The association between low 50 g glucose challenge test values and adverse pregnancy outcomes

Ha Yan Kwon

Department of Medicine

The Graduate School, Yonsei University

The association between low 50 g glucose challenge test values and adverse pregnancy outcomes

Directed by Professor Young-Han Kim

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Ha Yan Kwon

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YONSEI UNIVERSITY

This certifies that the Master's Thesis of
Ha Yan Kwon is approved.

Thesis Supervisor : Young-Han Kim

Thesis Committee Member#1 : Joonho Lee

Thesis Committee Member#2 : Byung-Wan Lee

The Graduate School
Yonsei University

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Ha Yan Kwon
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ABSTRACT

The association between low 50 g glucose challenge test values and adverse pregnancy outcomes

Ha Yan Kwon

Department of Medicine
The Graduate School, Yonsei University

(Directed by Professor Young-Han Kim)

Objective: To compare the pregnancy outcomes in pregnant women with low 50 g glucose challenge test (GCT) values to those of pregnant women with normal values.

Methods: This retrospective study was conducted in pregnant women undergoing gestational diabetes mellitus (GDM) screening tests at 24-28 weeks gestational age between January 2010 and December 2016. Women with multifetal pregnancies, type I or II diabetes before pregnancy, GCT performed prior to 24 or after 28 weeks of gestational age, and women undergoing multiple GCTs in the same pregnancy were excluded. Pregnancy outcomes in women with low GCT values [<tenth percentile (≤85 mg/dL)] were compared with those of women with normal GCT values (86-130 mg/dL).

Results: Of 3875 screened subjects, 519 (13.4%) women were included in the low GCT group and 3356 (86.6%) were included in the normal

GCT group. Women in the low GCT group had a significantly higher rate of small for gestational age (SGA) infants than did women in the normal GCT group (10.8% vs. 7.9%, p=0.02). Cesarean section and postpartum hemorrhage (PPH) were less frequent in the low GCT group than in the normal group (32.6% vs. 42.8%, p<0.01 and 0.2% vs. 1.2%, p=0.03, respectively). Women with low GCT values had a 1.38-fold increased independent risk of bearing SGA infants (95% CI: 1.01-1.88, p=0.04).

Conclusion: Women with low 50 g GCT values had significantly higher rates of SGA infants and significantly lower rates of cesarean delivery and PPH. Low GCT values were independently associated with increased risk of SGA.

Key words: 50 g oral glucose challenge test (GCT), low glucose value, pregnancy outcome

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I. INTRODUCTION

Remarkable metabolic changes in glucose metabolism occur during pregnancy to support fetal development and to maximize maternal efficiency. Abnormal glucose metabolism may result in an adverse intrauterine environment and lead to increase obstetrical complications. Oral glucose challenge testing (GCT) is widely used in the second trimester to assess maternal glucose status and screen for gestational diabetes (GDM). Hyperglycemia on the oral GCT is associated with macrosomia, cesarean delivery, preeclampsia, and an increased risk of long-term complications in the offspring including childhood obesity, insulin resistance, and type 2 diabetes later in life.[1-4] However, there have been limited studies regarding the implications of low 50 g GCT values, and there is no consensus on the association between an isolated low GCT value and adverse pregnancy outcomes. Some investigators have reported that maternal low GCT values are

linked to an increased risk of intrauterine growth restriction and neonatal intensive care unit (NICU) admissions,[5,6] whereas other investigators have found no relationship between low GCT values and perinatal morbidity.[7] The oral 50 g GCT has been used extensively in nearly all pregnant women, and a better understanding of the association between adverse pregnancy outcomes and low GCT values would be helpful in reducing maternal and neonatal morbidity.

The purpose of this study was to compare the pregnancy outcomes in pregnant women with low 50 g glucose challenge test (GCT) values to those of pregnant women with normal values.

