

AGE AS A RISK FACTOR FOR GESTATIONAL DIABETES MELLITUS¹

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ABSTRACT

Objective: To investigate the age cutoff point for the detection of gestational diabetes mellitus (GDM). **Method:** Case-control study with 416 pregnant women served at a prenatal outpatient clinic of a maternity hospital in Rio de Janeiro, RJ, Brazil. The analysis of the receiver operating characteristic curve was performed with the data to determine values with sensitivity optimization according to the specificity. **Results:** It is estimated that the odds ratio in a woman aged ≥ 25 years for developing gestational diabetes mellitus is 2.3 times higher. The age ≥ 22.5 years was determined as a point that maximizes the chance of developing gestational diabetes mellitus. The chance of finding this disease in a woman aged 22.5 years or older is three times greater than in younger women. **Conclusion:** The age cutoff point that suggests the need for greater glycemic monitoring in pregnant women was 22.5 years.

Keywords: Pregnant women. Glycemia. Risk factors. Diabetes gestational.

INTRODUCTION

During pregnancy, women's bodies undergo modifications in their metabolism for the development of the fetuses, considering their needs without interfering with the absorption of nutrients by the mothers^(1,2). Such changes are primordial for this development, given that hormonal changes are essential for the balance of the supply of glucose, amino acids, and lipids to the fetuses⁽²⁾.

During the first trimester, the estrogen and progesterone hormones act on the cells of the pancreas increasing insulin production and, consequently, lowering glucose levels and increasing glycogen levels^(1,3). In the second and third trimesters, with increased production of human placental lactogen, estrogen, progesterone, prolactin, cortisol, and placental insulinase which have a diabetogenic effect, and counteract the action of insulin there is resistance to its action, reduction of glycogen,

and consequent variation in blood glucose levels with respect to normal parameters^(1,3).

The Ministry of Health indicates that age over 35 years as a risk factor for gestational diabetes mellitus (GDM), while the Brazilian Society of Diabetes considers advanced maternal age, not determining a specific one. However, the Brazilian Federation of Gynecology and Obstetrics (FEBRASGO) and other health entities consider age above 25 years a risk factor for the development of GDM^(3,4-5).

Faced with this divergence in the literature regarding the age related to the increase in the risk factor for the development of GDM, the goal of the present study was to determine the age cutoff point that maximized sensitivity, specificity, and odds ratio for the detection of GDM. This research becomes relevant because it presents an analysis of this magnitude for the first time in the scenario and population studied, and provides data for screening and monitoring these pregnant women during the prenatal

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period, in order to minimize risks and complications related to GDM.

MATERIALS AND METHODS

Study design

This is an observational, case-control study that investigated the age of pregnant women with and without GDM. The hospital selected for the research was the Maternity School of the Federal University of Rio de Janeiro, Brazil. This unit was created by Decree No. 5,117 of 18th January 1904. It is located in Laranjeiras neighborhood, in the south region of the Municipality of Rio de Janeiro, and is a municipal reference for pregnant women at obstetric risk. Data collection was performed assessing medical records from September to December 2016. In order to obtain the population of the study, we performed a survey of the clients enrolled in the prenatal service of the maternity using the records of an institutional book called "Book of User Embrace - Nursing - Prenatal Registrations".

The present study included the medical records of all pregnant women who had started prenatal care at the hospital from 2009 to 2015, regardless of their gestational age. The previously defined inclusion criterion considered all pregnant women who had completed prenatal care at the hospital during that period. On the other hand, the exclusion criterion considered pregnant women who had been diagnosed with diabetes mellitus (DM) prior to gestation. The sample was selected after applying the eligibility criteria and performing the randomization of the numbers of the medical records.

The parameters used for GDM were: values above 92 mg/dl for fasting glycemia; values above 180 mg/dl after one hour of glucose overload; and values above 153 mg/dl after two hours of glucose overload in the postprandial glucose or TOTG test^(1,5-6).

For data collection, we used a three-step instrument, namely:

- First stage: Criteria for medical records eligibility (identification of DM diagnosis before the onset of pregnancy);
- Second stage: Identification data of pregnant women, such as, medical record

number, age, and sociodemographic data;

- Third stage: Obstetric and birth history, such as number of pregnancies, births, and abortions, history of malformations in previous pregnancies, family history of DM, history of current diseases, previous diseases, anthropometric data, and results of laboratory tests, such as fasting glycemia and postprandial glycemia, and/or oral glucose tolerance test.

