Perinatology
pISSN 2508-4887 • eISSN 2508-4895

Original article
Perinatology Vol. 28, No. 4, December, 2017
https://doi.org/10.14734/PN.2017.28.4.151

Perinatal Outcomes according to Screening Timing in Gestational Diabetic Women with Family History of Diabetes

Han-Sung Kwon, MD
Seo-Yeon Kim, MD
JiEun Park, MD
Han-Sung Hwang, MD
In-Sook Sohn, MD

Department of Obstetrics and Gynecology, Konkuk University School of Medicine, Seoul, Korea

Objective: To compare perinatal outcomes of gestational diabetic women with a family history of type 2 diabetes mellitus (DM), who were diagnosed through early or late screening.
Methods: After 2010, women with a family history of DM underwent 2-step screening at the initial visit, mostly before 16 weeks of gestation. The perinatal outcomes were compared with those of historical cohort screened at 24-28 weeks of gestation between 2005 and 2009. The primary outcomes were complications associated with maternal hyperglycemia such as primary cesarean delivery, large for gestational age (LGA), neonatal hypoglycemia, and fetal anomaly.
Results: The risk of gestational diabetes mellitus (GDM) was 20.8% (67/322) in women with a history of DM in a first-degree relative. Women who were screened before 16 weeks of gestation were more likely to have a high level of hemoglobin A1C at diagnosis and receive insulin therapy for glycemic control than the Late-screen group. But odds ratios of LGA, primary cesarean delivery and fetal anomalies compared with normal control were highest in the Late-screen group than in the Early screen group and the Low risk GDM group.
Conclusion: Some perinatal outcomes may be more favorable in women with GDM and a family history of DM who were screened before 16 weeks of gestation rather than routinely.

Key Words: Diabetes, gestational, Family, History, Prognosis

Received: 14 September 2017
Revised: 24 October 2017
Accepted: 25 October 2017

Correspondence to
Han-Sung Kwon, MD
Department of Obstetrics and Gynecology, Konkuk University School of Medicine, 120 Neungdong-ro, Gwangjin-gu, Seoul 05029, Korea

Tel: +82-2-2030-7645
Fax: +82-2-2030-7749
E-mail: 20050024@kuh.ac.kr

Introduction

Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance of variable severity that begins or is first recognized during pregnancy.[1] Almost 7–18% of pregnancies are complicated by GDM in the United States. In Korea, 2–5% of all pregnant women reportedly develop GDM, and the prevalence is increasing.[2] Any degree of glucose intolerance during pregnancy is associated with adverse maternal and fetal outcome. The adverse maternal complications include polyhydramnios, hypertension, preeclampsia, increased operative delivery and future diabetes mellitus. In the fetus and neonate, it is associated with macrosomia, metabolic abnormalities, respiratory distress syndrome, congenital anomalies, metabolic abnormalities and subsequent childhood and adolescent obesity.[3] Therefore, it is important to diagnose early and treat promptly to prevent complications. Among women with pregestational diabetes mellitus (DM) or early-onset GDM, increased perinatal morbidities are undoubtedly proportional to the degree and duration of maternal hyperglycemia.[2]

The American College of Obstetricians and Gynecologists includes previous history of GDM, known impaired glucose metabolism, and obesity as high-risk factors for GDM.[3] However, history of DM in a first-degree relative is also a risk factor for pregestational DM or early onset GDM.[4,5] A recent systematic review and meta-analysis revealed that the

overall odds ratio (OR) of family history for developing GDM was 3.46 (95% confidence interval [CI] 2.80–4.27).[6] And Kuti et al.[7] reported that a family history of DM was consistently and strongly associated with a GDM diagnosis. To date, however, few studies have demonstrated the benefits of early screening in high-risk groups, including those with a history of DM in a first-degree relative. Recently, Hong et al.[8] reported no benefit from early screening for high-risk women. D'Anna et al.[9] reported myo-Inositol supplementation in pregnant women with a family history of type 2 diabetes reduced GDM incidence and the delivery of macrosomia fetuses. They suggested earlier intervention might be effective in reducing complications of GDM in women with a family history of type 2 diabetes. Most previous studies, however, have focused on the diagnostic performances of early screening rather than the benefits of early detection and intervention of GDM.[10-15]

Therefore, this study aimed to compare perinatal outcomes of gestational diabetic women with a family history of type 2 DM, who were diagnosed through early or late screening.

