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Vol. 31 No. 6 NOVEMBER - DECEMBER 2023

CONTENTS

Thai Journal of Obstetrics and Gynaecology
November 2023, Vol. 31, No. 6, pp. 387.

EDITORIAL

This sixth issue of Thai Journal of Obstetrics and Gynaecology 2023 contains many interesting articles. One special article is "Nutrition during pregnancy". This article provides the information of nutrition requirement in pregnant women of normal weight and the optimal weight gain in pregnancy.

Editor in Chief and managing staff of the Thai Journal of Obstetrics and Gynecology already attended the meeting "The 2nd System Development and Quality Improvement of Thai Journals Indexed in Scopus, Phase 2" On Thursday, October 19, 2023 from 9:00 a.m. - 3:00 p.m. at the Eastin Grand Hotel, Phayathai. This meeting included editors and working groups of journals in the project. A total of 250 people attended the meeting (93 journals). This meeting mentioned the overall picture of the project: TCI-TSRI-Scopus Collaboration Project phase 1 and 2. The meeting also aimed to carry out journal work, to improve quality and increase the number of research articles and raise the quartile level of Thai journals in the Scopus database, to push journals into international databases and improve the quality of Thai journals and to create knowledge and understanding about the evaluation process of the Thai Local Board to work efficiently.

For the coming New Year 2024, we would like to extend our warmest wishes to The Royal Thai College of Obstetricians and Gynaecologists members, editorial board, reviewers, authors and families. We thank to all the authors, readers, reviewers, and editors for your contributions to Thai Journal of Obstetrics and Gynecology this past year and look forward to receiving your valuable contributions in 2024.

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

Thai Journal of Obstetrics and Gynaecology
November 2023, Vol. 31, No. 6, pp. 388-398.

SPECIAL ARTICLE

Nutrition during Pregnancy

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ABSTRACT

Maternal nutrition is the only source of support fetal growth and has effects on offspring health. Nutrition management is important during pregnancy, and this should start from preconception. Women should have a normal prepregnancy BMI and optimal gestational weight gain to have favorable pregnancy outcomes. It is suggested that pregnant women have a healthy balanced diet with adequate calories. The proportion of total daily energy should consist of carbohydrate 45 - 65%, protein 10 - 15%, and fat 20 - 35% from various sources to ensure a sufficient intake of macronutrients and micronutrients. Because of increased demand during pregnancy, some supplements may be necessary. Folic acid and iron supplementation is generally recommended. Supplementation with iodine and calcium should be considered in pregnant women at risk of low dietary intake. Pregnant women should concern about food safety, foods to avoid during pregnancy, and beware of excessive vitamin A and iodine intake.

Keywords: Nutrition, preconception, pregnancy.

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Having good obstetric care and healthy pregnancy lifestyles consisting of good nutritional status, staying physically active and good mental well-being, can lead to favorable pregnancy outcomes. Maternal nutritional status is important due to growing fetuses can only receive nutrition through their mothers. Recently, the 'early life programming' theory has indicated that environmental factors and lifestyles during pregnancy determine the risk of developing chronic diseases later in life and influence lifelong health in offspring. Nutrition in early life may be one mechanism that programs through epigenetic phenomena or deoxy-ribonucleic acid (DNA) methylation and affects gene expression. Either maternal undernutrition or overnutrition can result in reprogramming of fetal tissue[1].

A singleton pregnancy requires an additional 80,000 kcal, 46% for the fetus and placental, 27% for blood volume, extravascular volume, including breast tissue, and 27% for maternal accumulation. Excess caloric intake leads to maternal fat accumulation, whereas inadequate caloric intake results in protein

metabolism[2,3]. To determine maternal nutritional status, gestational weight gain (GWG) can be one of the important anthropometric assessments.

Optimal gestational weight gain

The National Academy of Medicine (NAM), formerly called the Institute of Medicine (IOM), has recommended optimal GWG in singleton pregnancy according to prepregnancy body mass index (BMI) categories (Table 1)[4, 5].

Table 1. The recommended optimal gestational weight gain in singleton pregnancy according to prepregnancy body mass index categories[4, 5].

Pre-pregnancy BMI (kg/m^2)	Pre-pregnancy weight category	Total weight gain range (kg)	Weight gain rate in the second and third trimesters (kg/week)
< 18.5	Underweight	12.5 - 18.0	0.51 (0.44 - 0.58)
18.5 - 24.9	Normal weight	11.5 - 16.0	0.42 (0.35 - 0.50)
25.0 - 29.9	Overweight	7.0 - 11.5	0.28 (0.23 - 0.33)
≥ 30	Obesity	5.0 - 9.0	0.22 (0.18 - 0.27)

Inadequate GWG was associated with low birth weight (LBW), small for gestational age (SGA), and preterm birth. In contrast, excessive weight gain during gestation could result in macrosomia, large for gestational age (LGA), increased rate of cesarean sections, pregnancy-induced hypertension, gestational diabetes, postpartum weight retention and the obesity in both mother and offspring[6,7]. These consequences were more evident in underweight women with inadequate GWG and in overweight women with excessive GWG. Currently, pregnant women tend to be overweight and have an excessive GWG. Some randomized control trials had shown that interventions, for example, diet control, exercise, in person visits, text messages, mobile application or combination, could decrease GWG, but did not affect perinatal outcomes[3]. Furthermore, in women with obesity, gestational weight loss could cause increased risks of SGA, LBW, and preterm delivery without any benefit in reducing the risk of preeclampsia and gestational diabetes3. As a result, IOM has recommended that all women should have a normal BMI before becoming pregnant and have appropriate GWG.

However, the IOM recommendations for optimal GWG came from studies in western countries that included a small proportion of Asian women. Furthermore, the World Health Organization (WHO) had issued different weight categories for Asian8 (underweight BMI < 18.5 kg/m^2, normal weight BMI 18.5 - 22.9 kg/m^2, overweight BMI 23.0 - 27.5 kg/m^2, obese BMI ≥ 27.5 kg/m^2). Some Asian countries such as Japan and Vietnam had developed the national guideline for optimal GWG due to concerns that the IOM classification might not be appropriate for Asian women. In Australia, different recommendations have been used for non-Asian and Asian women9. However, the IOM classification is still used in most countries, Thailand included[9,10].

In 2016, a retrospective study in China had compared pregnancy outcomes between 13,717 subjects with optimal GWG according to the IOM BMI cut-off points and the WHO Asian BMI cut-off points. The result showed that although the rate of preterm birth, pregnancy induced hypertension, and gestational diabetes was not significantly different between groups, there was a significantly lower risk of macrosomia and LGA in women with optimal GWG

according to the WHO Asian BMI cut-offs. Therefore, it was possible that GWG ranges based on IOM BMI cut-offs would classify some women in lower prepregnancy BMI categories and suggest they gain more weight, which can put them at higher risk for macrosomia and LGA[6].

Nutrition management in pregnant women of normal weight

Macronutrients

Macronutrients, consisting of carbohydrates, protein, and fat, are the nutrients that provide energy to the body and are needed in large quantities. The energy requirement in Thai women adults (aged 19 to 60) is approximately 1,500 - 1,800 kcal/day. Pregnant women require additional energy for 50 to 100 kcal/day in the first trimester, 250 to 300 kcal/day in the second trimester, and 450 to 500 kcal/day in the third trimester[10,11]. The main energy sources of the body are carbohydrates and fats, which are needed for 45 - 65% and 20 - 35% of the total daily energy requirement, respectively. On the other hand, proteins that should account for 10 - 15% of total daily energy are used mainly for the structure, function, and regulation of tissues and organs rather than for energy[10-12].

Carbohydrates

Carbohydrates are important for developing fetuses because glucose is used as an energy-producing substrate in fetal tissues, especially the brain[10,12]. Carbohydrates are classified into simple carbohydrates consisting of monosaccharides and disaccharides, and complex carbohydrates, which are starch, glycogen, and dietary fiber. In addition to the appropriate proportion of energy from carbohydrates, the IOM has also recommended that metabolically available dietary carbohydrate intake be not less than 175 grams/day or approximately 12 portions[12]. One carbohydrate portion is equal to 15 grams of carbohydrate, which can be found in a slice of bread, one third cup of cooked rice or noodles, a cup or 8 ounces of low-fat milk, a small banana or apple for examples[13]. Good sources of carbohydrates are whole grains, brown rice, whole wheat, and starchy vegetables. Fruits have a high level of simple sugar but are rich in micronutrients and dietary fibers, thus regular consumption of a variety of fruits is suggested. Foods to avoid are sweets, candy, soda pop, cake and bakery[10,12].

There was concern that non-nutritive sweeteners (NNS) could be consumed during pregnancy or not. Non-nutritive sweeteners such as saccharin, acesulfame-K, and sucralose can be transferred to fetuses through the placenta, while aspartame is completely metabolized in the maternal body, and there is insufficient data for steviosides. To date, no studies have investigated maternal glycemic outcomes of NNS consumption. No studies show the teratogenicity or fetal toxicity of NNS; however, some studies have revealed that NNS may cause an alteration in the maternal gut microbiome and the induction of fetal tissue programming. Regular consumption of maternal NNS has been associated with a higher risk of having overweight or obese offspring[14,15]. Currently, there is no recommendation on NNS consumption during pregnancy.

Dietary fibers are non-metabolically available carbohydrates. IOM recommends that pregnant women consume 28 grams/day of dietary fiber from whole grains, legumes, fruits, and vegetables. Adequate fiber consumption and water intake of 2 - 3 liters/day from both foods and beverages can improve constipation during pregnancy; however, excessive fiber intake can result in gastrointestinal distress and mineral absorption disturbance[10,12].

Proteins

The Thai Bureau of Nutrition has recommended that Thai adults should have 1 gram/kilogram body weight/day of protein intake with additional protein intake in pregnant women for 1 gram/day in the first trimester, 10 grams/day in the second trimester and 31 grams/day in the third trimester. However, for convenience, the Thai Bureau of Nutrition suggests the consumption of 12 tablespoons of a variety of lean

meat, legumes, eggs and tofu per day, together with a low-fat or fat-free milk consumption[10].

A whole egg contains 6 grams of protein. The yolk egg is rich in micronutrients but has a high level of fat. However, the consumption of 1-2 whole eggs a day in healthy people does not affect blood lipid concentration[16]. During pregnancy, low-fat and fat-free pasteurized or ultra-high temperature (UHT) milk is recommended. Milk is not only a source of protein and calcium, but it also has a growth promoting effect in offspring. The Danish National Birth Cohort showed that daily maternal milk consumption of more than 150 milliliters had a protective effect on SGA, while consumption of more than 1,200 milliliters increased the risk of LGA[17]. A recent systematic review and meta-analysis of 18 studies found a curved relationship between maternal dairy consumption and birth anthropometrics, which increased first and then decreased, suggesting that there was an optimal amount of dairy consumption during pregnancy[18]. However, no interventional study has investigated this issue. The US Department of Agriculture (USDA) dietary guideline recommends consuming dairy products 3 cups/day (720 milliliters)[19], but this is still controversial among dietary experts. The dietary reference intake by the Thai Bureau of Nutrition has suggested that daily milk consumption of 1-2 cups should be appropriated[10]. There is concern about maternal milk consumption and the risk of food allergy in offspring, but there is insufficient evidence to determine the relationship between restricted consumption of cow milk products during pregnancy and the risk of childhood allergy at present[20].

Fats

In addition to being a source of body energy, fat aids in the absorption of fat-soluble vitamins. There is insufficient data to determine a definite level of fat intake, but approximately 20-35% of the total daily energy requirement is recommended[10,12]. Although saturated fatty acids, which can be found in meat, dairy products, coconut oil, and palm oil, should be consumed less than 10% of total daily energy, moderate intake of monounsaturated and polyunsaturated fatty acids is known to have a positive effect on health. Olive oil is an example of food high in monounsaturated fatty acids. Linoleic acid (omega-6) and α-linolenic acid (omega-3) are essential since these two polyunsaturated fatty acids (PUFA) cannot be synthesized in the body but are only derived from the consumption of nuts and vegetable oil such as soybean oil, rice bran oil, and canola oil. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are also omega-3 PUFAs, but can be synthesized from α-linolenic acid, or directly derived from eating seafood, especially cold-water fatty fish such as salmon[10,12].

EPA and DHA are precursors of a variety of compounds that help resolve inflammatory responses and oxidative stress. Furthermore, DHA is involved in the development of retinal and brain function[12,21]. Many studies have investigated the effects of fish oil supplements and certain issues, for example: preterm labor, preeclampsia, neurodevelopment, childhood allergy, and risk of bleeding. In 2018, a Cochrane systematic review that included 70 randomized trials that included participants in 19,927 showed that 500 - 1,000 milligrams/day of fish oil supplement started before 20 weeks of gestation significantly reduced the risk of preterm birth but could increase the rate of postterm pregnancy without increasing the rate of cesarean section and induction of labor[21]. In the following year, a multicenter randomized double-blind controlled trial that included 5,544 participants revealed a contradictory result. The 900 milligrams / day fish oil supplement did not appear to reduce preterm birth even after a subgroup analysis of baseline DHA levels[22]. The fish oil supplement did not prevent preeclampsia and did not increase blood loss during delivery or postpartum hemorrhage[21]. Regarding neurodevelopment, a single center randomized double-blind controlled trial in Denmark showed that a 2.4 gram/day fish oil supplement continued from 24 weeks of gestation to 1 week postpartum significantly improved language development at 1 year. Interestingly, only boys in the

fish oil supplement group could achieve gross motor milestones at a younger age, had a greater cognitive improvement at 2.5 years and had less impact on emotional and behavioral problems at 6 years. It is possible that the involvement of testosterone in the inhibition of DHA synthesis may be involved in this sex preference benefit[23]. In the same study, the effect of fish oil on asthma prevention was also investigated and appeared to significantly reduce risk at 3 and 6-year of follow-up[24]. There is insufficient data from the interventional study to determine the effect of the fish oil supplement on the prevention of food allergy in childhood[25].

Despite controversy surrounding the fish oil supplement, regular consumption of fish during pregnancy is highly recommended. Fish is an excellent source of protein, is low in saturated fat, and contains a high amount of EPA and DHA compared to other types of meat. The US Food and Drug Administration (FDA) and the US Environmental Protection Agency (EPA) advise fish intake 8 - 12 ounces/week (227 - 340 grams) from choices lower in mercury[2,19]. The Thai Bureau of Nutrition recommends that pregnant women consume 2 tablespoons of fish every day or 4 tablespoons of fish every other day from various types of sea fish and freshwater fish[10]. As mentioned above, fish together with other lean meats, legumes, eggs, and tofu should be 12 tablespoons in total daily amount.

In summary, the eating pattern during pregnancy should be a healthy balanced diet that is rich in nutrients and has optimal calories. Meals should consist of whole grains, a variety of protein foods, low-fat or fat-free dairy products, soy products and a variety of fruits and vegetables in the appropriate amount (Fig. 1)[19].

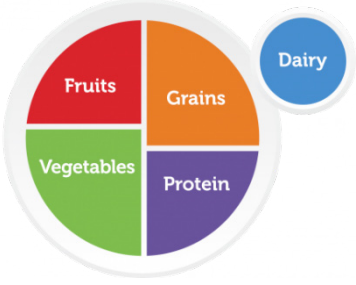

Fig. 1. The appropriate amount of each composition in meal[19].

Micronutrients

Minerals and vitamins are needed in a very small amount, but they have a critical impact on health. Dietary reference intake (DRI) is usually indicated as recommended dietary allowance (RDA), which is the average daily dietary intake level that is sufficient to meet the nutrient requirement of 97 - 98% of healthy individuals in a group, or adequate intake (AI), which is a value based on observed or experimentally determined approximations of nutrient intake by a group of healthy people. Another reference value that must be considered is tolerable upper intake level (UL), the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population[26].

The RDA or AI of minerals and vitamins for a singleton pregnancy suggested by IOM is shown in Table 2[26]. However, pregnant women who have healthy balanced meals should meet almost of these requirements and may need only several supplements, such as calcium, iron, iodine, and folic acid.

Table 2. The recommended dietary allowance or adequate intake of minerals and vitamins for a singleton pregnancy[26].

Minerals	Amount (mg/day)	Vitamins	Amount (mg/day)
Calcium	1,000	Vitamin A	0.77 (2,567 IU)
Iron	27	Vitamin D	600 IU/day
Iodine	0.22	Vitamin E	15
Chromium	0.03	Vitamin K	0.09
Copper	1.5	Thiamin (B1)	1.4
Fluoride	3	Riboflavin (B2)	1.4
Magnesium	300	Niacin (B3)	18
Manganese	2.5	Pantothenic acid (B5)	6
Molybdenum	0.05	Pyridoxine (B6)	1.9
Phosphorus	700	Biotin (B7)	0.03
Selenium	0.06	Folic acid (B9)	0.6
Zinc	11	Cobalamin (B12)	0.002
Potassium	4,700	Choline	450
Sodium	1,500	Vitamin C	85
Chloride	2,300		

Minerals

Calcium

Fetal skeletal development requires approximately 30 grams of calcium throughout pregnancy, primarily in the last trimester. Calcium-regulating hormones adjust maternal calcium absorption, so that the adequate calcium intake level does not increase during pregnancy[10,26]. IOM recommends 1,000 milligrams of calcium per day, while the Thai Bureau of Nutrition suggests that the 800 milligrams per day intake should be sufficient for Thai adults[10]. However, it was found that Thai people usually had suboptimal dietary calcium intake which was approximately 360 milligrams/day on average. Although pregnant women consume milk 1-2 cups a day, without adjustment of the diet, the dietary calcium intake may not meet the requirement. In addition to dairy products, pregnant women should consume high-calcium foods, for example tofu, fortified soy products, dried shrimp, crispy anchovy, beans, sesame, and leafy greens. High-oxalate vegetables such as spinach, noni leaf, betel leaf, and turkey berries should be avoided due to the inhibitory effect on calcium absorption[10].

Insufficient calcium intake, especially an intake of less than 500 milligrams/day for a long time, can lead to reduced bone mass during pregnancy. Excess calcium intake may cause kidney stone and interfere with other mineral absorption[10,26]. The WHO recommends calcium supplementation in pregnant women who have low dietary calcium intake to reduce the risk of preeclampsia and gestational hypertension[28,29]. There are several forms of calcium supplements which have a different amount of elemental calcium. Calcium carbonate has the highest elemental calcium which is 40%, while calcium citrate, calcium lactate, and calcium gluconate have elemental calcium 21%, 13%, and

9%, respectively. Calcium absorption is approximately 30%[10].

Iron

In a healthy pregnant woman, 1,000 milligrams of iron are required during pregnancy, mainly after mid-trimester, but few women have sufficient iron stores or dietary intake to supply this amount[29]. Dietary iron in the form of heme iron found in meat and blood curd has better bioavailability, which is 20-30% absorption. On the other hand, the absorption of nonheme iron which is found in egg, milk, beans, and leafy greens is only 2 - 10%. Furthermore, the phytate in beans and vegetables usually interferes with iron absorption, causing the total iron bioavailability on a Thai meal to be 10% in average[10,26].

Pregnant women with inadequate iron intake can cause iron deficiency anemia and increase the risk of prematurity and low birth weight, while those with excessive iron intake can have gastrointestinal effects such as nausea, vomiting, constipation, and diarrhea[10, 26, 29]. Dietary reference intake of iron and recommendations for supplementation vary across countries. Some countries have promoted the fortification of foods with iron and do not routinely recommend iron supplement except for pregnant women who are at risk of iron deficiency. However, the WHO recommends iron supplementation of 30 - 60 milligrams/day to all pregnant women to prevent anemia[30]. Accordingly, Thai Bureau of Nutrition also recommends 60 milligrams/day iron supplementation during pregnancy[10]. There are four types of oral iron supplement, ferrous fumarate which has 33% elemental iron, ferrous sulfate which has 20% elemental iron in hydrated form and 30 - 37% in desiccated form, ferrous gluconate which has 12% elemental iron, and lastly, iron hydroxy polymaltose complex, which is a non-ionic preparation with better bioavailability and less gastrointestinal side effects.

Iodine

Iodine is an essential component to produce thyroid hormone that plays an important role throughout pregnancy. The adequate level of iodine increases 50 micrograms/day during pregnancy due to increased maternal thyroid hormone production, fetal and placental iodine uptake, and increased renal excretion. Iodine deficiency has potentially harmful effects, for example, goiter, maternal and/or neonatal hypothyroidism, greater risk of abortion, stillbirth, and cretinism[10, 26]. People in Bangkok and southern Thailand generally have adequate iodine intake, as well as in central and northern Thailand where people have borderline sufficiency in iodine consumption. However, people in some area of northeastern Thailand have a suboptimal iodine intake[10].

Iodine is high in seafood, seaweed, and iodized salt. Most prenatal multivitamins and minerals usually consist of iodine. The RDA for iodine is in the range of 0.20 to 0.25 milligrams/day, slightly varying between recommendations. The American Thyroid Association (ATA) recommends a 0.15 milligram/day iodine supplement during pregnancy unless pregnant women consume levothyroxine regulary[10, 26, 31]. The tolerable upper intake level of iodine is 1.1 milligrams/day. Excessive iodine intake, uncommon, but may be a result of supplements, can lead to fetal goiter and thyroid dysfunction[10, 26].

Vitamins

Folic acid

Folate or folic acid is an essential coenzyme in the metabolism of nucleic acids, and the amino acid, methionine cycle and involves in DNA replication and cell division process[10, 26]. Generally, a daily 0.1 - 0.2 milligrams of folate is derived from natural foods such as meat, beans, and leafy greens. The folic acid found in fortified foods and dietary supplements has greater bioavailability, with 80 - 90% absorption. The Thai Bureau of Nutrition recommends 0.55 mg/day of folic acid intake. Inadequate folic acid intake can lead to macrocytic anemia, but excessive intake can mask vitamin B12 deficiency and lead to persistent neurological damage. For pregnant women, folic acid

supplementation is recommended to reduce the risk of neural tube defect (NTD) in the fetus[10, 26]. A previous study in Thailand found that preconception folic supplementation was used in only 9.7%[32].

In all women with an average risk of fetal NTD, a daily 0.4 mg folic acid supplement is recommended at least 1 month before conception to 12 weeks of gestation. A history of NTD in a previous child or a personal history of NTD in either parent poses a high risk of NTD, therefore a high dose of folic acid supplement for 4-5 milligrams/day is strongly recommended 1-3 months before conception to 12 weeks of gestation to reduce the risk of NTD in a fetus for 70%[33-36]. For women with moderate risk, for example: having a family history of other folic acid-sensitive congenital anomalies including cleft lip/palate, heart defect, and limb reduction defect, and having maternal medical conditions related to folic acid depletion, recommendations vary regarding these conditions. However, after 12 weeks of gestation, it is recommended to reduce the dose of folic acid supplement to 0.4 milligrams/day[33-37].

