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A comparison of predictive performances between OLD vs. NEW criteria in risk based screening strategy for gestational diabetes mellitus

임신성 당뇨 위험기반 선별전략의 구(舊)기준과 신(新)기준의 임신성 당뇨 예측 비교

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Abstract

A comparison of predictive performances between OLD vs. NEW criteria in risk based screening strategy for gestational diabetes mellitus

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Objective: Patients at high risk for developing gestational diabetes (GDM) should be screened for GDM in early pregnancy, ideally at the first prenatal visit. The definition of high-risk group for GDM defined by ACOG was changed from the criteria composed of 5 historic/demographic factors (severe

obesity, family history of diabetes, previous history of GDM, impaired glucose metabolism, glucosuria) [OLD criteria] to the criteria consisting of 11 factors [NEW criteria] in 2017. However, these two criteria have not been compared in terms of their ability to predict the development of GDM. In this study, we compare the predictive performances between these two sets of criteria.

Materials and Methods: This is a secondary analysis of a large prospective cohort study of healthy (nondiabetic) Korean women with singleton pregnancies designed to examine the risk of GDM in women with nonalcoholic fatty liver disease. Maternal fasting blood was taken at 10–14 weeks and measured for glucose and lipid parameters. GDM was diagnosed by the two step approach, 50g screening oral glucose tolerance

test (OGTT) followed by diagnostic 100g OGTT. The ability of these clinical/demographic risk factors for the development of GDM was compared between the OLD and NEW criteria.

Results: Among 820 women, 42 (5.1%) were diagnosed with GDM. Using the OLD criteria, 29.8% (244) of women would have been identified as high risk vs 16.0% (131) using the NEW criteria. Of the 42 women who developed GDM, 45.2% (19) would have been mislabeled as not high risk by the OLD criteria vs 50.0% (21) using the NEW criteria (1−sensitivity, 45.2% vs 50.0%, p=NS). Among the 778 patients who did not develop GDM, 28.4% (221) would have been identified as high risk using the OLD criteria vs 14.1% (110) using the NEW criteria (1−specificity, 28.4% vs 14.1%, p<0.001).

Conclusion: Compared with the OLD criteria, use of the NEW criteria would have decreased the number of patients identified as high risk and thus requiring early GDM screening by half (from 244 [29.8%] to 131 [16.0%]). Similarly, use of the NEW criteria would have decreased the number of patients who did not develop GDM from having to undergo early screening by half (from 221 [28.4%] to 110 [14.1%]). Both criteria would have missed around half of patients (45% vs 50%) who subsequently developed GDM. More studies are needed to confirm the clinical utility of using the NEW criteria.

Key words: Diabetes, Gestational, Diagnostic Screening Programs, Pregnancy, High-Risk

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Contents

List of Tables

List of Figures

Introduction

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance that is first recognized during pregnancy.[1] GDM is one of the most common complications during pregnancy, with the reported prevalence of 5.7−9.5% in Korean pregnant women.[2,3] GDM is related to not only maternal complication but also fetal/neonatal adverse outcome, therefore diagnosis of GDM in appropriate period and adequate glucose control is helpful to minimize these complications.[4−6]

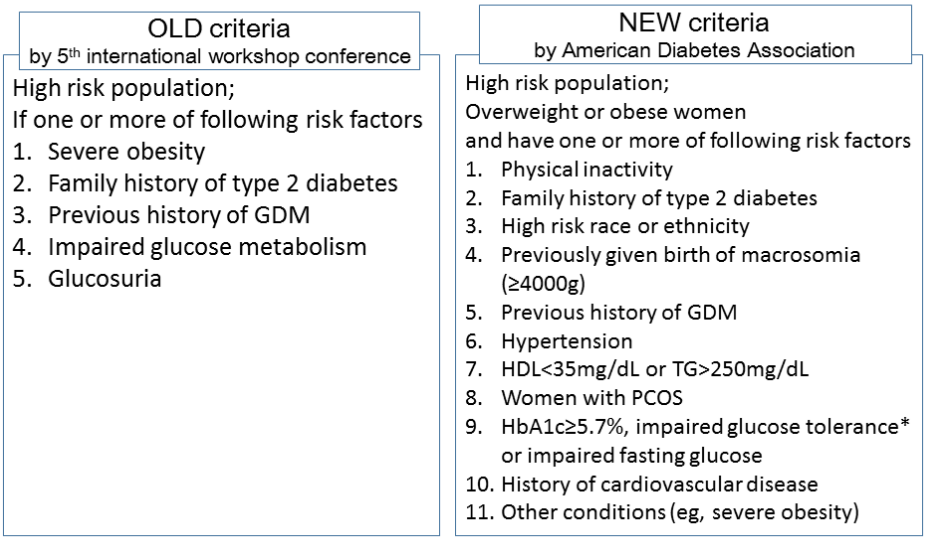
In 4th international workshop conference on GDM in 1998, classifying pregnant women according to the risk for GDM into low, intermediate and high risk group and differential screening strategy in each risk group was recommended. High risk group was defined as those with maternal demographic risk factors

(strong family history, marked obesity, history of GDM, glucose intolerance, glucosuria) and glucose intolerance test at their first prenatal visit was recommended for this high risk group.[7] These criteria for high risk group were reaffirmed in 5th international workshop conference in 2005 and have been also used in the clinical guideline by American College of Obstetricians and Gynecologists (ACOG).[8,9] Until now, the clinical effectiveness of the criteria for high risk group has not been well evaluated in previous studies, although this strategy has been widely implemented in clinical practice.[10-14]

Otherwise, American Diabetes Association (ADA) recommended early testing for diabetes at the first prenatal visit in women with risk factors for type 2 diabetes in 2012.[15] The criteria for high risk of diabetes in asymptomatic adult was exactly applied to pregnant women, because of increasing prevalence of type 2 diabetes in women with child bearing

age.[16] Therefore, criteria for high risk for GDM suggested in this recommendation were different with those in ACOG guidelines, consisting of 11 clinical factors (Fig 1). In 2017, ACOG adopted this ADA recommendation and recommended early screening for GDM according to these new criteria.[1] Unlike criteria of high risk population in 5th international workshop on GDM [OLD criteria], criteria of high risk population by ADA [NEW criteria] includes the degree of obesity and laboratory results.[8,17]

In Korea, the screening strategy for the high risk group and diagnosis of GDM has been conducted upon the ACOG guidelines. Although the acceptance of NEW criteria is a paramount important issue in clinical practice, these two criteria have not been compared in terms of their ability to predict the development of GDM until now. In this study, we compared the predictive performances for detecting GDM between OLD and NEW criteria.



