Research Square

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Glycated Albumin in Pregnancy: Reference Intervals Establishment and Its Predictive Value in Adverse Pregnant Outcomes

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Abstract

Background As one of the most common pregnant complications, the gestational diabetes mellitus (GDM) is associated with significant adverse pregnant outcomes and it is crucial to accurately monitor the glycemic states of GDM patients. The HbA1c which is a traditional long-term glycemic marker used in diabetic patients, is not recommended in GDM patients during pregnancy. Recently, many efforts have been focused on the alternative marker glycated albumin (GA) and its application in pregnancy during which profound physiological changes take place. Our objective was to determine the reference intervals (RIs) of GA in healthy Chinese pregnant women and to assess the predictive value of serum GA in adverse pregnant outcomes.

Methods Totally 479 healthy subjects including 153 in the first trimester, 174 in the second trimester, and 152 in the third trimester were enrolled from March to July 2019, for the purpose of establishing the trimester-specific RIs of GA. The diagnostic value of GA for GDM patients was evaluated and compared with that of fasting plasma glucose (FPG) at 24-28 weeks of gestation. The association between GA in the late pregnancy and the adverse pregnant outcomes was analyzed retrospectively with the data collected from January to June 2018 at our hospital.

Results The estimated RIs of GA in present study were 10.87-15.09 %, 10.04-13.50 %, and 9.78-13.03 % in the first, second, and third trimesters respectively. The areas under receiver operating characteristic (ROC) curves were 0.503 for GA and 0.705 for FPG. More importantly, the GA levels of the third trimester did not show significant changes in women with large-for-date birth weight, preterm delivery, postpartum hemorrhage or hypertension when compared in women with normal pregnancy outcomes. The exception was that the GDM patients who developed preeclampsia did have a lower GA level in their late pregnancy.

Conclusions Our results show that the GA was continuously decreased as the gestational age went up. It has limited value in diagnosing GDM and predicting adverse pregnancy outcomes.

Background

Gestational diabetes mellitus (GDM) is defined as any degree of glucose tolerance impairments with onset or first recognition during pregnancy [1]. As one of the most common pregnant complications, the prevalence of GDM is about 7 % worldwide and this rate is estimated to continue to increase in the future [2]. According to a research based on over 125 million pregnant subjects between 1979 and 2010, the increasing prevalence of GDM can be mainly attributed to increasing maternal age and body mass index (BMI) [3]. Adverse pregnancy outcomes of GDM affect both mothers and newborns in short and long terms. The women who were diagnosed with GDM have higher risk of type 2 diabetes and cardiovascular diseases after pregnancy [4]. In addition, GDM is closely associated with metabolism disorders, hypertensive disorders, preeclampsia, large for gestational age (LGA), birth weight above the 90th centile for gestational age), cesarean delivery and related birth injury in perinatal period [3,4].

Strict glycemic control is the key to prevent or decrease adverse perinatal complications. With a half-life of 8–12 weeks for red blood cells, the glycated hemoglobin A1c (HbA1c) can reflect ambient blood glucose

level in the past 2–3 months [5]. It has been widely used in monitoring glycemic state and guiding clinical therapy for diabetes patients. The HbA1c threshold of 6.5% for diabetes mellitus diagnosis is supported by the DETECT–2 collaboration [6]. However, the glycemic control may not be accurately monitored by the HbA1c level in some situations such as hemolytic anemia, iron deficiency anemia, uremia, hemoglobinopathies and pregnancy [7]. In normal pregnancy, the HbA1c level presents biphasic changes, including a significant decrease in the second trimester and a slowly elevation to its peak level in the third trimester [8]. For example, Richard et al. who observed this phenomenon found that the HbA1c concentration reached the nadir level at the 24 week's gestation [9]. Alternatively, glycated albumin (GA) is formed through a nonenzymatic reaction between blood glucose and serum albumin. As not affected by hemoglobin metabolism or iron-deficient anemia, GA is often recommended for clinical practice on glycemic control in pregnancy where HbA1c is not appropriate to implement [7,10].