II. MATERIALS AND METHODS

Study population

This retrospective study was conducted at Severance Hospital, a tertiary referral center affiliated with Yonsei University College of Medicine, Seoul, Korea, between January 2010 and December 2016. The study was approved by the hospital institutional review board. All women without known diabetes were screened for GDM with a 50 g GCT between 24 and 28 weeks of gestational age. Women who had a serum 1-hour glucose value obtained after a 50 g oral glucose load were eligible for this study. A low GCT value was defined as a serum glucose level below the tenth percentile in our study population (≤ 85 mg/dL). The normal GCT group consisted of women with a GCT value between 86 and 130 mg/dL. Data regarding maternal demographics, neonatal data, and pregnancy outcomes were obtained from the medical records. Data regarding the following adverse pregnancy outcomes were obtained: preeclampsia, abnormal amniotic fluid index (AFI), preterm labor, preterm premature rupture of membranes (PPROM), postpartum hemorrhage (PPH), small for gestational

age (SGA), admission to the neonatal intensive care unit (NICU), abnormal placental implantation, and preterm delivery. Women with multifetal gestations, type I or II diabetes before pregnancy, GCTs performed prior to 24 weeks or after 28 weeks of gestation, and women undergoing multiple GCTs during the same pregnancy were excluded. Women with 1-hour glucose levels > 130 mg/dL following the 50 g oral glucose load were not included in the study to limit false negatives for GDM.

Definitions

Neonate birthweight percentiles were calculated according to Korean reference standards.[8] SGA was defined as a neonatal birthweight below the tenth percentile for that gestational age and large for gestational age (LGA) was defined as a neonatal birthweight above the 90th percentile for that gestational age. Low birthweight was defined as birthweight < 2500 g and macrosomia was defined as a birthweight > 4000 g. Obesity was defined as a pre-pregnancy body mass index (BMI) ≥ 25 kg/m2. Preterm delivery was defined as delivery occurring prior to 37 weeks of gestational age and early preterm delivery was defined as delivery occurring prior to 34 weeks of gestational age. Preeclampsia was diagnosed if the patient presented with a persistent blood pressure elevation above 140/90 mmHg with additional systemic features after 20 weeks of gestation.[9] PPROM was confirmed by history and visualization of vaginal pooling of amniotic fluid before the onset of labor prior to 37 weeks of gestation. Oligohydramnios was defined as a four-quadrant amniotic fluid index (AFI) of ≤ 5 cm, and polyhydramnios was defined as an AFI ≥ 25 cm. PPH was defined as the loss of more than 1000 mL of blood within the first 24 hours following childbirth. Placenta previa was defined as abnormal placentation near or covering the internal cervical os, and placenta accreta was diagnosed if the placenta attached abnormally to the myometrium, and additional interventions

such as uterine artery embolization or cesarean hysterectomy were needed. Placental abruption was defined as the premature separation of the placenta from the uterus.

Statistical analysis

For a comparison of categorical variables, Pearson's chi-square test or Fisher's exact test were used. Continuous variables were analyzed using Student's t-test. To evaluate the crude association between low GCT levels and adverse pregnancy outcomes, logistic regression analysis was used to calculate the unadjusted odds ratios (OR) and 95% confidence intervals (95% CI). We also calculated the adjusted ORs after adjusting for potential confounding factors, including maternal age, parity, gestational age at delivery, pre-pregnancy BMI, weight gain during pregnancy, and others. A p value < 0.05 was considered statistically significant. All analyses were performed using SPSS version 23.0 (SPSS Inc. Chicago, IL, USA).

III. RESULTS

Initially, the medical records of 6257 women were reviewed for this study. Figure 1 shows the GCT values of the present study population. Of these, 579 (9.2%) had a low glucose value at one hour following a 50 g oral glucose load ($\leq$ 85 mg/dL). A total of 3875 women were ultimately enrolled into this study. Among these women, 519 (13.4%) had a low GCT value and 3356 (86.6%) had a normal GCT value (86-130 mg/dL).