GDM, gestational diabetes mellitus; HDL, high density lipoprotein; TG, triglyceride; PCOS, polycystic ovarian syndrome
* The results of HbA1c and 75g oral glucose tolerance test were not available in this study.

Figure 1. High risk group for gestational diabetes by OLD and NEW criteria

Material and Methods

Study design: This study is a secondary analysis of the large prospective cohort study designed to examine the risk of GDM in women with nonalcoholic fatty liver disease ("Fatty Liver in Pregnancy" registry, NCT02276144).[18] The subjects of this study are non-diabetic Korean women with singleton pregnancy whose data contains the information for assessing clinical and demographic risk by both OLD and NEW criteria and the results of the diagnostic tests for GDM during pregnancy. The predictive ability of these risk criteria for the development of GDM was compared between the OLD and NEW criteria.

Ethics: This study conforms to the STROBE guidelines for cohort studies.[19] The current study was approved by the Institutional Review Board of Seoul National University Hospital

(IRB No. 1810-047-977). Written informed consent was obtained from all participants at the time of enrollment of the original study.

The setting of prospective cohort study: There had been a large prospective cohort study of fatty liver pregnancy conducted in three centers (Incheon Seoul Women Hospital, Seoul Metropolitan Government Seoul National University Boramae Medical Center and Seoul National University Hospital) in South Korea to examine the risk of GDM in women with nonalcoholic fatty liver disease since 2014. Incheon Seoul Women Hospital as primary obstetric care center has approximately 4000 deliveries annually, and Seoul National University Boramae Medical Center as referral center has approximately 500 deliveries annually. Participants were recruited at these two hospitals, and investigators at Seoul

National University Hospital designed study protocol and analyzed data. The protocol of the original research is detailed in the previous report.[18]

Study population of current study: The women enrolled from October 2014 to October 2017 were included in current study. All participants visiting antenatal care centers before 14weeks of gestation were enrolled after obtaining informed consent. Women who agreed secondary analysis and who completed diagnostic tests (2 step approach) for GDM were included. Women with pregestational DM or who wanted to withdraw the study were excluded. Among them, eligible study population were fulfilled the all of data of clinical/demographic risk factors in OLD and NEW criteria. Cases with no information about at least one of the risk factors consisting OLD and NEW criteria

were excluded to compare sensitivity and specificity between OLD and NEW criteria.

The evaluation of risk factors of GDM: The presence of each risk factor included in the OLD or NEW criteria was evaluated in the study population. Among the risk factors, clinical characteristics including pre-pregnancy body mass index (BMI), family history of diabetes, history of gestational diabetes in prior pregnancy, maternal underlying disease such as pre-pregnancy diabetes, hypertension, and cardiovascular disease were collected routinely at the time of enrollment. At 10-14 weeks of gestation, the degree of physical activity was also evaluated by The International Physical Activity Questionnaire (IPAQ)[20] and the blood samples after 8 hour fasting were collected at the time of liver ultrasound (which was conducted for the original cohort study) for measurement

of fasting glucose level and lipid parameters such as triglyceride (TG), high density lipoprotein (HDL) cholesterol. In addition, the presence of glucosuria in early pregnancy and the delivery history of macrosomia and the diagnosis of polycystic ovarian syndrome (PCOS) before pregnancy were evaluated by review of medical record. The presence of glucosuria is routinely evaluated in early pregnancy in our institutions.

The definition of risk factors of GDM: For BMI classification, World Health Organization (WHO) criteria for Asian population were adopted, because the study population consisted of only Korean pregnant women.[21,22] Overweight and obese was defined as BMI $\geq$23kg/m^2 and BMI $\geq$25kg/m^2, respectively, and severe obesity was defined as BMI $\geq$30kg/m^2, suggested criteria for obesity class II (severe obesity) in Asian population.

Glucosuria was defined as +1 or more a dipstick at urinary analysis in early pregnancy.[23] Physical inactivity was defined as no leisure time physical activity in the last 7 days.[24] Impaired glucose metabolism was defined as fasting blood glucose ≥100mg/dL.[25] Other criteria of impaired glucose metabolism (HbA1c and impaired glucose tolerance) were not available in the current study.

Diagnosis of GDM: GDM was diagnosed by the two step approach, 50g screening oral glucose tolerance test (OGTT) followed by diagnostic 100g OGTT according to the guidelines of the ACOG.[1] Women with measured plasma glucose level ≥140 mg/dL at 50g OGTT were examined for 100g OGTT. A diagnosis for GDM required two or more elevated glucose values in 100g OGTT with the cut off values of the Carpenter and Coustan thresholds. (95mg/dL for fasting glucose

180mg/dL for 1-hour glucose, 155mg/dL for 2-hour glucose, and >140mg/dL for 3-hour glucose)[26]

Statistical analysis: Continuous variables were described by median and interquartile range (IQR), categorical variables described by numbers and percentage. Comparison of continuous variables was performed using the independent *t*-test or the Mann-Whitney *U*-test. Categorical variable were compared with the Chi-square test or the Fisher's exact test, where appropriate. Using univariable logistic regression analysis, odds ratios (OR) and 95% confidential interval (CI) of risk factors for GDM were evaluated. For determining independent risk factors, multivariable logistic regression analysis was conducted using variables chosen with a p-value of <0.05 in the univariable analysis with backward elimination. In the multivariable logistic regression, Firth's penalized