Methods

1. Data selection & Patient population

This was a retrospective cohort study. The Konkuk University Hospital institutional review board approved the study. Demographic and clinical data were collected through electronic medical record review.

Singleton pregnant women who had a history of DM in a first-degree relative and delivered from 2005 to 2012 were included in the study. Women with a history of GDM in a prior pregnancy, multifetal pregnancy, and known impaired glucose metabolism were excluded. In our institution, the GDM screening protocol had been changed for women with a family history of DM. Before 2010, all women with a family history of DM were screened for GDM with a 1-hour 50-g glucose challenge test (GCT) at 24–28 gestational weeks. An abnormal GCT was followed by a 3-hour 100-g glucose tolerance test to diagnose GDM. The cut-off value for abnormal GCT was ≥140 mg/dL and GDM was diagnosed when two abnormal values were obtained using the Carpenter-Coustan criteria. This was defined as the Late-screen GDM group. After 2010, women with a family history of DM underwent a 1-hour 50-g GCT at the initial visit, mostly before 16 weeks of gestation. If results of the first screen performed <16 weeks were normal but the final diagnosis of GDM was made after 24 weeks, women were categorized as the Early-screen GDM group. Women with normal results in both groups were considered as the Normal group. The Low-risk GDM group was defined as women diagnosed with GDM at age <25 years, with normal body weight, no family history of DM, no history of abnormal glucose metabolism, and no history of poor obstetric outcomes. After the diagnosis of GDM, management of patients was based on a multidisciplinary team approach with diverse healthcare professionals including endocrinologists and dieticians to monitor and control blood glucose levels.

The primary study outcomes were complications associated with maternal hyperglycemia such as primary cesarean delivery, large for gestational age (LGA), neonatal hypoglycemia, and fetal anomaly. Secondary outcomes included gestational age at birth, birth weight, labor induction, preterm birth, preeclampsia, and polyhydramnios. Preeclampsia was defined as the presence of hypertension and proteinuria after 20 weeks of pregnancy. LGA was defined as a birth weight higher than the 90th percentile for gestational age, sex, and fetal number according to Korean reference values.[16] Polyhydramnios was defined as an amniotic fluid index greater than 24 cm.

2. Statistics

Data were expressed as the mean±standard deviation for continuous variables and percentages for categorical variables. One-way analysis of variance and multiple comparisons with the Scheffe test were used for continuous values. A multivariate logistic regression analysis model was used to compare pregnancy complications and neonatal outcomes between groups. Results were considered statistically significant for $P<0.05$. Statistical analyses were performed using SPSS software version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

1. Study population

A total of 322 women had a history of DM in a first-degree relative. Of these, 38 (11.8%) were screened before 16 weeks

of gestation and 14 (36.8%) were diagnosed with GDM. Of the 14 with GDM, 11 were diagnosed before 16 weeks; 3 passed an initial test before 16 weeks but were diagnosed with GDM at 24 to 28 weeks of gestation. Screening with the GCT was performed in 284 of 322 (88.2%) women at 24 to 28 weeks of gestation, and 53 of 284 (18.7%) were verified to have GDM. In the same study period, 47 low-risk GDM patients were identified. Mean gestational age at the time of GDM diagnosis was 14.9 weeks in the Early-screen GDM group and 27.0 weeks in the Late-screen GDM group. The 4 groups did not differ significantly in terms of nulliparity, chronic hypertension, prior spontaneous abortion, or previous cesarean delivery. However, women in the Early-screen group were more likely to have higher age and body mass index (BMI). In the Early-screen group, 29% had hemoglobin A1C (HbA1C) >6.5%, with a rate of 6% in the Late-screen group and 4% in the Low-risk GDM group. In the Early-screen group, 64% received insulin therapy, compared with 43% in the Late-screen group and 28% in the Low-risk GDM group (Table 1).