Few articles focused on establishing GA reference range in pregnancy women. In a multi-center study base on the Japanese population, the GA level was significantly decreased in the second and the third trimesters compared with the first trimester [8]. In another study with 1479 normal pregnant women, the mean levels of GA were 11.53 % in the 24–28 weeks and 10.23 % in the 36–38 weeks [11]. Considering the fact that the GA level is continuously decreased during pregnancy, it is important to establish trimester-specific reference intervals (RIs). Moreover, it is still controversial if GA level is higher in diabetic pregnant women with neonatal complications such as LGA [12,13].The purpose of this study was to determine the RIs of GA in Chinese pregnant women, and to assess the predictive value of GA in adverse pregnant outcomes.

Methods

Study population

For the GA RI establishment, the singleton pregnant women attending routine check-ups in the Beijing Obstetrics and Gynecology Hospital from March to July 2019 were recruited with the following exclusion criteria: liver dysfunction with elevated transaminases, abnormal kidney function with elevated Cr and Bun, serum albumin lower than 32 g/L, elevated fasting plasma glucose (FPG) (normal range of 3.9–6.1 mmol/L in the first trimester) or impaired glucose intolerance, lipid metabolism disorders, clinical or subclinical thyroid dysfunction. In total, 479 healthy subjects including 153 in the first trimester, 174 in the second trimester, and 152 in the third trimester were enrolled in our study.

The GDM patients (n = 67) were diagnosed with the 75-gram oral glucose tolerance test (OGTT) according to the International Association of Diabetes and Pregnancy study Groups (IADPSG) 2010 criteria. Specifically, GDM was determined by meeting one of the three following criteria: FPG ≥5.1 mmol/L, 1-hour postprandial blood glucose ≥10.0 mmol/L, or 2-hour postprandial blood glucose ≥8.5 mmol/L. The collected serum samples of the recruited healthy and GDM subjects were stored at −80℃ before the GA testing.

In addition, 894 pregnant subjects that were diagnosed with GDM between January and June 2018 and delivered live newborns at our hospital were retrospectively analyzed in the association study with the

recorded adverse pregnant outcomes, including preterm delivery, postpartum hemorrhage, preeclampsia, hyper tension and neonatal birth weight3500 g.

GA measurement

The GA testing results were calculated as the ratio of glycated albumin over albumin. Specifically, the glycated albumin and albumin were assayed on the fully automated biochemical analyzer Abbott C16000 (Abbott Park, IL, USA) using the peroxidase method (Glycated albumin assay kit, Beijing Strong Biotechnologies Inc., Beijing, China). Total albumin was quantified by the bromocresol purple method (Glycated albumin assay kit, Beijing Strong Biotechnologies Inc., Beijing, China).

Statistical analysis

The Dixon method was applied to remove the outliers from the dataset in the RI study. The numerical data of GA level was presented as the meanstandard deviation (SD) if it was normally distributed or was expressed as median followed with interquartile range if the data was skewed. The RIs were estimated by the IBM SPSS Statistic 21 (SPSS Inc., Chicago, IL, USA) using the nonparametric approach according to the Clinical and Laboratory Standards Institute (CLSI) guideline EP28-A3C. To examine the statistical significance of GA levels between any two patient groups (with or without adverse pregnant outcomes), the Student's t test was used and $P < 0.05$ was considered to be statistically significant. The receiver operating characteristic (ROC) curve analysis was performed to compare the diagnostic power between GA and fasting plasma glucose at the 24–28 weeks of gestation. The correlation between GA and FPG was determined by the linear regression.

Results

With normal distributions examined by the Kolmogorov-Smirnov test (data not shown), the means of the GA level were 13.13±1.00 % in the first trimester (less than 13 weeks), 11.81±0.90 % in the second trimester (14–27 weeks), and 11.29±0.86 % in the third trimester (28–40 weeks). According to the CLSI guideline EP28-A3C [14] (original GA data available in Supplementary Table 1), in the GA RIs establishment study, the 2.5th and 97.5th were used as the lower and upper limits of RIs respectively. The 95% confidence interval (CI) of the two limits was calculated with bootstrap method. As a result, the RIs of GA were 10.87–15.09 %, 10.04–13.50 %, and 9.78–13.03 % in the first, second and third trimesters respectively (Table 1).