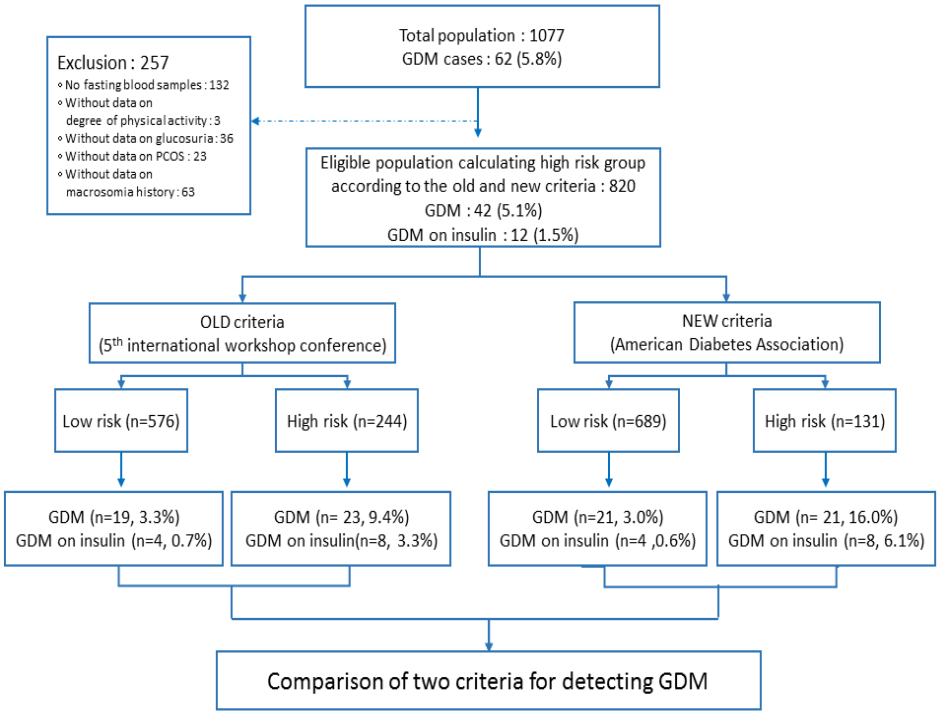
likelihood bias reduction was considered due to the sparseness of the data.[27] For comparison predictive performance such as detection rate and false positive rate between OLD and NEW criteria, the McNemar test was applied. Missing data were treated as missing observations. A *P*-value of <.05 was considered statistically significant. IBM SPSS Statistics version 23.0 software (IBM Inc., Armonk, NY) and R version 3.5.1 (http://www.r-project.org) were used for the analyses.

Result

Study population: During the study period, a total of 1077 women without pre-gestational diabetes were recruited between October 2014 and October 2017 and completed test for GDM. Among these women, 257 subjects (132 women who did not have a fasting blood sample at 10-14weeks of gestation, 3 women who did not report degree of physical activity, 36 women without data on glucosuria, 23 women without data on the history of polycystic ovarian syndrome, 63 women without data on macrosomia history in previous gestation) were excluded from the final analysis.

In 820 women in the final study population, 42 (5.1%) women were diagnosed for GDM and 12 (1.5%) women with GDM were managed on insulin (Fig 2). Among them, 29.8% (244) of

women would have been identified as high risk using the OLD criteria, whereas 16.0% (131) would have been identified as high risk using the NEW criteria. Among 244 women who were assessed as high risk by OLD criteria, 9.5% (23) of women were diagnosed GDM and 3.3% (8) of women were managed on insulin. Among the 131 women who were assessed as high risk by NEW criteria, 16.0% (21) of women was diagnosed GDM and 6.1% (8) of women were managed on insulin.



PCOS, polycystic ovarian syndrome; GDM, gestational diabetes mellitus

Figure 2. Study diagram

Basal characteristics and obstetric outcome according to the presence of GDM: Table 1 shows basal characteristics and obstetric outcome of the study population according to the GDM status. The median maternal age and the frequency of nulliparity were not different between the two groups. Women who developed GDM had a higher median pre-pregnancy BMI and a higher rate of previous history of GDM and chronic hypertension. The gestational age at delivery, birthweight, and the risk of macrosomia or Cesarean delivery were not different between the two groups. Women with GDM were more likely to have large-for-gestational age neonates, but this difference did not reach statistical significance.

Table 1. Basal characteristics and pregnancy outcome

	GDM (n=42)	Non-GDM (n=778)	p-value
Basal characteristics			
Age	32 (29-34)	32 (29-34)	0.699
Nulliparity	27 (64.3%)	417 (53.6%)	0.176
Pre-pregnancy BMI	24.8 (22.0-29.1)	21.5 (19.6-23.4)	<0.001
Previous GDM	6 (14.3%)	15 (1.9%)	<0.001
Chronic HTN	5 (11.9%)	23 (3.0%)	0.011
Pregnancy outcomes			
GAD (weeks)	38.9 (38.3-40.1)	39.3 (38.4-40.1)	0.426
Birthweight (kg)	3.21 (2.95-3.66)	3.23 (3.00-3.48)	0.328
LGA	8/40 (20.0%)	74/754 (9.8%)	0.056
Macrosomia (>4kg)	2/40 (5.0%)	25/756 (3.3%)	0.641
Cesarean section	16/40 (40.0%)	272/756 (36.0%)	0.606

Data are presented as median and interquartile range (IQR) for continuous variables, and numbers and percentage for categorical variables.
GDM, gestational diabetes mellitus; BMI, body mass index; HTN, hypertension; GAD, gestational age at delivery; LGA, Large for gestational age

Odds ratio of risk factors for GDM: Table 2 presents the odds ratio of individual risk factors consisting of the OLD or NEW criteria for high risk of GDM. BMI ≥23kg/m^2, first-degree relative with diabetes, chronic hypertension, previous history of GDM, impaired fasting glucose and TG >250mg/dL were associated with the development of GDM. Similarly, BMI ≥23kg/m^2, chronic hypertension, previous history of GDM, glucosuria, impaired fasting glucose, HDL cholesterol <35 mg/dL and TG >250mg/dL were associated with the development of GDM on insulin. However, PCOS history, physical inactivity, previously given birth of macrosomia, glucosuira and HDL cholesterol <35mg/dL were not related to the risk of GDM.

