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SENSITIVITY ANALYSIS OF THE SCREENING TEST FOR GESTATIONAL DIABETES MELLITUS AND THE EFFECT ON WEIGHTS OF NEWBORNS

Tay, Sandra (1), Murillo-Salas, Antonio (2), Quintana-Vargas, Silvia (3)

1 [Ms. Statistics and Operation Research, New Mexico Tech] [stay2254@gmail.com]

2[Departamento de Matematicas, Division de Ciencias Naturales y Exactas, Campus Guanajuato, Universidad de Guanajauto] [amurillos@ugto.mx]

3 [Hospital Regional de Alta Especialidad del Bajio][squintana2423@gmail.com]

Resumen

I**ntroducción:** la diabetes mellitus gestacional (DMG) representa un problema de salud pública con una prevalencia mundial desconocida, aunque su tasa de incidencia ha ido en aumento. El estándar de oro para el diagnóstico es la curva de tolerancia a la glucosa; sin embargo, el sistema de salud es inaccesible para algunas de las mujeres embarazadas. La prueba de detección de glucosa resulta ser rentable, accesible e inclusiva. Se pretende demostrar su utilidad en la identificación de mujeres embarazadas con diabetes gestacional. **Materiales y métodos:** se estudió una muestra de 1963 embarazadas de las cuales se tienen 275 casos de DMG. El área de estudio fue el estado de Guanajuato,México. La prueba de detección se clasificó en dos grupos y los dos grupos se estudiaron en función de su influencia en el peso de los recién nacidos. **Resultados:** Hubo una diferencia significativa en el peso al nacer de los dos grupos en detección. El peso al nacer para el tamiz> 200 fue sesgado a la derecha. El peso promedio de los bebés de las madres tamiz> 200 mg / dl fue 3351.5 ± 552.5 g. **Conclusión:** la prueba de tamiz es útil para predecir DMG y la prueba de tamiz superior a 200 mg / dL se puede utilizar para predecir el peso del recién nacido, pero no lo suficiente como para diagnosticar DMG en las madres. La prueba de diagnóstico (curva de tolerancia a la glucosa) es muy recomendable para valores de tamiz en el rango de 140 mg / dL a 200 mg / dL.

Abstract

Introduction: Gestational diabetes mellitus (GDM) represents public health problem with an unknown global prevalence yet its incidence rate has been on the increase. The gold standard for diagnosis is the glucose tolerance curve; however, the health system is inaccessible for some of the pregnant women. The glucose screening test turns out to be cost effective, accessible inclusive. It is intended to demonstrate its usefulness in identifying pregnant women with GDM. From this point of view, this study aims to determine the usefulness of the screening test to predict pregnant women who develop GDM. **Materials and methods**: A sample of 1963 pregnant women were studied with 275 GDM cases. The study area was the State of Guanajuato in Mexico. Screening test was categorized into two groups and the two groups were studied based on their influence on the weights of babies. The explanatory variables were identified by a multiple linear regression. **Results:** There was a significant difference in birth weights of the two screening groups. The birth weights for screening > 200 was skewed to the right. The mean weight of babies of screening > 200mg/dL mothers was 3351.5 ± 552.5g. **Conclusion:** The screening test is useful in predicting GDM and screening test above 200mg/dL can be used in the weight prediction of newborns but not sufficient enough to base a conclusion. Diagnostic test is highly recommended for screening values of 140mg/dL to 200mg/dL.

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Kerwords: Gestational diabetes; Macrosomia; Gestational age

INTRODUCTION

Background of study

Gestational diabetes mellitus (GDM) is a type of diabetes diagnosed during pregnancy. It is usually detected in the second and third trimester [1].

The World Health Organization (WHO) defines GDM as “hyperglycemia with blood glucose values above normal but below those diagnostic of diabetes, occurring during pregnancy”. According to (WHO), women with gestational diabetes tend to have a greater risk of delivery complications as well as complications during pregnancy. Children born by mothers with GDM and their mothers are also at increased risk of type 2 diabetes in the future [1]. Uncontrolled gestational diabetes causes the baby to have high blood glucose and this leads the baby’s pancreas to produce extra insulin to tame the blood glucose. The extra glucose produce is stored as fat [2].