Vitamin A

Vitamin A is important for vision, gene expression, reproduction, immune function, embryo development, and growth[10,26]. It can be found as retinoids in meat, eggs, milk, and as carotenoids in fruits and vegetables. Thai Bureau of Nutrition recommends vitamin A intake of 0.7 mg/day[10]. Inadequate vitamin A intake results in xerophthalmia, night blindness, and decreased immune function. Vitamin A deficiency is not a serious problem in Thailand; therefore, the importance of the recommendation for vitamin A intake is mainly based on tolerable upper intake level, which must not exceed 3 mg/day or 10,000 IU. A higher amount than this reference can cause defects in the cranial neural crest in fetuses, and a very large amount of vitamin A intake can lead to hypervitaminosis A[10, 26, 38]. However, carotenoids do not lead to vitamin A toxicity and teratogenicity. A prenatal multivitamin tablet always contains vitamin A at a lower level than 10,000 IU unless pregnant women have multiple supplements.

Vitamin D

Vitamin D plays an important role in calcium and phosphate homeostasis. It also supports cellular processes, neuromuscular function, and bone ossification. Eighty to ninety percent of derived vitamin D is synthesized from UVB in the skin and 10-20% comes from foods, found mainly in fortified milk and dietary supplements. A small amount of vitamin D is found in natural food sources[10, 26, 39].

The IOM and the Thai Bureau of Nutrition recommend a vitamin D intake of 600 IU/day, while the US endocrine society recommends 1,500 - 2,000 IU/day. The difference between both recommendations from the US IOM report and the US Endocrine Society guideline reflects different definitions of vitamin D deficiency and the goals of treatment. Insufficient vitamin D consumption causes impaired bone mineralization and can lead to rickets or osteomalacia. Excess vitamin D consumption may lead to hypervitaminosis D, which is a rare condition[10, 40, 41].

Regarding the effects of vitamin D intake on pregnancy outcomes, there was no difference in pregnancy duration, birth weight, stillbirth, and neonatal death between pregnant women who received vitamin D and placebo[39]. Recent evidence suggested that women with vitamin D deficiency were at increased risk of miscarriage, but there was limit data to determine whether vitamin D would decrease the risk[42]. Due to the actions of vitamin D that are involved not only in calcium homeostasis and suppression of vascular smooth muscle cell proliferation but also regulate renin-angiotensin system and have immunomodulatory effects, vitamin D supplementation for the prevention of preeclampsia has been investigated. However, the advantage of supplementation is still inconclusive. It was also found that co-administration of vitamin D and calcium did not bring any additional benefit compared to vitamin D or calcium supplementation alone[43, 44].

To what extent micronutrient supplementation is necessary may still be difficult to conclude. Although

there was evidence that micronutrient deficiencies negatively affected maternal health and pregnancy outcomes, no single micronutrient was responsible for adverse effects. Furthermore, most of the interventional studies on supplementation had been conducted in developed countries where severe deficiencies were rare[45]. Therefore, some effects of supplementation may not be clearly seen.

Food safety concerns

During pregnancy, food safety recommendations should be followed to prevent foodborne illness. Good hand hygiene is the first step, as well as kitchen utensils that must be clean before preparing food or having meals. The knives used with meat and those used with fruits or vegetables should be separated to prevent cross-contamination. The ingredients should be thoroughly cooked at proper cooking temperatures. Uneaten or leftover foods should be immediately stored in the refrigerator. Lastly, there are some foods to avoid during pregnancy. Cold cuts, smoked seafood, uncooked bean sprouts, ready-to-eat foods such as salads and sausages can be contaminated with listeria, as well as soft cheeses such as brie cheese blue cheese, and feta cheese which are usually made from unpasteurized milk. These foods should be avoided or cooked properly to prevent listeriosis. Undercooked meat, raw seafood, and unwashed fruits and vegetables can be contaminated with toxoplasma and salmonella. Sometimes salmonella may be contained in raw eggs, particularly from a low-quality source. Therefore, only cooked eggs should be consumed and some desserts that include raw eggs such as tiramisu, mousse, and frozen egg ice cream should be avoided. In addition, alcohol consumption should be prohibited during pregnancy. Liver and liver sausage consumption should be limited in early pregnancy due to the high level of vitamin A. Caffeine, not only found in coffee and tea, but also in chocolate and soda pop, should be limited to not exceed 200 milligrams/day due to the increased risk of miscarriage[36, 46].

Conclusion

Maternal nutrition is the only source of support fetal growth and has effects on offspring health. Nutrition management is important during pregnancy, and this should start from preconception. For favorable pregnancy outcomes, women should have a normal prepregnancy BMI and optimal gestational weight gain. It is suggested that pregnant women have a healthy balanced diet with adequate calories. The proportion of total daily energy should consist of carbohydrate 45 - 65%, protein 10 - 15%, and fat 20 - 35% from various sources to ensure a sufficient intake of macronutrients and micronutrients. Because of increased demand during pregnancy, some supplements may be necessary. Folic acid and iron supplementation is generally recommended. Supplementation with iodine and calcium should be considered in pregnant women at risk of low dietary intake. Although vitamin D is known to be involved in many cellular processes, now there is no evidence that vitamin D supplement has a positive effect on pregnancy outcome. Supplementation with DHA or fish oil is still controversial and further evidence may be needed to determine the advantage of supplementation. Pregnant women should concern about food safety, foods to avoid during pregnancy, and beware of excessive vitamin A and iodine intake.

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OBSTETRICS

Assessment of Fetal Cardiac Function in Women with Chronic Hypertension

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ABSTRACT

Objectives: The primary objective was to compare the fetal myocardial performance index (MPI) among pregnant women with chronic hypertension and women with normal blood pressure. The secondary objectives were to evaluate whether the fetal MPI can predict adverse perinatal outcomes and to assess uterine, middle cerebral, and umbilical arteries in pregnant women with chronic hypertension and normal blood pressure.

Materials and Methods: A cross-sectional study enrolled singleton pregnancies with a gestational age of 28-32 weeks in the antenatal clinic at King Chulalongkorn Memorial Hospital between April 2020 - April 2021. This study divided pregnant women into two groups, those with normal blood pressure and those with chronic hypertension. The fetuses were evaluated for growth, amniotic fluid volume, and fetal cardiac function.

Results: The median of modified MPI was not different between chronic hypertension and control groups (0.49 vs 0.47, p = 0.691, adjusted p = 0.299). The median of the Doppler studies showed no differences between groups in the left uterine artery pulsatility index (PI) (0.78 vs 0.76, p = 0.085, adjusted p = 0.902), right uterine artery PI (0.83 vs 0.75, p = 0.159, adjusted p = 0.442), umbilical artery PI (0.94 vs 0.93, p = 0.982, adjusted p = 0.060), middle cerebral artery PI (1.86 vs 1.80, p = 0.311, adjusted p = 0.05). The chronic hypertension group developed more maternal adverse outcomes, such as gestational age at birth (36.8 ± 2.19 vs 38.2 ± 1.31, p < 0.001, adjusted p < 0.001). Women in the chronic hypertension group also experienced more neonatal adverse outcomes, including length of hospital stays (4.0 vs 3.0, p < 0.001, adjusted p = 0.001). No differences were found in other neonatal adverse outcomes.

Conclusion: There was no difference in the median of the MPI between pregnant women with normal blood pressure and women with chronic hypertension. The Doppler studies of the umbilical artery, middle cerebral artery, and uterine artery were not different between the chronic hypertension group and the control group. The modified MPI may not be predictive of perinatal outcomes.

Keywords: adverse perinatal outcome, chronic hypertension, fetal cardiac function, modified myocardial performance index (Mod-MPI).

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การตรวจคลื่นเสียงความถี่สูงเพื่อประเมินการทำงานของหัวใจของทารกในสตรีตั้งครรภ์ที่มีภาวะความดันโลหิตสูงก่อนการตั้งครรภ์

ธัญลักษณ์ บุญประสิทธิ์, ธีระภัทร เจริญวิทย์

บทคัดย่อ

วัตถุประสงค์: เพื่อเปรียบเทียบการทำงานของหัวใจทารกในครรภ์ระหว่างสตรีตั้งครรภ์ที่มีภาวะความดันโลหิตสูงก่อนการตั้งครรภ์กับสตรีตั้งครรภ์ที่มีความดันโลหิตปกติในช่วงอายุครรภ์ 28-32 สัปดาห์ เพื่อศึกษาค่าการทำงานของหัวใจทารกในสตรีตั้งครรภ์ที่มีภาวะความดันโลหิตสูงก่อนการตั้งครรภ์ในช่วงอายุครรภ์ 28-32 สัปดาห์ สามารถทำนายภาวะแทรกซ้อนต่อทารกในครรภ์ และเพื่อศึกษาความต้านทานของเส้นเลือด uterine artery, middle cerebral artery, umbilical artery ในสตรีตั้งครรภ์ที่มีความดันโลหิตสูงก่อนการตั้งครรภ์โดยเปรียบเทียบกับสตรีตั้งครรภ์ที่มีความดันโลหิตปกติในช่วงอายุครรภ์ 28-32 สัปดาห์

วัสดุและวิธีการ: รูปแบบการศึกษาเป็นการศึกษาแบบ cross sectional study ในสตรีตั้งครรภ์เดี่ยวที่มีอายุครรภ์ระหว่าง 28-32 สัปดาห์ ที่มารับการตรวจฝากครรภ์ที่โรงพยาบาลจุฬาลงกรณ์ ในช่วงเดือน เมษายน พ.ศ.2563 - เมษายน 2564 ในการศึกษานี้แบ่งสตรีตั้งครรภ์เป็น 2 กลุ่ม คือ กลุ่มสตรีตั้งครรภ์ที่มีภาวะความดันโลหิตสูงก่อนการตั้งครรภ์หรือมีความดันโลหิตสูงก่อนอายุครรภ์ 20 สัปดาห์ และกลุ่มสตรีตั้งครรภ์ที่มีความดันโลหิตปกติ สตรีตั้งครรภ์ทั้ง 2 กลุ่มจะได้รับการตรวจคลื่นเสียงความถี่สูงประเมินน้ำหนักทารก ปริมาณน้ำคร่ำ ความต้านทานของเส้นเลือด uterine artery, middle cerebral artery, umbilical artery และการทำงานของหัวใจทารก (modified myocardial performance index)

ผลการศึกษา: ค่าการทำงานของหัวใจทารก (modified myocardial performance index) ไม่แตกต่างกันระหว่างสตรีตั้งครรภ์ที่มีความดันโลหิตสูงก่อนการตั้งครรภ์กับสตรีตั้งครรภ์ที่มีความดันโลหิตปกติ (0.49 vs. 0.47, p=0.691, adjusted p=0.299) ค่ามัธยฐานของค่าความต้านทานของเส้นเลือด left uterine artery PI (0.78 vs. 0.76, p=0.085, adjusted p=0.902), right uterine artery PI (0.83 vs. 0.75, p=0.159, adjusted p=0.442), umbilical artery PI (0.94 vs. 0.93, p=0.982, adjusted p=0.060) และ middle cerebral artery PI (1.86 vs. 1.80, p=0.311, adjusted p=0.050) ไม่แตกต่างกันระหว่างสตรีตั้งครรภ์ทั้งสองกลุ่ม ในกลุ่มสตรีตั้งครรภ์ที่มีความดันโลหิตสูงก่อนการตั้งครรภ์มีภาวะแทรกซ้อนต่อมารดามากกว่ากลุ่มสตรีตั้งครรภ์ที่มีความดันโลหิตปกติ ได้แก่ อายุครรภ์ที่คลอดบุตร (36.8 ± 2.19 vs 38.2 ± 1.31, p < 0.001, adjusted p < 0.001) และมีภาวะแทรกซ้อนต่อทารกหลังคลอดมากกว่า ได้แก่ ระยะเวลานอนโรงพยาบาลนานกว่า (4.0 vs 3.0, p < 0.001, adjusted p=0.001) ส่วนภาวะแทรกซ้อนอื่นๆ ต่อทารกพบว่าไม่แตกต่างกัน

สรุป: ค่าการทำงานของหัวใจทารก (modified myocardial performance index) ความต้านทานของเส้นเลือด umbilical artery, middle cerebral artery และuterine artery ไม่แตกต่างกันระหว่างสตรีตั้งครรภ์ที่มีความดันโลหิตสูงก่อนการตั้งครรภ์กับสตรีตั้งครรภ์ที่มีความดันโลหิตปกติ และจากการศึกษาแสดงให้เห็นว่าค่าการทำงานของหัวใจทารกในสตรีตั้งครรภ์ที่มีภาวะความดันโลหิตสูงก่อนการตั้งครรภ์ไม่สามารถทำนายภาวะแทรกซ้อนต่อทารกในครรภ์

คำสำคัญ: ภาวะแทรกซ้อนต่อทารกในครรภ์, ภาวะความดันโลหิตสูงก่อนการตั้งครรภ์, ค่าการทำงานของหัวใจทารก, Modified myocardial performance index (Mod-MPI)

Introduction

When hypertension is diagnosed before pregnancy or before 20 weeks of gestation, it is defined as chronic hypertension. Chronic hypertensive disease is reported in 0.5 - 5% of pregnancies[1,2]. The prevalence of chronic hypertension at King Chulalongkorn Memorial Hospital was 3.24% in 2017. The risk of chronic hypertension increases with obesity and advanced maternal age.

Chronic hypertension is related to insulin resistance and endothelial dysfunction. Correspondingly, pregnancy complications such as preeclampsia and gestational diabetes mellitus (GDM) are also associated with insulin resistance and endothelial dysfunction[3,4,5]. The most common comorbidities are pregestational diabetes, thyroid disorders, chronic renal disease, and collagen vascular disease[6].

Chronic hypertension is a risk factor for many adverse maternal and neonatal outcomes. Significant maternal morbidities are stroke, renal failure, pulmonary edema, severe preeclampsia, and placental abruption. Neonatal morbidities are fetal growth restriction, prematurity, low birth weight, respiratory distress syndrome, and stillbirth[7, 8, 9,10]. Pregnant women with this condition should be managed with appropriate maternal and fetal surveillance.

Chronic hypertension in pregnancy has also been attributed to placenta abnormalities such as decreased placenta vessel numbers, placental infarction, villous fibrinoid necrosis, and avascular villi. When the placenta is abnormal, it can cause fetal hemodynamic change, which can induce changes in fetal cardiac function.

Currently, fetal surveillance is conducted by a nonstress test (NST) and ultrasound. Ultrasound assesses fetal weight, amniotic fluid, Doppler waveform of vessels, and the myocardial performance index (MPI). MPI can be considered a direct parameter of cardiac dysfunction. In combination with other venous and arterial parameters, MPI helps define the fetal condition[11].

Studies have previously used the MPI to evaluate fetal cardiac function and predict adverse neonatal outcomes in conditions such as fetal growth restriction and preeclampsia. In 2019, Lina Zhang et al. reported that fetal growth restriction fetuses had an increased modified MPI which could predict adverse perinatal outcomes[12]. Alici Davutoglu et al[13] found that early-onset fetal growth restriction and late-onset fetal growth restriction fetuses have significantly higher modified MPI values demonstrating prenatal cardiac dysfunction. Sevket Balli et al[14] also demonstrated that the isovolumic relaxation time and the right and left MPI were higher in fetuses of preeclamptic mothers than in fetuses of non-preeclamptic mothers. Bhorat et al[15] also reported higher MPI values in the preeclamptic group. Fetal cardiac function was significantly impaired in pregnancies complicated by severe early-onset preeclampsia. They concluded that the MPI could be integrated into routine fetal surveillance techniques. No studies have used MPI to evaluate fetal cardiac status in pregnant women with chronic hypertension. This study was performed to compare the MPI of pregnant women with chronic hypertension to those with normal blood pressure and evaluate whether the MPI can predict adverse perinatal outcomes.

Materials and Methods

A cross-sectional study design recruited pregnant patients at the King Chulalongkorn Memorial Hospital antenatal clinic between April 2020 and April 2021. The inclusion criteria were singleton pregnant women above 18 years old with 28 - 32 weeks gestational age. The exclusion criteria were fetal structural or chromosome anomaly, underlying maternal disease (renal, liver, connective tissue disease), and tocolytic agents.

This study was divided into a control group of

pregnant women with normal blood pressure and a case group of pregnant women with chronic hypertension. Chronic hypertension in pregnancy was defined as hypertension diagnosed or present before pregnancy or before 20 weeks of gestation with a systolic blood pressure of 140 mm Hg or more, a diastolic blood pressure of 90 mm Hg or more, or both documented by a minimum of two determinations taken at least 4 hours apart[16].

No study had previously evaluated fetal cardiac function in pregnant women with chronic hypertension. This pilot study estimated the mean MPI in pregnant women with chronic hypertension. The sample size was calculated following Sevket Balli et al[14] and using a sample size calculation from two independent means. A minimum of 34 pregnant women corresponding to the criteria were required for the case and control groups.

The primary outcome of this study was to compare the fetal MPI between pregnant women with chronic hypertension and women with normal blood pressure. The secondary outcomes were to evaluate whether the fetal MPI in pregnant women with chronic hypertension can predict adverse perinatal outcomes and assess the uterine artery, middle cerebral artery, and umbilical artery in pregnant women with chronic hypertension and pregnant women with normal blood pressure.

All the women gave informed consent before enrolling in the study. The study was approved by the Institutional Review Board (IRB) at King Chulalongkorn Memorial Hospital. The fetuses were evaluated for growth, amniotic fluid volume, and fetal cardiac function. Fetal biometric measurements included biparietal diameter, head circumference, abdominal circumference, and femur length. Fetal weight was estimated. Doppler measurements of the umbilical artery (UA), middle cerebral artery (MCA), and uterine artery were assessed. Fetal cardiac function was evaluated using a modified MPI. A single operator (well-trained Maternal-Fetal medicine fellow under supervision by MFM staff) measured all parameters using the GE Voluson E10 (GE Medical Systems, Kretztechnik, Zipf, Austria). The intraclass correlation coefficient was 0.860 (95% confidence interval (CI) 0.578-0.962).

Modified myocardial performance index

A cross-sectional image of the five-chamber view of the fetal heart and an apical projection of the heart were obtained. The Doppler sample volume was placed on the lateral wall of the ascending aorta, below the aortic valve (AV), and above the mitral valve (MV). The ascending aorta aligns with an angle of insonation < 20 degrees. The Doppler trace showed an echo corresponding to the opening and closure of the mitral valve and aortic valve waveforms. The periods were estimated as follows: the isovolumetric contraction time (ICT) was estimated from the closure of the mitral valve to the opening of the aortic valve, the ejection time (ET) from the opening to the closure of the aortic valve, and the isovolumetric relaxation time (IRT) from the closure of the aortic valve to the opening of the mitral valve. The modified MPI was calculated as (ICT + IRT)/ET[17, 18].

Uterine artery Doppler assessment

The probe was placed longitudinally in the lower lateral quadrant of the abdomen. Color flow mapping is useful for identifying the uterine artery as it crosses the external iliac artery. The pulsed-wave Doppler sampling gate should be narrow (~ 2 mm). The insonation angle should be < 30°, and the peak systolic velocity should be > 60 cm/s. The PI was measured when at least three identical waveforms were obtained[19, 20].

Middle cerebral artery Doppler assessment

An axial brain section, including the thalami and the sphenoid bone wings, should be obtained and magnified. The circle of Willis and the proximal MCA was identified using color flow mapping. The pulsed-wave Doppler gate should then be placed at the proximal third of the MCA, and the angle of insonation should be kept as close as possible to 0°. The PI was measured when at least three identical

waveforms were obtained[20, 21].

Umbilical artery Doppler assessment

The umbilical cord was visualized in a longitudinal section in a free loop and magnified to the maximum possible extent without fetal movements or breathing. The angle of insonation was less than 60°. The PI was measured when at least three identical waveforms were obtained[20,22].

Statistical analysis

SPSS (IBM Corp. IBM SPSS Statistics for Windows, version 22.0, Armonk, NY: IBM Corp) was used for statistical analysis. The Kolmogorov-Smirnov test was used to check the normality of the variable distribution. Data are presented with mean ± standard deviation (SD) and median (interquartile range, IQR). Pearson's chi-square or Fisher's exact test was used to compare categorical data. An independent t-test was used in a comparison of parametric variables, and a Mann-Whitney U test was used for comparing continuous data with non-normal distributions. Multiple regression was used to model the effect of different baseline characteristics on each response variable. Multiple logistic regression was established to determine the association between binary outcomes and chronic hypertension group adjusted with maternal age, gestational diabetes (GDM) and body mass index (BMI). A p-value of < 0.05 was considered statistically significant.

Results

A total of 140 pregnant women were enrolled in this study. Forty women had chronic hypertension, and 100 women had normal blood pressure. All the fetuses were evaluated for growth, amniotic fluid volume, fetal cardiac function, and Doppler measurement between 28-32 weeks of gestational age and followed up by adverse maternal and neonatal outcomes.

The two groups' baseline characteristics were compared (Table 1). The chronic hypertension group were older (35.73 ± 4.27 vs 32.81 ± 5.50, p = 0.003) and had a higher BMI (32.42 ± 6.15 kg/m^2 vs 21.95 ± 3.69 kg/m^2, $p < 0.001$). Gestational diabetes mellitus was also more prevalent in the chronic hypertension group compared to the normal group (45% vs 0%, $p < 0.001$) (Table1).

Table 1. Baseline characteristics.

	Chronic hypertension (n = 40)	Normal blood pressure (n = 100)	p value
Maternal age (years)	35.73 ± 4.27	32.81 ± 5.50	0.003†
Gravida (%)			0.433*
- Primigravida	12 (30.0%)	37 (37%)	
- Multigravida	28 (70.0%)	63 (63%)	
Other underlying disease (%)			
- Heart disease	0 (0%)	2 (2%)	1.000*
- Chronic Hepatitis B infection	0 (0%)	1 (1%)	1.000*
- GDM	18 (45.0%)	0 (0%)	< 0.001*
- No underlying disease	22 (55.0%)	97 (97%)	< 0.001*
BMI (kg/m^2)	32.42 ± 6.15	21.95 ± 3.69	< 0.001†

BMI: body mass index, GDM: gestational diabetes mellitus

Data are presented as the mean ± standard deviation or n (%).

* Fisher's exact test or Pearson's chi-square test. † Independent t-test.

Sonographic data, including the mean of gestational age at the time of ultrasound (29.70 ± 1.29 vs 30.05 ± 0.97, p = 0.082, adjusted p = 0.108), median estimated fetal weight (1389.50 vs 1521.00, p = 0.039, adjusted p = 0.006), median deep vertical pocket (5.50 vs 4.90, p = 0.109, adjusted p = 0.698) as well as the median of the Doppler studies including left uterine artery PI (0.78 vs 0.76, p = 0.085, adjusted p = 0.902), right uterine artery PI (0.83 vs 0.75, p = 0.159, adjusted p = 0.442), umbilical artery PI (0.94 vs 0.93, p = 0.982, adjusted p = 0.060), middle cerebral artery PI (1.86 vs 1.80, p = 0.311, adjusted p = 0.05), were not different between chronic hypertension group and control group (Table 2).