Table 2. Odds ratio of risk factors for GDM and GDM on insulin using univariable logistic regression analysis

	GDM (n=42)	Non GDM (n=778)	Odds ratio (95% CI)	GDM on insulin (n=12)	Odds ratio (95% CI)
BMI					
≥23 kg/m^2	28 (66.7%)	234 (30.1%)	4. 65 (2.40−8.99)	9 (75.0%)	6.97 (1.87−25.99)
≥25 kg/m^2	21 (50.0%)	118 (15.2%)	5.59 (2.96−10.56)	7 (58.3%)	7.83 (2.44−25.09)
≥30 kg/m^2	8 (19.0%)	29 (3.7%)	6.08 (2.59−148.29)	2 (16.7%)	5.17 (1.08−24.65)
First−degree relative with diabetes	15 (35.7%)	165 (21.2%)	2.06 (1.07−3.97)	4 (33.3%)	1.86 (0.55−6.25)
Chronic hypertension	5 (11.9%)	23 (3.0%)	4.44 (1.60−12.33)	2 (16.7%)	6.57 (1.36−31.68)
Women with PCOS	1 (2.4%)	12 (1.5%)	1.56 (0.20−12.27)	0 (0.0%)	0.00 (0.00−26.17)
History of CVD	0 (0.0%)	0 (0.0%)	(−)	0 (0.0%)	−
Previous GDM	6 (14.3%)	15 (1.9%)	8.48 (3.11−23.14)	3 (25.0%)	16.96 (4.17−68.97)
Previously given birth of macrosomia	1 (2.4%)	10 (1.3%)	1.87 (0.23−14.99)	0 (0.0%)	0.00 (0.00−12.39)
Physical inactivity	3 (7.1%)	103 (13.2%)	0.50 (0.15−1.66)	0 (0.0%)	0.00 (0.00−2.40)
Glucosuria	3 (7.1%)	26 (3.3%)	2. 23 (0.65−7.67)	2 (16.7%)	5.79 (1.21−27.74)
Impaired fasting glucose	7 (16.7%)	5 (0.6%)	30.92 (9.35−102.31)	5 (41.7%)	110.43 (26.01−468.80)
HDL cholesterol <35 mg/dL	1 (2.4%)	0 (0.0%)	1.87 (0.23−14.99)	1 (8.3%)	Inf (1.66−Inf)
TG >250 mg/dL	4 (9.5%)	8 (1.0%)	10.13 (2.92−35.14)	3 (25.0%)	32.08 (7.30−141.04)

Data are presented as numbers and percentage.
GDM, gestational diabetes mellitus; CI, confidence interval; BMI, body mass index; PCOS, polycystic ovarian syndrome; CVD, cardiovascular disease; HDL, high density lipoprotein; TG, triglyceride

Odds ratio of risk factors by OLD and NEW criteria: Table 3 shows that the risk factors in OLD criteria were significantly associated with the development of GDM, except glucosuria. Overall, the odds ratio of high risk group for GDM by the OLD criteria was 3.05 (1.63-5.71). By NEW criteria, overweight women who had one of the risk factors such as first degree relative with diabetes, previous GDM, chronic hypertension, TG>250mg/dL, impaired fasting glucose or severe obesity increased risk of the development of GDM, significantly. Overall, the odds ratio of high risk group by the NEW criteria was 6.07 (3.21-11.49), higher than those by the OLD criteria.

Table 4 also presents the odds ratio of individual risk factors for GDM requiring insulin treatment according to the OLD or NEW criteria. The odds ratio of high risk group by the OLD criteria and the NEW criteria was 5.04 (1.50-16.91) and 12.15 (3.60-41.02), respectively.

Table 3. Odds ratio of risk factors by OLD and NEW criteria for detecting GDM using univariable logistic regression analysis

	GDM (n=42)	Non GDM (n=778)	Odds ratio (95% CI)	P-value
High risk according to OLD criteria	23 (54.8%)	221 (28.4%)	3.05 (1.63-5.71)	<0.001
Severe obesity (BMI ≥30 kg/m^2)	8 (19.0%)	29 (3.7%)	6.08 (2.59-148.29)	<0.001
First-degree relative with diabetes	15 (35.7%)	165 (21.2%)	2.06 (1.07-3.97)	0.027
Previous gestational diabetes	6 (14.3%)	15 (1.9%)	8.48 (3.11-23.14)	<0.001
Impaired fasting glucose	7 (16.7%)	5 (0.6%)	30.92 (9.35-102.31)	<0.001
Glucosuria	3 (7.1%)	26 (3.3%)	2. 23 (0.65-7.67)	0.181
High risk according to NEW criteria	21 (50.0%)	110 (14.1%)	6.07 (3.21-11.49)	0.000
BMI ≥23kg/m^2 and have one or more of the following risk factors				
Physical inactivity	1 (2.4%)	23 (3.0%)	0.80 (0.11-6.08)	1.000
First-degree relative with diabetes	11 (26.2%)	54 (6.9%)	4.76 (2.27-9.99)	<0.001
Previously given birth of macrosomia	1 (2.4%)	8 (1.0%)	2.35 (0.29-19.22)	0.378
Previous gestational diabetes	4 (9.5%)	6 (0.8%)	13.54 (3.67-50.02)	<0.001
Chronic hypertension	4 (9.5%)	13 (1.7%)	6.19 (1.93-19.90)	0.009
HDL cholesterol <35 mg/dL	0 (0.0%)	0 (0.0%)	(-)	-
TG >250 mg/dL	3 (7.1%)	3 (0.4%)	19.87 (3.88-101.66)	0.002
Women with PCOS	1 (2.4%)	6 (0.8%)	3.14 (0.37-26.68)	0.309
Impaired fasting glucose	6 (14.3%)	3 (0.4%)	43.06 (10.35-179.13)	<0.001
Severe obesity (BMI ≥30 kg/m^2)	8 (19.0%)	29 (3.7%)	6.08 (2.59-148.29)	<0.001
History of CVD	0 (0.0%)	0 (0.0%)	(-)	-

Data are represented as numbers and percentage.
GDM, gestational diabetes mellitus; CI, confidence interval; BMI, body mass index; HDL, high density lipoprotein; TG, triglyceride; PCOS, polycystic ovarian syndrome; CVD, cardiovascular disease

Table 4. Odds ratio of risk factors by OLD and NEW criteria for detecting GDM on insulin using univariable logistic regression analysis