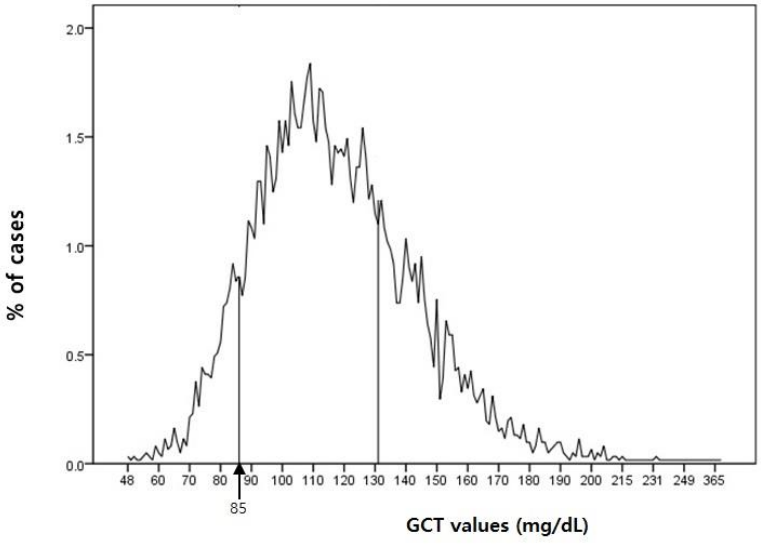

Figure 1. Distribution of the glucose challenge test values in the study population.

Compared to women with a normal GCT value, women with a low GCT value were younger ($p < 0.01$) and had greater gestational age at delivery ($p < 0.01$). The proportions of women with a maternal age > 35 years and with maternal obesity (pre-pregnancy ≥ 25 kg/m2) were lower in the low GCT group than in the normal group. Other characteristics between the two groups were similar (Table 1).

The cesarean section rate was lower in the low GCT group than that seen in the normal GCT group ($p < 0.01$) as was the emergency cesarean section rate ($p = 0.01$). PPH also occurred less frequently in women with a low GCT value than in women with a normal GCT value ($p = 0.03$). There were no significant differences in other adverse pregnancy outcomes including preeclampsia, oligohydramnios, polyhydramnios, PPROM, preterm labor, preterm delivery, placenta previa, placenta accreta, and placental abruption between the two groups (Table 2).

Table 1. Maternal characteristics of the low and normal GCT level groups

	GCT level		*p*-value
	Low (n=519)	**Normal (n=3356)**	
Age (years)	31.7±3.4	32.6±3.7	<0.01
> 35 years	105 (20.2)	990 (29.5)	<0.01
Parity			0.11
0	461 (59)	1667 (53.9)	
1	275 (35.2)	1181 (38.2)	
2	43 (5.5)	213 (6.9)	
≥ 3	3 (0.4)	32 (1.1)	
Gestational weeks at delivery	39.2±1.5	38.9±1.7	<0.01
50g GCT value(mg/dL)	77.1±7.2	108.6±12.1	<0.01
Pre-pregnancy BMI (kg/m^2)	21.6±29.7	21.5±13.2	0.89
BMI ≥ 25	22 (4.2)	298 (8.9)	<0.01
Weight gain during pregnancy (kg)	12.6±4.0	12.6±4.7	0.74
Any pre-existing medical conditions			0.24
Chronic hypertension	4 (0.8)	49 (1.5)	
Hyperthyroidism	6 (1.2)	39 (1.2)	
Hypothyroidism	11 (2.1)	87 (2.6)	
Thrombocytopenia	7 (1.3)	26 (0.8)	
Other conditions[(1)]	22 (4.2)	95 (2.8)	

Data expressed as number(%) or mean±SD. GCT, glucose challenge test; BMI, body mass index. [(1)] Other conditions include epilepsy, asthma, antiphospholipid syndrome, renal disease, Behcet's disease and myasthenia gravis.