2. Primary outcomes

Women in the Late-screen GDM group had a higher incidence of primary cesarean delivery than women in the Normal group (OR 2.11, 95% CI 1.11-4.03). Higher incidence was also shown in the Early-screen GDM group (OR 1.84, 95% CI 0.56-6.20) and Low-risk GDM group (OR 1.87, 95% CI 0.95-3.67), but this was not significant. The risk of LGA was also significantly higher in the Late-screen GDM group (OR 2.75, 95% CI 1.31-5.76) than in the Normal group, even after adjustment for significant confounding factors (adjusted OR 2.23, 95% CI 1.02-4.84). However, women in the Early-screen GDM group (OR 0.65, 95% CI 0.08-5.16; adjusted OR 0.45, 95% CI 0.05-3.78) and Low-risk GDM group (OR 1.52, 95% CI 0.62-3.72; adjusted OR 0.81, 95% CI 0.29-2.25) did not differ significantly with respect to LGA compared to the Normal group. The incidence of neonatal hypoglycemia was significantly higher in the Low-risk GDM group (OR 4.00, 95% CI 1.19-13.1) than in other groups, compared with the Normal group. No anomalies were found in the Early-screen group, but compared to the Normal group, the OR (4.86, 95% CI 1.60-14.7) in the Late-screen GDM group was higher than in the Low-risk GDM group (Table 2).

3. Secondary outcomes

Other than labor induction, no difference was found in the incidence of gestational age at birth, birth weight, preterm birth, preeclampsia, and polyhydramnios among groups. Induction of labor was more frequent in the Early-screen GDM group (50%) and Late-screen GDM group (35%) than in the Low-risk GDM group (21%) (Table 3).

Discussion

The present study revealed that the risk of GDM was 20.8%

Table 1. Maternal Characteristics

	Early screen GDM (n=14)	Late screen GDM (n=53)	Normal group (n=255)	Low risk group (n=47)	*P*-value
Gestataional age at diagnosis (weeks)	14.9±9.0	27.0±1.9	26.4±2.1	26.0±3.4	<0.01
Age (years)	34.8±4.1	32.9±4.5	31.5±3.7	31.1±1.9	<0.01
Pregestational BMI (kg/m^2)	25.2±4.3	23.4±3.8	21.3±3.2	20.8±2.1	<0.001
Gestational BMI at delivery (kg/m^2)	28.6±3.6	27.8±3.8	26.5±3.5	25.3±2.5	<0.001
Nulliparous	7 (50)	32 (60)	155 (61)	29 (62)	NS
Previous spontaneous abortion	3 (21)	13 (25)	5 9 (23)	16 (34)	NS
Previous cesarean delivery	4 (29)	10 (19)	42 (17)	7 (15)	NS
Nulliparous	7 (50)	32 (60)	155 (61)	29 (62)	NS
Chronic HTN	0 (0)	1 (2)	2 (1)	1 (2)	NS
HbA1C>6.5	4 (29)	3 (6)	-	2 (4)	<0.05
Insulin therapy	9 (64)	23 (43)	-	13 (28)	<0.05

Values are presented as mean±standard deviation or number (%).
Abbreviations: GDM, gestational diabetes mellitus; BMI, body mass index; NS, not significant; HTN, hypertension.

Table 2. Primary Perinatal Outcomes

	Normal control (n=255)	Early screen GDM (n=14)	Late screen GDM (n=53)	Low risk GDM (n=47)
Primary cesarean delivery	1	1.84 (0.56-6.20)	2.11 (1.11-4.03)	1.87 (0.95-3.67)
LGA (adjusted OR)*	1	0.65 (0.08-5.16) 0.45 (0.05-3.78)	2.75 (1.31-5.76) 2.23 (1.02-4.84)	1.52 (0.62-3.72) 0.81 (0.29-2.25)
Neonatal hypoglycemia	1	2.10 (0.09-18.6)	1.07 (0.16-5.55)	4.00 (1.19-13.1)
Fetal anomaly	1	-	4.86 (1.60-14.7)	1.22 (0.18-6.33)

Abbreviations: GDM, gestational diabetes mellitus; LGA, large for gestational age; OR, odds ratio.
*Adjusted for maternal body mass index in pregnancy