As shown in Figure 1, the GA level was significant lower in the second trimester than that in the first trimester ($P<0.001$). This decreasing tendency was also recognized when comparing the GA in the second with that in the third trimesters (P□0.001).

Interestingly, there was no statistic difference of the GA levels between the GDM group and the healthy controls at 24–28 weeks of gestation (Figure 2) (Supplementary Table 2). When compared with the GA, the FPG had a better discrimination power for GDM patients. The areas under ROC curve (AUC) were 0.503 for GA and 0.705 (P□0.001) for FPG (Figure 3) (Supplementary Table 2). Furthermore, our data showed the GA

level did not have a linear correlation with the FPG concentration in women with GDM (R2 = 0.021; P = 0.245).

In the association analyses, the GA levels measured in the third trimester for the GDM patients (n = 894) were not significantly different between the groups with and without adverse pregnant outcomes, suggesting the limited predictive value of the GA testing in the late pregnancy. The only exception was made with the GDM subjects who developed preeclampsia (PE). A lower GA mean level was observed compared with the control group without PE (P<0.05). (Table 2).

Discussion

The GA is considered a more sensitive blood glucose indicator than the HbA1c in pregnancy with a shorter half-life of around 2–3 weeks [7,15]. Takuji et al. [16] reported that the GA reference interval in the non-pregnant Americans with normal glucose tolerance was 11.9–15.8 %. However with the observation made in present study, the GA level was gradually decreased when the gestation age went up. This physiological change of serum GA level during pregnancy has been reported both in healthy pregnant women and in those diagnosed with GDM [11]. Hiramatsu et al. [8] showed that the normal ranges of GA in healthy Japanese women were 12.2–16.6 % in first trimester, 11.8–15.6 % in second trimester and 11.3–15.5 % in third trimester with both lower and upper limits higher than those reported in our study, suggesting the lack of the GA reagent uniformity and the potential impact of different ethnic background. Even with the same GA reagent (Lucica GA-L, Asahi Kasei, Tokyo) that was used by the above Japanese research group, the mean GA value of the 24–28 weeks gestations with Chinese pregnant women was still lower than that of the Japanese pregnant women [11].

Both BMI and urinary protein have been reported as two important factors influencing GA levels during pregnancy. The GA concentrations were found much lower in the high BMI group (BMI25 kg/m^2) than in the low BMI group (18.5 and 25 kg/m^2); the GA was also lower in the pregnant women with elevated urinary protein [8]. Selvin et al. [17] also reported an inverse association between GA and BMI. However, the underlying mechanism for decreased GA level in the subjects with higher BMI still remains unknown. One hypothesis was that the chronic inflammation related turnover of negative acute-phase proteins might have led to the decrease of GA [18]. Glomerular filtration rate (GFR) could also be attributed to the changes of GA level during pregnancy. It has been reported that the GA level was inversely increased when the estimated GFR (eGFR) was decreased due to renal dysfunction in both diabetic and nondiabetic population [19]. Similarly, as pregnancy progressed, physiologically elevated eGFR may also lead to the decrease of GA concentration.

We compared the GA levels of pregnant women with and without GDM at the 24–28 weeks of gestation and found no significant difference (P = 0.824) between the two groups. This result was consistent with a study conducted by Zhu et al. [20], in which no statistical GA difference was observed between the patients with and without GDM who were less than 28 weeks of gestations. Therefore, lack of difference between normal and GDM women did not support the universal use of GA before 28 weeks of gestation for glucose monitoring.