Table 2. Pregnancy outcomes of the low and normal GCT level groups

	Low GCT (n=519)	**Normal GCT (n=3356)**	***p*-value**
Delivery mode			< 0.01
Vaginal delivery	350 (67.4)	1919 (57.2)	
Cesarean section	169 (32.6)	1437 (42.8)	
Emergency c-section	61 (36.0)	527 (36.7)	
Preeclampsia	6 (1.2)	49 (1.5)	0.58
Abnormal AFI			
Oligohydramnios	5 (1.0)	36 (1.1)	0.82
Polyhydramnios	2 (0.4)	22 (0.7)	0.46
Preterm delivery			
< 34 weeks	3 (0.6)	56 (1.7)	0.06
< 37 weeks	25 (4.8)	239 (7.1)	0.05
PPROM	6 (1.2)	62 (1.8)	0.26
Placental abruption	1 (0.2)	13 (0.4)	0.49
Placenta previa	8 (1.5)	61 (1.8)	0.65
Placenta accreta	1 (0.2)	18 (0.6)	0.29
PPH	1 (0.2)	40 (1.2)	0.03

Data expressed as number (%). GCT, glucose challenge test; C-section, cesarean section; AFI, amniotic fluid index; PPROM, preterm premature rupture of membranes; PPH, postpartum hemorrhage

Neonatal outcomes are shown in Table 3. There was a significant difference in the rate of SGA neonates between the two groups (10.8% vs. 7.9%, p = 0.02). The number of neonates with low birthweight (LBW), macrosomia, low Apgar score (5-minute Apgar score < 7), admission to the NICU, and intrauterine fetal death were not significantly different between the two groups (Table 3).

Table 3. Neonatal outcomes of the low and normal GCT groups

	Low GCT (n=519)	**Normal GCT (n=3356)**	***p*-value**
Birthweight (g)	3175.2 ± 439.7	3187.1 ± 471.1	0.58
SGA	56 (10.8)	266 (7.9)	0.02
LBW[(1)]	22 (4.2)	199 (5.9)	0.12
LGA	40 (7.7)	319 (9.5)	0.18
Macrosomia[(2)]	12 (2.3)	109 (3.2)	0.25
Five minute APGAR <7	11 (2.1)	84 (2.5)	0.59
NICU admission	64 (12.3)	455 (13.6)	0.74
IUFD	2 (0.4)	4 (0.1)	0.15

Data expressed as number(%) or mean±SD. SGA, small for gestational age; LBW, low birthweight; AF, amniotic fluid; NICU, neonatal intensive care unit; IUFD, intrauterine fetal death. [(1)] birthweight <2500g; [(2)] birthweight >4000g

Multivariable logistic regression analysis was used to access the associations between a low GCT value and certain adverse pregnancy outcomes while controlling for potential confounders (Table 4). Neonates born to mothers with a low GCT value had a significantly higher risk of SGA (OR = 1.38, 95% CI 1.01-1.88) and a significantly lower risk of cesarean delivery (OR = 0.75, 95% CI 0.61-0.92). In addition, a low GCT level was independently associated with a decreased risk for PPH (OR = 0.17, 95% CI 0.02-0.91).

Table 4. Association of low GCT values with adverse pregnancy outcomes by multivariable logistic regression analysis

	Adjusted OR	95% CI	*p* value
Cesarean section	0.75 [(1)]	0.61-0.92	<0.01
Emergency C-section	0.71 [(1)]	0.53-0.95	0.02
Preeclampsia	0.99 [(2)]	0.40-2.40	0.98
Preterm delivery	0.81 [(3)]	0.44-1.51	0.52
Early preterm delivery	0.32 [(3)]	0.09-1.14	0.08
PPROM	0.77 [(2)]	0.31-1.91	0.58
Placental abruption	0.57 [(2)]	0.07-4.48	0.60
PPH	0.17 [(2)]	0.02-0.91	0.03
SGA	1.38 [(4)]	1.01-1.88	0.04
Five minute APGAR <7	0.93 [(2)]	0.47-1.85	0.85
NICU admission	1.34 [(2)]	0.28-6.28	0.70
IUFD	5.73 [(2)]	0.95-34.31	0.05