Table 3. Secondary Perinatal Outcomes

	Early screen GDM (n=14)	Late screen GDM (n=53)	Normal group (n=255)	Low risk GDM (n=47)	*P*-value
Gestational age at birth (weeks)	39.1±1.4	38.1±1.4	38.9±1.9	38.4±1.3	NS
Birth weight (kg)	3.42±0.25	3.27±0.53	3.20±0.53	3.13±0.57	NS
Labor induction	7 (50)	18 (35)	74 (29)	10 (21)	<0.05
Preterm births	0 (0)	7 (13)	22 (9)	5 (11)	NS
Preeclampsia	0 (0)	1 (2)	7 (3)	2 (4)	NS
Polyhydramnios	0 (0)	2 (4)	6 (2)	0 (0)	NS

Values are presented as mean±standard deviation or number (%).
Abbreviations: GDM, gestational diabetes mellitus; NS, not significant.

(67/322) in women with a history of DM in a first-degree relative, which was relatively high compared with a reported GDM incidence of around 5%. Women who were screened before 16 weeks of gestation were more likely to have a high level of HbA1C and receive insulin therapy for glycemic control than the Late-screen group and Low-risk group. Higher pregestational and gestational BMI were also shown in the Early-screen GDM patients. These results suggest that women in the Early-screen group may have a more severe form of DM than women in the Late-screen GDM group. Nonetheless, favorable outcomes can be expected in the Early-screen GDM group with intensive management. In contrast, the Late-screen GDM group may include women with pregestational DM, early-onset GDM, and late-onset GDM. This heterogeneous composition may lead to insufficient treatment in women with a probability of more severe DM. In fact, the current study showed that the risk of LGA, primary cesarean delivery, and fetal anomalies was significantly higher in the Late-screen GDM group than in the Early-screen GDM and Low-risk GDM groups. This reflects longer exposure to hyperglycemia, which may cause increased perinatal complications in women with delayed diagnosis of pregestational DM or Early-onset GDM. Tisi et al.[17] reported that fetuses were exposed to increased amniotic fluid glucose before 15 weeks of gestation and suggested that metabolic perturbations were underway before diagnosis and that earlier screening and intervention might be warranted.

The early screening and treatment of DM in asymptomatic high-risk women with a family history of DM is controversial. Syngelaki et al.[18] noted early effective screening for GDM could be achieved based on maternal characteristics and history including a family history of DM. However, the U.S. Preventive Services Task Force concluded that the evidence was insufficient to assess the balance of benefits and harms of screening for GDM in asymptomatic pregnant women before 24 weeks of gestation.[19] Few studies have been published on the benefits or harms of early diagnosis and treatment. Hong et a1.[8] reported that they did not find a benefit to early screening in high-risk women. However, they noted it was somewhat promising that several adverse pregnancy outcomes were not increased in the early screening group because of DM care starting in early pregnancy. To the best of our knowledge, the current study may be the first to show more favorable perinatal outcomes in women with a family history of DM as a result of early screening and treatment for GDM. Another strength of this study is the inclusion of perinatal outcome data for Low-risk GDM and Normal groups for comparison with the Late-

screen GDM group. The limitations of this study include the small study population, especially for the Early-screen GDM group and the lack of data on shoulder dystocia, which is an important complication of DM in pregnancy.

In conclusion, some perinatal outcomes including LGA and primary cesarean delivery may be more favorable in women with GDM and a family history of DM who were screened before 16 weeks rather than routinely at 24 to 28 weeks of gestation. The Early-screen GDM group had outcomes similar to those in the Low-risk GDM group due to intensive management starting in early gestation. This study is limited, however, to demonstration of the benefits of early screening and treatment in patients with a family history of type 2 DM. A randomized controlled trial with a larger study population will be needed in the future.

Acknowledgments

This paper was written as part of the Konkuk University research support program for its faculty on sabbatical leave in 2014.