In current practice, GDM was diagnosed during 24–28 weeks of gestations by FPG and postprandial blood glucose levels. As the HbA1c concentration was influenced by the half-life of red blood cell which could be prolonged by iron-deficiency during pregnancy, its application in GDM diagnosis has not been widely recommended [1,21]. As a non-traditional glycemic marker, the limited diagnostic value of GA in GDM has been reported in several articles. In a study of 114 patients with GDM [22], the cut-off value of GA5.8 %, which was derived from the ROC curve had optimal specificity (100%) and poor sensitivity (17.1%) for diagnosing GDM. Zhu et al. [20] reported that the AUC values were 0.726 for FPG and only 0.542 for GA in the second trimester. Similarly, observation was made by Saglam et al. [23] with the AUC of GA being 0.550 in the GDM diagnosis. In our study, we also found a higher diagnostic value of FPG (AUC = 0.705) than that of GA (AUC = 0.503) during the 24–28 weeks of gestation. Besides, there was no linear correlation between the GA and the FPG with the collected serum samples. Huang et al. [24] reported that the FPG and the GA values had exhibited a significant correlation in all pregnant women although the linear coefficient was only 0.103. In the non-pregnant population, the linear correlation between GA and FPG had been observed with a better coefficient factor (R^2 = 0.41) [25]. Therefore, whether GA and FPG is linearly related during pregnancy remains questionable and further study is warranted to explore their relations.

Fetal macrosomia which is defined as infant birth weight more than 4000 g, is a common adverse neonatal outcome of GDM. The incident rate is 15–45% of women diagnosed with GDM compared with 12% of normal women [26]. The Pedersen's hypothesis explaining the pathophysiology of macrosomia is that maternal hyperglycemia leads to fetal hyperglycemia and hyperinsulinemia which further result in protein and fat stores in fetus [26]. Here we explored the association between GA and birth weight to evaluate the value of GA in predicting large-for-date status. Our results showed that the GA levels in third trimester had no significant difference between the groups with birth weight3500 g and≥3500 g in both GDM and normal pregnancy groups (Table 2). Interestingly, Zhang et al. [27] conducted a study involving 242 Chinese pregnant women with GDM and they found the GA level had no association with neonate birth weight in the late pregnancy. Another similar study with Chinese women diagnosed with GDM showed that the GA level at 36–38 weeks of gestation was comparable and had no difference between the maternal group with birth weight of 3000–3499 g and the group with birth weight of 3500–3999 g [11]. In a multicenter study including 136 Japanese diabetic pregnant women, the incidence of large-for-date showed no statistical difference between the group of GA15.8% group and the group of GA≥15.8% group with P = 0.071[13]. However, the above negative findings about the GA prediction on birth weight have been controversial. In a retrospective study of 42 Japanese women with GDM, the maternal GA level was significantly higher in the group of infants with large-for-date status [28]. It has been also reported that an average increase of 76.1 g in birth weight was observed per 1% maternal GA elevation [10]. According to the work by Catalano et al. [29], although no significant difference of the infant birth weight between the GDM and the normal groups was found, the fat mass of infants was changed in the same direction as the maternal blood glucose level. Therefore, the blood glucose or GA may have a better predictive value for neonatal body compositions (such as fat mass) than simple body weight.

To our best knowledge, there has been no relevant report focused on the GA level and the maternal pregnancy outcomes of women diagnosed with GDM. As shown in Table 2, our results demonstrated that the maternal GA levels in the third trimester had little value in predicting adverse pregnancy outcomes

including preterm delivery, postpartum hemorrhage or hypertension in the GDM or the non-diabetic group. However, we found that the GA level was significantly lower in the women who suffered from preeclampsia. Interestingly, in another study focused on the relationship between the serum albumin and the preeclampsia, it was found that women in the preeclampsia group displayed significantly lower level of serum albumin than those in the normal group. It was proposed that albumin might function in suppressing vascular oxidative stress and preventing endothelial dysfunction [30]. In our study, the decreased albumin and the resulting decreased GA may have made the patients more vulnerable to preeclampsia.

Conclusions

The trimester-specific RIs of GA showed an obvious decreasing trend throughout the entire pregnancy. As a short-term glycemic control indicator, the GA level has limited value in diagnosing GDM at the 24–28 weeks of gestation and in predicting adverse pregnancy outcomes.

