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The Comparative Study of The Large for Gestational Age Prevalence in Neonate of Diabetic Pregnant Women Between The Optimal and Suboptimal Glycemic Control Groups

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ABSTRACT

Objective: To compare the prevalences of LGA (large for gestational age) newborns in diabetic pregnant women between the optimal glycemic control and suboptimal glycemic control.

Materials and Methods: Total of 228 women, delivered at Ramathibodi Hospital between March 2010-December 2012, 114 women in each group, were enrolled. The medical records were reviewed for necessary data. The primary outcome were the prevalences of LGA in both groups and the secondary outcome were the prevalences of neonatal hypoglycemia.

Results: The prevalence of LGA newborns in suboptimal controlled group was higher than in optimal controlled group (n = 33, 28.95% and n = 7, 6.14%, respectively) with the relative risk of 4.71 (95% CI; 2.18, 10.21). The factors that found the association with LGA newborns were prepregnant BMI and types of DM. Adjusted relative risk for both factors of the LGA in suboptiamal controlled group was 3.59 (95% CI; 1.60, 8.06). The prevalence of neonatal hypoglycemia were not different. (7.02% in suboptimal controlled group and 3.51% in optimal controlled group)

Conclusion: Suboptimal glycemic controlled pregnant women were found increase risk of LGA newborns. The prevalence of neonatal hypoglycemia was not different.

Keywords: GDM, glycosylated hemoglobin concentration, HbA1c, LGA

Introduction

The prevalence of gestational diabetes mellitus (GDM) has been increasing in developed countries form 2.9% to 8.8% over 20 year[1,2]. Both GDM and overt DM have been shown to impact pregnancy outcomes. Perinatal morbidities includes macrosomia, birth trauma, hypoglycemia, hyperbillirubinemia, and polycythemia. Perinatal outcomes associated with poor glycemic control in mothers are associated with as high as 42.9% mortality[3] Neonatal adiposity similarly increases. Researches also reported future risk of childhood obesity and development of type 2 diabetes

and cardiovascular disease as a result of increased neonatal hyperinsulinemia and increase fat mass. While the well controlled maternal GDM could decrease the risk of large for gestational age infant[4].

The glycosylated hemoglobin concentration, also called hemoglobin A1c (HbA1c), reflects a longer duration of glycemic control, generally about 3 months, which approximated the life span of the red blood cell. The glycosylated hemoglobin was used to study the relationship between maternal glycemic control and the effect to neonates[5].

Large for gestational age (LGA) is a result from maternal GDM or overt DM especially in women who poor glycemic control and it may result in difficult delivery, shoulder dystocia, birth trauma or increased rate of caesarean section. Fetal hyperglycemia and hyperinsulinemia result from poor glycemic control of diabetic pregnant women also result in neonatal hypoglycemia. It is interesting whether the prevalence of LGA infants in optimal glycemic control groups is lower than suboptimal glycemic control groups and the prevalence of neonatal hypoglycemia is lower in optimal glycemic control groups too.

Materials and Methods

This retrospective and prospective cohort study was approved by the Ethical Clearance Committee on Human Rights Related to Researches Involving Human subjects, Faculty of Medicine Ramathibodi Hospital. From the result of our pilot study of 26 GDM mothers at DM clinic of ANC clinic. The prevalence of LGA in optimal and suboptimal glycemic control groups were 7.6% and 19.23%. Power of 95% at type I alpha error of 0.05 and type II error of 0.2 were used. The calculated sample size was 114 eligible subjects in each group.

A study comprising all women with GDM and overt DM delivering at Ramathibodi hospital during March 2010-December 2012. GDM was diagnosed if fasting plasma glucose (FPG) ≥ 92 mg/dl but < 126 mg/dl or HbA1c < 6.5% at the first ANC or abnormal only 1 of 75 gm OGTT (normal limits were FPG < 92 mg/dl , 1 hr postprandial (PPD) <180 mg/dl, 2 hr PPD < 153 mg/dl). Overt DM was diagnosed if there was the history of diabetic mellitus before pregnancy or FPG ≥ 126 mg/dl and/or HbA1c ≥ 6.5 at the first ANC visit.