	GDM on insulin (n=12)	Non GDM (n=778)	Odds ratio (95% CI)	P-value
High risk according to OLD criteria	8 (66.7%)	221 (28.4%)	5.04 (1.50-16.91)	0.007
Severe obesity (BMI ≥30 kg/m^2)	2 (16.7%)	29 (3.7%)	5.17 (1.08-24.65)	0.077
First-degree relative with diabetes	4 (33.3%)	165 (21.2%)	1.86 (0.55-6.25)	0.297
Previous gestational diabetes	3 (25.0%)	15 (1.9%)	16.96 (4.17-68.97)	0.002
Impaired fasting glucose	5 (41.7%)	5 (0.6%)	110.43 (26.01-468.80)	<0.001
Glucosuria	2 (16.7%)	26 (3.3%)	5.79 (1.21-27.74)	0.064
High risk according to NEW criteria	8 (66.7%)	110 (14.1%)	12.15 (3.60-41.02)	<0.001
BMI ≥23kg/m^2 and have one or more of the following risk factors				
Physical inactivity	0 (0.0%)	23 (3.0%)	1.29 (0.01-10.31)	0.868
First-degree relative with diabetes	3 (25.0%)	54 (6.9%)	4.47 (1.18-16.99)	0.049
Previously given birth of macrosomia	0 (0.0%)	8 (1.0%)	3.63 (0.03-32.08)	0.463
Previous gestational diabetes	2 (16.7%)	6 (0.8%)	25.73 (4.62-143.36)	0.006
Chronic hypertension	1 (8.3%)	13 (1.7%)	5.35 (0.64-44.54)	0.194
HDL cholesterol <35 mg/dL	0 (0.0%)	0 (0.0%)	(-)	-
TG >250 mg/dL	2 (16.7%)	3 (0.4%)	51.67 (7.77-343.65)	<0.001
Women with PCOS	0 (0.0%)	6 (0.8%)	4.75 (0.04-44.16)	0.392
Impaired fasting glucose	4 (33.3%)	3 (0.4%)	129.17 (24.78-673.28)	<0.001
Severe obesity (BMI ≥30 kg/m^2)	2 (16.7%)	29 (3.7%)	5.17 (1.08-24.65)	0.077
History of CVD	0 (0.0%)	0 (0.0%)	(-)	-

Data are represented as numbers and percentage.
GDM, gestational diabetes mellitus; CI, confidence interval; BMI, body mass index; HDL, high density lipoprotein; TG, triglyceride; PCOS, polycystic ovarian syndrome; CVD, cardiovascular disease

Predictive performance of NEW vs. OLD criteria: As shown in table 5, detection rate and false positive rate were compared between two criteria. Of the 42 women who developed GDM, OLD criteria would have classified 54.8% of women as high risk whereas NEW criteria would have classified 50% of women as high risk (p=NS). Among the 778 patients who did not develop GDM, 28.4% (221) would have been identified as high risk using the OLD criteria vs. 14.1% (110) using the NEW criteria ($p<0.001$). For prediction of GDM requiring insulin treatment, detection rate was 66.7% of both criteria and false positive rate was lower when using the NEW criteria than OLD criteria. (29.2% vs 15.2%, $P<0.001$)

Table 5. Predictive performance of OLD vs NEW criteria

For GDM	N of high risk	Detection rate (%)	P-value*	False Positive rate (%)	P-value*
OLD criteria	244 (29.8%)	54.8%†	-	28.4%‡	-
NEW criteria	131 (16.0%)	50%†	0.754	14.1%‡	<0.001
For GDM on insulin					
OLD criteria	244 (29.8%)	66.7%§	-	29.2%‖	-
NEW criteria	131 (16.0%)	66.7%§	1.000	15.2%‖	<0.001

Data are presented as number and percentage
*P values are for the comparison of NEW criteria with OLD criteria
† Values are based on a total of 42 women with GDM
‡ Values are based on a total of 778 women without GDM
§ Values are based on a total of 12 women with GDM on insulin
‖ Values are based on a total of 808 women without GDM on insulin
GDM, gestational diabetes mellitus

Independent risk factors of GDM: Table 6 shows multivariable logistic regression analysis conducted to determine independent risk factors of GDM. Among various risk factors consisting of OLD or NEW criteria, only 4 factors [BMI, previous gestational diabetes, TG >250mg/dL and impaired fasting glucose] were independent risk factors.

Table 6. Multivariable logistic regression analysis of risk factors for GDM *

Risk factors	Odds ratio	95%CI	P-value
BMI (kg/m^2)			<0.001
23-25	2.251	0.864-5.861	0.097
25-30	4.779	2.065-11.061	<0.001
≥30	6.492	2.202-19.140	0.001
Previous GDM	6.137	1.862-20.228	0.003
TG >250 mg/dL	11.117	2.900-42.613	<0.001
Impaired fasting glucose	14.305	3.744-54.656	<0.001

*Multivariable logistic regression analysis is conducted using variables chosen with a p-value of <0.05 in the univariate analysis with backward elimination. (BMI, previous gestational diabetes, first-degree relative with diabetes, chronic hypertension, TG >250 mg/dL and impaired fasting glucose)

GDM, gestational diabetes mellitus; CI, confidence interval; TG, triglyceride; HDL, high density lipoprotein

Discussion

Principal findings of the study: (1) The prevalence of GDM and GDM managed on insulin was 5.1% and 1.5%, respectively. (2) Compared with the OLD criteria, use of the NEW criteria would have decreased the number of patients identified as high risk and thus requiring early GDM screening by half (from 29.8% to 16.0%). (3) Detection rate for GDM was similar between two criteria, however false positive rate is significantly lower by the NEW criteria compared with the OLD criteria. (4) Among the suggested risk factors, only BMI, previous gestational diabetes, TG >250mg/dL and impaired fasting glucose were independent risk factors.

High risk criteria for GDM: There has been so much effort to establish criteria which the high risk group of GDM can be

classified by, for the number of pregnant women who are examined unnecessary screening tests could be reduced. The previous studies had researched for validating the performances of the risk based screening guidelines or scoring systems of GDM.[28-30] According to the current systematic review study evaluating the association of risk factors with GDM, it was hardly possible to make the gold standard screening methods for detecting of GDM.[31] To this day, the criteria for the high risk group of GDM used in each country are not unified.[15,32,33]

The aim of the present study was to investigate which criteria had better predictive performances for developing GDM between OLD and NEW criteria adopted by ACOG. In the current study, the detection rate of NEW criteria is similar to OLD criteria, but the false positive rate is lower in NEW criteria than in OLD criteria. According to these, fewer people are

classified as high risk and can receive unnecessary screening tests. However, pregnant women should have their laboratory results such as TG, HDL cholesterol level for their risk assessment by NEW criteria. Therefore, for applying NEW criteria in clinical setting, cost effective analysis is necessary.