Aside GDM increasing the risk of type 2 diabetes for the baby and mother in future, there are other health issues it could lead to if not treated or controlled. Some of the effect of untreated or uncontrolled GDM on the baby are the baby might be born with jaundice, perinatal death, respiratory distress syndrome, and macrosomia which means being born larger than normal. Macrosomia usually leads to delivery difficulty and it is more dangerous for the baby. The mother is also at an increased risk of having high blood pressure, depression, preeclampsia, and may have to go through a caesarean section to deliver baby [2].

Over the years, there have been several criteria for GDM and due to the differences there is no fixed rate for the world’s prevalence. In 2014, DeSisto et al in their work “Prevalence estimates of gestational diabetes mellitus in the United States, Pregnancy Risk Assessment Monitoring System (PRAMS), 2007 - 2010” concluded on a 9.2% GDM prevalence rate after sampling 16 states in the United States [2]. A study on the Australian population should that GDM affects 5-10% of pregnant women [5]. Ethnicity is one of the risk factors of GDM and racial groups like African Americans, Asian Americans, Hispanics/Latina (including Mexican women), and American Indians are at increased risk [3]. In 1983, diabetes mellitus was listed as the number driving cause of death in Mexico and also gestational diabetes increase the risk of perinatal mortal [4].

WHO stated in one of their newsletters that GDM has a high association with women whose BMI (≥ 25kg/m^2) is high. Some other risk factors include maternal age, family history of GDM or type 2 diabetes, ethnicity, personal history of GDM, previous pregnancy which resulted in a child with high birth weight [1].

Problem statement

Gestational diabetes mellitus represents public health problem prevalence ranges from 4 to 12% according to the population studied. The gold standard for diagnosis is the glucose tolerance curve; however, the health system is inaccessible for some of the pregnant women. It requires a reliable accessible method, inclusive, cost effective universal coverage.

The glucose screening test turns out to be cost effective, accessible inclusive. It is intended to demonstrate its usefulness in identifying pregnant women with gestational diabetes. From this point of view, this study aims to determine the usefulness of the screening test to predict pregnant women who develop GDM.

Objectives

- To determine the usefulness of the screening test in predicting pregnant women who develop GDM.

- To show if there is a difference in the weights of the newborns based on the screening groups.
- To determine the sensitivity and specificity of the screening test
- To determine if the glucose screen greater than 200 predicts 95% of women with diabetes and the altered weights of newborns.

MATERIALS AND METHODS

Study design

The study established association between variables rather than causality. The research design used in the study was descriptive and inferential. The objective of descriptive statistics was to get quantifiable information such as the percentiles of the gestational age groups, the sensitivity of the screening test and others. Inferential analysis in this research was used to make judgments based on the observed differences.

Procedure

First, a principal component analysis was performed on the variables (fasting, 1-hour, 2-hours, and 3-hours) for the oral glucose tolerance test (OGTT) to check the contribution of each variable and to decide if it is necessary to reduce the variables. Based on Carpenter and Coustan's (CC) criteria, GDM was diagnosed if two or more values from the diagnostic test exceeds their threshold values: fasting ≥ 95mg/dL, 1-hour ≥ 180mg/dL, 2-hour ≥ 155mg/dL, and 3-hours ≥ 140mg/dL [6]. Studies have proved that pregnant women whose screening test value is > 200mg/dL stand 99% chance of having gestational diabetes. GDM in this research was diagnosed by the CC criteria for cases with screening greater than 130mg/dL but less than 200mg/dL plus screening > 200mg/dL.

Study variables

Screening for GDM is usually preformed at 24 – 28 weeks of gestation. In this study some of the pregnant women had their an early screening test (from the 14th week of gestation) before their 24th gestational week and had a rescreening after the 24th week so screening was put together by taking the latest screening of each patient. In order to confirm that screening test > 200mg/dL shows 99% chance of getting gestational diabetes, the variable screening was categorized in two groups. High screening was defined as screening test > 200mg/dL and low screening was screening test ≤ 200mg/dL. Birth weights of the babies were compared by the means of the two screening groups.