The inclusion criteria were pregnant women who were delivery at Ramathibodi hospital with gestational age ≥ 37 week, diagnosed gestational diabetic mellitus or overt diabetic mellitus, followed up at DM clinic of ANC clinic and evaluated HbA1c at least 1 time in third trimester. The exclusion criteria were multiple pregnancy or pregnancy with medical complications that resulted in alter blood glucose level such as using steroid drug

GDM or overt DM patients were attended DM clinic and advised by specialized nurses for diet control and self-monitoring of blood glucose, good control was defined that fasting blood glucose < 95 mg/dl and/or 1 hour postprandial < 140 mg/dl. The pregnant women recorded their blood glucose levels in the diabetic clinic book and the doctors reviewed their records every ANC visit. The pregnant women who are well controlled by diet control at first time were classified as GDMA1. The poor controlled GDM pregnant outcome was consulted to endocrinologist for insulin therapy. The GDM patient who was treated with insulin was classified as GDMA2. In overt DM, the insulin was started by endocrinologists if they used oral diabetic drugs before pregnancy. During ANC visit, GDMA1 were followed by obstetricians in DM clinic and GDMA2 and overt DM women followed up with obstetricians and endocrinologists. Timing of the appointment depended on patient condition, gestational age and glycemic controlled. HbA1c was measured at the third trimester between 32-38 week of gestation.

In our study, the optimal glycemic control was defined as the HbA1c level < 6% at the third trimester and the suboptimal glycemic control group was defined as the patient who had HbA1c level ≥ 6% at the third trimester, which was recommended by American Diabetes Association 2012 recommendation[6].

The primary outcome was the prevalence of LGA, which was defined as a birth weight > 95th percentile, adjusted for gestational age of Chart of Division of Maternal Fetal Medicine, Department of Obstertircs and Gynecology Faculty of Medicine Chulalongkorn University, Thai version[7-8]. Secondary outcome was

the prevalence of neonatal hypoglycemia which was defined as blood glucose < 40 mg/dl at 1 hour after delivery and no early feeding.

Statistical analysis

All analysis were conducted using the STATA version 1.2. Normally distributed continuous variables were reported by mean (± standard deviation) and student-T test was used for comparing. Chi- spuare-test was used for comparing the proportion data. The significant factors were analyzed by multivariate logistic analysis and presented as p-value, risk ratio (RR) and 95% confidence interval. P < 0.05 was considered statistically significant.

Results

In this study include all women follow by the inclusion criteria, total 228 women were separated to optimal and suboptimal glycemic control groups by HbA1c level in third trimester. Demographic data of the study population were presented in Table 1. There were neither difference in maternal age, gestational age at the time of HbA1c nor the total weight gain. Mean prepregnant BMI was higher in the suboptimal control group (25.7 versus 22.4 kg/m^2 in optimal glycemic control group). There was more GDMA1 in optimal glycemic control group than suboptimal glycemic control group. (87.72% and 73.68% respectively.)

Table 1. Demographic data

Characteristics	Optimal control group n = 114	Suboptimal control group n = 114	p
- Age (y)	31.5 ± 5.4	32.1 ± 5.1	0.36
- Prepregnant BMI (Kg/m^2)	22.4 ± 4.0	25.7 ± 5.0	< 0.001*
- Gestational age at HbA1c was measured (week)	35.8 ± 2.0	35.7 ± 2.5	0.95
- Total weight gain (kg)	11.7 ± 3.9	12.0 ± 4.4	0.51
- Type of DM [I]			0.001*
GDMA1	100, 87.72%	84, 73.68%	
GDMA2	13, 11.40%	17, 14.91%	
Overt DM	1, 0.88%	13, 11.40%	

Data were presented in mean ± standard deviation, *statistic significant,

[I] Data were presented as number (%), *statistic significant

Table 2. showed the prevalence of LGA and neonatal hypoglycemia. LGA in suboptimal control group that was higher than in optimal control group (RR = 4.71, 95% CI = 2.18-10.21). After adjusted risk ratio by type of GDM and prepregnant BMI, the prevalence of LGA in suboptimal control group was higher than in the optimal control group (RR = 3.59, 95%CI;1.60-8.06). The prevalences of neonatal hypoglycemia in suboptimal control group and optimal control group were not different (7.02% and 3.51%), p = 0.375.

Table 2. The prevalence of LGA and neonatal hypoglycemia in optimal and suboptimal glycemic control group.