GCT, glucose challenge test; OR, odds ratio; CI, confidence interval; C-section, cesarean section; PPROM, preterm premature rupture of membrane; PPH, postpartum hemorrhage; SGA, small for gestational age; NICU, neonatal intensive care unit; IUFD, intrauterine fetal death. [(1)] Adjusted for age, parity, gestational age, birthweight, fetal sex, pre-pregnancy body mass index (BMI), and weight gain during pregnancy; [(2)] Adjusted for age, parity, gestational age, birthweight, fetal sex, pre-pregnancy BMI, and weight gain during pregnancy; [(3)] Adjusted for age, parity, birthweight, fetal sex, pre-pregnancy BMI, weight gain during pregnancy, preeclampsia, preterm premature rupture of membranes, and preterm labor; [(4)] Adjusted for age, parity, gestational age, fetal sex, pre-pregnancy BMI, and weight gain during pregnancy.

IV. DISCUSSION

The GCT is a screening tool for GDM that has been proven to be effective in nearly the entire population of pregnant women, and nearly all pregnant women undergo a 50 g GCT between 24 and 28 weeks of gestation, except

those with a high risk of diabetes. Hyperglycemia is associated with morbidity during pregnancy, and recently it has been reported that obstetrical complications increase proportionally with the continuum of maternal hyperglycemia.[10] However, the significance of a low maternal GCT value remains uncertain. In this study, we found that a low GCT value has significant clinical implications.

A low GCT value was significantly associated with an increased risk of SGA neonates compared to that of the normal GCT group. Consistent with our study, several previous studies have shown an association between a low GCT value and SGA neonates or low birthweight. One study reported that women with a low GCT value have a 2.65 times greater risk of having an SGA baby than women with a normal GCT value ($p = 0.002$).[11] Melamed et al. reported that a low GCT value was independently associated with an increased risk for low birthweight (< 2500 g) and birthweights < the tenth, fifth, and third percentiles.[5] Other studies have shown a relationship between maternal low GCT values and SGA infants.[12,13] Topçu et al. reported that neonatal birth weight was correlated with GCT results, and that this relationship was more prominent in male infants.[14]

Maternal glucose metabolism changes dramatically during pregnancy since glucose is the principal fetal nutrient. Glucose is provided to the fetus through the placental circulation and the maternal-fetal glucose gradient. Insulin is a key growth factor for fetal development, and the fetus produces its own insulin in response to glucose stimulation. Fetal growth restriction may be directly linked to a deficiency of glucose as a nutrient source and may be indirectly related with excess insulin sensitivity. Rogne and Jacobsen reported that an insufficient increase in maternal glucose levels after a glucose challenge was associated with an increased risk for impaired fetal growth.[15] Furthermore, several studies have reported an increased insulin sensitivity in pregnancies with intrauterine growth restriction.[16-18] In an animal study, maternal low

glucose values during pregnancy were associated with a decrease in fetal glucose, which lead to diminished fetal growth rates and decreased fetal insulin.[19] Although there are controversies regarding the association between low maternal glucose levels and fetal growth restriction, many studies have reported a high proportion of SGA neonates in women with low GCT values.

We found that the low GCT value group had lower cesarean section and emergency cesarean section rates compared to that seen in the normal group. These findings are consistent with those of other studies.[5,14] This phenomenon may be related to the lower maternal obesity rates in the low GCT level group. In our study, the most common indications for emergency cesarean delivery were cephalopelvic disproportion (292/588, 49.6%) and failure to progress (96/588, 16.3%). Compared to women with normal GCT values, those with low GCT values were less likely to be obese (pre-pregnancy BMI $\geq$ 25) ($p <$ 0.01). Maternal obesity is associated with a risk of cesarean section because of pelvic narrowing from adipose tissue and inefficient uterine contractions due to the release of inflammatory mediators from adipose tissue.[20,21] Similarly, other studies have reported that the incidence of cesarean section and pre-pregnancy BMI is lower in women with low GCT values in comparison to women with normal GCT values.[5,14]

We also demonstrated that the low GCT group had a lower rate of PPH than did the normal GCT group. The reason for this relationship is not clear and this observation has not been previously reported to the best of our knowledge. One can speculate that lower rates of maternal obesity and LGA in women with low GCT levels is associated with a decreased risk of PPH, since maternal obesity and LGA are risk factors of PPH, and these two factors are less common in women with low GCT levels.