Table 2. Sonographic data and comparison of UtAPI, UAPI, MCA PI.

	Chronic hypertension (n = 40)	Normal blood pressure (n = 100)	p value	Adjusted p value[ψ]
GA at USG (weeks)	29.70 ± 1.29	30.05 ± 0.97	0.082[†]	0.108
EFW (grams)	1389.50 (1232.00 - 1623.00)	1521.00 (1368.75 - 1637.75)	0.039[‡]	0.006
DVP (cm)	5.50 (4.45 - 6.28)	4.90 (4.35 - 5.85)	0.109[‡]	0.698
Left Uterine artery PI	0.78 (0.61 - 1.31)	0.76 (0.59 - 0.92)	0.085[‡]	0.902
Right Uterine artery PI	0.83 (0.63 - 1.31)	0.75 (0.63 - 1.30)	0.159[‡]	0.442
Umbilical artery PI	0.94 (0.86 - 1.03)	0.93 (0.82 - 0.93)	0.982[‡]	0.060
Middle cerebral artery PI	1.86 (1.62 - 2.37)	1.80 (1.63 - 2.07)	0.311[‡]	0.050

USG: ultrasound, EFW: estimate fetal weight, DVP: deep vertical pocket, PI: pulsatility index

Data are presented as the mean ± standard deviation or median (interquartile range) or n (%).

[†] Independent t-test. [‡] Mann Whitney U test, [ψ] Adjusted p value for maternal age, GDM, BMI, using multivariate linear regression.

No significant differences were found in the median MPI (0.49 vs 0.47, p = 0.691, adjusted p = 0.299), isovolumetric relaxation time (44.00 vs 47.00, p = 0.785, adjusted p = 0.232), ejection time (173.00 vs 178.00, p = 0.133, adjusted p = 0.179) but isovolumetric contraction time was decreased in chronic hypertension group (36.00 vs 36.00, p = 0.380, adjusted p = 0.019) (Table 3).

Table 3. Modified myocardial performance index.

	Chronic hypertension (n = 40)	Normal blood pressure (n = 100)	p value	Adjusted p value[ψ]
ICT, ms	36.00 (29.25 - 40.00)	36.00 (27.00 - 49.00)	0.380[‡]	0.019
IRT, ms	44.00 (40.00 - 53.00)	47.00 (40.00 - 58.00)	0.785[‡]	0.232
ET, ms	173.00 (157.00 - 182.00)	178.00 (169.00 - 187.00)	0.133[‡]	0.179
Modified MPI	0.49 (0.40 - 0.55)	0.47 (0.40 - 0.57)	0.691[‡]	0.299

ICT: isovolumetric contraction time, IRT: isovolumetric relaxation time, ET: ejection time, modified MPI: modified myocardial performance index. Data are presented as the median (interquartile range)

[‡] Mann Whitney U test. [ψ] Adjusted p value for maternal age, GDM, BMI, using multivariate linear regression

Thirty-seven pregnant women delivered and collected data for maternal and neonatal outcomes in the chronic hypertension group. Results showed that pregnant women with chronic hypertension had more maternal adverse outcomes, such as the mean gestational age at delivery was lower in the chronic hypertension group (36.8 ± 2.19 vs 38.2 ± 1.31, p < 0.001, adjusted p < 0.001). The other maternal adverse outcomes were not different (Table 4).

The chronic hypertension group showed more neonatal adverse outcomes, including length of hospital stays (4.0 vs 3.0, p < 0.001, adjusted p = 0.001). Although, other neonatal adverse outcomes were not distinct (Table 5).

Table 4. Maternal adverse outcomes.

	Chronic hypertension (n = 37)	Normal blood pressure (n = 100)	p value	Adjusted p value
GA at birth (weeks)	36.8 ± 2.19	38.2 ± 1.31	< 0.001†	< 0.001Ψ
Preterm delivery indicated from preeclampsia with severe features (%)	3 (8.1%)	0 (0%)	0.019*	0.996τ
Preeclampsia with severe feature (%)	7 (18.9%)	1 (1.0%)	< 0.001*	0.382τ
Preterm delivery (%)	5 (13.5%)	8 (8.0%)	0.337*	0.536τ
Placenta previa (%)	0 (0%)	1 (1.0%)	1.000*	1.000τ

Data are presented as the mean ± standard deviation or n (%).

* Fisher's exact test or Pearson's chi-square test. † Independent t-test.

Ψ Adjusted p value for maternal age, GDM, BMI, using multivariate linear regression.

τ Adjusted p value for maternal age, GDM, BMI, using multiple logistic regression.

Table 5. Maternal adverse outcomes.

	Chronic hypertension (n = 37)	Normal blood pressure (n = 100)	p value	Adjusted p value
TTNB (%)	1 (2.7)	1 (1.0)	0.469*	0.571τ
RDS (%)	3 (8.1)	4 (4.0)	0.387*	0.309τ
EOS (%)	5 (13.5)	4 (4.0)	0.060*	0.638τ
IUGR (%)	0 (0)	0 (0)	1.000*	1.000τ
Jaundice (%)	7 (18.9)	5 (5.0)	0.017*	0.148τ
Hypoglycemia (%)	4 (10.8)	1 (1.0)	0.019*	0.444t
No adverse outcome (%)	17 (45.9)	85 (85.0)	< 0.001*	0.042t
NICU admission (%)	1 (2.7)	3 (3.0)	1.000*	0.633t
Need for ventilator (%)	6 (16.2)	4 (4.0)	0.024*	0.225t
Length of hospital stay (days) median (IQR)	4.00 (3.00 - 7.00)	3.00 (3.00 - 3.50)	< 0.001‡	0.001t

TTNB: transient tachypnea of newborn, RDS: respiratory distress syndrome, EOS: early onset neonatal sepsis, IUGR: intrauterine growth restriction

Data are presented as the median (interquartile range) or n (%). * Fisher's exact test or Pearson's chi-square test. ‡ Mann Whitney U test.

Ψ Adjusted p value for maternal age, GDM, BMI, using multivariate linear regression.

τ Adjusted p value for maternal age, GDM, BMI, using multiple logistic regression.

Discussion

Chronic hypertension is a risk factor for many adverse maternal and neonatal outcomes. Pregnant women with this condition should be managed with appropriate maternal and fetal surveillance. A nonstress test and ultrasound should be performed to assess fetal weight, amniotic fluid, Doppler waveform of vessels and to calculate the MPI.

Pregnancy with chronic hypertension can cause fetal growth restriction that decreases and impairs fetal cardiac function, such as MPI, from cardiac growth interference caused by nutrient supply and oxygen reduction, rising placental impedance, and chronic fetal cardiac afterload[23]. We conducted a study comparing fetal cardiac function between pregnant women with chronic hypertension and women with normal blood pressure. Our study found differences in baseline characteristics between the two groups. The prevalence of GDM was higher in the chronic hypertension group, related to insulin resistance and endothelial dysfunction. Maternal age and BMI were also higher in the chronic hypertension group. Both groups also differed in data collected by sonograph, including gestational age at the time of ultrasound, estimated fetal weight, deep vertical pocket, and Doppler studies.

Our results corresponded with a study from Api et al[24] that fetal global myocardial functioning assessed by modified MPI did not change in mild or severe preeclampsia between the two groups, which might have resulted from fetuses in the study not having complications that impacted fetal cardiac function such as placental insufficiency or fetal growth restriction. In contrast, Sevket Balli et al[14] and Bhorat et al[15] reported higher fetal MPI values in pregnant women with preeclampsia.

Our Doppler studies of the UA, MCA, and uterine artery did not reveal any differences between the chronic hypertension group and control group due to the absence of placental insufficiency or fetal growth restriction in both groups, which do not affect placental impedance and fetal cardiac afterload. On the contrary, Sevket Balli et al[14] found a decreased MCA PI in the preeclampsia group compared to the healthy group. Api et al[24] reported that uterine artery PI increased, and MCA PI decreased in severe preeclampsia mothers due to redistribution of fetal cardiac output secondary to increased placental vascular resistance. Our study showed that compared to women with normal blood pressure, pregnant women with chronic hypertension experienced more maternal adverse outcomes. The mean gestational age at the delivery time was lower in the chronic hypertension group (36.8 ± 2.19 vs 38.2 ± 1.31, $p < 0.001$, adjusted $p < 0.001$). The chronic hypertension group was also associated with more neonatal adverse outcomes, including length of hospital stay; however, other neonatal adverse outcomes were not different. Six newborns needed ventilators in the chronic hypertension group. Three newborns were diagnosed with respiratory distress syndrome, and others were diagnosed with early onset of neonatal sepsis, transient tachypnea of newborns, and hypoglycemia. Most were put in an oxygen box at 5 liters per minute (LPM) for 1-2 days. Only one preterm newborn with respiratory distress syndrome was on continuous positive airway pressure (CPAP) for two days. There were two newborns with respiratory distress syndrome in the normal blood pressure group, one newborn with transient tachypnea of the newborn, and one newborn with early onset of neonatal sepsis. All of them were put in an oxygen box at 5 LPM for 1-2 days. However, the two groups had no significant correlations in the MPI with neonatal adverse outcomes.

In addition to the lack of significant difference in the MPI between chronic hypertension and normal blood pressure groups (0.49 vs 0.47, $p = 0.691$, adjusted $p = 0.299$), we also found no difference in the MPI between chronic hypertension with neonatal adverse outcomes and chronic hypertension without neonatal adverse outcomes (0.47 vs 0.49, $p = 0.784$, adjusted $p = 0.710$).

This study's strength was that no studies had used MPI to evaluate fetal cardiac status in pregnant women with chronic hypertension, and few have used MPI to predict perinatal outcomes. Since our study

only enrolled 40 women with chronic hypertension and some variables of interest had low incidence, our results need to be confirmed by a more extensive study with a larger sample.

Conclusion

There was no difference in the modified MPI between pregnant women with normal blood pressure and women with chronic hypertension. The Doppler studies of the UA, MCA, and uterine artery were also not different between chronic hypertension and control groups. Based on our results, the modified MPI may not be predictive of perinatal outcomes.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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OBSTETRICS

Pregnancy Outcomes among Singleton Pregnant Women with Coronavirus Disease 2019 Infection: A single-center study in Thailand

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ABSTRACT

Objectives: We aimed to describe the outcomes between singleton pregnant women with and without coronavirus disease 2019 (COVID-19) infection.

Materials and Methods: A retrospective study of pregnancy outcomes was conducted among pregnant women delivered in Khon Kaen Hospital with universal nasopharyngeal swab realtime reverse transcription polymerase chain reaction (RT-PCR) tested for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) between August 1, 2021, and August 31, 2022. A total of 230 pregnant women were included in this study: the COVID-19-positive group (n = 115) and the COVID-19-negative group (n = 115). Adverse pregnancy outcomes were determined, including preterm delivery, preeclampsia, cesarean delivery, placental abruption, clinical chorioamnionitis, stillbirth, intensive care unit (ICU) admission, and maternal length of stay. In addition, neonatal outcomes recorded included birth weight, meconium-stained amniotic fluid, 5-min Apgar score, neonatal intensive care unit (NICU) admission, mechanical ventilation used in the first 24 h, required continuous positive airway pressure (CPAP) in the first 24 h, neonatal sepsis and a result of neonatal SARS-CoV-2 RT-PCR tested.

Results: Preterm delivery was significantly greater among the COVID-19-infected women (35.6%) than among the non-COVID-19-infected women (27.8%) (odds ratio 6.36, 95% confidence interval (CI) 1.71-8.15, p = 0.026). The length of hospital stay was also significantly longer in the COVID-19-infected group (7.89 ± 3.26 vs 2.82 ± 0.79 days, odds ratio 11.46, 95%CI 3.85-34.12, p < 0.001). Most pregnant women with COVID-19 infection had mild symptoms (36.5%). Two (1.7%) had severe pneumonia and required mechanical ventilation. No significant differences in neonatal outcomes and no vertical transmission were detected in this study.

Conclusion: Pregnant women with COVID-19 infection were at significantly increased risk of preterm delivery and had a longer hospital stay.

Keywords: coronavirus disease 2019, pregnancy outcomes, preterm delivery, COVID-19.

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ผลลัพธ์การตั้งครรภ์ในสตรีตั้งครรภ์เดี่ยวที่ติดเชื้อไวรัสโคโรนา 2019 : การศึกษาในสถาบันเดียว

วศวัตติ์ พัฒนะชัยรุจน์, ธัญธร ศรีสถาพร, อุษณีย์ สังคมกำาแหง, ทุมวดี ตั้งศิริวัฒนา

บทคัดย่อ

วัตถุประสงค์*: เพื่อศึกษาผลลัพธ์การตั้งครรภ์ในสตรีตั้งครรภ์ที่ติดเชื้อโควิด-19 เปรียบเทียบกับสตรีตั้งครรภ์ที่ไม่ติดเชื้อ***วัสดุและวิธีการ****: การศึกษาแบบ Retrospective study ระหว่างวันที่ 1 สิงหาคม 2564-31 สิงหาคม 2565 ในสตรีตั้งครรภ์ที่มาคลอดบุตร ณ โรงพยาบาลขอนแก่นและได้รับการตรวจหาเชื้อไวรัสโคโรนา 2019 จากเยื่อโพรงจมูกและคอหอยด้วยวิธี RT-PCR (Real time reverse transcription polymerase chain reaction) ทำการเก็บข้อมูลจากสตรีตั้งครรภ์ที่ติดเชื้อโคโรนาไวรัส 2019 จำนวน 115 คน เปรียบเทียบกับกลุ่มที่ไม่ติดเชื้อจำนวน 115 คน ข้อมูลที่ศึกษา ได้แก่ ข้อมูลพื้นฐานของมารดา ผลลัพธ์ของการตั้งครรภ์และการคลอด ภาวะแทรกซ้อน และผลลัพธ์ในทารกแรกเกิด*

ผลการศึกษา: *สตรีตั้งครรภ์ที่ติดเชื้อไวรัสโคโรนา 2019 มีอัตราการคลอดก่อนกำหนดสูงกว่าสตรีตั้งครรภ์ที่ไม่ติดเชื้อ (ร้อยละ 35.65 และร้อยละ 27.83 ตามลำดับ, อัตราส่วนออด 6.36, ช่วงความเชื่อมั่นร้อยละ 95 1.71-8.15) และมีระยะเวลาการนอนโรงพยาบาลที่ยาวนานกว่า (7.89 ± 3.26 วัน และ 2.82 ± 0.79 วัน ตามลำดับ, อัตราส่วนออด 11.46, ช่วงความเชื่อมั่นร้อยละ 95 3.85-34.12) สตรีตั้งครรภ์ที่ติดเชื้อส่วนใหญ่ (ร้อยละ 36.52) มีอาการไม่รุนแรง แต่พบสตรีตั้งครรภ์ 2 ราย (ร้อยละ 1.74) มีอาการปอดติดเชื้อรุนแรง ต้องใช้เครื่องช่วยหายใจและเข้ารับการรักษาตัวในหอผู้ป่วยหนัก ทั้งนี้ ไม่มีความแตกต่างกันอย่างมีนัยสำคัญในผลลัพธ์ของทารกแรกเกิด และไม่พบว่ามีการถ่ายทอดเชื้อไวรัสโคโรนา 2019 จากมารดาสู่ทารก*

สรุป*: สตรีตั้งครรภ์ที่ติดเชื้อไวรัสโคโรนา 2019 เพิ่มอัตราการคลอดก่อนกำหนดและมีระยะเวลาในการนอนโรงพยาบาลนานกว่าสตรีตั้งครรภ์ที่ไม่ติดเชื้ออย่างมีนัยสำคัญ*

คำสำคัญ*: โคโรนาไวรัส 2019, ผลลัพธ์การตั้งครรภ์, สตรีตั้งครรภ์, การคลอดก่อนกำหนด, โควิด-19*

Introduction

The COVID-19 pandemic has spread worldwide since the first case in Wuhan City (Hubei Province, China) in December 2019. By 2021, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) had infected more than 182 million people globally, with more than 3.9 million deaths[1].

Thailand was the first country to report a case outside China. On January 13, 2020, the Ministry of Public health reported the first confirmed COVID-19 case in a Wuhan resident who traveled to Bangkok. Subsequently, the first locally transmitted cases were reported on January 31, and cases continued to increase, and the epidemic was widespread. As of April 2022, the country had reported a cumulative total of 3,684,755 confirmed cases, with 25,318 deaths from the disease[2].

SARS-CoV-2 is an enveloped, positive-stranded RNA beta-coronavirus, the International Committee on Taxonomy of Viruses Study Group proposed that this virus be designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The virus infects host respiratory epithelial cells through the angiotensin-converting enzyme-2 (ACE2) receptor, predominantly within type II alveolar lung cells. Extrapulmonary sites also occur in the heart, blood vessels, kidneys, liver, and gastrointestinal tract.

The estimated incubation period is up to 14 days from the time of exposure, with a median incubation period of 4 to 5 days[3]. The spectrum of illness can range from asymptomatic infection to severe pneumonia with acute respiratory distress syndrome and death. The mortality rate is higher in those older than 70 years, regardless of chronic medical conditions. Among those with available data on health conditions, 32% had cardiovascular diseases, 30% had diabetes, and 18% had chronic lung diseases. Other conditions that may lead to a high risk for severe COVID-19 include cancer, kidney diseases, obesity, and other immunocompromising conditions. Pregnant women are also at increased risk for severe illness associated with COVID-19[4] due to their susceptibility to respiratory pathogens such as decreased lung capacity, immunologic changes, and increased risk for thromboembolic diseases. Furthermore, the pregnancy bias toward T-helper 2 (Th2) system dominance protects the fetus but leaves the mother vulnerable to viral infections, more effectively contained by the Th1 system.

The association between COVID-19 and adverse pregnancy outcomes was unclear. Some evidence indicated that an unfavorable cluster of differentiation 4 (CD4) cell phenotype raised concerns about disordered implantation and placentation[5] and the possibility of developing fetal growth restriction, preeclampsia, and other consequences of placental dysfunction. COVID-19 is also associated with a profound prothrombotic state, particularly with the formation of immunogenic thrombi in the microvasculature[6], and there is also an increased risk of poor obstetric outcomes among pregnant women[7]. Symptomatic maternal COVID-19 is associated with an increased likelihood of preterm birth. It may also be associated with an increased incidence of small for gestational age babies[8], and it seems likely that neonatal morbidity for babies born to mothers with COVID-19 infection is linked to preterm birth, while stillbirth remains a rare outcome.

Many studies showed the adverse effects of COVID-19 infection to pregnancy outcomes, but some data are still controversy[9]. We thus aimed to compare pregnancy outcomes among pregnant patients with and without COVID-19 infection at the delivery time.

Materials and Methods

This was a case-control study of pregnancy outcomes among pregnant patients who delivered

at Khon Kaen Hospital between August 1, 2021 to August 31, 2022. The research protocol was approved by the Khon Kaen Hospital Institute Review Board in Human Research (KEXP65052).

The sample size was calculated using the formula for case-control studies and based on previous data[10]. The estimated rate of preterm birth in COVID-19 pregnant women was 0.22, and the rate of preterm birth in pregnant women without COVID-19 was 0.08 with an acceptable error (alpha) of 0.05, beta of 0.20, Z1-$\propto$/2 of 1.96 and Z1-β of 0.80. The continuity correction sample size thus included 230 cases, 115 pregnant women with COVID-19 and 115 pregnant women without COVID-19. The authors selected the ratio (case: control) of 1:1 based on maternal age, gestational age at delivery, and delivery date.

Pregnant women admitted to the labor room or delivery units during the study period were included, and universal SARS-CoV-2 RT-PCR testing was performed. Diagnosis of COVID-19 infection was made by real-time reverse transcription polymerase chain reaction (RT-PCR) detected SARS-CoV-2 nucleic acid from nasopharyngeal specimens. Eligible patients were then divided into two groups, a positive-COVID-19 group, and a negative-COVID-19 group. Pregnancy with multifetal gestations was excluded from this study. In addition, hospital admission logs were reviewed to ensure complete data capture of all delivered women.

Baseline characteristics were recorded, including maternal age, body mass index (BMI), parity, comorbidities, and doses of COVID-19 vaccination. Among women with COVID-19 infection, our study classified maternal disease severity at presentation according to the National Institutes of Health (NIH) COVID-19 illness severity classification[11], including asymptomatic, mild, moderate, severe, and critical illness. Asymptomatic or presymptomatic infection was defined as individuals who test positive for SARS-CoV-2 using a virologic test (i.e., a nucleic acid amplification test [NAAT] or an antigen test) but with no symptoms consistent with COVID-19. Mild illness was defined as individuals with any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but with no shortness of breath, dyspnea, or abnormal chest imaging. Moderate illness was defined as individuals showing evidence of lower respiratory disease during clinical assessment or imaging and with oxygen saturation (SpO2) ≥ 94% on room air at sea level. Severe illness was defined as individuals with a SpO_2 < 94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) < 300 mm Hg, respiratory frequency > 30 breaths/min, or lung infiltrates > 50% and critical illness was defined as individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.

Treatment of COVID-19 during pregnancy depended on the severity of the illness. In our hospital treatment policy, COVID-19-infected women were admitted to the obstetrics cohort ward with standard intrapartum care and delivered by an obstetrician staff or resident doctor with a multidisciplinary team. We classified pregnant women according to the NIH illness severity scale. In mild and moderate illnesses, symptomatic treatment was given, including hydration, antipyretics, analgesics, and antitussives. Medical consultation with internal medicine and infectious disease staff was obtained in severe and critical illness cases. Those patients who required mechanical ventilation were admitted to the intensive care unit (ICU), and therapeutic management included respiratory support, antiviral drugs, and corticosteroids.

Preterm labor was treated with the same protocol in both groups. Pregnant women

admitted with preterm labor underwent universal RT-PCR testing for SARS-CoV-2. Women infected with COVID-19 were moved to an isolation room and treated with tocolytic agents. Per our hospital guidelines, Nifedipine was the first line drug, and terbutaline (Bricanyl) was the second choice when nifedipine was failed unless contraindicated (i.e., in cardiac disease, maternal tachycardia, or poorly controlled diabetes mellitus (DM). Magnesium sulfate was given for neuroprotection in case of preterm labor at gestational age less than 32 weeks. A dexamethasone dose of 6 mg intramuscular injection (IM) was given every 12 h: 4 doses were given in case of preterm labor with a gestational age of fewer than 34 weeks with a high risk for preterm delivery in the next 7 days.

