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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).

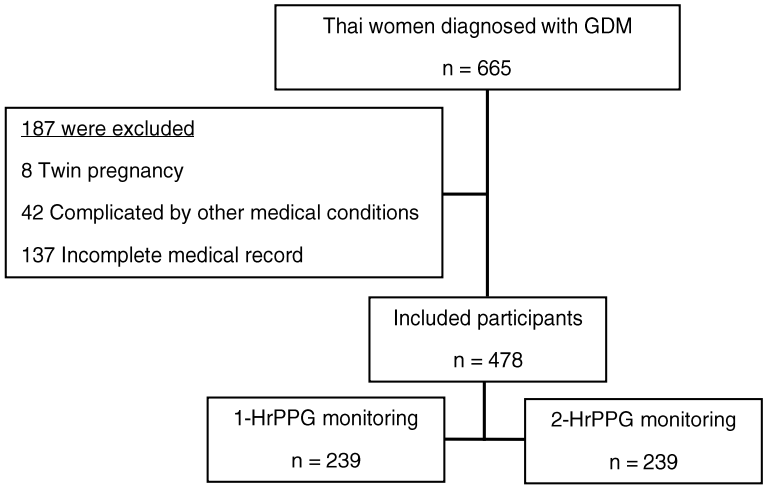

Fig. 1. The study flowchart.

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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