The sample size was estimated in 400 pregnant women, based on a pilot study conducted with 17 pregnant women with glycemic instability and 31 pregnant women who did not exhibit that disorder. This way, considering 95% confidence level and error margin of 5%, we used the SPSS (Statistical Package for the Social Sciences) software, version 22.0, and Microsoft Excel 2007®. We obtained a sample of 416 pregnant women, divided into control group and case group.

The data collected were used to prepare a database in a spreadsheet to perform the analysis using the SPSS software and Microsoft Excel 2007®. For the characterization of the sample and the descriptive analysis of the variables behavior, the data were synthesized through calculations of descriptive statistics (mean, median, minimum, maximum, standard deviation, coefficient of variation, and proportions of interest), simple frequency distributions, and cross-tabulated tables, always comparing the results of the two groups, case and control.

The chi-square test was used to assess the significant association between a given factor and the diagnosis of glycemic instability. The measure (estimator) used to express the risk was odds ratios. The receiver operating characteristic (ROC) curve was used to determine an optimal age cutoff point that maximized the risk of the diagnosis of glycemic instability. In addition to the significance test, an asymptotic confidence interval was obtained for the area under the ROC curve (AUC-ROC), which is expected not to contain value 0.5.

The present study was approved by the Research Ethics Committee of the Maternity School, under Protocol No. 1,705,122.

RESULTS

Among the 416 pregnant women of the sample, 320 were younger than 35 years, and 139 of them exhibited GDM, i.e., 43.4%. Regarding the other 96 pregnant women aged 35 years or older, 61 (63.5%) exhibited GDM. It is estimated that the odds ratio for developing GDM in women aged 35 or older is 2.3 times greater than in younger women.

We classified the pregnant women with

reduced intervals of age. Subsequently, 129 pregnant women under the age of 25, and 287 pregnant women aged 25 or older were selected. Among the women who were younger than 25 years, 44 (34.1%) had GDM, whereas among the 287 pregnant women aged 25 years or older, 156 (54.4%) had GDM ($p < 0.001$). It is estimated that the chance of developing GDM in women aged 25 years or older is 2.3 times greater than in women aged less than 25 years.

Table 1. Synthesis of risks for glycemic instability in pregnant women. Rio de Janeiro, RJ, Brazil, 2009-2015.

Variables	Cases/Group size	Incidence of glycemic instability	<i>p</i> -value - chi-square test	Odds ratios
Age*				
<35 years	139/320	43.4%	<0.001	2.3
≥35 years	61/96	63.5%		
Age*				
<25 years	44/129	34.1%	<0.001	2.3
≥25 years	156/287	54.4%		

In this scenario, we found an age group with lower risk factor for GDM than what is suggested in the literature. Therefore, we chose to apply the ROC curve to determine the age cutoff point that would maximize the odds ratios.

Figure 1 illustrates the ROC curve, which

indicated the age of 22.5 as an optimal cutoff point. Therefore, the sensitivity and the specificity reached their simultaneous maximum likelihood and the results suggest a diagnostic test that classifies positive GDM for women aged 22.5 years or older, concluding that this is the cutoff point that maximized the odds ratios.

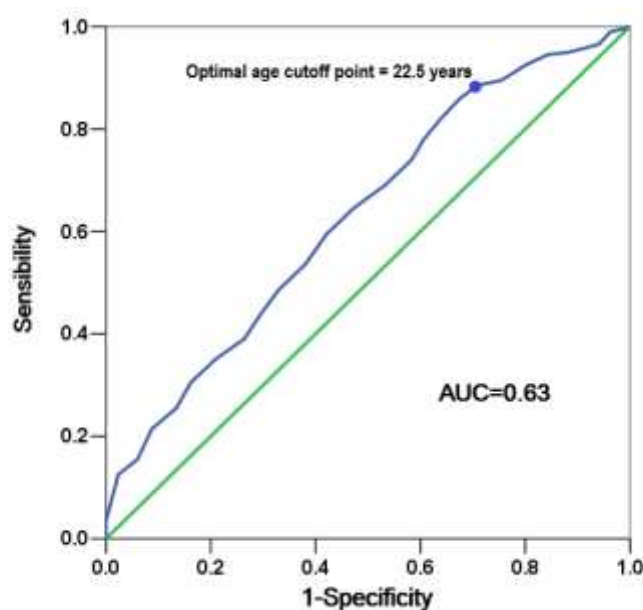


Figure 1. ROC curve using age as indicator of GDM.