The primary outcome was preterm delivery (delivery before 37 weeks gestation, including spontaneous and indicated preterm delivery) and the secondary outcomes were cesarean delivery, placental abruption, clinical chorioamnionitis, stillbirth, gestational hypertension, preeclampsia, ICU admission, mechanical ventilation, length of stay and the neonatal outcomes including birth weight, meconium-stained amniotic fluid, 5-min Apgar score, Neonatal Intensive Care Unit (NICU) admission, mechanical ventilation used in the first 24 h, required continuous positive airway pressure (CPAP) in the first 24 h, neonatal sepsis, and results of neonatal SARS-CoV-2 RT-PCR tests.

Statistical analyses were done using STATA 16 computer software. Baseline characteristics were analyzed using chi-square or Fisher's exact test and presented as numbers and percentages. Continuous data were analyzed using the student's t-test and presented as means with standard deviation (SD). Pregnancy outcomes were compared between women with and without SARS-CoV-2 infection. Logistic regression analyses were performed using the t-test for continuous outcomes and the Pearson $\chi 2$ test for categorical outcomes. The p values for all hypotheses were 2-sided, and the statistical significance was set at $p < 0.05$. Effect sizes were presented as odds ratio (OR) with 95% confidence intervals (CIs).

Results

Two hundred and thirty pregnant women were included between August 1, 2021, and August 31, 2022, comprising a COVID-19 positive group (n = 115) and a COVID-19 negative group (n = 115). The baseline characteristics of the participants are shown in Table 1. The mean age of pregnant women with a COVID-19 infection was 27.7 ± 5.7 years, most of whom were multiparous (73.91%). The median gestational age at delivery was 37 1/7 weeks (interquartile range (IQR) 321/7 to 406/7) in COVID-19 positive group and 37 3/7 (IQR 32 to 41) weeks in COVID-19 negative group (p = 0.92). The two groups had no significant differences in maternal age, BMI, parity, or co-morbidities but in the number of COVID-19 vaccination doses (p = 0.020). Pregnant women who got COVID-19 infection had never get vaccination in higher percentage (19.13% vs 14.78%) compared with those who did not get infection. However, 40% of those who got COVID-19 infection had received two or more vaccination doses. Women who received 2 or more vaccine doses were less common in the COVID-19-positive group (40.0% vs 58.3%) than in the COVID-19-negative group. Among pregnant women with COVID-19 infection, 36.5% had a mild illness, 33.0% had no symptoms, 26.1% had moderate illness, 2.6% had severe illness, and 1.7% had critical illness. In cases of severe and critical illness, there were three pregnant patients with COVID-19 pneumonia that required mechanical ventilation and two patients had septic shock with respiratory and kidney failure.

Table 1. Baseline characteristics.

Characteristic	COVID-19 positive (n = 115)	COVID-19 negative (n = 115)	p value
Age (years), mean ± SD	27.70 ± 5.66	27.21 ± 5.41	0.498
Gestational age at delivery (weeks), median (IQR)	$37^{1/7}$ ($32^{1/7}$ to $40^{6/7}$)	$37^{3/7}$ (32 to 41)	0.92
BMI (kg/m^2), n (%)			0.758
< 18.5	22 (19.13)	18 (15.65)	
18.5-24.9	18 (15.65)	23 (20.00)	
25-25.9	51 (44.35)	48 (41.76)	
≥ 30	24 (20.87)	26 (22.61)	
Parity, n (%)			0.761
Nulliparous	30 (26.09)	28 (24.35)	
Multiparous	85 (73.91)	87 (75.65)	
Comorbidities, n (%)			0.904
Chronic hypertension	8 (6.96)	10 (8.70)	
Diabetes mellitus	10 (8.70)	12 (10.43)	
Asthma	5 (4.35)	4 (3.48)	
None	92 (80.00)	89 (77.39)	
COVID Vaccination, n (%)			0.020*
None	22 (19.13)	17 (14.78)	
1 dose	47 (40.87)	31 (26.96)	
2 doses or more	46 (40.00)	67 (58.26)	
NIH severity classification, n (%)			NA
Asymptomatic	38 (33.04)		
Mild illness	42 (36.52)		
Moderate illness	30 (26.09)		
Severe illness	3 (2.61)		
Critical illness	2 (1.74)		

BMI: body mass index, NIH: National Institute of Health, SD: standard deviation, IQR: interquartile range, n: number of patients

Pregnancy outcomes are presented in Table 2. In the COVID-19-positive group, term delivery accounted for 64.4% of births, and preterm delivery 35.7%. In the COVID-19-negative group, term delivery accounted for 72.2%, while preterm delivery was lower (27.8%). In the COVID-19-positive group, 56.5% of pregnant women (65/115 cases) were delivered by cesarean section, and emergency cesarean section accounted for 87.7% of cases. In the COVID-19-positive group, the indications for cesarean delivery were previous cesarean delivery (29 cases, 44.6%), cephalopelvic disproportion (22 cases, 33.9%), non-reassuring fetal status (7 cases, 10.8%), abnormal presentation (5 cases, 7.7%) and other 2 cases accompanying severe maternal COVID-19 pneumonia included septic shock to improve maternal hemodynamic stability.

In the COVID-19-positive women, the proportion of cesarean section in the term delivery group was 78.5% (51/65 cases), and the indications were previous cesarean delivery (24 cases, 36.9%), cephalopelvic disproportion (20 cases, 30.8%), non-reassuring fetal status (4 cases, 6.15%) and abnormal presentation (3 cases, 4.6%). Whereas cesarean section in the preterm delivery group was 21.5% (14/6 cases), and the indications were previous cesarean delivery (5 cases, 7.7%), non-reassuring fetal status (3 cases, 4.6%), cephalopelvic disproportion (2 cases, 3.1%), abnormal presentation (2 cases, 3.1%) and others (2 cases, 3.1%).

In addition, the maternal length of stay of women with COVID-19 infection was significantly longer than women without COVID-19 infection (7.89 ± 3.26 vs 2.82 ± 0.79 days, OR 11.46, 95%CI 3.85-34.12, p < 0.001).

Finally, there were no statistically significant differences between the two groups in maternal outcomes

of placental abruption, clinical chorioamnionitis, stillbirth, gestational hypertension, preeclampsia, ICU admission, and mechanical ventilation. In addition, there were no statistically significant differences between groups in infants born to COVID-19-positive mothers. No vertical transmission of COVID-19 was detected in this study.

Table 2. Obstetrics and neonatal outcomes among delivered women with and without SARS-CoV-2 infection.

Outcome	COVID-19 positive (n = 115)	COVID-19 negative (n = 115)	p value	Odds ratio (95% CI)
Term delivery, n (%)	74 (64.35)	83 (72.17)	0.439	-
37 - 38^{+6}	42 (36.52)	55 (47.83)		
39 - 39^{+6}	25 (21.74)	23 (20.00)		
40 or more	7 (6.09)	5 (4.35)		
Preterm delivery, n (%)	41 (35.65)	32 (27.83)	0.026	6.36 (1.71-8.15)
Mode of delivery, n (%)				
Vaginal delivery	50 (43.48)	42 (36.52)	0.508	-
Spontaneous	49 (98.00)	36 (85.71)		
Operative (V/E, F/E)	1 (2.00)	6 (14.29)		
Cesarean delivery	65 (56.52)	73 (63.48)	0.282	-
Elective	8 (12.31)	54 (73.97)		
Emergency	57 (87.69)	19 (26.03)		
Indications for C/S, n (%)				
Non-reassuring fetal status	7 (10.77)	5 (6.85)	0.514	-
Abnormal presentation	5 (7.69)	2 (2.74)	0.274	-
CPD	22 (33.85)	19 (26.03)	0.104	-
Previous cesarean delivery	29 (44.62)	42 (57.53)	0.273	-
Others	2 (3.08)	5 (6.85)		
Placental abruption, n (%)	1 (0.87)	3 (2.61)	0.313	-
Clinical chorioamnionitis, n (%)	1 (0.87)	2 (1.74)	0.561	-
Stillbirth, n (%)	0 (0.00)	2 (1.74)	0.155	-
Gestational hypertension, n (%)	2 (1.74)	4 (3.48)	0.408	-
Preeclampsia, n (%)	8 (6.96)	14 (12.17)	0.808	-
Without severe feature	5 (62.50)	8 (57.14)		
With severe feature	3 (37.50)	6 (42.86)		
ICU admission, n (%)	3 (2.61)	0 (0.00)	0.081	-
Mechanical ventilation used, n (%)	2 (1.74)	0 (0.00)	0.498	-
Maternal length of stay (days); mean ± SD	7.89 ± 3.26	2.82 ± 0.79	< 0.001	11.46 (3.85-34.12)
Neonatal outcomes				
Birthweight (grams); mean ± SD	2920.69 ± 561.60	2876.43 ± 568.97	0.552	-
5-min APGAR score, n (%)				
7 - 10	112 (97.39)	113 (98.26)	0.651	-
< 7	3 (2.61)	2 (1.74)	0.449	-
Meconium-stained amniotic fluid, n (%)	8 (6.96)	15 (13.04)	0.765	-
NICU admission, n (%)	9 (7.83)	12 (10.43)	0.492	-
Mechanical ventilation in first 24 hr, n (%)	4 (3.48)	4 (3.48)	0.229	-
CPAP in first 24 hr, n (%)	13 (11.30)	8 (6.96)	0.547	-
Neonatal sepsis, n (%)	8 (6.96)	10 (8.70)	0.706	-
Neonatal RT-PCR for SARS-CoV-2, n (%)				
Detected	0 (0.00)		NA	
Not detected	115 (100.00)			

SD: standard deviation, n: number of patients, V/E: vacuum extraction, F/E: forceps extraction, C/S: cesarean section, CPD: cephalopelvic disproportion, NA: not applicable, NICU: neonatal intensive care unit, CPAP: continuous positive airway pressure, RT-PCR: real-time reverse transcription polymerase chain reaction

Discussion

Our results showed that the rate of preterm delivery was significantly higher among the COVID-19-positive group, 35.7% (41/115) vs 27.8% (32/115) in the COVID-19-negative group (OR 6.36, 95%CI 1.71-8.15, p= 0.026). Our results agreed with a systematic review by Maryamsadat et al[12], who reported that preterm birth was more likely among pregnant women with COVID-19 than pregnant women without COVID-19. Similarly, Shu et al[13] found that having COVID-19 while pregnant was associated with preterm birth and a higher maternal and neonatal morbidity risk. Allotey et al[14] likewise found that pregnant women with covid-19 were more likely to deliver preterm. Finally, Oralkhan et al[15] performed a systematic review from twenty-six cohort studies and found that COVID-19 was associated with a significantly increased risk of preterm birth, corresponding with a study by Anggraini et al[16] who showed that there was a significant relationship between COVID-19 and increased incidence of preterm birth. Notwithstanding, Adhikari et al[17] performed a large, single-institution cohort study and found no differences in preterm birth composite outcomes. Similarly, Barbara et al[18] reported that preterm births before 37 weeks' gestation were not significantly changed. Similarly, Pirjani et al[19] and Mullin et al[20] found that the prevalence of preterm birth did not differ significantly during the COVID-19 pandemic compared to the pre-pandemic period.

Preterm delivery was influenced by multiple factors, and it is critical to understand the mechanism that explains the link between preterm delivery and SARS-CoV-2 infection and identifies effective prevention methods to avoid COVID-19-caused adverse pregnancy outcomes. Numerous studies have demonstrated that the pathogen may cause exaggerated systemic inflammatory responses, which may interfere with the placenta's optimal condition for fetal growth and development[21] and vascular malperfusion of the placental-fetal unit may be another contributing factor to developing adverse pregnancy outcomes.

According to Thresa et al[22] the COVID-19 pandemic has had a disproportionate impact on the mental health of pregnant women, including stress, worry, and anxiety. As such, mental health disorders are associated with intrauterine growth restriction or preterm delivery due to the activation of the human platelet antigen (HPA) axis by mothers who experience stress during pregnancy. Consequently, the fetus may be stressed by increased concentrations of corticotropin-releasing hormone (CRH) in the fetal plasma, amniotic fluid, and maternal plasma compared to levels in normal pregnancy. In the current study, however, the exact cause of preterm birth in COVID-19-infected pregnant women is unknown. Future research is required to collect additional data to further validate or corroborate these findings, to better comprehend these associations, and to identify effective strategies to prevent adverse outcomes in pregnant women infected with COVID-19.

More than half of COVID-19 pregnant women (65/115 cases, 56.52%) were delivered by cesarean section. Most cases were emergency cesareans (57/65 cases, 87.7%). The indications for cesarean section among COVID-19 pregnant patients were previous cesarean delivery (29 cases, 44.6%), cephalopelvic disproportion (22 cases, 33.9%), non-reassuring fetal status (7 cases, 10, 8%), and abnormal presentation (5 cases, 7.7%). Other conditions accompanying severe maternal COVID-19 pneumonia included septic shock to improve hemodynamic stability. Compared with non-infected women, our study showed that the cesarean section rate was not significantly higher (56.5% vs 63.5%, p = 0.282), unlike Maryamsadat et al[12], Jean et al[23], and Phabhu et al[24], who reported that cesarean delivery occurred more often among pregnant women with COVID-19. Further studies on changing cesarean section trends during the pandemic are needed.

The current study found that the maternal length of hospital stay of women with COVID-19 infection was significantly longer than women without COVID-19 infection (7.89 ± 3.26 vs 2.82 ± 0.79 days, p < 0.001). This might be because during the early pandemic in

Thailand, and accordance with our hospital treatment policy, all infected patients, regardless of symptoms, were required to be hospitalised to ensure they received proper care and prevent the spread of the virus to the community. In contrast, hospital stays for patients with moderate to critical illnesses requiring oxygen therapy, mechanical ventilation, or intensive care, should be longer. However, the latest wave (the omicron wave - the sixth) led to a sharp rise in the number of new COVID-19 cases, and this increase in the number of patients overwhelmed many hospitals. In addition, hospitals had already reached full capacity with asymptomatic patients or those with mild illnesses who did not require oxygen therapy. Home isolation had then become a suitable option for those caring for themselves.

According to our hospital policy during the pandemic, all infants born to COVID-19-positive mothers were isolated, and a nasopharyngeal RT-PCR swab test was performed at 24 and 72 hours postpartum. In our study, no vertical transmission was detected. Although vertical transmission of SARS-CoV-2 is possible, the current data suggest it is rare. Chen et al[25] showed that SARS-CoV-2 was negative in all the amniotic fluid, cord blood, breast milk and neonatal nasopharyngeal swabs. By contrast, few cases of intrauterine SARS-CoV-2 transmission have been documented by the study of Vivanti et al[26] reported a proven case of transplacental transmission of SARS-CoV-2 from a pregnant woman affected by COVID-19 during late pregnancy. In addition, infection in neonates is more likely due to close contact after delivery according to the findings of Martinez-Perez et al[27], PCR analysis was performed on samples of the nasopharynx and oropharynx of 147 newborns during the first 12 and 48 hours of life, 3 of which were positive in the first 12 hours and all three newborns who had an initial positive result were retested at 48 hours, with a final negative result.

There were no significant differences in the baseline characteristics of the two groups vis-à-vis maternal age, BMI, parity, and co-morbidities. However, this study showed that pregnant women who were never vaccinated were more likely to be infected with COVID-19 (19.1% vs 14.8%), while women who received 2 or more doses were less likely (40.0% vs 58.3%). These results provide further evidence that vaccination against COVID-19 is protective for all pregnant women and that the vaccines are safe and effective during pregnancy. In addition, Atsuyuki et al[28] performed a systematic review, and the results showed that vaccination during pregnancy was not associated with an increased the risk of adverse peripartum outcomes, but decreased risk of NICU admission, intrauterine fetal death, and maternal infection. Thus, COVID-19 vaccination should be encouraged for all pregnant. Furthermore, in 2021 Shimabukuro et al[29] reported that the production of IgG antibodies and their subsequent transfer improved after the second dose of either vaccine. Baoqi Zeng et al[30] showed that booster vaccination doses were more effective against Delta and Omicron variants and women who got booster vaccination were less likely to suffered from severe COVID-19 diseases. In addition, according to Phupong[31], prevention is the best way to avoid COVID-19. Regular hand washing, covering the mouth and nose when coughing and sneezing, and avoiding close contact with anyone showing symptoms of respiratory illness such as coughing and sneezing are all standard recommendations for coronavirus infections.

As of March 2022, the country had reported number of pregnant women with COVID-19 infection are more than 7,210 and 110 patients were dead. The reports of disease severity among pregnancy with COVID-19 infection by Torri et al[32] found that most patients with a positive SARS-CoV-2 test were asymptomatic and according to a study by Phupong[31], the clinical characteristics of COVID-19 in pregnant women were the same as those of non-pregnant adults in the general population and Seema et al[33] compared maternal clinical characteristics during first and second waves of COVID-19 in pregnant women in India, the results found that fever and sore throat were common presenting symptoms and most women

with underlying disease such as asthma and cardiac disease progressed to severe or critical illness. In our study, among women with COVID-19 infection, most had mild symptoms (36.5%) (i.e., cough, myalgia, fever, sore throat, or nasal stuffiness), importantly, our findings revealed that 4.4% of all delivered women with SARS-CoV-2 infection developed severe and critical illness, which are lower than rates reported by Andrikopoulou et al[34].

Although our study period included the two different waves of infection (Delta and Omicron), which may have influenced disease severity, a study by Birol et al[35] found that disease severity was comparable between the two waves, and infection in unvaccinated pregnant women carried a considerable risk of morbidity and mortality regardless of variant, in the same way. Seema et al[33] showed that the clinical characteristics and severity of the disease did not differ significantly in the first and second waves of COVID-19. However, Kensuke et al[36] reported the clinical manifestations of COVID-19 in pregnant women differed between the Delta and Omicron periods, and Sarah et al[37] discovered that infection during the Omicron-dominant period (compared with the Delta-dominant period) was associated with significantly lower risk for critical care admission and preterm birth.

The present study showed no differences between the two groups in obstetric complications (viz. placental abruption, clinical chorioamnionitis, stillbirth, gestational hypertension, preeclampsia, ICU admission, and mechanical ventilation). In addition, no statistically significant differences were found among infants born to mothers with COVID-19 infection. This observation may be due to a small sample size that could not detect the difference. In contrast, Fhabian et al[38] investigated maternal and fetal outcomes in pregnant women hospitalized with COVID-19 in Venezuela; the findings revealed that the most common maternal complications were anemia, oligohydramnios, hypertensive disorders of pregnancy, and low birth weight. There was furthermore an increased risk of stillbirth and abortions in pregnant women with COVID-19 infection. Furthermore, studies by Wong[39] and Alfaraj[40] showed that SARS and Middle East respiratory syndrome coronavirus (MERS-CoV) infection were associated with a high incidence of maternal and neonatal complications such as spontaneous abortion, intrauterine growth restriction, and ICU admission. Notwithstanding, in pregnant women with COVID-19 (SARS-CoV-2) has fewer adverse maternal and neonatal complications than those viruses.

The strengths of our study were that it was a matched case-control and a single-center study, despite the limitations of a retrospective design, a small sample size, and a study period that included different clinical manifestations of disease (viz., the Delta and Omicron waves).

Conclusion

Pregnant women with COVID-19 infection were at significantly increased risk of preterm delivery and had a longer hospital stay.

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Potential conflict of interest

The authors declare no conflicts of interest.

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OBSTETRICS

Rate of Large for Gestational Age Newborn Between Gestational Diabetes Mellitus followed-up by One-hour Postprandial Plasma Glucose and Two-hour Postprandial Plasma Glucose

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ABSTRACT

Objectives: To compare the rate of large for gestational age (LGA) newborns, adverse perinatal, and obstetrical outcomes in gestational diabetes mellitus (GDM) followed-up by one-hour postprandial glucose (1-HrPPG) and two-hour postprandial glucose (2-HrPPG), and to study the risk factors increasing the rate of LGA newborns.

Materials and Methods: In this retrospective cohort study, Thai singleton pregnancies with GDM diagnosed by using the Carpenter and Coustan criteria who were regularly followed-up and delivered a live birth after 28 weeks of gestation at Prapokklao Hospital between October 2017 to July 2022 were enrolled. The participants were classified into two groups based on the follow-up method. The data were collected from the medical records and analyzed by SPSS version 26.0.

Results: Four hundred and seventy-eight participants were included and divided into two groups of 239 participants each. There were no differences in the baseline characteristics. In the obstetrical outcomes, metformin was used more (16.3% vs 4.2%, $p < 0.001$) in the 1-HrPPG group, but the others were not different. For the neonatal outcomes, the mean birthweight was higher in the 1-HrPPG group (3180.8 ± 460.6 vs 3098.0 ± 434.9 grams, $p = 0.044$), but the rate of LGA was not different (20.5% vs 20.1%, $p = 0.909$). After the logistic regression analysis, the excessive gestational weight gain doubled the risk of LGA.

Conclusion: The rate of LGA newborns in GDM who were followed-up by 1-HrPPG or 2-HrPPG was not different, and the appropriate gestational weight gain could reduce the rate of LGA.

Keywords: LGA, GDM, 1-HrPPG, 2-HrPPG.