To get the predictive factors for the model of birth weight (normal) the following variables were used maternal age, caesarean section, whether or not mother gained 15kilos during pregnancy, mother's current weight, maternal height, body mass index (BMI), sex of the baby, gestational age, baby's height, baby's weight at birth, mother's previous weight and GDM status. Birth weight was defined as a factor $(normal \rightarrow 2500 \leq baby's\ weight \leq 4000)$g and $(abnormal \rightarrow 2500 > baby's\ weight > 4000)$g. BMI was also defined as underweight (BMI ≤ 18.4kg/m^2), normal (18.4kg/m^2 < BMI < 25kg/m^2), overweight (25kg/m^2 ≤ BMI < 30kg/m^2), and obesity (BMI ≥ 30 kg/m^2) and this definition was based on WHO references. And lastly, gestational age at birth was classified into preterm (< 37weeks), normal-term (≥ 37weeks to 40weeks) and post-term (>40weeks to 42weeks). Other predictive variables used in this research include number of pregnancies, previous GDM, family history of type II diabetes and if baby weighed over 4000grams in previous pregnancy.

Statistical analysis

R console version 3.1.2 was used the analyses. Pearson's correlation was performed on the continuous variables to find the association between the predictive variables (continuous) and birth weight as well as correlation between the independent variables. Continuous variables were expressed as mean ± standard deviation. Exploratory data analysis used to maximize insight into the dataset, extract important variables, and to test underlying assumptions for hypothesis testing and model fitting. Difference in means of birth weights based on the two screening groups was checked using student's t-test.

Sensitivity analysis was used to determine the sensitivity, specificity and the false positive rate of the screening test. The optimal cut-off point of the screening test in predicting GDM was determined using the receiver operator characteristic (ROC) curve. To select the risk factors that significantly contributes to GDM, backward stepwise regression analysis was used. Logistic regression analysis was performed to develop a predictive variables for GDM and a multivariate linear regression for a predictive model for birth weight. Stepwise regression procedure was used as a diagnostic for the model. The model was refitted till the best model was obtained. To ensure that the results are related to the population and not just our sample a training and validation test was performed on the final model.

Sample size

The study began by cleaning the data. The data had a sample size of 2038 with quite over 83 variables and quite a number of missing values. After the data was cleaned the sample sized reduced to 1963 data points by eliminating the values. Since not all the variables from the original data was useful in this study a subset was created for the needed variables.

RESULTS AND DISCUSSION

The PCA plot showed that fasting together with 1-hour and 2-hours explains about 94% of the variance and the 6% is explained by 3-hours FPG (Figure 1). Not wanting a variability less than 95% we stuck to all four OGTT variables and used the CC criteria. The sample size used was 1963 gestational mothers out of whom 275 were with GDM which made up 14% prevalence rate. Of the 275 women with GDM based on CC criteria, 76 of them had a screening value above 200mg/dL. 27.6% of the women with GDM had a screening test value greater than 200mg/dL. The weights of babies for mothers without GDM was fairly normal whereas those of mothers with GDM left skewed. Student's t-test showed a difference in the means of the weights of babies for the two screening groups with a p-values of 0.001807. This means that the screening test > 200 has a significant effect on the weight of the baby. The mean weight of these babies was 3351.5 ± 552.5g. The 95% CI was (3277.3 to 3475.7), implying that 95% of the time a gestational mother with a screening test value > 200mg/dL will have a baby weighing within the interval.

Table 1 shows the sensitivity and specificity of the screening test at some selected cut-offs. From the table a moderate cut-off value for screening test will be 160mg/dL. The sensitivity and specificity for the cut-off at 140mg/dL were 84.4% and 50.7% respectively. At this cut-off accurate prediction rate is about 60% and the false negative rate is about 81%. The ROC curve as shown in Figure 2 has an area under the curve of 0.7726. Hence for the best screening test cut-off for a fairly significant prediction is 160mg/dL.

The average maternal age was 25.4 ± 6.3 years. Women with GDM had an average maternal age of 28.3 ± 6.4 years. About 41.5% of the women with GDM were obese and 36.4% were overweight (Table 2). 32.1% of the babies weighing more than 4000g at birth were by mothers with GDM. About 19% of the women with GDM gained 15kilos during pregnancy and 42.5% of them had history of Macrosomia. Out of the total sample 1017 (51.8%) have family history of type II diabetes and 173 of them were women with GDM which constitute 62.9% of GDM cases. The average weights of babies was 3172.5 ± 510.8g and the average weights of babies of GDM mothers was 3253.5 ± 584.3g. Table 5 and Table 6 shows the percentiles of the weights of babies of mothers with and without GDM by the gestational age groups. It was observed that in each percentile for all