Independent risk factors of GDM: Among risk factors consisting of NEW criteria, physical inactivity, macrosomia history, low HDL cholesterol and PCOS were not significant risk factors for GDM. After analyzing multivarialbe logistic regression, only 4 factors including BMI $\geq$25kg/m^2, previous gestational diabetes, TG >250 mg/dL and impaired fasting glucose were independent risk for GDM.

There have been previous studies evaluating predictable markers for GDM using maternal blood sample in early pregnancy. Elevated fasting glucose level in early pregnancy

has been well known as a risk factor of GDM.[34-36] The previous studies about the relationship of lipid concentrations in early pregnancy and GDM revealed that only elevated triglyceride is significantly associated with GDM while other lipids are not.[37,38] These results are consistent with our findings. Thus, evaluating level of TG and fasting blood glucose at their early pregnancy visit might be clinically useful marker for predicting GDM. It is expected to help build a new model for GDM prediction.

Non-significant risk factors of GDM: In this study, we found that history of PCOS, macrosomia history, physical inactivity, glucosuria and HDL cholesterol <35mg/dL did not increase risk for GDM significantly.

History of PCOS was regarded as a risk factor for GDM in previous studies.[39-41] From a recent research which based on the public health data of South Korea, the odds ratio of PCOS to

prevalence of GDM was reported 1.31 (1.24−1.38).[42] According to the study, PCOS prevalence was 1.68% and 1.29% in cases with GDM patients and cases without GDM, respectively. It is similar with the prevalence of PCOS in our study. Determining the association between PCOS and GDM, further studies upon a larger size of cases should be necessary.

As a risk factor of GDM, history of macrosomia was included in a number of risk based screening strategy. Currently, meta−analysis to examine risk factors of GDM in Asian reported the odds ratio of history of macrosomia was 4.41 (3.09−6.31).[43] In our study, although odds ratio of history of macrosomia was 1.87(0.23−14.99) in total study population, it was 2.51 (0.30−20.97) in primiparous and multiparous women (the data are not shown). Since the number of cases was so small, we could not obtain the statistical significance.

Although physical inactivity is one of the risk factors by NEW

criteria, the association between physical activity and GDM has been inconsistent.[44-46] In our results, the proportion of physically inactive women was even lower in women with GDM, although this difference was not statistically significant. Interestingly, the proportion of physically inactive women was lower in obese women than normal weight women (the data are not shown), and it could affect the result that physical inactivity was not associated with GDM.

Glucosuria has been considered a risk factor for GDM as a finding from hyperglycemia.[47] However, the predictive power of glucosuria for GDM was too low in previous studies.[48,49] Our study showed the similar results.

History of cardiovascular disease and low HDL cholesterol level are known to be risk factors. However, prevalence of those is so low in young women. Because we verified it with a small number of cases, the results were not significant in our study.

Strength: This is the first study validating both NEW and OLD criteria adopted by ACOG. According to the study protocol which was designed to determine the risk of GDM in patients with NAFLD, we prospectively collected the clinical factors which are known as risk factors for GDM, such as previous history of GDM or family history of diabetes. In addition, we also collected fasting blood sample at 10–14 weeks of gestation, and measured HDL cholesterol, TG, and glucose in these blood samples. This prospective collection of clinical data and laboratory result allowed accurate determination of the predictability of OLD and NEW criteria for GDM. It is highly different from other previous studies validating risk–based screening strategies.

In addition, the current study evaluated the risk factors for

GDM in Asian population. As the frequency or risk factors for diabetes may be different among races or ethnicities, it is necessary to evaluate the effectiveness of the risk-based GDM screening strategies in Asian population. Until now, there had been no research about risk based screening strategies for GDM in Asian countries. Comparing to the previous meta-analysis analyzed risk factors for GDM in Asian, the prevalence of GDM and the distributions of risk factors of GDM are similar to that of the subjects of our study.[43] We expect that our study provides clinical information of risk based screening strategy to other Asian countries.

Limitation: There are several points to be considered. First, statistical power comparing sensitivity between two sets of criteria could be not enough because the number of patients with GDM was so small in the current study. According to the

previous studies, the sensitivity of OLD criteria was 60%[23,28,50,51] and that of NEW criteria was 85%.[29] When we assumed the proportions of predicting developed GDM from both high risk criteria was expected lower than 0.4 due to large discrepancy between two criteria, the statistical power of the analysis was calculated less than 50% with our 42 GDM cases. It means, even if the sensitivity is resulted same as that we assume, the power is less than 50%. Second, we evaluated the false positive rate and detection rate for GDM diagnosed during any period of gestation, although the high risk criteria targeted selection of high risk group for GDM diagnosed early in pregnancy or pre-gestational diabetes. Third, the criteria with laboratory result are based on the result of the blood taken at 10-14 weeks of gestation. The optimal blood testing period for judgment of high risk (i.e. pre-gestational blood test vs. blood test in early pregnancy) is not clear in the guidelines.

Further study: To confirm clinical utility of NEW criteria or selective risk based screening for early GDM, more prospective studies and randomized controlled trials will be needed comparing outcome between populations managed according to the strategy and not. For suggestion appropriate screening strategy for GDM, comparison and validation of various screening strategies are needed.

Conclusion

Compared with the OLD criteria, use of the NEW criteria would have decreased the number of patients identified as high risk and thus requiring early GDM screening by half. Similarly, use of the NEW criteria would have decreased the number of patients who did not develop GDM from having to undergo early screening by half. More studies are needed to confirm the clinical utility of using the NEW ADA criteria.

Reference

1. Practice Bulletin No. 180: Gestational Diabetes Mellitus. *Obstetrics and gynecology.* 2017;130(1):e17-e37.
2. Koo BK, Lee JH, Kim J, Jang EJ, Lee C-H. Prevalence of gestational diabetes mellitus in Korea: a National Health Insurance Database study. *PLoS One.* 2016;11(4):e0153107.
3. Nguyen CL, Pham NM, Binns CW, Duong DV, Lee AH. Prevalence of Gestational Diabetes Mellitus in Eastern and Southeastern Asia: A Systematic Review and Meta-Analysis. *Journal of diabetes research.* 2018;2018.
4. Catalano PM, McIntyre HD, Cruickshank JK, et al. The hyperglycemia and adverse pregnancy outcome study: associations of GDM and obesity with pregnancy outcomes. *Diabetes care.* 2012:DC_111790.
5. Group HSCR. Hyperglycemia and adverse pregnancy outcomes. *New England Journal of Medicine.* 2008;358(19):1991-2002.
6. González-Quintero VH, Istwan NB, Rhea DJ, et al. The impact of glycemic control on neonatal outcome in singleton pregnancies complicated by gestational diabetes. *Diabetes care.* 2007;30(3):467-470.
7. Metzger BE, Coustan DR, Committee O. Summary and recommendations of the fourth international workshop-conference on gestational diabetes mellitus. *Diabetes care.* 1998;21:B161.
8. Metzger BE, Buchanan TA, Coustan DR, et al. Summary and recommendations of the fifth international workshop-conference on gestational diabetes mellitus. *Diabetes care.* 2007;30(Supplement 2):S251-S260.
9. Practice Bulletin No. 137: Gestational diabetes mellitus. *Obstetrics*

and gynecology. 2013;122(2 Pt 1):406-416.