We did not detect any significant association between low GCT values and other complications such as preterm delivery, low Apgar score, and the rate of admission to the NICU. It is tempting to speculate that a prolonged decrease in

maternal glucose levels might lead to decreased fetal glucose levels, increased protein breakdown, and increased oxidative metabolism, adversely affecting the intrauterine environment. Although the mechanisms are not clear and there are many confounding factors, one possible explanation is that a low glucose value with a 50 g glucose load does not accurately reflect maternal glucose levels. However, because hyperglycemia in 50g GCT reflects abnormal maternal insulin resistance, low glucose values with a 50g glucose load may reflect increased maternal insulin sensitivity. Further research regarding a relative increase in maternal insulin sensitivity and other factors affecting maternal glucose metabolism are needed to more clearly define the relationship between a low GCT value and adverse perinatal outcomes such as preterm delivery and perinatal morbidities.

A strength of our study is the large homogeneous sample. In addition, we evaluated various maternal and neonatal outcomes in order to define the relationships between low GCT values and maternal and neonatal complications. Our study is limited by its retrospective design. The study design was limited to an evaluation of long-term complications associated with a low GCT level. Additionally, our study has a potential selection bias because the study was conducted in a tertiary referral center that has high proportion of high-risk pregnancies. Some pre-referral data were also incomplete.

V. CONCLUSION

We found that maternal low glucose levels following a 1-hour oral GCT are associated with a higher incidence of SGA infants and a lower incidence of cesarean section and PPH. A low GCT was independently associated with an increased risk for SGA infants. We suggest that a low 50 g GCT glucose value may be useful for predicting the birth of an SGA infant. Careful attention should be paid to women with low GCT values.

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50g 경구 당부하 검사에서 저혈당인 산모의 임신 결과

<지도교수 김영한>

연세대학교 대학원 의학과

권하얀

목적: 임신성 당뇨 선별을 위해 시행한 50g 경구 당부하검사에서 저혈당인 경우 산모와 태아에게 미치는 영향을 밝히고자 하였다.

연구방법 : 2010년 1월에서 2016년 12월까지 임신 24-28주에 50g 경구 당부하검사를 시행한 산모를 대상으로 하였다. 전체 연구에 참여한 산모 중 혈장 혈당치가 10 백분위수 미만인 85 mg/dL 이하인 산모를 저혈당 산모군, 86 mg/dL 이상 130 mg/dL 미만인 산모를 대조군으로 선정하였다. 다태임신, 임신 전 당뇨를 진단받은 경우, 임신 24주 이전 또는 28주 이후에 경구 당부하검사를 시행한 경우는 제외하였다.

결과: 연구기간 중 경구 당부하 검사상 저혈당이 나온 산모는 9.2% (579/6257) 였으며 그 중 연구에 적합한 저혈당군 519명, 대조군 3356명를 대상으로 비교하였다. 저혈당 군은 대조군에 비해 저체중출생아의 빈도가 높았고(10.8% vs 7.9%, p=0.02) 제왕절개술의 빈도는 적었다 (32.6% vs 42.8%, p<0.01). 조기분만, 조기양막파수, 양수과소증, 태반조기박리, 낮은 아프가 점수, 신생아 중환자실 입원 빈도와 자궁내 태아사망빈도는 두 군사이에 통계학적인 차이는 없었다.

결론: 임신 중 혈당은 태아의 발육에 영향을 줄 수 있다. 특히 임신 중 저혈당이 지속되는 경우 저체중아를 출생하는 발생하는 빈도가 더 높으므로 주의깊게 관찰해야 한다.

핵심되는 말 : 50g 당부하 검사, 저혈당산모, 임신 합병증