the gestational age groups except the 5th percentile for preterm, the weights of the babies for mothers with GDM were higher than that of mothers without GDM. All the factors for predicting risk of GDM were moderately correlated with each but BMI and current weight had a correlation of 0.85 which is considered high and could lead to multicollinearity. Table 3 shows predictor variables relating to GDM from logistic regression. All predictors except age ($p < 0.00$), history of macrosomia ($p = 0.023$), BMI ($p = 0.003$) and family history of type II diabetes ($p = 0.002$) were not significant. Multicollinearity was the suspected cause so a backward stepwise regression was run using the AICs. The diagnostic test showed number of pregnancies to be a significant factor. Hence the significant factors in predicting GDM were age ($p < 0.00$), history of macrosomia ($p = 0.023$), BMI ($p < 0.00$), family history of type II diabetes ($p =0.002$) and number of pregnancies ($p =0.13$).

Weight of baby for mothers with screening test > 200 had a low correlation with predictor variables: 0.23 with height of the baby, 0.30 with number of pregnancies and about 0.15 with BMI. From the multiple regression analysis of babies weights for mothers with screening test > 200, using their AICs, history of macrosomia ($p = 0.11$), maternal history of GDM ($p =0.004$), number of pregnancies ($p = 0.005$), mother gained over 15kilos during pregnancy ($p =0.09$) and the height of baby ($p = 0.04$) were statistically significant in predicting the weight of babies. The final model with the best explanatory variables is shown in (Table 4). A validation test was perform by training 80% of the data and testing with the 20% and it showed an accuracy of about 90.8%. Thus, this prediction accurately works on 90% of the population and not limited to the sample.

CONCLUSIONS

3-hours OGTT fasting gives a minimum performance in GDM diagnosis. The screening test is useful in predicting GDM and screening test above 200mg/dL can be used in the weight prediction of newborns but not sufficient enough to base a conclusion on the GDM status of mothers. The OGTT is recommended for screening test > 140mg/dL. Percentiles for the weights of newborns for mothers with GDM are higher than the weights of babies of mothers based on the gestational groups. And also a preterm baby weighing > 3500g has a high risk of type II diabetes in future. Diagnostic test is highly recommended for screening values of 140mg/dL to 200mg/dL. Family history of type II diabetes, BMI ≥ 25 kg/m^2 and history of macrosomia has high significant effect on GDM.

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Figure 1: PCA for OGTT variables

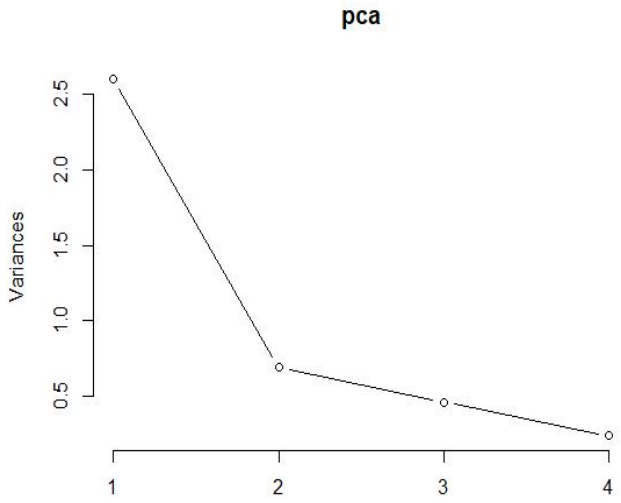

Table 1: Screening test for GDM capacity at different cut-off

Cut-off (mg/dL)	Sensitivity (%)	Specificity (%)	Pred. Value (%)
200	28	99.8	38.8
195	29.5	98.9	36.5
180	39.6	94.7	29.6
160	60	81	20.3
155	62.5	62.5	18.0
140	84.4	50.7	11.1
130	90.2	29.6	6.5

Characteristics	**Total gestational mothers n=1963**	**%**

GDM	1963	…
Yes	275	14
No	1688	86
Screening test	…	…
≤200	1887	97
>200	76	3
P(GDM = YES | Screening > 200)	76	27.6
BMI Status | GDM = YES (n= 275)	…	…
Underweight	1	0.36
Normal weight	60	21.8
Overweight	100	36.4
Obesity	114	41.5
Birth weight | GDM = YES (n= 275)	…	…
Low & high	47	20
Normal	188	80
Gestational age | GDM = YES (n= 275)	…	…
Preterm	15	5.5
Normal term	244	88.7
Post term	16	5.8
Gained over 15kilos during pregnancy| GDM = YES (n= 163)	31	19
Macrosomia history | GDM = YES (n= 87)	26	42.6
Family history of type 2 diabetes (n=1963)	1017	51.8
Family history of type 2 diabetes | GDM = YES (n=275)	173	62.9