The AUC-ROC was 0.63, showing satisfactory performance of the proposed test

with the new age cutoff point.

Chart 1 shows the significance analysis of this AUC. The results indicate that the area was

significantly different from 0.5 (p -value <0.001), which was confirmed by the confidence interval of the area (0.577 to 0.683).

Chart 1. Significance analysis of the area under the ROC curve.

Area under the ROC curve	Standard error	p -asymptotic value	Asymptotic confidence interval for the area under the curve	
			Lower limit	
0.63	0.027	<0.001	0.577	0.63

The test based on the proposed cutoff point had a sensitivity of 0.86 and $(1-\text{specificity}) = 0.676$, which implies a specificity equal to 0.324. Sensitivity equal to 0.86 means that 86% of pregnant women with GDM would be correctly identified by the proposed test, considering this age cutoff point; and $(1-\text{specificity})$ equal to 0.676 implies that the false-positive probability would include 67.6% of the cases that did not have GDM and would be classified as positive by the proposed test.

The accuracy of the proposed test would be 58.2%, i.e., it is estimated that it correctly determined (not-sick and sick) 58.2% among women. Considering the age cutoff point of 22.5 years, we obtained the cross-distribution illustrated in Chart 2.

Given that the ROC curve determined that 22.5 years was the optimal age cutoff point, the

sample was examined and it was observed that, among the 98 pregnant women aged less than 22.5 years, 28 (28.6 %) exhibited GDM. On the other hand, among the 318 pregnant women aged 22.5 or older, 172 (54.1%) had GDM. This incidence was significantly higher.

The p -value of the chi-square test <0.001 indicates that the association between GDM and age over 22.5 years was significant. The odds ratio of 3.0 was significant, given that its confidence interval (CI = 1.8-4.8) did not contain value 1. This way, it is estimated that the chance of finding GDM in a woman aged 22.5 or older is 3.0 times greater than in a woman aged less than 22.5 years. It should be noted that using the cutoff points of 35 and 25 years, the risk measure was smaller, i.e., equal to 2.3.

Chart 2. Number of GDM cases according to the age of pregnant women. Rio de Janeiro, Southeast region of Brazil, 2009-2015.

Variables	Cases/Group size	Cases of GDM	p -value - chi-square test	Odds ratio	Confidence interval for odds ratios
Age*			<0.001	3.0	(1.8; 4.8)
<22.5 years	28/98	28.6%			
≥ 22.5 years	172/318	54.1%			

Chart 3 shows different age cutoff points, which would be the false-positive $(1-\text{specificity})$ measure, the sensitivity, and the specificity, obtaining tests with more and less strict criteria. The chart includes age values that generate the least strict test, with a sensitivity of 1.00 and specificity of 0.000, in comparison to the strictest test, which had a sensitivity of 0.00 and specificity of 1.000.

The use of less strict criteria led to obtain higher values of $(1-\text{specificity})$ and sensitivity (points placed on the right corner of the curve); however, by contrast, there were smaller specificities for these cutoff points. The optimal age cutoff point was 22.5 years. It is the point that balances the needs for sensitivity and specificity, maximizing the risk for GDM. The use of the ages 25 and 35 years as risk factors

are stricter criteria and not ideal.

Chart 3. Age cutoff points for tests with less strict and stricter criteria. 1-Sp = (1-specificity).