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การศึกษาเปรียบเทียบอัตราการเกิดทารกน้ำหนักเกินเกณฑ์อายุครรภ์ในสตรีที่มีภาวะเบาหวาน ขณะตั้งครรภ์ ระหว่างกลุ่มที่ติดตามด้วยระดับน้ำตาลในเลือด 1 ชั่วโมงหลังอาหาร และ 2 ชั่วโมงหลังอาหาร

ปาริฉัตร มีประเสริฐ, สิริดา พิทยานนท์

บทคัดย่อ

วัตถุประสงค์: *เพื่อเปรียบเทียบอัตราการเกิดทารกที่มีน้ำหนักแรกคลอดเกินเกณฑ์ตามช่วงอายุครรภ์ ผลลัพธ์ไม่พึงประสงค์ปริกำเนิดในทารกและในสตรีที่มีภาวะเบาหวานขณะตั้งครรภ์ ที่ตรวจติดตามด้วยระดับน้ำตาลในเลือด 1 ชั่วโมงหลังอาหาร กับ 2 ชั่วโมงหลังอาหาร และเพื่อศึกษาปัจจัยที่เพิ่มการเกิดทารกน้ำหนักแรกคลอดเกินเกณฑ์ตามช่วงอายุครรภ์*

วัสดุและวิธีการ: *การศึกษาแบบ Retrospective cohort โดยเลือกหญิงไทยครรภ์เดี่ยวที่ถูกวินิจฉัยว่าเป็นเบาหวานขณะตั้งครรภ์ด้วยเกณฑ์ของ Carpenter and Coutan ตรวจติดตามต่อเนื่องและคลอดบุตรมีชีพหลังอายุครรภ์ 28 สัปดาห์ ที่โรงพยาบาลพระปกเกล้า ระหว่างเดือนตุลาคม พ.ศ. 2559 ถึงเดือนกรกฎาคม พ.ศ. 2565 โดยแบ่งประชากรออกเป็น 2 กลุ่ม อ้างอิงตามวิธีที่ใช้ตรวจติดตามระดับน้ำตาลในเลือด ข้อมูลทั้งหมดได้จากเวชระเบียนและวิเคราะห์ข้อมูลด้วยโปรแกรม SPSS รุ่น 26*

ผลการศึกษา: *หญิงไทยครรภ์เดี่ยว 478 คน แบ่งออกกลุ่มละ 239 คน ไม่พบความแตกต่างของลักษณะพื้นฐานของผู้เข้าร่วมวิจัย ในส่วนของผลลัพธ์ทางสูติศาสตร์พบว่ามีการใช้ยาเม็ดลดน้ำตาล(เมตฟอร์มิน)ในกลุ่ม1 ชั่วโมงหลังอาหารมากกว่า (ร้อยละ 16.3 vs 4.2, $p < 0.001$) แต่ไม่พบความแตกต่างกันอย่างมีนัยสำคัญทางสถิติในประเด็นการศึกษาอื่น และผลลัพธ์ปริกำเนิดของทารกพบว่าในกลุ่ม 1 ชั่วโมงหลังอาหารพบน้ำหนักแรกคลอดเฉลี่ยของทารกมากกว่า (3180.8 ± 460.6 vs 3098.0 ± 434.9 กรัม, $p = 0.044$) แต่อัตราการเกิดทารกน้ำหนักแรกคลอดเกินเกณฑ์อายุครรภ์ไม่แตกต่างกัน (ร้อยละ 20.5 vs 20.1, $p = 0.909$) และหลังจากการวิเคราะห์การถดถอยโลจีสติกพบว่าการที่สตรีตั้งครรภ์มีน้ำหนักขึ้นมากผิดปกติจะเพิ่มความเสี่ยงของการเกิดทารกน้ำหนักแรกคลอดเกินเกณฑ์ตามช่วงอายุครรภ์ 2 เท่า*

สรุป: *อัตราการเกิดทารกน้ำหนักแรกเกิดเกินเกณฑ์อายุครรภ์ไม่แตกต่างกันระหว่างสตรีตั้งครรภ์ที่ตรวจติดตามด้วยระดับน้ำตาลในเลือด 1 ชั่วโมงหลังอาหาร และ 2 ชั่วโมงหลังอาหาร และการควบคุมการเพิ่มของน้ำหนักขณะตั้งครรภ์อย่างเหมาะสมอาจจะช่วยลดการเกิดทารกน้ำหนักแรกคลอดเกินเกณฑ์ตามช่วงอายุครรภ์*

คำสำคัญ: *ทารกน้ำหนักแรกเกิดเกินเกณฑ์อายุครรภ์, เบาหวานขณะตั้งครรภ์, ระดับน้ำตาลในเลือดที่ 1 หรือ 2 ชั่วโมงหลังอาหาร*

Introduction

Gestational diabetes mellitus (GDM) is one of the major medical complications worldwide, including Thailand[1-3]. The worldwide prevalence has increased parallel to the obesity situation, increasing maternal age, and decreasing physical activity[1, 2, 4]. The data from the antenatal care clinic (ANC) of Prapokklao Hospital, Chanthaburi, Thailand between 2018 to 2020 showed that 11% of pregnancies were diagnosed with GDM.

GDM has many options for diagnosis and treatment without different outcomes[5-8]. The choice of management would depend on the institute's preferences and the patient's needs. The targeted plasma glucose is 140 mg/dL for a one-hour postprandial glucose (1-HrPPG) measurement and 120 mg/dL for a two-hour postprandial glucose (2-HrPPG) measurement[1]. GDM who can achieved target plasma glucose without medication classified as GDMA1 and who has to controlled with medication classified as GDMA2[1].

Women with GDM were also more likely to develop preeclampsia and experience a cesarean delivery[9]. Moreover, the children of women with GDM were more likely to be a large for gestational age (LGA) newborn which increases neonatal risks such as, shoulder dystocia, neonatal hypoglycemia, jaundice, neonatal intensive care unit (NICU) admission, and even stillbirth[1, 10-12]. Furthermore, LGA increases the maternal risks include higher cesarean section rates, postpartum hemorrhage and third or fourth degree tear of perineum[11, 12].

At Prapokklao Hospital, the postprandial plasma glucose (PPG) measurement has been the main follow-up method. In addition, the selection of 1-HrPPG or 2-HrPPG would depend on the doctor's preference, and if 1-HrPPG was greater than 140 mg/dL, 2-HrPPG would not be done again.

The reviewed literature found limited studies in Thailand[5, 6] on the rate of LGA newborns and adverse obstetrical or perinatal outcomes in GDM related to the follow-up method. Therefore, this study proposed to compare the rate of the LGA newborns, adverse neonatal, and obstetrical outcomes in GDM that were followed-up by 1-HrPPG and 2-HrPPG and to study potential factors increasing risk of LGA newborn in GDM.

Materials and Methods

Prapokklao Hospital has used a risk-based strategy for GDM screening. A two-step approach (50 g glucose challenge test followed by a selective 100 g oral glucose tolerant test) has been used for diagnosis. The follow-up method has mainly utilized 1-HrPPG. or 2-HrPPG depending on the doctor's preference. Initial treatments were lifestyle modification and nutritional therapy, such as informing the appropriate calories intake, preferred type of food and proper amount, and how to exercise properly. Medication would be started if PPG could not achieve the target. Additionally, the choice of medications and delivery timing would follow the American College of Obstetricians and Gynecologists (ACOG)'s recommendations[1].

The Ethics Committee for Research on Humans in Chanthaburi approved this retrospective cohort study (CTIREC 097/64). We enrolled Thai singleton pregnant women equal to or older than 18 years of age with GDM diagnosed by the Carpenter and Coustan criteria[13], regularly followed-up, and delivered a live birth after 28 weeks of gestation at Prapokklao Hospital, Chanthaburi, from October 2017 to July 2022. If the fetus was prenatally diagnosed with a congenital anomaly or abnormal chromosome, the participant would be excluded. To eliminate confounding factors, pregnant women with other medical conditions were also excluded too. The participants were divided into two groups according to their PPG measurement (1-HrPPG or 2-HrPPG). If any participant had a result of both follow-up methods, the arrangement was based on a follow-up method that used more than 80% of the overall measurement and only the value of that method was taken into the calculation.

The sample size was computed by G*POWER 3.1.9.2. with a power of 80% and a type I error of 5%

referring to the study of Weisz et al[5] The LGA in the 1-HrPPG group was 0.07 and 2-HrPPG was 0.15. The estimated sample size was 478 people and divided into 239 participants in each group.

For the baseline characteristic, the World Health Organization (WHO)'s criteria for the Asian population[14] was used to discriminate the body mass index (BMI) categories. The Institute of Medicine's weight gain recommendation for pregnancy[15] was used to diagnose the excessive gestational weight gain (GWG).

For obstetrical outcomes, the participants were graded as well-controlled if they achieved the target PPG at ≥ 80% of all the measurements. If not, they were graded as poorly controlled. Comorbidities, choice of treatment, route of delivery and complications such as postpartum hemorrhage, third- or fourth-degree perineal tear were recorded.

For neonatal outcomes, LGA was defined as a neonatal birth weight of more than a 90th percentile[16] and fetal macrosomia was defined if birthweight ≥ 4000 g.[11] The term newborns birth weight reference was a neonatal weight by the gestational age chart calculated from the fetal growth variation in selected healthy, low-risk pregnancies delivered at Prapokklao Hospital in 2020, and INTERGROWTH-21ST[17] was a reference for preterm newborns. Birth trauma and perinatal complications including shoulder dystocia, neonatal hypoglycemia, neonatal jaundice and NICU admission were recorded. Besides, shoulder dystocia was defined if timing of delivery head-to-body interval greater than one minute or needed additional maneuvers to success the delivery of the baby[18].

All the data were collected from the medical records at Prapokklao Hospital and SPSS version 26 was used for analyzing the data. The categorical data were reported as a number (%) and compared by the chi-square test or Fisher's exact test. For continuous data, Shapiro-Wilk test was used for checking the data distribution. If normal distribution, data were reported as a mean (standard deviation (SD)) and compared by an independent t-test. If not, the report would be a median (min; max) and compared by the Mann Whitney-U test. Logistic regression analysis was used to study the potential factors that affected the rate of the LGA newborns.

Results

Six hundred and sixty-five Thai pregnant women with GDM were enrolled, and 187 were excluded from the study due to twin pregnancy, complicated with other medical conditions, and incomplete medical record (Fig. 1).

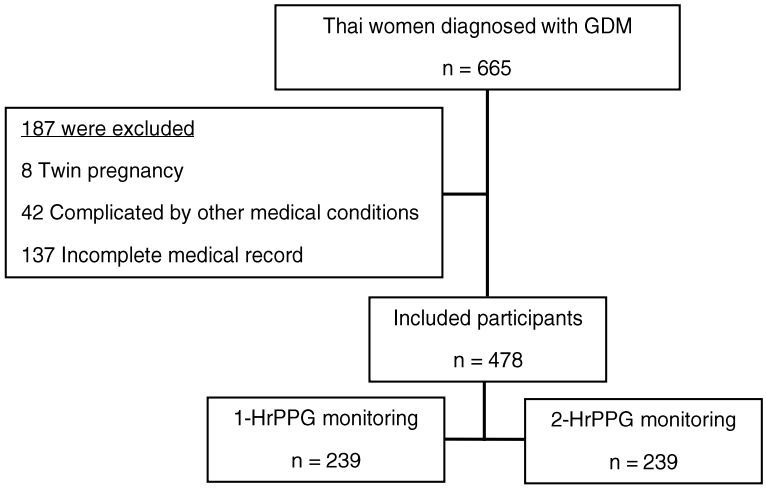

Fig. 1. The study flowchart.

The baseline characteristics were not different between the groups, but a family history of DM was found more in the 1-HrPPG group (14% vs 6%, p = 0.004). The mean age of the participants was around 31 years (p = 0.151), and 38% of the participants were older or equal to 35 years (p = 0.158). Around 80% of the participants were multiparity (p = 0.493), and 57% of the participants were categorized as obesity (p = 0.955) (Table 1).

Table 1. Baseline characteristics.

	1-HrPPG (n = 239)	2-HrPPG (n = 239)	p value
Mean age (years)	31.2 ± 6.2	32.0 ± 6.1	0.151
Age ≥ 35 years, n (%)	84 (35.1)	99 (41.4)	0.158
Parity			0.493
Multiparity, n (%)	188 (78.7)	194 (82.2)	
Pregestational weight, (kg)	67.2 ± 16.4	66.4 ± 14.2	0.541
Pregestational BMI	26.9 ± 7.6	26.9 ± 5.6	0.955
Parity			
BMI categories			
Underweight, n (%)	10(4)	7(3)	0.459
Normal, n (%)	51(21)	56(23)	0.583
Overweight, n (%)	47(20)	35(15)	0.145
Obesity, n (%)	131(55)	141(59)	0.356
Gestational age at diagnosis, wk.	19.4 ± 8.8	20.5 ± 9.9	0.204
Family History of DM*, n (%)	33(14)	14(6)	0.004
History of GDM, n (%)	5(2)	3(1)	0.724

HrPPG: hour postprandial glucose, BMI: body mass index, DM = Diabetes mellitus, GDM: gestational diabetes mellitus
BMI category (kg/m^2): underweight < 18.5, normal weight = 18.5-22.9, overweight = 22.9-24.9, obesity = ≥ 25

During the antepartum period, the participants were not different in progression or the obstetric outcomes, but the treatment method. The total weight gain was around 9 kgs (p = 0.369), and 31% of the participants had excessive GWG (p = 0.921). Gestational hypertension and preeclampsia coexisted in around 7.3% of the participants (p = 0.598) and 4% of the participants (p = 0.815), respectively. For the treatment, 74% of the participants could achieve target PPG without medication, which was significantly found in the 2-HrPPG group more than the 1-HrPPG group (82.8% vs 65.3%, p < 0.001). Insulin and metformin were the choices of medication for the participants who could not achieve the target PPG without medication. Metformin was used in the 1-HrPPG group more than the 2-HrPPG group (16.3% vs 4.2%, p < 0.001), but using insulin not different between groups (18.4% vs 12.6%, p = 0.077). For the intrapartum, there were no differences in the route of delivery. For the complications, postpartum hemorrhage was found in 2.7% of the participants (2% vs 3.3%, p = 0.399) and not found any of third-or fourth-degree perineal tear (Table 2).

Table 2. Obstetrical outcomes.

Outcomes	1-HrPPG (n = 239)	2-HrPPG (n = 239)	p value
Gestational weight gain (GWG), kg.	9.6 ± 6.3	9.1 ± 5.5	0.369
Excessive GWG, n (%)	74 (30.9)	75 (31.4)	0.921
Gestational age at delivery, wk.	38.1 ± 1.1	38.0 ± 1.5	0.462
Preterm labor, n (%)	14 (5.8)	25 (10.5)	0.066
Comorbidities			
Gestational hypertension, n (%)	19 (8)	16 (6.7)	0.598
Preeclampsia, n (%)	9 (3.7)	10 (4.2)	0.815
Treatments			< 0.001
Diet control only, n (%)	156 (65.3)	198 (82.8)	
Metformin, n (%)	39 (16.3)	10 (4.2)	
Insulin, n (%)	44 (18.4)	30 (12.6)	
Postprandial plasma glucose control			0.055
Well-controlled, n (%)	146 (61.1)	166 (69.5)	
Poor-controlled, n (%)	93 (38.9)	73 (30.5)	
Route of delivery			0.521
Vaginal delivery, n (%)	131 (54.8)	124 (51.9)	
Cesarean section, n (%)	108 (45.2)	115 (48.1)	
Indication for cesarean section			0.466
Primary cesarean section, n (%)	66 (27.6)	59 (24.7)	
Repeated cesarean section, n (%)	42 (18)	56 (23.4)	
Complications			
Postpartum hemorrhage, n (%)	5 (2)	8 (3.3)	0.399

HrPPG: hour postprandial glucose, GWG: gestational weight gain

For the neonatal outcomes, the mean birthweight was significantly higher in the 1-HrPPG group (3180.8 ± 460.6 vs 3098.0 ± 434.9 grams, p = 0.044). But the rate of the LGA newborns was not different (20.5% vs 20.1%, p = 0.91). For complications, there were two cases of shoulder dystocia that were found in the 2-HrPPG group only (0.8%, p = 0.499) and only one brachial plexus injury found in the 2-HrPPG group (0.4%, p = 1.000). Other adverse neonatal outcomes, such as neonatal hypoglycemia and neonatal jaundice, neither rate of the NICU admission were statistically different (Table 3).

After the comparison of the rate of LGA between the GDM follow-up by 1-HrPPG and 2-HrPPG, there was no relationship between them. Univariate and multivariate Logistic regression analysis were used to analyze factors that could affect the rate of the LGA newborns. The follow-up method, maternal age equal or older than 35 years, type of GDM, controlled with metformin, well-controlled PPG, overweight, obesity, and excessive GWG were included in the analysis. Only the excessive GWG increased the risk for the LGA newborns (adjusted odds ratio 2.04, 95% confidence interval 1.27-3.27, p = 0.003). Other factors did not significantly increase the risk of LGA (Table 4).

Table 3. Neonatal outcomes.

Outcomes	1-HrPPG (n = 239)	2-HrPPG (n = 239)	p value
Mean Birthweight, gram	3180.8 ± 460.6	3098.0 ± 434.9	0.044
Weight categories			0.909
LGA, n (%)	49 (20.5)	48 (20.1)	
AGA, n (%)	167 (69.9)	159 (66.5)	
SGA, n (%)	23 (9.6)	32 (13.4)	
Macrosomia, n (%)	7 (3)	4 (1.6)	
Birth injury			
Brachial plexus nerve injury, n (%)	0	1 (0.4)	1.000
Complications			
Shoulder dystocia, n (%)	0	2 (0.8)	0.499
Neonatal hypoglycemia, n (%)	71 (29.7)	72 (30.1)	0.920
Neonatal jaundice, n (%)	64 (26.8)	59 (24.7)	0.601
NICU admission, n (%)	4 (1.7)	5 (2.1)	1.000

HrPPG: hour postprandial glucose, LGA: large for gestational age, AGA: appropriate for gestational age, SGA: small for gestational age, NICU: neonatal intensive care unit

Table 4. Univariate and multivariate logistic regression analysis of large for gestational age and risk factors in GDM.

Factors	Crude OR	95%CI		p value	Adjusted OR	95%CI		p value
1-HrPPG	1.03	0.66	1.60	0.909	1.06	0.67	1.68	0.809
GDMA2	1.03	0.73	1.45	0.883	0.90	0.60	1.37	0.634
Metformin	1.31	0.66	2.63	0.442	1.34	0.59	3.08	0.483
Well-controlled	0.70	0.45	1.11	0.133	0.73	0.44	1.23	0.236
Maternal age ≥ 35 yrs.	1.45	0.92	2.27	0.109	1.44	0.89	2.31	0.137
BMI Categories	7 (3)	4 (1.6)						
Overweight	1.13	0.63	2.01	0.682	1.11	0.54	2.29	0.771
Obesity	1.10	0.70	1.73	0.679	1.07	0.60	1.91	0.827
Excessive GWG	2.07	1.30	2.37	0.002	2.04	1.27	3.27	0.003

OR: odd ratio, CI: confidence interval, HrPPG: hour postprandial glucose, GDM: gestational diabetes mellitus, BMI: body mass index, GWG:

Discussion

Thai pregnant women in Chanthaburi could be at risk of GDM due to the advanced maternal age, obesity, and excessive GWG, similar to other studies[1, 2, 19]. Even though the prevalence of GDM in Chanthaburi was quite high, more than 70% of the participants achieved the target PPG without medication.

GDM participants that were followed-up by 1-HrPPG or 2-HrPPG had similar obstetric and neonatal outcomes, including the rate of the LGA newborns, even with well-controlled PPG or

significantly higher mean birthweight in 1-HrPPG. This data strengthened the results of Weisz et al[5] and Ozgu-Erdinc et al[6] that found no difference in the rate of LGA in GDM that was followed-up by different methods. This may be due to plasma glucose peaks at approximately 90 minutes after a meal, between the two time points[1]. Therefore, no matter which followed-up method was used, this did not affect the obstetric and neonatal outcomes.

Although, metformin exposure in-utero increased the risk of SGA and may reduce the rate of LGA[20]. But it not showed in our study. Nevertheless, the CLUE study had done the additional analysis and found no relationship between metformin exposure in-utero and SGA or LGA[21]. So far, metformin in pregnancy and the adverse outcomes in the child is still inconclusive and need further assessment.

The most potential contributing factor for the LGA newborns was excessive GWG. This data emphasized the study of Kim et al that found a positive association between excessive GWG and LGA[22]. Likewise, Boriboonhirunsarn and Kasempipatchai showed that excessive GWG doubled the risk for LGA[23]. And Bhavadharini et al also found that excessive GWG increased the risk of LGA newborns[24]. GWG is a modifiable factor that would make excessive GWG be preventable. Hence, all pregnant women should be advised and encouraged to gain an appropriate GWG. Because this could reduce LGA which would decrease the morbidity and mortality in pregnant women and their children[24].

For the strength of this study, neonatal birth weight was compared to the local low-risk population, which could reflect the reality in the institute. Some limitations may be from selective bias of the method used and uncontrollable confounding factors such as choice of treatment, eating behavior, physical activities, or another lifestyle could affect the PPG levels. Further randomized controlled trial studies could correct these biases and flaws.

Conclusion

The rate of the LGA newborns, the obstetric and neonatal outcomes in GDM followed-up by 1-HrPPG or 2-HrPPG was not different. Any method could be individually chosen for follow-up in GDM. Excessive GWG doubled the risk for having LGA newborns. Encouragement for pregnant people to gain an appropriate GWG may reduce LGA.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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GYNAECOLOGY

Reliability and Validity of the Thai Version of the Pelvic Floor Bother Questionnaire

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ABSTRACT

Objectives: To develop a Thai version of the pelvic floor bother questionnaire (PFBQ) and to evaluate its reliability and validity. The correlation with the pelvic floor distress inventory-20 (PFDI-20) questionnaire was evaluated.

Materials and Methods: A Thai version of PFBQ was developed from the original English version by translation and back translation method. The psychometric properties of the questionnaire were evaluated in 100 Thai women with pelvic floor dysfunction (PFD). Internal consistency was measured by Cronbach's alpha coefficient for all items. Test-retest reliability was measured by intraclass correlation coefficient (ICCr). The agreement of each item between two visits (two-week interval) was measured by Kappa coefficient. Concurrent validity of the PFBQ was evaluated by assessing its correlation with the PFDI-20 using the Spearman's correlation coefficient (r).

Results: A total of 100 women who had PFD symptoms (mean age ± standard deviation = 61.89 ± 11.70 years) were enrolled in the study. All women completed the study. The Thai version of PFBQ demonstrated acceptable internal consistency (Cronbach's alpha = 0.76) and excellent test-retest reliability (ICCr = 0.90, 95% confidence interval 0.85-0.93). The agreement of each question between two visits ranged from moderate to substantial (Kappa = 0.43-0.69). There was a positive correlation between the Thai version of PFBQ and the PFDI-20 (r = 0.81).

Conclusion: The Thai version of the PFBQ is valid and reliable. It may be used as a tool to identify the presence of symptoms and assess the severity of bother of various pelvic floor dysfunction in Thai women. PFBQ can be used as a patient reported outcome instrument in both research and clinical practice.

Keywords: Thai version, pelvic floor bother questionnaire, PFBQ, pelvic floor dysfunction.