Abbreviations

GDM: gestational diabetes mellitus; BMI: body mass index; LGA: large for gestational age; HbA1c: glycated hemoglobin A1c; GA: glycated albumin; RI: reference interval; FPG: fasting plasma glucose; OGTT: oral glucose tolerance test; CLSI: Clinical and Laboratory Standards Institute; ROC: receiver operating characteristic; CI: confidence interval; AUC: areas under ROC curve; PE: preeclampsia; GFR: glomerular filtration rate.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Beijing Obstetrics and Gynecology Hospital, Capital Medical University (approval number: 2017-KY–070–01). The verbal consents from the participants were required as no clinical intervention was involved, which was approved by the ethical committee of our institute.

Consent for publication

Not applicable.

Availability of data and materials

The original GA and FPG datasets generated during the current study are available and provided as supplementary files. However, according the patients' verbal consents, their biometrics and pregnancy outcomes are only available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no conflict of interest.

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Authors' contributions

Y. D., Y. Z., J. W., X. X., C. Z., J. L., G. T., L. H. and Z. C. were involved in conception and design of the study, performing experiments, acquisition of data, analysis and interpretation of data. Y. D. and Z. C. were involved in drafting of the article and critical approval of the final article. Y. D., L. L., and Z. C. were involved in the statistical analysis and figure preparation.

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Tables

Table 1 The trimester-specific reference intervals of glycated albumin

	first trimester	second trimester	third trimester
No. of subjects	153	174	152
GA (%) , mean±SD	13.13±1.00	11.81±0.90	11.29±0.86
2.5% percentile (90% CI)	10.87 (10.75, 11.41)	10.04 (9.43, 10.39)	9.78 (9.62, 9.81)
97.5% percentile (90% CI)	15.09 (14.61, 15.54)	13.5 (13.20, 13.84)	13.03 (12.70, 13.32)

GA, glycated albumin; SD, standard deviation; CI, confidence interval.

Table 2 Comparisons of glycated albumin of pregnant women with and without adverse pregnancy outcomes.

normal group (n=114)	case		control		P-value
	number	GA (%±SD)	number	GA (%±SD)	
preterm delivery	4	10.54±0.48	110	11.31±0.83	0.067
postpartum hemorrhage	23	11.22±0.78	91	11.30±0.84	0.655
preeclampsia	6	10.87±0.77	108	11.31±0.83	0.210
hyper tension	3	10.87±0.51	111	11.30±0.83	0.381
birth weight □ 3500g	32	11.27±0.76	78	11.33±0.86	0.723
GDM group (n=894)	case		control		P-value
	number	GA (%±SD)	number	GA (%±SD)	
preterm delivery	63	12.01±1.43	831	12.18±1.52	0.410
postpartum hemorrhage	160	12.03±1.39	734	12.19±1.53	0.223
preeclampsia	60	11.79±1.82	834	12.19±1.48	0.049
hyper tension	45	11.79±1.51	849	12.18±1.51	0.090
birth weight □ 3500g	354	12.22±0.91	477	12.14±1.35	0.482