10. Moyer VA. Screening for gestational diabetes mellitus: US Preventive Services Task Force recommendation statement. *Annals of internal medicine.* 2014;160(6):414-420.
11. Danilenko-Dixon DR, Van Winter JT, Nelson RL, Ogburn PL. Universal versus selective gestational diabetes screening: Application of 1997 American Diabetes Association recommendations. *American Journal of Obstetrics and Gynecology.* 1999;181(4):798-802.
12. Cosson E, Benchimol M, Carbillon L, et al. Universal rather than selective screening for gestational diabetes mellitus may improve fetal outcomes. *Diabetes & metabolism.* 2006;32(2):140-146.
13. Cosson E, Benbara A, Pharisien I, et al. Diagnostic and prognostic performances over 9 years of a selective screening strategy for gestational diabetes mellitus in a cohort of 18,775 subjects. *Diabetes care.* 2012:DC_121428.
14. Hiéronimus S, Le JM. Relevance of gestational diabetes mellitus screening and comparison of selective with universal strategies. *Diabetes & metabolism.* 2010;36(6 Pt 2):575-586.
15. Association AD. Standards of medical care in diabetes—2012. *Diabetes care.* 2012;35(Supplement 1):S11-S63.
16. Lawrence JM, Contreras R, Chen W, Sacks DA. Trends in the prevalence of pre-existing diabetes and gestational diabetes mellitus among a racially/ethnically diverse population of pregnant women, 1999-2005. *Diabetes care.* 2008.
17. Association AD. 2. Classification and diagnosis of diabetes. *Diabetes care.* 2017;40(Supplement 1):S11-S24.
18. Lee SM, Kwak SH, Koo JN, et al. Non-alcoholic fatty liver disease in the first trimester and subsequent development of gestational diabetes mellitus. 2018:1-11.
19. Von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)

statement: guidelines for reporting observational studies. 2007;4(10):e296.

20. Craig CL, Marshall AL, Sjorstrom M, et al. International physical activity questionnaire: 12-country reliability and validity. *Medicine and science in sports and exercise.* 2003;35(8):1381-1395.
21. Organization WH. The Asia-Pacific perspective: redefining obesity and its treatment. In: Sydney: Health Communications Australia; 2000.
22. Kim Y, Suh YK, Choi H. BMI and metabolic disorders in South Korean adults: 1998 Korea national health and nutrition survey. *Obesity research.* 2004;12(3):445-453.
23. Pöyhönen-Alho MK, Teramo KA, Kaaja RJ, Hiilesmaa VK. 50 gram oral glucose challenge test combined with risk factor-based screening for gestational diabetes. *European Journal of Obstetrics & Gynecology and Reproductive Biology.* 2005;121(1):34-37.
24. Yadav K, Krishnan A. Changing patterns of diet, physical activity and obesity among urban, rural and slum populations in north India. *Obesity reviews.* 2008;9(5):400-408.
25. Nathan DM, Davidson MB, DeFronzo RA, et al. Impaired fasting glucose and impaired glucose tolerance: implications for care. *Diabetes care.* 2007;30(3):753-759.
26. Carpenter MW, Coustan DR. Criteria for screening tests for gestational diabetes. *American Journal of Obstetrics & Gynecology.* 1982;144(7):768-773.
27. Firth D. Bias reduction of maximum likelihood estimates. *Biometrika.* 1993;80(1):27-38.
28. Teh WT, Teede HJ, Paul E, et al. Risk factors for gestational diabetes mellitus: implications for the application of screening guidelines. 2011;51(1):26-30.
29. Avalos GE, Owens LA, Dunne F, care ADcJD. Applying current screening tools for gestational diabetes mellitus to a European population—is it time for change? 2013:DC_122669.

30. Syngelaki A, Pastides A, Kotecha R, et al. First-trimester screening for gestational diabetes mellitus based on maternal characteristics and history. 2015;38(1):14-21.
31. Farrar D, Simmonds M, Bryant M, et al. Risk factor screening to identify women requiring oral glucose tolerance testing to diagnose gestational diabetes: A systematic review and meta-analysis and analysis of two pregnancy cohorts. 2017;12(4):e0175288.
32. Women's NCCf, Health Cs. Diabetes in pregnancy: management of diabetes and its complications from preconception to the postnatal period. 2015.
33. Nankervis A, McIntyre H, Moses R, et al. ADIPS consensus guidelines for the testing and diagnosis of hyperglycaemia in pregnancy in Australia and New Zealand. 2014:1-8.
34. Riskin-Mashiah S, Younes G, Damti A, AUSLANDER RJDc. First trimester fasting hyperglycemia and adverse pregnancy outcomes. 2009.
35. Zhu W-w, Yang H-x, Wei Y-m, et al. Evaluation of the value of fasting plasma glucose in the first prenatal visit to diagnose gestational diabetes mellitus in China. 2013;36(3):586-590.
36. Riskin-Mashiah S, Damti A, Younes G, Auslender RJEJoO, Gynecology, Biology R. First trimester fasting hyperglycemia as a predictor for the development of gestational diabetes mellitus. 2010;152(2):163-167.
37. Enquobahrie DA, Williams MA, Qiu C, Luthy DAJDr, practice c. Early pregnancy lipid concentrations and the risk of gestational diabetes mellitus. 2005;70(2):134-142.
38. Li G, Kong L, Zhang L, et al. Early pregnancy maternal lipid profiles and the risk of gestational diabetes mellitus stratified for body mass index. 2015;22(6):712-717.
39. Ashrafi M, Sheikhan F, Arabipoor A, Hosseini R, Nourbakhsh F, Zolfaghari Z. Gestational diabetes mellitus risk factors in women

with polycystic ovary syndrome (PCOS). *European journal of obstetrics, gynecology, and reproductive biology.* 2014;181:195-199.