	Age cutoff point	1-Sp	Sensibility		Specificity	
			Value	95% CI	Value	95% CI
Less strict criteria	12	1.000	1	1.000 - 1.000	0.000	0.000 - 0.000
	13.5	0.995	1	1.000 - 1.000	0.005	0.000 - 0.014
	14.5	0.986	0.995	0.985 - 1.000	0.014	0.000 - 0.030
	15.5	0.963	0.99	0.976 - 1.000	0.037	0.012 - 0.062
	16.5	0.940	0.965	0.940 - 0.990	0.06	0.028 - 0.092
	17.5	0.884	0.95	0.920 - 0.980	0.116	0.073 - 0.159
	18.5	0.843	0.945	0.913 - 0.977	0.157	0.109 - 0.205
	19.5	0.801	0.925	0.888 - 0.962	0.199	0.146 - 0.252
	20.5	0.755	0.895	0.853 - 0.937	0.245	0.188 - 0.302
	21.5	0.708	0.885	0.841 - 0.929	0.292	0.232 - 0.352
Optimal cutoff point	22.5	0.676	0.86	0.812 - 0.908	0.324	0.262 - 0.386
Stricter criteria	23.5	0.639	0.82	0.767 - 0.873	0.361	0.297 - 0.425
	24.5	0.606	0.78	0.723 - 0.837	0.394	0.329 - 0.459
	25.5	0.583	0.74	0.679 - 0.801	0.417	0.351 - 0.483
	26.5	0.532	0.69	0.626 - 0.754	0.468	0.402 - 0.534
	27.5	0.472	0.645	0.579 - 0.711	0.528	0.462 - 0.594
	28.5	0.421	0.595	0.527 - 0.663	0.579	0.513 - 0.645
	29.5	0.380	0.535	0.466 - 0.604	0.62	0.555 - 0.685
	30.5	0.329	0.485	0.416 - 0.554	0.671	0.608 - 0.734
	31.5	0.296	0.44	0.371 - 0.509	0.704	0.643 - 0.765
	32.5	0.264	0.39	0.322 - 0.458	0.736	0.677 - 0.795
	33.5	0.208	0.35	0.284 - 0.416	0.792	0.738 - 0.846
	34.5	0.162	0.305	0.241 - 0.369	0.838	0.789 - 0.887
	35.5	0.134	0.255	0.195 - 0.315	0.866	0.821 - 0.911
	36.5	0.088	0.215	0.158 - 0.272	0.912	0.874 - 0.950
	37.5	0.060	0.155	0.105 - 0.205	0.94	0.908 - 0.972
	38.5	0.023	0.125	0.079 - 0.171	0.977	0.957 - 0.997
	39.5	0.019	0.105	0.063 - 0.147	0.981	0.963 - 0.999
	40.5	0.009	0.07	0.035 - 0.105	0.991	0.978 - 1.000
	41.5	0.000	0.035	0.010 - 0.060	1.000	1.000 - 1.000
	42.5	0.000	0.02	0.001 - 0.039	1.000	1.000 - 1.000
	43.5	0.000	0.01	0.000 - 0.024	1.000	1.000 - 1.000
	44.5	0.000	0.005	0.000 - 0.015	1.000	1.000 - 1.000
	46	0.000	0.000	0.000 - 0.000	1.000	1.000 - 1.000

DISCUSSION

The present study determined the age of 22.5 years as the best cutoff point for detecting increased risk for GDM in the Municipality of Rio de Janeiro, RJ, Brazil. A cross-sectional study conducted in Yemen divided 311 non-diabetic pregnant women, aged between 15 and 49 years, and gestational age between 24 and 40 weeks, into two groups. One of the groups consisted of pregnant women with risk factors, and the other group was formed by pregnant women without risk factors. The study determined the age ≥ 35 years as a risk factor for GDM, and confirmed that the probability of GDM increased by 8.97 times in women aged ≥ 35 years⁽⁷⁾.

A retrospective cohort study was conducted in Africa with 238 pregnant women divided into two groups, one composed of pregnant women

with GDM, and the other with pregnant women without GDM. The study found mothers with GDM, with a mean age of 33.06 years, family history of diabetes (62.67%), body mass index above normal, overweight (54.55%), and obesity (24.24%)⁽⁸⁾.

A longitudinal, descriptive and analytical study, conducted with 204 pregnant women in a prenatal outpatient clinic of a public maternity hospital in the northeast of Brazil, assessed the prevalence of risk factors during pregnancy and their relationship with unfavorable maternal-fetal outcomes. The mean age of the pregnant women was 26 ± 6.4 years. Among the maternal-fetal outcomes found, only 3.4% were characterized as GDM. The study concluded that overweight and obesity, in addition to excessive weight gain during pregnancy and anemia, were associated with inadequate outcomes such as: pre-eclampsia; cesarean delivery; and newborn weight change.⁽⁹⁾ There was no

significant association with GDM, considering that only 3.4% of the pregnant women had developed GDM, contradicting the findings of the present study.