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การศึกษาความเที่ยงและความตรงของแบบสอบถามการรบกวนในอุ้งเชิงกราน

เบญจมาภรณ์ เสรีนนท์ชัย, ปุริม เรือนภู่, กีรติ เชียงทอง, สุวิทย์ บุณยเวชชีวิน

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาการศึกษาความเที่ยงของแบบสอบถามการรบกวนในอุ้งเชิงกราน (Pelvic Floor Bother Questionnaire) ฉบับภาษาไทย และหาสหสัมพันธ์เทียบกับแบบสอบถาม Pelvic Floor Distress Inventory -20 (PFDI-20)*

วัสดุและวิธีการ: *การศึกษาแบบสอบถามทางจิตวิทยา (Psychometric test) โดยมีการแปลแบบสอบถามการรบกวนในอุ้งเชิงกรานเป็นฉบับภาษาไทย โดยมีการแปลแบบสอบถามโดยนักภาษาศาสตร์เป็นภาษาไทย และแปลฉบับภาษาไทยเป็นภาษาอังกฤษอีกครั้ง (translation-back translation method) เพื่อใช้ในการประเมินเรื่องของการรบกวนในอุ้งเชิงกราน*

ผลการศึกษา: *จากการศึกษาผู้เข้าร่วมวิจัย 100 คน ที่มีอายุเฉลี่ย 61.89 ± 11.70 ปี ค่าสัมประสิทธิ์สหสัมพันธ์ ของความสอดคล้องภายใน (Internal Consistency) อยู่ในเกณฑ์ที่ยอมรับได้ (α = 0.76) และมีค่าสัมประสิทธิ์ของความคงที่ (test-restet reliability) อยู่ในเกณฑ์ดีมาก (ICCr = 0.90 (0.85-0.93) โดยมีค่าสถิติแคปปาที่บ่งบอกถึงความไปด้วยกันของการตอบคำถามแต่ละข้อในการตอบคำถามครั้งแรกและครั้งที่สองเมื่อผ่านไป 2 สัปดาห์ อยู่ในเกณฑ์ปานกลางถึงมาก (k = 0.43-0.69) และมีค่าความสอดคล้องระหว่างแบบสอบถามการรบกวนในอุ้งเชิงกรานเป็นฉบับภาษาไทย และ PFDI-20 ฉบับภาษาไทย ในระดับสูง (r = 0.81)*

สรุป: *แบบสอบถามการรบกวนในอุ้งเชิงกรานฉบับภาษาไทย มีความเที่ยงและความตรง และสามารถใช้เป็นเครื่องมือที่ใช้ในการประเมินการมีอาการของภาวะอุ้งเชิงกรานผิดปกติ รวมทั้งประเมินความรุนแรงของอาการที่เกิดขึ้นจากภาวะอุ้งเชิงกรานผิดปกติ*

คำสำคัญ: *ฉบับภาษาไทย, แบบสอบถามการรบกวนในอุ้งเชิงกรานฉบับภาษาไทย, ภาวะอุ้งเชิงกรานผิดปกติ*

Introduction

Pelvic floor dysfunction (PFD) refers to a variety of conditions, including pelvic organ prolapse, lower urinary tract dysfunction such as urinary incontinence, defecatory dysfunction, and sexual dysfunction[1]. Even though, PFD rarely result in severe morbidity, this problem can significantly have the effect to the patient's quality of life[2]. The patient reported outcome instruments for self-assessment of symptoms by patients are important. As the most effective way is to assess the bother of patients by evaluating at the patient's point of view[3]. A questionnaire is a data collection tool that can provide objective measures of the patient's symptoms and other aspects of health, such as discomfort, bother, satisfaction, and quality of life. It can be used in clinical practice or in a research study. Questionnaire with scoring system is extremely useful to determine the most bothersome symptoms and grasp the impact of treatment. Currently, several questionnaires are used for evaluating pelvic floor dysfunction, of which many have been translated into Thai and validated. These questionnaires are used in both clinical and research settings. For example, the pelvic floor distress inventory-20 (PFDI-20) is a tool that evaluates the distress related to pelvic floor dysfunctions[4]. However, the tools that assess multiple conditions of PFD are mostly multi-item questionnaires which are difficult to use in the clinical setting. There are validated shorter questionnaires for single PFD problem such as the overactive bladder symptom score (OABSS). This four-item questionnaire evaluates four symptoms of overactive bladder, including daytime frequency, nighttime frequency, urgency, and urgency incontinence[5]. It is convenient to use but this questionnaire is specific for only one disorder of PFD.

The pelvic floor bother questionnaire (PFBQ) is a short questionnaire that assesses the presence of multiple common conditions of PFD that can evaluate the severity or bother of these pelvic floor problems. The original PFBQ questionnaire was developed in English language and demonstrated good validity and reliability[6]. The PFBQ has been translated and validated in many languages, including Arabic[7], Turkish[8] Portuguese[9] and Chinese[10]. The PFBQ was used as a tool to evaluate pelvic floor symptoms and level of bother in many research studies[11-15]. It can be used to evaluate prevalence of PFD in various populations[16-17].

In Thailand, the PFBQ was adopted and translated in Thai language in a tertiary care clinic without psychometric test (validity and reliability test) being studied or reported before[18]. The aim of this study was to translate the PFBQ into Thai and to assess the validity and reliability of the Thai version of the PFBQ for further use to assess multiple pelvic floor dysfunctions in clinical practice and for research purposes with one instrument.

Materials and Methods

This study was conducted at the Female Pelvic Medicine and Reconstructive Surgery Clinic, the King Chulalongkorn Memorial Hospital (KCMH), a tertiary care center in Bangkok, Thailand, between July 2020 and July 2021. The study was approved by the Research Ethics Committee, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand. Informed consent was obtained from all participants. The participants were invited into the study by convenient sampling technique. The inclusion criteria were: 1) Thai women who had any symptoms of pelvic organ prolapse, urinary incontinence, urinary urgency and frequency, urge incontinence, fecal incontinence, obstructed defecation or dyspareunia, 2) agree to have self-answering questionnaires. The exclusion criteria were: 1) pregnant, 2) age less than 18 years, 3) inability to read Thai language or mental incapacity to complete self-administered questionnaires.

All participants were evaluated by detailed medical history and complete physical examination, including pelvic organ prolapse assessment using pelvic organ prolapse quantification (POP-Q) system[19] during the initial visit. Participant's demographic data were recorded. The final diagnosis, additional investigation, and management of each participant were decided by the attending physicians without any influence from this study.

The participants completed the Thai version of the PFBQ at the initial visit by themselves. The self-answered PFDI-20 was also completed at the initial visit

in order to assess its correlation with the PFBQ. To evaluate test-retest reliability, all participants received a second copy of the Thai version of the PFBQ in a stamped envelope and were instructed to complete and return it by mail, two weeks after the initial visit.

Questionnaires

The pelvic floor bother questionnaire (PFBQ) consisted of nine items to assess the presence of symptoms and their degree of bother related to pelvic floor dysfunctions. Each item had dichotomous options, "yes" and "no", for identification of the presence of symptoms. If the answer of any symptom was "yes", the extent of its bother was reflected by the following options: not at all (1), only a little bit (2), somewhat (3), a moderate amount (4) and a lot (5). Each answer was scored in a range from 0 to 5 with a higher score indicated a more severe bother. The scoring system had the same weight for all questions. The total questionnaire score ranged from 0 to 45. In order to have a summary score ranging from 0 to 100, the total score was transformed by multiplying the mean score of the answered items by 20[20]. This transformed score was used in our study.

Translation of the PFBQ was processed as follows. After permission from the original study's authors, the English version of the PFBQ was translated into Thai by a linguist from the Language Institute, Chulalongkorn University and backward translated by another independent linguist. The final draft was accomplished after a small group interview with patients with PFD and content validation was ensured by two urogynecologists from our department.

The pelvic floor distress inventory-20 (PFDI-20) is a tool to evaluate distress related to pelvic floor dysfunction. The PFDI-20 has a total of 20 questions divided to three scales (urinary dysfunction, pelvic organ prolapse and defecatory dysfunction). The distress associated with each symptom ranges from 0 (not present) to 4 (quite a bit). The score of each subscale was calculated by multiplying the mean score by 25 (range 0-100). The summary score was the sum of the three subscale scores (range 0–300). A higher score indicated more symptom distress[13]. The PFDI-20 has been translated into Thai and validated (Cronbach's alpha coefficient 0.93, intraclass correlation (ICCr) 0.83)[4].

Statistical analysis

For baseline characteristics, the categorical data were presented with number and percentage. The continuous data were presented with mean and standard deviation (SD) or median with interquartile range (IQR) as appropriate.

Rule of thumb's formula was used to estimate the sample size of this psychometric test study[21-22]. Ninety participants were required for the nine-item questionnaire. After adding of 10% for dropouts, 100 participants in total were needed.

The PFBQ was assessed in terms of internal consistency and test-retest reliability. Internal consistency of the questionnaire was measured by Cronbach's alpha coefficient for all items. A Cronbach's alpha coefficient of < 0.50 was classified as 'unacceptable', 0.50-0.60 as 'poor', 0.60-0.70 as 'questionable', 0.70-0.80 as 'acceptable', 0.80-0.90 as 'good' and > 0.90 as 'excellent'[23]. Test-retest reliability was measured by ICCr with 95% confidence interval (CI). An ICCr of < 0.50 was classified as 'poor', 0.50-0.75 as 'moderate', 0.75-0.90 as 'good' and > 0.90 as 'excellent'[24]. The agreement of each item between two visits was measured by the kappa coefficient. A kappa coefficient of < 0 was classified as 'poor', 0-0.20 as 'slight', 0.21-0.40 as 'fair', 0.41-0.60 as 'moderate', 0.61-0.80 as 'substantial' and 0.81-1.00 as 'almost perfect'[25]. Concurrent validity of the PFBQ was evaluated by assessing the correlation between the PFBQ and the PFDI-20 with Spearman's correlation coefficient. The correlation coefficient of 0-0.30 was classify as 'negligible', 0.30-0.50 as 'low', 0.50-0.70 as 'moderate', 0.70-0.90 as 'high' and 0.90-1.00 as 'very high'[26].

All data were managed using the Statistical Package for the Social Sciences for Windows version 22.0 (SPSS, Chicago, IL USA). Statistical significance was considered if a p value was lower than 0.05.

Results

One hundred twenty-two women were invited

to participate in the study, of which 100 were enrolled. Twenty-two women declined to participate. All enrolled participants completed the questionnaires on both visits (Fig. 1). The mean ± SD age was 61.89 ± 11.70 years and mean ± SD body mass index was 25.36 ± 4.05 kg/m^2. The majority of participants were in menopause (84%). The initial complaints were demonstrated in Table 1.

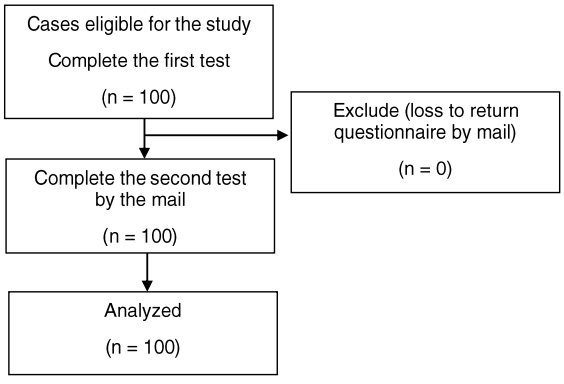

Fig. 1. Flow of participants.

Table 1. Participants' characteristic (n = 100).

Age (mean ± SD)	61.89 ± 11.70
BMI (mean ± SD)	25.36 ± 4.05
Number of children	n (%)
Nulliparous	12 (12%)
1	21 (21%)
2	33 (33%)
3	22 (22%)
> 3	12 (12%)
Education	n (%)
Under primary school	18 (18%)
Primary school	25 (25%)
Secondary school	30 (30%)
Bachelor's degree	23 (23%)
Higher than Bachelor's degree	3 (3%)
Marital status	n (%)
Single	8 (8%)
Married	89 (89%)
Divorced or widowed	3 (3%)
Menopausal status	n (%)
Menopause	84 (84%)
Premenopause	16 (16%)
Initial complaint	n (%)
Genital prolapse	72 (72%)
Stress urinary incontinence	7 (7%)
Urge urinary incontinence	8 (8%)
Mixed urinary incontinence	4 (4%)
Urinary frequency	9 (9%)

SD: standard deviation

The median (IQR) of the total PFBQ score at the first and second visits were 15.56 (7.22-32.78) and 17.78 (8.89-31.11), respectively (Table 2). The internal consistency of total questionnaire was acceptable (Cronbach's alpha = 0.76, Table3). The internal consistency of urinary symptoms was good (Cronbach's alpha = 0.80). The internal consistency of defecatory symptoms was questionable (Cronbach's alpha = 0.67, Table 3). The intraclass correlation coefficient for the total PFBQ score was excellent (ICCr = 0.90, Table 4).

Table 2. Participants' symptoms reported by the PFBQ.

	Frequency, n (%)
Stress urinary incontinence	49 (49)
Urinary frequency	69 (69)
Urinary urgency	51 (51)
Urinary urge incontinence	45 (45)
Voiding difficulty	25 (25)
Genital prolapse	31 (31)
Obstructed defecation	26 (26)
Fecal incontinence	28 (28)
Dyspareunia	17 (17)

PFBQ: pelvic floor bother questionnaire

Table 3. Internal reliability for the Thai version of PFBQ.

	Internal reliability (Cronbach's alpha coefficient)
Global	0.76
Urinary symptoms	0.80
Defecatory symptoms	0.67

PFBQ: pelvic floor bother questionnaire

Table 4. Test-retest reliability of Thai version of PFBQ.

	Estimate	95% Confidence interval
PFBQ total score		
Intraclass correlation	0.90	0.85-0.93
PFBQ items		
Kappa		
1.Stress urinary incontinence	0.61	0.55-0.67
2.Urinary frequency	0.55	0.49-0.61
3.Urinary urgency	0.60	0.54-0.66
4.Urinary urge incontinence	0.57	0.50-0.63
5.Voiding difficulty	0.43	0.35-0.50
6.Genital prolapse	0.59	0.52-0.66
7.Obstructed defecation	0.57	0.49-0.64
8.Fecal incontinence	0.59	0.52-0.67
9.Dyspareunia	0.69	0.60-0.77

PFBQ: pelvic floor bother questionnaire

The kappa statistics of each item ranged from 0.43-0.69 which indicated moderate to substantial agreement between the two visits. The median (IQR) of the total PFDI-20 score was 14.38 (7.50-25.94). The total PFBQ score had a high positive correlation with the total PFDI-20 score (Spearman's correlation coefficient = 0.81, $p < 0.001$).

Discussion

A total of 100 women participated in this study. All participants completed the protocol. The mean age of the participants was 61.89 ± 11.70 years. The reason that might explain this surprisingly young participants was the nature of self-answered questionnaires. Younger women might be more comfortable to complete the questionnaires by themselves than older women. However, we did not have data of the excluded women to confirm this hypothesis.

The PFBQ can identify the bother of all pelvic floor dysfunction problems (pelvic organ prolapse, urinary incontinence, fecal incontinence, and dyspareunia). We found other additional PFD apart from the patients' complaints (voiding difficulty, obstructed defecation, fecal incontinence, and dyspareunia) (Table 1 and 2). This benefit supported the use of this questionnaire as a screening tool for PFD problems in the clinical setting.

The internal consistency of Thai version of the PFBQ was acceptable (Cronbach's alpha = 0.76), similar to the original English version[6], Portuguese-Brazilian version[9] and Chinese version[10]. The PFBQ is a short questionnaire that assesses different symptoms of PFD, so the expected internal consistency is not relatively high. Some language translational versions such as Arabic version and Turkish version did not evaluate internal consistency because they expected that it would be low, due to each question of the PFBQ focused on different conditions[7, 8]. In the Turkish version, the authors performed confirmatory factor analysis to establish the construct validity of the PFBQ. They found that the factor loads of all items in the PFBQ were high, which supported the construct validity of the PFBQ[8]. In Arabic version, the authors calculated the construct validity by comparing scores of an affected population with those of a control population. They found significant differences in the scores of each PFBQ item between the two groups, with the exception of dyspareunia[7].

The Thai version of the PFBQ questionnaire had an excellent test-retest reliability (ICCr = 0.90) which was consistent with the original English version(6), and other language translation versions (Arabic, Turkish, Brazillian-Portuguese, and Chinese)[7-10]. The agreements the Thai version of PFBQ measured within each item ranged from moderate to substantial (kappa coefficient 0.43-0.69) which were lower than the original study[6] and Portuguese-Brazilian version[9]. This may be due to cultural and language difference. These reflected the consistent validity and reliability of the PFBQ after being translated into many languages. We found the good concurrent validity (high positive correlation of Thai version PFBQ and the Thai version of PFDI-20) (Spearman's correlation coefficient = 0.81). This was similar to the Turkish version of PFBQ[8].

Strengths of this study

This study was conducted with strict and validated processes. The questionnaire was translated by experienced linguists and its contents were confirmed by two urogynecologists. There were no dropouts in this study. This excellent cooperation from participants might result from understanding the objective of the study explained by the investigator team. This may reflect the ease of use of the questionnaire. We also assessed the correlation of the PFBQ with the PFDI-20 which was used in our routine clinical practice for concurrent validity.

Limitations of this study

There were no data on the time used for questionnaire completion included in this study. Apart from reliability and validity, the time used to complete the questionnaire is another factor to consider whether the questionnaire should be used in the clinical setting.

As this study was done as hospital based, in one teaching hospital in Bangkok, there might be some limitations for the generalization of our results for other women in different parts of Thailand with different ethnic and culture. There was also possibility of selective bias as we only included women with PFD at our clinic that can come for the treatment at hospital. These women might have better social status and living in the metropolitan city (Bangkok) who can easily access to the hospital service. There was no data on responsiveness because there was no follow up-of the score changes after the treatment compared to the other clinical symptoms. Future study on responsiveness by using the PFBQ before and after medical or surgical treatment and the time used for completion of different questionnaires are advocated.

Conclusion

The Thai version of the PFBQ is valid and reliable. It may be used as a tool to identify the presence of symptoms and assess the severity or bother of various pelvic floor dysfunctions in Thai women. PFBQ can be used as a patient reported outcome instrument in both research and clinical practice.

Potential conflicts of interest

The authors declare no conflicts of interest.

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OBSTETRICS

Sleep Quality and Associated Factors during Pregnancy

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ABSTRACT

Objectives: To assess the prevalence of poor sleep quality among Thai pregnant women and associated factors.

Materials and Methods: A multicenter cross-sectional study was conducted between October 2021 and June 2022. The sleep quality was evaluated using the Thai version of the Pittsburgh sleep quality index (T-PSQI). Factors associated with poor sleep quality (T-PSQI score > 5) were determined using logistic regression analyses.

Results: This study included 414 participants. The prevalence of poor sleep quality was 43.2% (95% confidence interval 38.4% - 48.2%). Prevalence of poor sleep quality was the highest among pregnant women in the third trimester (37.6%, 35.3%, and 51.0% for women in the first, second, and third trimesters, respectively). In multivariate analyses, only gestational trimesters were independently associated with poor sleep quality. There were no significant associations between poor sleep quality and maternal age, pre-pregnancy body mass index, or the number of prior conceptions.

Conclusion: Approximately 43% of Thai pregnant women in this study encountered poor sleep quality. The prevalence of poor sleep quality was the highest among pregnant women in the third trimester.

Keywords: sleep quality, pregnancy, associated factors, pittsburgh sleep quality index .

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คุณภาพการนอนหลับและปัจจัยที่เกี่ยวข้องในระหว่างตั้งครรภ์

พรศิริ คำภูแสน, ยุวดี อิฐรัตน์, พิรชา ตั้งตรงไพโรจน์, กนกพร บุตรมารศรี, วิรัชนี สุขวัฒนานนท์, น้ำเพชร จำปาทอง

บทคัดย่อ

วัตถุประสงค์: *เพื่อประเมินคุณภาพการนอนหลับของสตรีตั้งครรภ์แต่ละไตรมาสและปัจจัยที่มีความสัมพันธ์กับคุณภาพการนอนของสตรีตั้งครรภ์แต่ละไตรมาส*

วัสดุและวิธีการ: *การศึกษาแบบพหุสถาบัน เชิงพรรณนาแบบตัดขวาง ระหว่างเดือนตุลาคม พ.ศ.2563 ถึง เดือนมิถุนายน พ.ศ.2564 โดยการใช้แบบประเมินคุณภาพการนอนหลับแบบพิตส์เบอร์ก ฉบับภาษาไทย (Thai version of the Pittsburgh sleep quality index; T-PSQI) ในการประเมินคุณภาพการนอนหลับ รวมทั้งได้ศึกษาปัจจัยที่สัมพันธ์กับคุณภาพการนอนหลับที่ไม่ดี (T-PSQI score > 5) โดยใช้สถิติวิเคราะห์การถดถอยโลจิสติค (logistic regression analyses)*

ผลการศึกษา: *ในสตรีตั้งครรภ์ 414 คน พบว่า ความชุกของคุณภาพการนอนหลับที่ไม่ดี คือ ร้อยละ 43.2 (ช่วงเชื่อมั่นร้อยละ 95, 38.4 - 48.2) ซึ่งความชุกของคุณภาพการนอนหลับที่ไม่ดีนั้นพบสูงที่สุดในหญิงตั้งครรภ์ไตรมาสที่สาม (ร้อยละ 37.6, 35.3, 51.0 ในสตรีตั้งครรภ์ไตรมาสที่ 1, ไตรมาสที่ 2 และไตรมาสที่ 3 ตามลำดับ) และในการวิเคราะห์พหุตัวแปรพบว่าปัจจัยที่มีความสัมพันธ์กับคุณภาพการนอนหลับที่ไม่ดีคือ ช่วงอายุครรภ์แต่ละไตรมาส และปัจจัยที่ไม่มีความสัมพันธ์ทางสถิติกับคุณภาพการนอนหลับที่ไม่ดี ได้แก่ อายุ ดัชนีมวลกายก่อนตั้งครรภ์ และจำนวนการตั้งครรภ์ก่อนหน้า*

สรุป: *ประมาณร้อยละ 43 ของสตรีตั้งครรภ์ไทย พบว่ามีคุณภาพการนอนหลับที่ไม่ดี ซึ่งความชุกของคุณภาพการนอนหลับที่ไม่ดีนั้นพบสูงที่สุดในหญิงตั้งครรภ์ไตรมาสที่สาม*

คำสำคัญ: *คุณภาพการนอนหลับ, การตั้งครรภ์, ปัจจัยที่เกี่ยวข้อง, แบบประเมินคุณภาพการนอนหลับแบบพิตส์เบอร์ก*

Introduction

During pregnancy, there are significant anatomical and physiological adaptations to allow fetal growth and preparation for childbirth[1]. These changes sometimes may lead to common complaints, such as constipation, low back pain, palpitations, lessened exercise tolerance, and dizziness[1].

Sleep complaints are not uncommon among pregnant women[2]. Although sleep disturbances occurring during pregnancy are generally secondary to pregnancy-related anatomical and physiological changes, they can be due to certain pathological causes such as maternal obesity, cardiometabolic disorders, and preexisting respiratory tract disease[2]. Evidence suggests that suboptimal maternal sleep during pregnancy is related to maternal depression, hypertensive disorders, gestational diabetes mellitus, fetal growth impairment, and preterm birth[2-5]. Meticulous assessment and appropriate management of sleep disorders during pregnancy may prevent adverse perinatal outcomes.

Sleep characteristics vary across the population assessed[6]. This may be due to the differences in the prevalence of conditions constituting links to sleep disorders such as obesity, cardiometabolic disorders, and psychological illness[6]. Sleep patterns also can be mediated by various sociocultural factors[6]. Assessments of sleep quality that focus on certain populations are therefore mandatory. Gathering information relevant to a particular group helps tailor appropriate management. Accordingly, this study was conducted to assess the prevalence of poor sleep quality and associated factors among Thai pregnant women.