40. Zhang YJ, Jin H, Qin ZL, et al. Predictors of Gestational Diabetes Mellitus in Chinese Women with Polycystic Ovary Syndrome: A Cross-Sectional Study. *Gynecologic and obstetric investigation.* 2016;81(3):220-224.
41. Toulis KA, Goulis DG, Kolibianakis EM, Venetis CA, Tarlatzis BC, Papadimas I. Risk of gestational diabetes mellitus in women with polycystic ovary syndrome: a systematic review and a meta-analysis. *Fertility and sterility.* 2009;92(2):667-677.
42. Koo BK, Lee JH, Kim J, Jang EJ, Lee CH. Prevalence of Gestational Diabetes Mellitus in Korea: A National Health Insurance Database Study. *PLoS One.* 2016;11(4):e0153107.
43. Lee KW, Ching SM, Ramachandran V, et al. Prevalence and risk factors of gestational diabetes mellitus in Asia: a systematic review and meta-analysis. *BMC pregnancy and childbirth.* 2018;18(1):494.
44. ACOG committee opinion. Exercise during pregnancy and the postpartum period. Number 267, January 2002. American College of Obstetricians and Gynecologists. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics.* 2002;77(1):79-81.
45. Nobles C, Marcus BH, Stanek EJ, 3rd, et al. Effect of an exercise intervention on gestational diabetes mellitus: a randomized controlled trial. *Obstetrics and gynecology.* 2015;125(5):1195-1204.
46. Badon SE, Wartko PD, Qiu C, Sorensen TK, Williams MA, Enquobahrie DA. Leisure Time Physical Activity and Gestational Diabetes Mellitus in the Omega Study. *Med Sci Sports Exerc.* 2016;48(6):1044-1052.
47. Cersosimo E, Ajmal M, Naukam RJ, Molina PE, Abumrad NN. Role of the kidney in plasma glucose regulation during hyperglycemia. 1997;272(5):E756-E761.
48. Agbozo F, Abubakari A, Narh C, Jahn A. Accuracy of glycosuria,

random blood glucose and risk factors as selective screening tools for gestational diabetes mellitus in comparison with universal diagnosing. *BMJ open diabetes research & care.* 2018;6(1):e000493.

49. Tan PC, Ling LP, Omar SZ. Screening for gestational diabetes at antenatal booking in a Malaysian university hospital: the role of risk factors and threshold value for the 50-g glucose challenge test. *The Australian & New Zealand journal of obstetrics & gynaecology.* 2007;47(3):191-197.

50. Coustan DR, Nelson C, Carpenter MW, et al. Maternal age and screening for gestational diabetes: a population-based study. 1989;73(4):557-561.

51. Östlund I, Hanson UJAoegS. Occurrence of gestational diabetes mellitus and the value of different screening indicators for the oral glucose tolerance test. 2003;82(2):103-108.

국문초록

임신성 당뇨 위험기반 선별전략의 구(舊)기준과 신(新)기준의 임신성 당뇨 예측 비교

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연구목적: 임신성 당뇨의 고위험군에 해당하는 산모는 초기 임신 시기에 임신성 당뇨에 대해서 선별검사를 시행하는 것을 권고받고 있다. 미국 산부인과 학회 진료지침에 따르면 임신성 당뇨의 고위험 기준은 개정전 5가지의 위험인자(증증 비만, 당뇨 가족력, 이전 임신성 당뇨 과거력, 당 조절 장애, 포도당뇨)로 구성되어 있었는데 최근 11개의 당뇨 위험 인자들로 구성된 새로운 기준으로 바뀌었다. 그러나 새로운 기준이 임신성 당뇨의 고위험군을 더 잘 반영한다는 뚜렷한 증거가 없고 이 두 고위험 기준에 따른 임신성 당뇨 예측력

비교에 대한 연구는 없는 실정이다. 이 연구에서는 이 두 고위험 기준이 임신성 당뇨를 얼만큼 예측하는지 비교해보고자 하였다.

연구방법: 이 연구는 지방간과 임신성 당뇨의 연관성에 대한 다기관 전향적 코호트 연구의 이차 분석 연구이다. 이전에 당뇨를 진단받은 적 없는 단태 임신을 대상으로 하였다. 임신 10-14주에 공복혈액을 채취하여 혈당과 지단백등을 측정하였다. 임신성 당뇨는 50g 당부하 검사로 선별하고 100g 당부하 검사로 확진하였다. 구(舊)기준과 신(新)기준을 구성하고 있는 위험인자들을 분석하여 이 두 기준의 임신성 당뇨 발견율 및 위양성율을 비교하였다.

연구결과: 총 820명 중 42명 (5.1%)이 임신성 당뇨를 진단받았다. 구기준에 따르면 244명 (29.8%)이 고위험군으로 분류되었는데 반해 신기준에 따르면 131명 (16.0%)이 고위험군으로 분류되었다. 임신성 당뇨를 진단받은 42명 중 구기준에 의해 19명 (45.2%)이 고위험군으로 잘못 분류되었고 신기준을 적용하였을 때 21명

(50.0%)이 고위험군으로 잘못 분류되었다. (p=NS) 임신성 당뇨가 아닌 778명 중 구기준에 의해 221명 (28.4%)가 고위험군으로 분류된 것에 반해, 신기준에 의하면 110명 (14.1%)가 고위험군으로 분류되었다. (p<0.001)

결론: 구기준에 비해 신기준을 적용하였을 때 고위험군 환자 수가 감소하여 임신성 당뇨를 조기 선별해야 하는 환자수가 224명에서 131명으로 대략 반으로 줄어들게 된다. 또한, 신기준을 사용함으로써 임신성 당뇨가 발생하지 않은 환자들 중에서도 불필요한 선별검사를 시행하는 산모 수가 221명에서 110명으로 대략 반으로 줄어들게 된다. 그러나 두 고위험 기준 모두 임신성 당뇨의 발견율은 대략 50% 정도였다. 새로운 임신성 당뇨 고위험 기준의 임상적 적용에 대한 더 많은 연구가 필요하다.

주요어: 임신성 당뇨, 선별 방법, 고위험 임신

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