Age differs between studies. In the present study, the age cutoff point (22.5 years) and the chance of exhibiting GDM was 3.0 times higher. A study conducted in the State of Paraná, Brazil, between 2013 and 2014, with 592 women that had recently given birth, including young women (72.5%), with mean age of 25 years, adolescents (17.2%), and mothers aged 35 years or older (10.3%) aimed to describe the sociodemographic and obstetric profile of this population. It revealed that, among the gestational interurrences, urinary tract infection (37.3%), anemia (27.2%), and arterial hypertension (19.3%) were the most frequent, whereas GDM was present in only 6.1% of the mothers, and the incidence of GDM was not significant in this population. We concluded that this study contradicts the present study, which determined the age of 22.5 years as a risk factor for GDM⁽¹⁰⁾.

A cross-sectional study carried out in 2013 with 217 pregnant women aged 13 to 43 years, in a public maternity hospital in Maceió, State of Alagoas, Brazil, assessed the prevalence and the factors associated with the outcomes hypertensive pregnancy syndrome and GDM. It found that the age group ≥ 35 years (OR = 4.33; 95% CI = 1.61-11.69) and gestational overweight (OR = 2.97; 95% CI = 1.05-8.37) were significantly associated with the presence of GDM. In that study, the age group < 35 years was associated with the presence of GDM, which is in contrast to the findings of our study⁽¹¹⁾.

A study conducted in China from June to August 2015, with 2,345 pregnant women in 16 hospitals, aimed to determine the prevalence of GDM and assess its association with social and behavioral factors. It found that women aged between 26 and 35 years (OR = 2.33, 95% CI = 1.22-4.45) and between 36 and 45 years (OR = 5.87; 95% CI = 2.53-13.62) were more likely to exhibit GDM than pregnant women aged 18 to 25 years. The results of that study are not in line with the results of the present study⁽¹²⁾.

Another cross-sectional study, conducted from March to November 2012 in the prenatal outpatient clinic of Hospital das Clínicas, Federal University of Pernambuco, Brazil, assessed a sample of 50

adult pregnant women within the age group of 20 to 45 years. The goal was to evaluate the nutritional status of pregnant women with GDM, associating it with demographic, socioeconomic, obstetrical, and clinical variables. The study found a greater frequency of age over 25 years as a risk factor in 88% of the pregnant women, i.e., 44 of the 50 women assessed. That study used the age of 25 years as a parameter and found a high number of pregnant women with the diagnosis of GDM.⁽¹³⁾

A cross-sectional study was performed with 50 patients (pregnant women and others that had given birth) hospitalized for GDM control from November 2012 to September 2013 at a public maternity hospital in Fortaleza, CE, Brazil. The study had a loss of five women, because they did not meet the inclusion criteria. The goal of that study had been to determine the sociodemographic and clinical-obstetric profile, as well as prenatal care provided to women with GDM. It was found that GDM had occurred predominantly in women aged between 28 and 37 years (25; 50%), whereas in the age group between 18 and 27 years, the study found 14.28% of the women, and age above 37 years (11; 22.0%). We found that the highest age group had a lower incidence, compared with an incidence of 78% in women younger than 37 years⁽¹⁴⁾.

A documentary study of medical records of 32 pregnant women with GDM conducted from September 2015 to June 2016 in Itanhaém, State of São Paulo, Brazil, aimed to identify risk pregnancies during user embracement performed by nurses. It was found that 18 pregnant women (56.2%) were aged between 26 and 35 years, only five (13.7%) were aged up to 25 years, and nine (28.1%) were older than 35 years. This study refutes the data found in our research and, still, disagrees with studies that have considered advanced age as a risk factor, since its incidence occurred in the age group between 26 and 35 years, corroborating the statements of FEBRASGO and other studies⁽¹⁵⁾.

A study conducted in Turkey between January 2011 and July 2015 aimed to investigate the impact of advanced maternal age on the perinatal and neonatal outcomes of single pregnancies in nulliparous women. They formed a control group with 471 pregnant women aged 18 to 34 years, and two other groups with 399 pregnant women of advanced maternal age (35 to 39 years) and 87

women with very advanced maternal age (>40 years). That study found a significant increase in GDM rates (OR = 2.41; 95% CI = 2.13-3.76) and cesarean sections (OR = 2.67; 95% CI = 1.90-3.82) in the group of very advanced age⁽¹⁶⁾.

The American Diabetes Association recommends that risk factors for GDM should be investigated in the first prenatal visit, and considers age equal to or greater than 25 years.⁽¹⁷⁾ Although the recommendation points to age as an indicator of risk for GDM, the present study showed that, in Brazil, cautious evaluations during prenatal care provided to pregnant women aged 22 years or older would have indicated early risk for the development of GDM and allowed the professionals involved in the process to monitor glucose levels and other interventions necessary to prevent obstetric and neonatal complications.