Outcome	Optimal control group n = 114	Suboptimal control group n = 114	p
LGA (n,%)			
No LGA	107, 93.86%	81, 71.05%	< 0.001*
LGA	7, 6.14%	33, 28.95%	
Neonatal hypoglycemia (n, %)			
No hypoglycemia	110, 96.49%	106, 92.98%	0.375
Hypoglycemia	4, 3.51%	8, 7.02%	

Data were presented as number (%), *statistic significant

Discussion

In this study, the result show different of LGA prevalence in between suboptimal and optimal glycemic control groups similar to other study but prevalence of neonatal hypoglycemia was not different between two groups that different from prior study

LGA pregnancies were complicated by postpartum hemorrhage, shoulder dystocia, cesarean section delivery, neonatal hypoglycemia and had a longer hospitalization period[9].

Maternal hyperglycemia significantly increase the risk perinatal morbidity including LGA and macrosomia. The prevalence of LGA range between 9.5–26.1%[10-13].

Previous study reports that as maternal age increased the birthweight increased and maternal age was significantly higher in LGA[14]. The prepregnant maternal BMI and the total weight gain may influence the risk of LGA pregnancy[15,16]. The factors of maternal age and total weight gain were similar in our study for both optimal and suboptimal control group, nevertheless the prepregnant BMI was higher in suboptimal control group. This maybe due to increased demands on maternal metabolism during pregnancy form excess weight, resulting in imbalance in hormonal carbohydrate regulation mechanisms and insulin sensitivity. Previous study reported the prevalence of LGA newborns was higher among overweight, obese, and obese class II women as compared with normal weight women[15].

Several methods have been used to evaluate the diagnosis of diabetic mellitus. Oral glucose tolerance test (OGTT) is the gold standard test for diagnosing GDM with different criteria and values for OGTT for diagnosing GDM[16-18]. OGTT is a cumbersome procedure for participants as well as health care providers, which requires fasting state, waiting time for minimum two blood samples taken and depends on participant's compliance. World Health Organization (WHO) in 2011 as well as American Diabetic Association (ADA) has accepted HbA1c as a diagnostic tool for diagnosing diabetic mellitus[19,20]. There are no recommendations available for use of HbA1c as a diagnostic tool for GDM. The mean HbA1c value in women with GDM was significantly higher than women without GDM[21]. Cut off value of ≥ 5.95% had sensitivity of 28.6% and specificity of 97.2% in diagnosing GDM. Other studies report that HbA1c are lower in pregnancy comparing to non-pregnancy state[22,23] with trimester-specific reference interval[24]. High maternal HbA1c is associated with overweight in neonates[25] and poor pregnancy outcome[26].

There was no cut off point of HbA1c to monitor the glycemic control. In this study use HbA1c level 6% for separate groups of glycemic control. According to recommendation of ADA 2012, the optimal control of HbA1c level should be less than 6%[6], in diabetic women who become pregnant.

Our study showed the suboptimal glycemic control group had 4.71 – fold increased prevalence of LGA and the factors that associated with the LGA were prepregnant BMI and type of DM. After adjusting for both factors suboptimal glycemic control group remained have 3.59 fold increased risk of neonatal LGA.

This finding was also report from previous study[25].

The strength of this study may be the measurement of HbA1c was found excellent reliability within the same individual[27]. The value reflects the glycemic condition three months prior the measurement which should have effect towards developing fetus, and is not fluctuated according to daily diet consumption before the test. Using HbA1c in also likely to be more acceptable to pregnant women as a single non-fasting blood sample. The result of our study can support that controling blood sugar level in GDM and over DM is important because poor glycemic control results in increasing risk of LGA. HbA1c level in the third trimester useful for predict LGA infant, this study suggest to monitor HbA1c in the third trimester in clinical practice.

The limitations of the study were HbA1c reflected the mean glycemic condition but not the blood glucose fructuations whice may had some effects deleterious on the fetal development[25]. Although HbA1c had advantage of good intra-individual reliability, the measurement of HbA1c is affected by anemia which associated with accelerated red blood cell turnover and some hemoglobinopathies[21], these condition were not analysed in this study.

The optimal control glycemic status in GDM women may prevent the adverse maternal and fetal outcomes. Further studies of optimal cut off point of HbA1c for well control GDM that will have the impact on the mentioned outcomes should be evaluated.

The risk of neonatal hypoglycemia increase with birth wight, both in diabetic and in non-diabetic pregnancies[9]. In our study, no significant difference hypoglycemic newborns in both optimal and suboptimal glycemic control groups were found due to insufficient calculated sample size. Other study reported more neonatal hypoglycemia in suboptimal glycemic control GDM women[25].

Conclusion

Suboptimal glycemic control GDM and overt DM women, defined by HbA1c ≥ 6%, had prevalence of LGA newborn and increased risk of LGA for 3.59 fold. The prevalence of neonatal hypoglycemia was not different.