Materials and Methods

Settings and participants

This multicenter cross-sectional study was conducted in four hospitals (two provincial hospitals and two tertiary hospitals) in Thailand from October 2021 to June 2022 and was approved by the review boards of the individual participating hospital. Participants were consecutive Thai pregnant women who attended antenatal care department during the study period. This study recruited only singleton pregnant women.

As the tool for assessing the quality of sleep in this study was a self-administered questionnaire, we, therefore, excluded pregnant women with limited reading ability. The research assistant provided study information to all potential participants. Only women who provided written consent were enrolled.

Data and measurements

Baseline demographic characteristics were extracted from medical records. To assess the sleep quality among the participants, this study applied the Thai version of the Pittsburgh sleep quality index (T-PSQI) developed by Sitasuwan et al[7] with permission obtained from the authors. The Pittsburgh sleep quality index (PSQI) is a tool to measure sleep quality during the previous month. The PSQI has been originally published by Buysse et al[8] in 1989. The PSQI is a self-rating questionnaire comprised of seven component scores, each rated from zero (no difficulty) to 3 (severe difficulty). The component scores are summed, resulting in a global score between 0 and 21, with higher scores implying greater sleep difficulty[8]. The PSQI global score greater than 5 indicates poor sleep quality[8].

Data analysis

Sample size was calculated based on an anticipated rate of poor sleep quality across trimesters of pregnancy of 40% with an absolute error of 10%, a type I error of 5%, and 10% of incomplete data. Overall, each participating hospital required at least 103 participants[9-11]. This multicenter cross-sectional study was undertaken in different level of participating hospitals to ensure that the sample of this study was representative for Thai pregnant women.

Descriptive statistics were used to present the background demographic characteristics of the participants. Factors potentially associated with an increased risk of poor sleep quality were identified by reviewing the existing literature. The subsets of participants that had no such potential factors were applied as reference groups during analysis.

The purposeful selection method was used for variable selection process. Variables that were noted to

have p value < 0.25 in simple logistic regression analysis were included for a multiple logistic regression analysis. Collinearity between the covariates in a multiple logistic regression model was assessed to ensure the exclusion of a significant degree of relationship among these variables. Adjusted odds ratio (aOR) and 95% confidence interval (CI) were computed to represent the magnitude of the association. Statistical analyses were performed with STATA version 14.

Results

This study recruited 414 women. The mean age was 29.02 years with a standard deviation (SD) of 5.83 years. One hundred and fifty-nine women (38.4%) were primigravida. Eighty-five pregnant women were in the first trimester. The remaining 133 and 196 pregnant women were in the second and third trimesters, respectively. Table 1 displays the baseline characteristics of the participants.

Table 1. Baseline characteristics of the participants.

Characteristics	All participants (n = 414)	Participants by gestational trimester		
		1st trimester (n = 85)	2nd trimester (n = 133)	3rd trimester (n = 196)
Maternal age mean ± SD (years)	29.02 ± 5.83	29.05 ± 5.59	29.40 ± 5.85	28.77 ± 5.94
Educational level				
No formal education	13 (3.14)	3 (3.53)	4 (3.01)	6 (3.06)
Primary education	24 (5.80)	4 (4.71)	12 (9.02)	8 (4.08)
Secondary education	200 (48.31)	34 (40.00)	63 (47.37)	103 (52.55)
Bachelor's degree or higher	177 (42.75)	44 (51.76)	54 (40.60)	79 (40.31)
Marital status				
Single	40 (9.66)	8 (9.41)	10 (7.52)	22 (11.22)
Married	371 (89.61)	77 (90.59)	122 (91.73)	172 (87.76)
Widowed, divorced, separated	3 (0.72)	0 (0.00)	1 (0.75)	2 (1.02)
Occupation				
None	86 (20.77)	14 (16.47)	28 (21.05)	44 (22.45)
Agriculturist	25 (6.04)	6 (7.06)	14 (10.53)	5 (2.55)
Employee/shop owner	220 (53.14)	47 (55.29)	63 (47.37)	122 (62.24)
Civil servant	55 (13.29)	16 (18.82)	21 (15.78)	19 (9.69)
Others	28 (6.76)	2 (2.35)	7 (5.26)	6 (3.06)
Adequacy of income[a]				
Adequate	305 (73.67)	65 (76.47)	98 (73.68)	142 (72.45)
Inadequate	109 (26.33)	20 (23.53)	35 (26.32)	54 (27.55)
Pre-pregnancy BMI mean ± SD (kg/m^2)	23.04 ± 5.03	23.04 ± 4.39	23.89 ± 5.22	22.46 ± 5.11
Primigravida	159 (38.41)	34 (40.00)	42 (31.58)	83 (42.35)
Complications				
Gestational diabetes mellitus	37 (8.94)	4 (4.71)	8 (6.02)	25 (12.76)
Anemia	27 (6.52)	6 (7.06)	8 (6.02)	13 (6.63)
Hypertensive disorders	9 (2.17)	0 (0.00)	2 (1.50)	7 (3.57)
Others	8 (1.93)	2 (2.35)	3 (2.26)	3 (1.53)

Data are presented as number (percentage) unless stated otherwise. SD: standard deviation, BMI: body mass index

Table 2 shows the global score of sleep quality assessed by using T-PSQI. The mean global score of the entire cohort was 5.62 with an SD of 2.91. The mean global score of sleep quality was the highest among pregnant women in the third trimester. A PSQI global score greater than 5 which indicated poor sleep quality was noted in 179 women (43.24%, 95% CI 38.41% - 48.16%). Of 179 women experiencing poor sleep quality, 83 (20.05%) reported that disturbed sleep led to dysfunction in daily life.

The changing trend in the rate of poor sleep quality throughout pregnancy was similar to the PSQI mean score. The prevalence of poor sleep quality in the third trimester was the highest of the three gestational trimesters (51.02%, 95% CI 43.80% - 58.21%). The prevalence of poor sleep quality in the first trimester (37.6%, 95% CI 27.36% - 48.16%) was comparable to that noted in the second trimester (35.3%, 95% CI 27.25% - 44.09%) (Table 2).

Table 2. Global score of sleep quality by T-PSQI.

Sleep quality score	All participants (n = 414)	Participants by gestational trimester		
		1st trimester (n = 85)	2nd trimester (n = 133)	3rd trimester (n = 196)
Mean global score, SD	5.62 (2.91)	5.53 (2.91)	4.91 (2.63)	6.14 (2.99)
Median global score, IQR	5 (4 - 7)	5 (4 - 7)	5 (3 - 7)	6 (4 - 8)
Number of women with global score > 5 (%, 95% CI)	179 (43.24%, 95% CI 38.41 - 48.16)	32 (37.65; 95% CI 27.36 - 48.82)	47 (35.34, 95% CI 27.25 - 44.09)	100 (51.02; 95% CI 43.80 - 58.21)

T-PSQI: Thai- Pittsburgh Sleep Quality Index, SD: standard deviation, IQR: interquartile range, CI: confidence interval

Table 3 displays the factors associated with poor sleep quality among pregnant women. Multivariate analysis showed that the gestational trimester was independently associated with poor sleep quality. Women in the third trimester carried a higher risk of poor sleep quality compared to those in the first trimester (aOR 1.70, 95% CI 10.1 - 2.87). The risk of encountering poor quality of sleep among women in the second trimester was not significantly different from that reported among women in the first trimester (aOR 0.91, 95% CI 0.52 - 1.61).

There were no significant associations between poor sleep quality during pregnancy and maternal age, adequacy of household income, educational attainment, pre-pregnancy body mass index (BMI), and the number of prior conceptions (Table 3).

Table 3. Factors associated with poor sleep quality during pregnancy.

Factors	Poor sleep quality (%) n = 179	Unadjusted OR (95% CI)	Adjusted OR[a] (95% CI)
Gestational trimesters			
First trimester (<14 weeks) (n = 85)	32 (37.65)	Reference	Reference
Second trimester (14-28 weeks) (n = 133)	47 (35.34)	0.91 (0.51 – 1.59)	0.91 (0.52 – 1.61)
Third trimester (>28 weeks) (n = 196)	100 (51.02)	1.73 (1.03 - 2.90)	1.70 (1.01 – 2.87)
Gravidity			
Multigravida (n = 255)	104 (40.78)	Reference	Reference
Primigravida (n = 159)	75 (47.17)	1.30 (0.87 – 1.93)	1.26 (0.84 – 1.90)
Adequacy of household income by self-rating			
Adequate (n = 305)	125 (40.98)	Reference	Reference
Inadequate (n = 109)	54 (49.54)	1.41 (0.91 – 2.19)	1.42 (0.91 - 2.22)
Educational attainment			
Lower than bachelor's degree (n = 237)	97 (40.93)	Reference	Reference
Bachelor's degree or higher (n = 177)	82 (46.34)	1.25 (0.84 – 1.85)	Variable removed
Maternal age			
< 35 years (n = 345)	151 (43.77)	Reference	Reference
≥ 35 years (n = 69)	28 (40.58)	0.88 (0.52 - 1.48)	Variable removed
Maternal pre-pregnancy BMI			
Underweight (< 18.5 kg/m^2) (n = 69)	30 (43.48)	Reference	Reference
Normal weight (18.5-23.0 kg/m^2) (n = 178)	76 (42.70)	0.97 (0.55 – 1.70)	Variable removed
Overweight (23.0-27.5 kg/m^2) (n = 92)	34 (36.96)	0.76 (0.40 – 1.44)	
Obesity (≥ 27.5 kg/m^2) (n = 75)	39 (52.00)	1.41 (0.73 – 2.72)	

OR: odds ratio, CI: confidence interval, BMI: body mass index
a Variance inflation factor =1 indicated no evidence of multicollinearity existed in a regression model

Discussion

This study assessed subjective sleep quality using the T-PSQI questionnaire. The prevalence of poor sleep quality among Thai pregnant women was 43.2% (95% CI 38.4% - 48.2%). Prevalence of poor sleep quality was the highest among women in the third trimester (37.6%, 35.3%, and 51.0% in the first, second, and third trimesters, respectively). Approximately 20% of women with poor sleep quality reported dysfunction in daily life. Multivariate analysis showed that the gestational trimester was independently associated with poor sleep quality. There were no significant associations between maternal age, pre-pregnancy BMI, number of prior conceptions, and poor sleep quality.

In a previous systematic review published in 2018 which included 24 studies assessing poor sleep quality among pregnant women using PSQI, with a total of 11,002 women contributing data, the prevalence of poor sleep quality varied from 20.8% to 76.3% with a pooled rate of 45.7% (95% CI 36.5% - 55.2%)[10]. In the subsequent systematic review published in 2020 which included 42 studies, the pooled prevalence of poor sleep quality during pregnancy captured by PSQI was 44.5% (95% CI: 37.6–51.6%)[11]. Our finding was consistent with previous studies. Poor sleep quality was also prevalent among Thai pregnant women with a rate of 43.2% (95% CI 38.4% - 48.2%).

The prevalence of poor sleep was different among the three gestational trimesters. In this study, the prevalence of poor sleep quality was found to be highest among women in the third trimester (51.0%). Women in the third trimester were 1.7 times more likely to encounter poor sleep quality compared to those in the first trimester (aOR 1.70, 95% CI 1.01 - 2.87). The finding of the highest rate of poor sleep quality in the last trimester noted in our study was in line with previously reported findings[10-13]. Sleep quality that worsens in the third trimester appears to be partly associated with the increased strength of perceived fetal movements and backache secondary to a rapid increase in the size of the uterus during the third trimester[12].

In the existing literature, various maternal characteristics have been noted to be potentially related to sleep quality during pregnancy i.e., socioeconomic status, level of educational attainment, maternal age, parity status, and maternal BMI[10-16]. This study, however, found no significant impact of these factors on the quality of sleep among our participants.

Sleep disturbance can be assessed by either objective measures (i.e., actigraphy, in-laboratory and in-home polysomnography, and the multiple sleep latency test) or subjective measures (i.e., PSQI, Epworth Sleepiness Scale, Functional Outcomes of Sleep Questionnaire)[17]. For screening purposes, subjective assessment is more practical because of less time-consuming and less expensive[17]. PSQI was applied in this study because it can measure a broad range of subjective sleep quality indicators including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, daytime sleep dysfunction, sleep disturbance, and use of sleeping medications. The PSQI has been primarily developed by Buysse et al[8]. Nowadays, it is widely utilized in both clinical practice and research settings. The PSQI has been translated into several languages[18-20]. This questionnaire has been translated into the Thai language by Sitasuwan et al[7]. The validity and reliability of the Thai version of PSQI are noted to be comparable to the original English version[7].

Findings from this study should be interpreted in light of some limitations. Firstly, this study was a cross-sectional design. Change in PSQI scores over time therefore cannot be determined. The highest rate of mean PSQI score in the last trimester noted in this study however was congruent with previous longitudinal studies[10-12]. Secondly, although the PSQI enables us to identify pregnant women experiencing poor quality of sleep with high sensitivity and specificity, this tool only designates good or poor sleep quality thus precluding our ability to differentiate the severity of disturbed sleep[21]. As a result, further studies determining the severity of sleep disturbance

among pregnant women who reported having poor sleep quality are warranted. However, approximately one-fifth of women with poor sleep quality in this study reported dysfunction in daily life which might represent a group of women suffering from severe sleep disturbances.

Conclusion

In conclusion, approximately 43% of Thai pregnant women in this study reported having poor sleep quality. Prevalence of poor sleep quality was the highest (51.0%) among those who were in the third trimester. These findings underlined poor sleep quality as one of the common problems among pregnant women in our setting. Screening for poor sleep quality by using T-PSQI may be crucial to lessen the risks of adverse perinatal outcomes related to sleep

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Potential conflicts of interest

The authors declare no conflicts of interest.

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The 3 Years Overall Survival Rate in the Women with Stage III Endometrial Cancer across Different Sequences of Adjuvant Chemotherapy or Radiation Therapy

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ABSTRACT

Objectives: To analyze the three years overall survival (OS) and progression free survival (PFS) in women with stage III endometrial cancer across different sequences of chemotherapy (CT) and radiotherapy (RT).

Materials and Methods: A total of 110 stage III endometrial cancer (EC) patients treated with surgically staging and postoperatively received adjuvant therapy in the sandwich method were retrospectively analyzed. Treatment protocols were divided into three groups (Group A: 1-2 cycles of CT followed by RT and 4-5 cycles of CT, Group B: 3 cycles of CT before RT and 3 cycles of CT, and Group C: 4-5 cycles of CT before RT and 1-2 cycles of CT). Survival analysis was analyzed by log-rank test and Cox regression analysis.

Results: After 68 months of median follow-up time, the three years OS and PFS in all patients were 90.0% and 93.5%, respectively. There was no statistical difference in OS and PFS among the three groups. The three years OS was 100%, 86.8%, and 94.7% in groups A, B, and C. In addition, consecutively, the three years PFS was 100%, 91.88%, and 94.7% in groups A, B, and C.

Conclusion: Different adjuvant chemotherapy or radiation therapy sequences offer excellent clinical efficacy and no treatment-related mortality in stage III EC. Moreover, sequences of CT and RT in the sandwich method did not impact the three years OS and PFS.

Keywords: endometrial cancer, adjuvant therapy, sandwich method.

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อัตราการอยู่รอดโดยรวมที่ระยะเวลา 3 ปีของผู้ป่วยมะเร็งเยื่อบุโพรงมดลูกระยะที่ 3 ที่ได้รับการรักษาเพิ่มเติมหลังการผ่าตัด ที่แตกต่างกันในลำดับขั้นตอนการให้เคมีบำบัดและการฉายรังสี ในโรงพยาบาลราชวิถี

กมัยธร เทียนทอง, ฉัตรภัสร์ กล่ำนาค

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาอัตราการอยู่รอดโดยรวมและอัตราการปลอดโรคที่ระยะเวลา 3 ปี ของผู้ป่วยมะเร็งเยื่อบุโพรงมดลูกระยะที่ 3 ที่ได้รับการรักษาเพิ่มเติมหลังการผ่าตัด ที่แตกต่างกันในลำดับขั้นตอนการให้เคมีบำบัดและการฉายรังสี*

วัสดุและวิธีการ: *ผู้ป่วยมะเร็งเยื่อบุโพรงมดลูกระยะที่ 3 จำนวน 110 คน ซึ่งได้รับการรักษาโดยการผ่าตัดเพื่อกำหนดระยะของโรค ได้รับการรักษาเพิ่มเติมหลังการผ่าตัดแบบแซนวิชเทคนิค การรักษาเพิ่มเติมหลังการผ่าตัดแบบแซนวิชเทคนิค แบ่งเป็น 3 กลุ่ม ได้แก่ กลุ่ม A คือ ผู้ป่วยที่ได้รับยาเคมีบำบัด 1-2 ครั้ง ก่อนได้รับการฉายรังสี และตามด้วยยาเคมีบำบัด 4-5 ครั้ง, กลุ่ม B คือ ผู้ป่วยที่ได้รับยาเคมีบำบัด 3 ครั้ง ก่อนได้รับการฉายรังสี และตามด้วยยาเคมีบำบัด 3 ครั้ง และกลุ่ม C คือ ผู้ป่วยที่ได้รับยาเคมีบำบัด 4-5 ครั้ง ก่อนได้รับการฉายรังสี และตามด้วยยาเคมีบำบัด 1-2 ครั้ง วิเคราะห์อัตราการอยู่รอดด้วยวิธีการทางสถิติ*

ผลการศึกษา: *หลังจากการตรวจติดตามเป็นระยะเวลาเฉลี่ย 68 เดือน พบว่าอัตราการอยู่รอดโดยรวมและอัตราการปลอดโรคเฉลี่ย 3 ปี ของผู้ป่วยมะเร็งเยื่อบุโพรงมดลูกระยะที่ 3 คือ ร้อยละ 90.0 และ 93.5 ตามลำดับ โดยอัตราการอยู่รอดโดยรวมของผู้ป่วยกลุ่ม A, B, C คือร้อยละ 100, 86.8 และ 94.7 ตามลำดับ อัตราการปลอดโรคของผู้ป่วยกลุ่ม A, B, C คือร้อยละ 100, 91.9 และ 94.7 ตามลำดับ ทั้งนี้ไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติระหว่างทั้ง 3 กลุ่ม*

สรุป: *ลำดับของการให้ยาเคมีบำบัดและการฉายรังสีที่แตกต่างกันมีประสิทธิภาพที่ดีในการรักษา และไม่พบว่ามีอัตราเสียชีวิตที่เกิดจากการรักษา นอกจากนี้ลำดับการรักษาที่แตกต่างกันของแซนวิชเทคนิคไม่ส่งผลถึงอัตราการอยู่รอดและปลอดโรคที่ระยะเวลา 3 ปี*

คำสำคัญ: *มะเร็งเยื่อบุโพรงมดลูก, การรักษาเสริมหลังการผ่าตัด, ลำดับของการให้ยาเคมีบำบัดและการฉายรังสี*

Introduction

Endometrial cancer (EC) is one of the most common gynecologic malignancies. The incidence has continually increased due to aging, obesity, and metabolic syndrome[1]. Generally, EC is recognized as a disease related to a favorable prognosis since most patients are diagnosed at the early stage of the disease. Conversely, locally advanced EC patients tend to develop loco-regional and distant recurrence, subsequently lower survival[2]. Several adjuvant therapies are given to improve the outcome of these patients[3]. Adjuvant pelvic radiation (RT) is effective for loco-regional control, while adjuvant chemotherapy (CT) administration reduces distant metastatic risk[4]. Several studies in recent years have shown that the combination of these two treatment modalities may be the most promising option for patients with advanced disease[5]. The primary concern regarding the combination of RT and CT is the optimal timing of RT and CT. Patients receiving RT before CT may develop tumor progression outside the radiation field[6]. On the contrary, when CT is initially administered, patients may be suffering from the toxicity of CT, and the capacity to complete RT may be limited[7]. Many studies have been sequentially the timing of RT and CT to lessen toxicity and achieve optimal survival outcomes[8-11]. To date, the optimal sequence of administering RT and CT for locally advanced stage EC patients, either sequentially or sandwiched (adjuvant CT followed by RT and subsequent CT), remains controversial. The sandwich approach is one of the potential techniques with high efficacy and acceptable toxicity. Various studies supported the sandwich method for treating stage III EC and reported three years progression free survival (PFS) rates of 53%-80% and three years overall survival (OS) rates of 52%-91%[7, 12-15]. However, there is limited data about a sequence of CT and RT in the sandwich method. Therefore, we conducted a retrospective study to analyze the three years OS and PFS rates in women with stage III EC across different sequences of CT and RT in the sandwich method.

Materials and Methods

Patient selection

Electronic data of 110 FIGO stage III EC patients treated between January 2012 and June 2018 at the Department of Obstetrics and Gynecology, Rajavithi Hospital, Thailand, were retrospectively reviewed. Institutional review board (IRB) approval was obtained. All patients were surgically staged with total hysterectomy, bilateral salpingo-oophorectomy, and bilateral pelvic and paraaortic lymph node (LN) sampling or dissection. A sequence of CT and RT in the sandwich method was postoperatively administered. Exclusion criteria were women who had received neoadjuvant therapy (CT or RT) before hysterectomy and had not completed RT and six cycles of CT. Data regarding date of surgery, cytoreduction status, pathological factor, number of CT cycles received before and after RT, type of radiation therapy received, date of recurrence, and date of death was extracted. Optimal cytoreduction was total residual tumor less than or equal to one cm in diameter, and suboptimal debulking was defined as tumor more than one cm of disease.

Treatment protocol

Adjuvant CT was given within 2 weeks after surgery. The CT regimens composed of carboplatin (area under curve 5) plus paclitaxel (175 mg/m^2) and doxorubicin (60 mg/m^2) plus cisplatin (50 mg/m^2) every 21 days. Treatment toxicities-related death was assessed. At present, the optimal sequences of adjuvant therapy have yet to be determined. Therefore, there is no consensus guideline in our hospital. The treatment protocol is depended on the surgeon's preference. The adjuvant CT and RT were determined using the different sequences of the number of CT

cycles before and after RT initiation. Three sequence groups were identified.

- Group A: Patients received 1-2 cycles of CT followed by RT and additional 4-5 cycles of CT

- Group B: Patients received three cycles of CT followed by RT and additional 3 cycles of CT

- Group C: Patients received 4-5 cycles of CT followed by RT and additional 1-2 cycles of CT

External beam RT was provided to all patients, using a total dose of 50-50.4 Gy to the pelvis with a daily fraction of 1.8-2 Gy. In cases of para-aortic lymph node metastasis, para-aortic fields were routinely irradiated. Vaginal brachytherapy was provided when patients were considered at high risk of local recurrence or the discretion of the treating radiation oncologist, using two fractions of 6 Gy.