In January 2011, the American Diabetes Association in combination with the International Association of the Diabetes and Pregnancy Study Groups published new modifications in the diagnostic protocol of GDM, aiming at two main issues: the diagnosis of overt diabetes; and the possibility of confirming a greater number of women who would benefit from the control of hyperglycemia during pregnancy, considering an age cutoff point of pregnant women⁽¹⁸⁾.

The Ministry of Health advises health professionals about high-risk pregnancies in the technical manual⁽⁴⁾ (2012), and considers the maternal age equal to or greater than 35 years a cutoff point for screening and diagnosis of GDM. However, it states that, in Brazil, the prevalence of gestational diabetes is 7.6% in women aged over 20 years and served by the Unified Health System. This perspective corroborates the results found in the population of our study.

In 2016, the Pan American Health Organization⁽¹⁹⁾ published guidelines for the screening and diagnosis of GDM in Brazil. According to the guidelines, women's age is a risk factor associated with hyperglycemia during pregnancy, and there is a progressive risk increase as maternal age increases. However, it does not establish the age cutoff point for these women.

As limitations of the study, we mention: (a) the case-control method, which allows that observed associations may be due to the effect of confounding variables; and (b) baseline measurements may have been affected by pre-existing clinical conditions.

CONCLUSION

The present study assessed the age cutoff point for detecting GDM. It found that, in the assessed population, pregnant women older than 22.5 years were three times more likely to exhibit GDM than younger women.

It is recommended that professionals working in prenatal care be aware of this risk performing early screening and constant monitoring, in order to minimize complications and damage caused to the health of pregnant women and their children.

It is suggested that further studies with prospective methods and measures of sensitivity and specificity in other scenarios and with other populations are conducted in order to minimize the biases related to the case-control method.

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IDADE COMO FATOR DE RISCO PARA DIABETES MELLITUS GESTACIONAL

RESUMO

Objetivo: Investigar o ponto de corte da idade para detecção de diabetes mellitus gestacional (DMG). **Método:** Estudo caso-controle com 416 gestantes acompanhadas no ambulatório de pré-natal de uma maternidade no Rio de Janeiro, RJ, Brasil. A análise da curva *receiver operating characteristic* foi aplicada aos dados para evidenciar valores com otimização da sensibilidade em função da especificidade. **Resultados:** Estima-se que a razão de chance de uma mulher com idade ≥ 25 anos desenvolver diabetes mellitus gestacional é 2,3 vezes maior. A idade $\geq 22,5$ anos foi identificada como ponto que maximiza a chance para a diabetes mellitus gestacional. A chance de uma mulher com idade maior ou igual a 22,5 anos apresentar esta doença é 3,0 vezes maior do que em outra mulher com idade menor. **Conclusão:** O ponto de corte de idade que sugere necessidade de maior monitoramento de glicemia em gestantes é de 22,5 anos.

Palavras-chave: Gestantes. Glicemia. Fatores de risco. Diabetes gestacional.

EDAD COMO FACTOR DE RIESGO PARA DIABETES MELLITUS GESTACIONAL

RESUMEN

Objetivo: investigar el punto de corte de la edad para detección de la diabetes mellitus gestacional (DMG). **Método:** estudio caso-control con 416 gestantes acompañadas en el ambulatorio de prenatal de una maternidad en Rio de Janeiro, RJ, Brasil. El análisis de la curva receiver operating characteristic fue aplicada a los datos para evidenciar valores con optimización de la sensibilidad en función de la especificidad. **Resultados:** se estima que la razón de la probabilidad de que una mujer con edad ≥ 25 años desarrolle diabetes mellitus gestacional es 2,3 veces mayor. La edad $\geq 22,5$ años fue identificada como punto que maximiza la probabilidad para la diabetes mellitus gestacional. La posibilidad de que una mujer con edad mayor o igual a 22,5 años presente esta enfermedad es 3,0 veces mayor que en otra mujer con menor edad. **Conclusión:** el punto de corte de edad que sugiere la necesidad de un mayor monitoreo de glucemia en gestantes es de 22,5 años.

Palabras clave: Gestantes. Glucemia. Factores de riesgo. Diabetes gestacional.

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