References

1) Metzger BE, Coustan DR. Summary and recommendations of the Fourth International Workshop-Conference on Gestational Diabetes Mellitus. The Organizing Committee. Diabetes Care 1998;21 Suppl 2: B161-7.
2) Jang HC. Gestational diabetes in Korea: incidence and risk factors of diabetes in women with previous gestational diabetes. Diabetes Metab J 2011;35:1-7.
3) Committee on Practice Bulletins--Obstetrics. Practice bulletin no. 137: gestational diabetes mellitus. Obstet Gynecol 2013;122(2 Pt 1):406-16.
4) Metzger B, Buchanan T, Coustan DR, de Leiva A, Dunger DB, Hadden DR, et al. Summary and recommendations of the fifth international workshop-conference on gestational diabetes mellitus. Diabetes Care 2007; 30 Suppl 2:S251-60.
5) American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2010; 33 Suppl 1:562-9 .
6) Moosazadeh M, Asemi Z, Lankarani KB, Tabrizi R, Maharlouei N, Naghibzadeh-Tahami A, et al. Family history of diabetes and the risk of gestational diabetes mellitus in Iran: a systematic review and meta-analysis. Diabetes Metab Syndr 2016 Dec 13 [Epub]. https://doi.org/10.1016/j.dsx.2016.12.016.
7) Kuti MA, Abbiyesuku FM, Akinlade KS, Akinosun OM, Adedapo KS, Adeleye JO, et al. Oral glucose tolerance testing outcomes among women at high risk for gestational diabetes mellitus. J Clin Pathol 2011; 64:718-21.
8) Hong WY, Biggio JR, Tita A, Harper LM. Impact of early screening for gestational diabetes on perinatal outcomes in high-risk women. Am J Perinatol 2016;33:758-64.
9) D'Anna R, Scilipoti A, Giordano D, Caruso C, Cannata ML, Interdonato ML, et al. Myo-inositol supplementation and onset of gestational diabetes mellitus in pregnant women with a family history of type 2 diabetes: a prospective, randomized, placebo-controlled study. Diabetes Care 2013;36:854-7.
10) Watanabe N, Morimoto S, Fujiwara T, Suzuki T, Taniguchi K, Mori F, et al. Prediction of gestational diabetes mellitus by soluble (pro)renin receptor during the first trimester. J Clin Endocrinol Metab 2013;98:2528-35.
11) Smirnakis KV, Plati A, Wolf M, Thadhani R, Ecker JL. Predicting gestational diabetes: choosing the optimal early serum marker. Am J Obstet Gynecol 2007;196:410.e1-6.
12) Smirnakis KV, Martinez A, Blatman KH, Wolf M, Ecker JL, Thadhani R. Early pregnancy insulin resistance and subsequent gestational diabetes mellitus. Diabetes Care 2005;28:1207-8.
13) Rasanen J, Quinn MJ, Laurie A, Bean E, Roberts CT Jr, Nagalla SR, et al. Maternal serum glycosylated fibronectin as a point-of-care biomarker for assessment of preeclampsia. Am J Obstet Gynecol 2015;212:82.e1-9.
14) Plasencia W, Garcia R, Pereira S, Akolekar R, Nicolaides KH. Criteria for screening and diagnosis of gestational diabetes mellitus in the first trimester of pregnancy. Fetal Diagn Ther 2011;30:108-15.
15) Bartha JL, Martinez-Del-Fresno P, Comino-Delgado R. Gestational diabetes mellitus diagnosed during early pregnancy. Am J Obstet Gynecol 2000;182:346-50.
16) Lee JJ. Birth weight for gestational age patterns by sex, plurality, and parity in Korean population. Korean J Pediatr 2007;50:732-9.
17) Tisi DK, Burns DH, Luskey GW, Koski KG. Fetal exposure to altered amniotic fluid glucose, insulin, and insulin-like growth factor-binding protein 1 occurs before screening for gestational diabetes mellitus. Diabetes Care 2011;34:139-44.
18) Syngelaki A, Pastides A, Kotecha R, Wright A, Akolekar R, Nicolaides KH. First-trimester screening for gestational diabetes mellitus based on maternal characteristics and history. Fetal Diagn Ther 2015;38:14-21.
19) Moyer VA; U.S. Preventive Services Task Force. Screening for gestational diabetes mellitus: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2014;160:414-20.