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การศึกษาเปรียบเทียบความชุกของทารกแรกเกิดที่มีน้ำหนักตัวเกินเกณฑ์ปกติของมารดาที่เป็นเบาหวานในกลุ่มที่ควบคุมน้ำตาลได้ตามเป้าหมายกับกลุ่มที่ควบคุมน้ำตาลไม่ได้ตามเป้าหมาย

ขวัญสุดา เย็นศรี, พัญญู พันธ์บูรณะ, ณัฐพงศ์ อิศรางกูร ณ อยุธยา, ประชา นันท์นฤมิต

วัตถุประสงค์ *: เพื่อศึกษาเปรียบเทียบความชุกของทารกแรกเกิดที่มีน้ำหนักตัวเกินเกณฑ์ปกติของมารดาที่ได้รับการวินิจฉัยว่าเป็นเบาหวานขณะตั้งครรภ์และมารดาผู้ป่วยเบาหวานมาก่อนการตั้งครรภ์ในกลุ่มที่ควบคุมน้ำตาลได้ตามเป้าหมายและกลุ่มที่ควบคุมไม่ได้ตามเป้าหมาย*

เครื่องมือและระเบียบวิธีการวิจัย *: การศึกษาแบบเก็บข้อมูลหญิงที่ได้รับการวินิจฉัยเบาหวานก่อนและขณะตั้งครรภ์ที่มาคลอดที่โรงพยาบาลรามาธิบดีระหว่างเดือน มีนาคม 2553 - ธันวาคม 2555 จำนวนทั้งสิ้น 228 คน โดยแบ่งเป็นกลุ่ม คือกลุ่มที่ควบคุมน้ำตาลได้ตามเป้าหมาย (ค่า HbA1c < 6%) และกลุ่มที่ควบคุมน้ำตาลไม่ได้ตามเป้าหมาย (ค่า HbA1c ≥ 6%) โดยมีการตรวจ HbA1c ในช่วงไตรมาสที่สามของการตั้งครรภ์ โดยแต่ละกลุ่มมีประชากลุ่มละ 114 คน จากนั้นนำมาศึกษาเปรียบความชุกของภาวะทารกแรกเกิดที่มีน้ำหนักตัวเกินเกณฑ์ปกติ และความชุกของภาวะน้ำตาลต่ำหลังคลอดของทารก*

ผลการศึกษา *: ความชุกของภาวะทารกแรกเกิดมีน้ำหนักตัวเกินเกณฑ์ปกติในกลุ่มมารดาที่ควบคุมน้ำตาลไม่ได้ตามเป้าหมายนั้นสูงกว่ากลุ่มที่ควบคุมน้ำตาลได้ตามเป้าหมายคิดเป็น 28.95% และ 6.14% ตามลำดับ โดยความเสี่ยงคิดเป็น 4.71 เท่า จากการศึกษาพบว่ามีปัจจัยที่มีผลต่อภาวะทารกแรกเกิดมีน้ำหนักตัวเกินเกณฑ์ปกติ ได้แก่ ดัชนีมวลกายก่อนการตั้งครรภ์และชนิดของเบาหวาน โดยหลังจากการคำนวน โดยตัดปัจจัยดังกล่าวก็ยังพบว่า กลุ่มที่ควบคุมน้ำตาลไม่ได้ตามเป้าหมายยังคงมีความเสี่ยงต่อการเกิด ภาวะทารกแรกเกิดน้ำหนักตัวเกินเกณฑ์มากกว่ากลุ่มที่ควบคุมน้ำตาลได้ตามเป้าหมาย 3.59 เท่า ในด้านของภาวะน้ำตาลต่ำหลังคลอดในทารกพบว่าทั้งสองกลุ่มมีความชุกไม่ต่างกัน*

สรุป*: ค่า HbA1c ในช่วงไตรมาสที่สามของการตั้งครรภ์สัมพันธ์กับความชุกของภาวะทารกแรกเกิดน้ำหนักตัวเกินเกณฑ์ปกติในกลุ่มที่ควบคุมน้ำตาลไม่ได้ตามเป้าหมายจะเพิ่มความเสี่ยงมากกว่ากลุ่มที่ควบคุมน้ำตาลได้ตามเป้าหมาย ความชุกของภาวะน้ำตาลต่ำหลังคลอดในทารกทั้งสองกลุ่มนั้นไม่แตกต่างกัน*