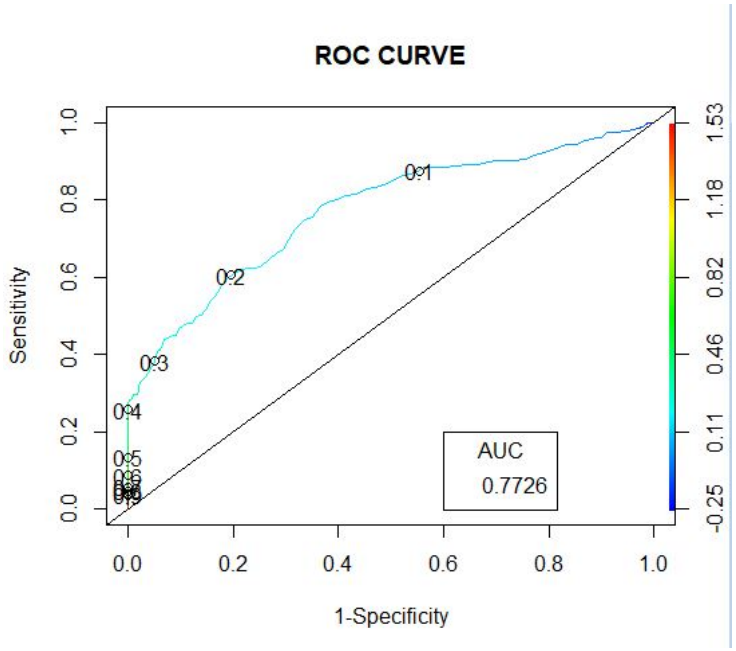

Figure 2: Receiver operating characteristic curve with an AUC of 0.77

Table 2: Character of gestational mothers and newborns

Characteristics	Total gestational mothers n=1963	%
GDM	1963	…
Yes	275	14
No	1688	86
Screening test	…	…
≤200	1887	97
>200	76	3
P(GDM = YES | Screening > 200)	76	27.6
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Table 3: Predictive factors of GDM

VARIABLES	ESTIMATES	P-VALUE
MATERNAL AGE	0.0727	<0.00
FAMILY HISTORY OF TYPE II DIABETES	-0.4215	0.002
HISTORY OF GDM	-0.6152	0.187
BMI	0.0717	0.003
CURRENT WEIGHT	-0.0012	0.903
NUMBER OF PREGNANCY	-0.0722	0.133
GAINED OVER 15KILOS DURING PREGNANCY	0.1014	0.650
HISTORY OF MACROSOMIA	-0.6052	0.023

Table 4: Final predictive model for weight of babies of mothers with screening test value > 200mg/dL

VARIABLES	ESTIMATES	P-VALUE
INTERCEPT	4006.86	<0.00
HISTORY OF MACROSOMIA	114.13	0.117
GAINED OVER 15KILOS DURING PREGNANCY	-120.57	0.098
NUMBER OF PREGNANCY	34.54	0.005
HISTORY OF GDM	-557.50	0.001
HEIGHT OF BABY	23.57	0.039

Table 5: Percentiles of the weights of babies for mothers with GDM by the gestational age groups

PERCENTILE/ GESTATIONAL AGE GROUPS	95^{th}	90^{th}	10^{th}	5^{th}
PRETERM	3477.5	3375.0	1530.0	1215.0
NORMAL TERM	4200.0	4007.0	2678.0	2487.5
POST TERM	4060.0	3868.0	3082.0	3050.0

Table 6: Percentiles of weights of babies for mothers without GDM by the gestational age groups

PERCENTILE/ GESTATIONAL AGE GROUPS	95^{th}	90^{th}	10^{th}	5^{th}
PRETERM	3240.5	3114.5	1517.5	1249.6
NORMAL TERM	3948.5	3790.0	2650.0	2500.0
POST TERM	3935.5	3852.5	2900.0	2642.5