Statistical analysis

The sample size was estimated based on a previous study 15 that revealed 80% of the three years OS. The estimated single proportion with an alpha error of 5% and delta of 10% was tested with a dropout rate of 10%. Therefore, the number of participants was 107. All statistical analyses were evaluated using standard software (SPSS version 22; SPSS Inc., Chicago, IL, USA). The primary objective of this study was the three years OS in stage III EC across different sequences of adjuvant CT or RT. In addition, the secondary purposes were to evaluate the three years PFS and the optimal sequence of CT and RT in the sandwich method. Time to death or progression was calculated as the period from the date of surgery to the date of death or the first clinical or imaging evidence of disease recurrence. Clinicopathological data were summarized and presented as frequencies (number, percent) or means ± standard deviations. Both OS and PFS rates were estimated by the Kaplan-Meier method. The Pearson chi-square test was used to analyze the clinical and pathological factors differences among the groups. Univariate analysis was performed via the log-rank test. Multivariate analysis was done using the Cox proportional hazards model, using covariates with a p value less than 0.1 based on univariate analysis. All p values < 0.05 were statistically significant.

Results

This study enrolled 110 patients with stage III EC who underwent surgical staging and adjuvant CT and RT in the sandwich method. Table 1 shows the clinicopathological characteristics of the patients stratified by different sequences of CT and RT in the sandwich method. The patients were divided into three groups according to the number of CT cycles before and after RT. Of these, 15 (13.6%), 76 (69.1%), and 19 (17.3%) received adjuvant treatment in groups A, B, and C, respectively. The mean age at the time of surgery was 60.9 years old. The most common tumor histology was endometrioid adenocarcinoma (80.9%). On histologic examination, the majority of patients had deep myometrial invasion (84.5%), presence of LVSI (88.2%), and pelvic LN metastasis (63.6%). Approximately 27% of patients had paraaortic LN metastasis. Positive fluid for cytology was noted in 90% of patients. After surgical staging, optimal cytoreductive status was documented in 87.3% of patients. In group A, all patients had optimal cytoreductive status. Overall, there was no statistical significance of clinicopathological factors among the three groups. The most frequent chemotherapy regimen (108, 98.2%) was paclitaxel plus carboplatin. Doxorubicin plus cisplatin was only given to two patients (1.8%) in group B because of paclitaxel hypersensitivity in the first cycle of CT and a personal history of supraventricular tachycardia (SVT).

Table 1. Clinicopathological characteristics stratified by different sequences of CT and RT in the sandwich method.

Characteristics	All patients (n= 110)	Group A (n= 15)	Group B (n= 76)	Group C (n= 19)	p value
Age (years) at surgery (mean ± SD)	60.9 ± 8.5	60.2±9.6	62.1±8.5	56.6±6.6	0.970
Cytoreductive status					
Optimal	96 (87.3%)	15 (100%)	64 (84.2%)	17 (89.5%)	0.294*
Suboptimal	14 (12.7%)	0 (0%)	12 (15.8%)	2 (10.5%)	
Histology type					
Endometrioid	89 (80.9%)	14 (93.3%)	60 (79.0%)	15 (79.0%)	0.454*
Non-endometrioid	21 (19.1%)	1 (6.7%)	16 (21.0%)	4 (21.0%)	
Tumor size (cm) (mean ± SD)	5.9±2.5	6.3±2.1	5.9±2.5	5.3±2.5	0.610
Myometrial invasion					
< 50%	17 (15.5%)	2 (13.3%)	14 (18.4%)	1 (5.3%)	0.465*
≥ 50%	93 (84.5%)	13 (86.7%)	62 (81.6%)	18 (94.7%)	
LVSI					
Absent	13 (11.8%)	1 (6.7%)	10 (13.2%)	2 (10.5%)	0.904*
Present	97 (88.2%)	14 (93.3%)	66 (86.8%)	17 (89.5%)	
Isthmic involvement					
Absent	55 (50.0%)	7 (46.7%)	37 (48.7%)	11 (57.9%)	0.743+
Present	55 (50.0%)	8 (53.3%)	39(51.3%)	8 (41.2%)	
Cervical involvement					
Absent	72 (65.5%)	10 (66.7%)	49 (64.5%)	13 (68.4%)	0.944+
Present	38 (34.5%)	5 (33.3%)	27 (35.5%)	6 (31.6%)	
Uterine serosal involvement					
Absent	92 (83.6%)	11 (73.3%)	64 (84.2%)	17 (89.5%)	0.449+
Present	18 (16.4%)	4 (26.7%)	12 (15.8%)	2 (10.5%)	
Adnexal involvement					
Absent	67 (60.9%)	8 (53.3%)	45 (59.2%)	14 (73.7%)	0.416+
Present	43 (39.1%)	7 (46.7%)	31 (40.8%)	5 (26.3%)	
Pelvic LN metastasis					
Yes	70 (63.6%)	8 (53.3%)	45 (59.2%)	16 (84.2%)	0.094+
No	40 (36.4%)	7 (46.7%)	31 (40.8%)	3 (15.8%)	
Paraaortic LN metastasis					
Yes	30 (27.3%)	4 (16.7%)	21 (27.6%)	6 (31.6%)	0.934+
No	80 (72.7%)	11 (73.3%)	55 (72.4%)	13 (68.4%)	
Peritoneal cytology					
Positive	99 (90.0%)	14 (93.3%)	67 (88.2%)	18 (94.7%)	0.839*
Negative	7 (6.7%)	0 (0.0%)	6 (7.9%)	1(5.3%)	
Not done	4 (3.6%)	1 (6.7%)	3 (3.9%)	0 (0.0%)	

* Fisher's Exact Test, + Pearson chi-square test
Group A: 1-2 cycles of CT followed by RT and additional 4-5 cycles of CT
Group B: 3 cycles of CT followed by RT and additional 3 cycles of CT
Group C: 4-5 cycles of CT followed by RT and additional 1-2 cycles of CT
CT: chemotherapy, RT: radiotherapy, SD: standard deviation, LVSI: lymphovascular space invasion, LN: lymph node

Fig. 1. reveals Kaplan-Meier survival analysis in all patients. After 68 (8-113) months of median follow-up time, the three years OS and PFS were 90.0% and 93.5%, respectively. Fig. 2. demonstrates the Kaplan-Meier survival analysis by treatment group. Consecutively, the three-year OS was 100%, 86.8%, and 94.7% in groups A, B, and C. In addition, the three-year PFS was 100%, 91.88%, and 94.7% in groups A, B, and C.

Of 110 patients, 25 patients (22.7%) experienced the recurrent disease. Three patients (2.7%) had local recurrence, and 22 patients (20%) had distant metastasis. Disease recurrence was 6.7% (1 patient), 25% (19 patients), and 26.3% (5 patients) in groups A, B, and C, respectively. Furthermore, the death rate was highest in group B (11 patients, 14.5%), followed by one patient (5.3%) in group C. However, recurrence and survival did not statistically differ among the three groups. Ninety-eight patients (89.1%) remained alive at the analysis time. For the toxicities, there were no treatment-related deaths in this cohort.

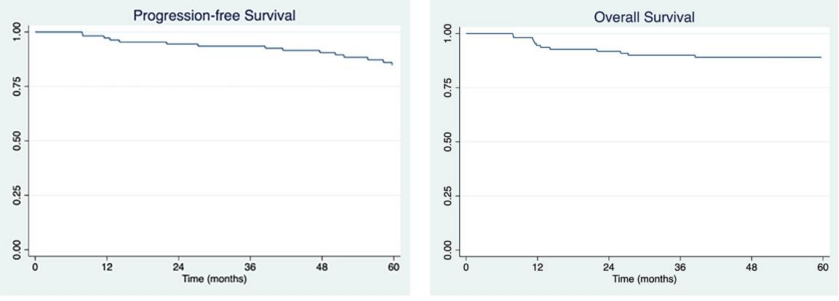

Fig. 1. Kaplan–Meier survival analysis in all patients (PFS analysis and OS analysis).

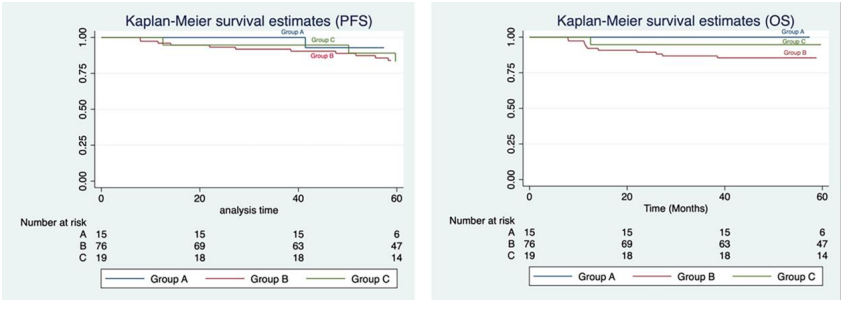

Fig. 2. Kaplan–Meier survival analysis by treatment group (PFS analysis and OS analysis).
Group A: 1-2 cycles of CT followed by RT and additional 4-5 cycles of CT
Group B: 3 cycles of CT followed by RT and additional 3 cycles of CT
Group C: 4-5 cycles of CT followed by RT and additional 1-2 cycles of CT

Table 2. establishes a univariate analysis of the prognostic factor of OS and PFS. The sequence of CT and RT in the sandwich method was not the predictive factor for OS and PFS. Paraaortic LN metastasis resulted in significantly worse survival, 2.70 times than no paraaortic LN metastasis. Moreover, the patients with an age of more than 60 years old, suboptimal cytoreductive status, non-endometrioid adenocarcinoma, and isthmic involvement had a statistical risk of disease recurrence compared to those under 60 years old, endometrioid adenocarcinoma, and non-isthmic

involvement for 2.17, 0.40, 2.40, and 2.36 times, respectively. As shown in table 3, no prognostic factor predicted both OS and PFS in a multivariable model.

Table 2. Univariate analysis of prognostic factors for OS and PFS.

Characteristics	PFS	HR (95% CI)	p value	OS	HR (95% CI)	p value
Adjuvant treatment						
B vs A	0.32	0.04, 2.40	0.267	0.00	0.00, ∞	1.000
B vs C	0.99	0.37, 2.70	0.996	0.35	0.04, 2.68	0.309
Age (yrs) (≤ 60 vs > 60)	2.17	0.89, 5.29	0.088	3.52	0.77, 16.08	0.104
BMI (kg/m²) (≤ 25 vs > 25)	0.95	0.42, 2.13	0.897	0.44	0.13, 1.46	0.178
Cytoreductive status (Optimal vs suboptimal)	0.40	0.16, 1.00	0.050	0.41	0.11, 1.50	0.178
Endometrioid Histology (yes vs no)	2.40	1.02, 5.68	0.046	2.15	0.64, 7.13	0.213
Tumor size (cm) (≤ 2 vs > 2 cm)	1.01	0.14,7.56	0.990	0.41	0.05,3.17	0.392
Myometrial invasion (< 50 % vs ≥ 50 %)	0.92	0.31, 2.74	0.888	2.09	0.27, 16.20	0.480
LVSI (no vs yes)	1.34	0.31, 5.72	0.694	0.00	0.00, ∞	1.000
Isthmic involvement (no vs yes)	2.36	1.03, 5.41	0.042	2.03	0.61, 6.75	0.246
Cervical involvement (no vs yes)	1.72	0.78, 3.79	0.182	1.90	0.61, 5.89	0.267
Uterine serosal involvement (no vs yes)	0.92	0.27, 3.12	0.897	1.87	0.51, 6.90	0.349
Adnexal involvement (no vs yes)	0.53	0.22, 1.28	0.159	0.49	0.13, 1.81	0.286
Pelvic LN metastasis (no vs yes)	1.47	0.61, 3.53	0.385	1.14	0.34, 3.79	0.828
Paraaortic LN metastasis (no vs yes)	1.14	0.50, 2.61	0.758	2.70	0.87, 8.37	0.086

Group A: 1-2 cycles of CT followed by RT and additional 4-5 cycles of CT

Group B: 3 cycles of CT followed by RT and additional 3 cycles of CT

Group C: 4-5 cycles of CT followed by RT and additional 1-2 cycles of CT

OS: overall survival, PFS: progression free survival, HR: Hazard Ratio, CI: Confidence Intervals, BMI: body mass index, LVSI: lymphovascular space invasion, LN: lymph node

Discussion

Advanced stage EC is related to the unfavorable prognosis due to the tendency of disease progression. The rationale of multimodal treatment using CT and RT is to control local and distal relapse. Most publications demonstrated promising survival outcomes and toxicity safety of multimodal therapy. The fundamental concern about the combination of RT and CT is the optimal timing of RT and CT. Patients receiving RT before CT may develop tumor progression

outside the radiation field. Moreover, when CT is initially given, the patient may experience CT toxic effects, and the ability to complete RT may be limited. To balance the benefits of each treatment modality while limiting therapy toxicities, sandwich therapy has been investigated. In the sandwich method, several prospective and retrospective studies revealed the superior PFS (53-80%) and OS (52-91%) compared to those receiving RT followed by CT or CT followed by RT in the setting of advanced staged EC with acceptable toxicity profile[7-9, 13-19]. To date, there is uncertainty regarding the optimal number of CT cycles to administer before and after RT. Treatment in the sandwich method facilitates administration of both planned modalities, with the ability to provide at least some systemic therapy before initiating RT. Generally, three cycles of CT, followed by RT, and then three cycles of CT are frequently used.

In this study, all patients achieved complete surgery, CT, and RT without treatment-related mortality. The three years OS and PFS in all patients were 90.0% and 93.5%, respectively, and we found no statistical significance in the three years OS and PFS when compared among the three groups. Different CT and RT sequences in the sandwich treatment were feasible and accomplished the excellent three years OS and PFS rate in stage III EC patients. However, the three years OS and PFS in group A tended to be better than the other group. It is probably caused by the high percentage of an optimal cytoreductive status (100%) and histology of endometrioid adenocarcinoma (93.3%). As well as there was a lower rate of pelvic (53.5%) and paraaortic (16.7%) LN metastasis.

Differ from the other studies, there were very high OS and PFS rates in all patients. Furthermore, the three years OS was 100%, 86.8%, and 94.7% in groups A, B, and C, respectively. In addition, the 3-year PFS was 100%, 91.88%, and 94.7% in groups A, B, and C, respectively. We demonstrated an outstanding OS and PFS because of complete treatment, including surgery, CT, and RT in all patients with a significant number of optimal cytoreductive surgery[11, 14-19]. Moreover, we limited our selection of patients to only those with stage III disease, and the most common histologic subtype was endometrioid adenocarcinoma (80.9%). No negative prognostic factor was identified in the multivariate analysis for both OS and PFS.

The strengths of this study included only surgically complete staged patients and were well balanced in terms of clinic-pathological distribution and cytoreduction status. The present study had several limitations. First, it was retrospective in nature. Second, we collected only information about treatment-related death. Data of overall treatment-related toxicities, both short and long-term, were omitted. Third, the number of patients in group A and C was relatively small. It may need to be careful when the results are interpreted. Lastly, although most patients had endometrioid histology, patients with non-endometrioid histology were also included in the analyses. Further prospective randomized trials conducted on larger scales with well-defined patient populations and molecular classification analysis are needed to clarify the impact of various sequencing schedules on clinical outcomes.

Conclusion

In conclusion, the sandwich method offered excellent clinical efficacy and no treatment-related mortality in stage III EC. Different sequences of CT and RT in the sandwich method did not impact the three years OS and PFS in stage III EC. The trend of giving 1-2 cycles of CT, followed by RT, and additional 4-5 cycles of CT (group A) seemed to have the highest OS and PFS. However, the number of patients in group A and C was relatively small. It may need to be careful when the results are interpreted.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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CASE REPORT

Spontaneous Abortion due to Maternal Listeriosis: A case report

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ABSTRACT

Listeriosis is an infection caused by *Listeria monocytogenes*, which is a foodborne pathogen. Maternal listeriosis is clinically challenging to diagnose as gastrointestinal symptoms are not the main feature. Intrauterine infection can lead to spontaneous abortion, preterm delivery, and intrauterine foetal death. We report a case of maternal listeriosis that had presented to our emergency department with spontaneous abortion.

Keywords: listeria monocytogenes, listeriosis, foetus, foodborne, pregnancy.

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Introduction

Listeriosis is an infection caused by *Listeria monocytogenes*, which is a foodborne pathogen. Pregnant women, their fetuses, and the elderly are more susceptible to infection. Animals are the natural reservoir for this bacterium. However, it can also be found in soil, raw vegetables, uncooked meat, and unpasteurized dairy products. Infection occurs when the patient consumes food contaminated by it.

Intrauterine infection may lead to the mother having an abortion, stillbirth, premature delivery and chorioamnionitis. A recent study reported that *Listeria monocytogenes* was detected in 3.7% of women with spontaneous abortion[1]. In another study, mothers who had listeria infection were found to have a significantly higher rate of preterm delivery (61.3%) and stillbirth (13.5%) compared to those not infected[2]. Complications to the fetus include neonatal sepsis, neonatal meningitis, and neonatal death. A study reported that the morbidity in the fetus could go as high as 30%[3]. An umbrella review involving 330 studies reported that 66% of listeriosis infections occur in the third trimester, while only 3% occur in the first trimester of pregnancy[4].

We found only a limited number of case reports on maternal listeriosis from Malaysia. Therefore, we report here a case of maternal listeriosis that presented with a spontaneous abortion to the emergency department of Hospital Universiti Sains Malaysia.

Case Report

A 29-year-old Malay, para 2-0-0-2, at 20 weeks of gestation, presented to the Emergency Department (ED), Hospital Universiti Sains Malaysia complaining of fever with chills and rigors for 3 days. It was associated with lower abdominal pain and vaginal bleeding. Upon arrival at the ED, she passed out an abortus with the placenta, weighing 180 grams with minimal blood loss. The abortus appeared fresh and was non-viable upon delivery. The placenta was intact, appeared normal, and had no foul smell. She denied consumption of unpasteurised cheese, uncooked meat, or poultry. She also denied taking any medication. There were no other associated gastrointestinal, respiratory, cardiovascular, or urinary tract symptoms.

On physical examination, her temperature was 38.2°C. Her vital signs were stable, and there were no abnormalities seen. Full blood count showed leukocytosis (white blood cell count: 18.9 x 10^9/L). A differential count was not done. There was mild anemia (hemoglobin level: 10.2 g/dL) and normal platelet level (273 x 10^9/L). Her renal and liver function tests were within normal range.

Blood and placental tissue samples were sent to the microbiology laboratory for culture and sensitivity tests. Microscopy revealed short Gram-positive bacilli (Fig. 1). The catalase test was positive. The culture revealed small and smooth β-hemolytic colonies on blood agar incubated in 5% CO_2 (Fig. 2). An "umbrella" growth pattern was seen in a semisolid motility medium (Fig. 3). The Christie–Atkins–Munch-Peterson (CAMP) test was positive. Identification using VITEK® 2 system revealed *Listeria monocytogenes* with excellent identification (98%). The antibiotic susceptibility test showed that the isolate was sensitive to ampicillin and trimethoprim-sulfamethoxazole. Cefuroxime and metronidazole were not tested as these antibiotics are not included in the Clinical and Laboratory Standards Institute (CLSI) antimicrobial susceptibility testing standards guideline, hence do not have any reference cut-off point.

On admission, the patient was given intravenous (IV) cefuroxime 750 mg every 8 hours and IV metronidazole 500 mg every 8 hours as empirical treatment for septic miscarriage. The fever subsided, and the patient recovered well. There were no clinical sign or symptom of genitourinary infection. The patient was discharged on the third day of admission before the microbiological laboratory results were available. The patient was on IV antibiotics for three days. The antibiotic was changed to oral ampicillin and given to continue for one week after discharge. Follow-up was done at the post-natal clinic. A blood culture taken on the follow-up revealed no growth.

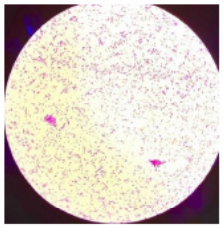

Fig. 1. Short Gram-positive bacilli on microscopy.

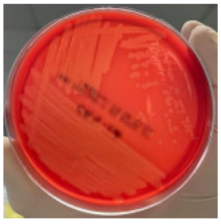

Fig. 2. Small and smooth β-hemolytic colonies on blood agar incubated in 5% CO_2.

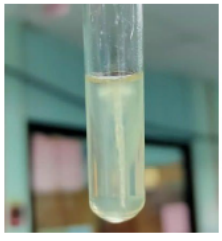

Fig. 3. "umbrella" growth pattern seen in a semisolid motility medium.

Discussion

The most common risk factor for infection is consuming unpasteurized dairy products due to the bacteria's ability to grow and multiply at low temperatures, such as in refrigerated food[5]. The patient denied consuming unpasteurised cheese, uncooked meat, or poultry. Trying to ascertain the food may be challenging, partly contributed by the extended incubation period, which may last up to 6 weeks in pregnancy[6]. A study done in Malaysia reported that 20% of the raw chicken meat sold at hypermarkets and wet markets had *Listeria monocytogenes*[7]. Another study found *Listeria monocytogenes* in ready-to-eat foods such as cooked satay, prawns, squids, clams, chicken dishes, cucumber and peanut sauce from street vendors, canteens, and restaurants[8].

Maternal listeriosis is clinically challenging to diagnose as gastrointestinal symptoms are not the main feature[6]. A study reported that women with maternal listeriosis had symptoms of a flu-like illness (32%), fever (65%), backache (21.5%), headache (10.5%), vomiting/diarrhea (7%), muscle pains (4%) and sore throat (4%) while 29% of the women were asymptomatic[9]. In another study, they found abdominal pain (88.2%), prolonged rupture of membranes (23%) and no fetal movement (13.7%) as the three most common symptoms in maternal listeriosis[10].

Hence, clinicians may miss the diagnosis. Therefore, the microbiology laboratory plays an important role. The organism grows well and can

be isolated from samples taken from the blood and placenta. Both VITEK® 2 system and matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) can be used to confirm the diagnosis[11].

The intracellular survival ability of the bacteria protects it from the host's innate and adaptive immune responses. Currently, no randomised controlled trial has yet demonstrated the most effective treatment of listeriosis[12]. However, it is usually susceptible to ampicillin.

Listeriosis usually causes a mild illness in the mother[13]. The patient was initially given cefuroxime and metronidazole as empirical treatment, following the national guideline for septic miscarriage[14]. The patient was discharged from hospital with 7 days of oral ampicillin and had recovered fully. Nevertheless, The American College of Obstetricians and Gynecologists and the Centres for Disease Control and Prevention (CDC) recommend a high dose of intravenous ampicillin (at least 6 g/day) for at least 14 days in non-allergic pregnant patients[15].

Conclusion

In conclusion, clinicians should be aware of maternal listeriosis due to the high risk of morbidity and mortality to the fetus so that prompt investigation and proper treatment can be given.

Potential conflicts of interest

The authors declare no conflicts of interest.

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