Figures

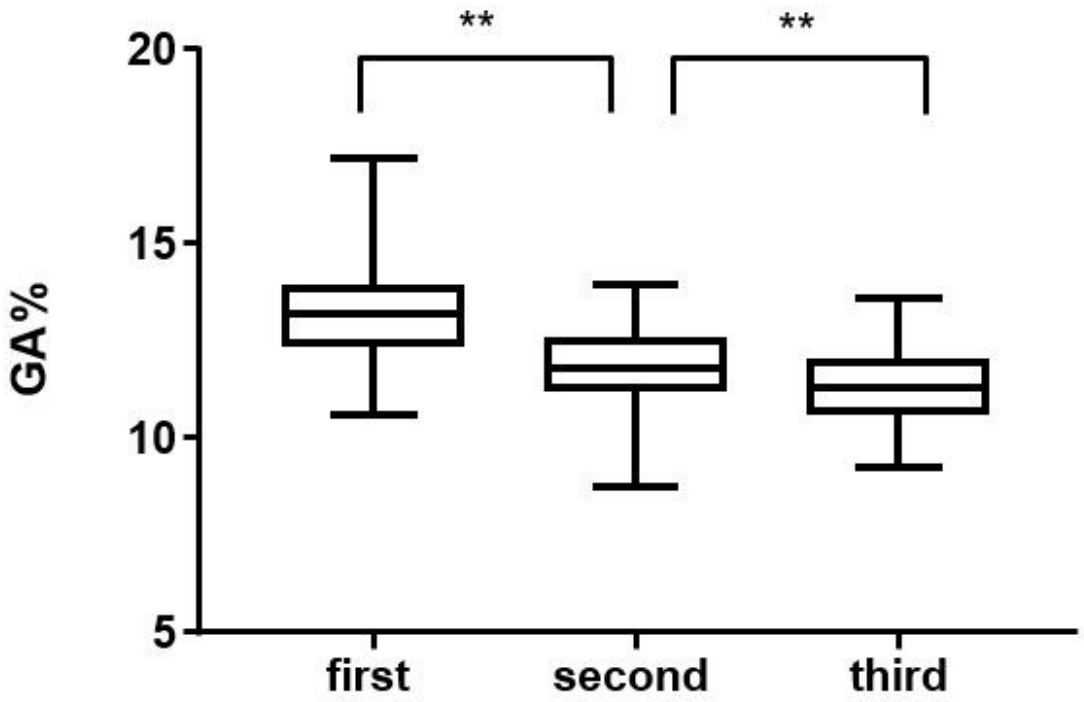

Figure 1

Box plots of glycated albumin in the healthy pregnant women recruited in present study. *indicates P□0.05; **indicates P□0.001.

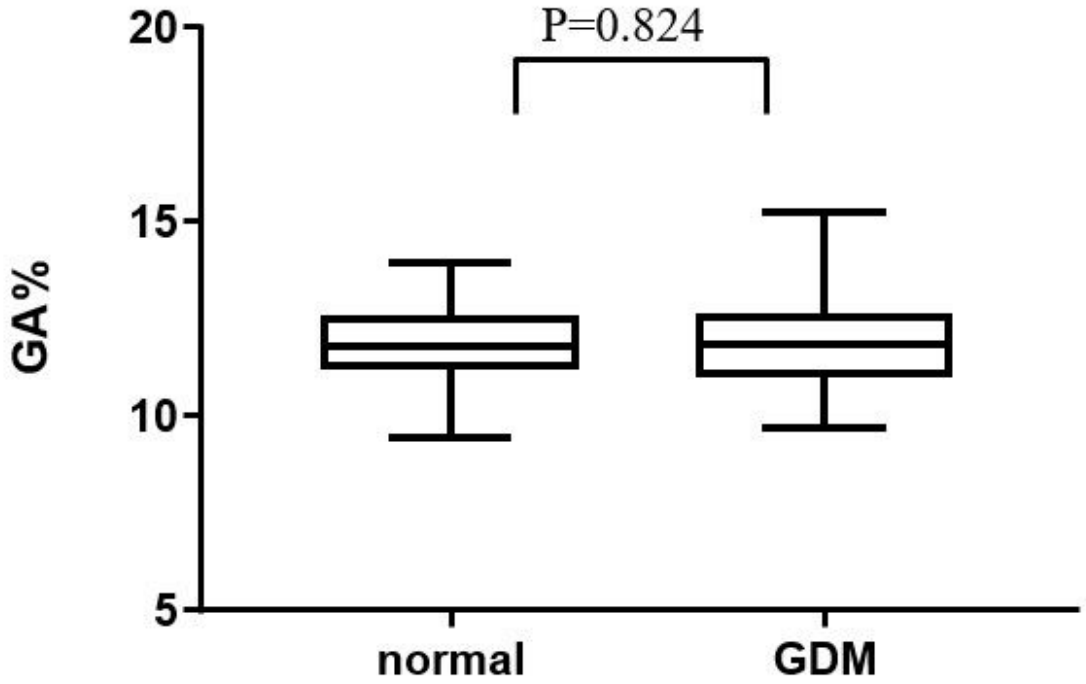

Figure 2

Box plots of glycated albumin in women with and without GDM at the 24-28 weeks of gestation.

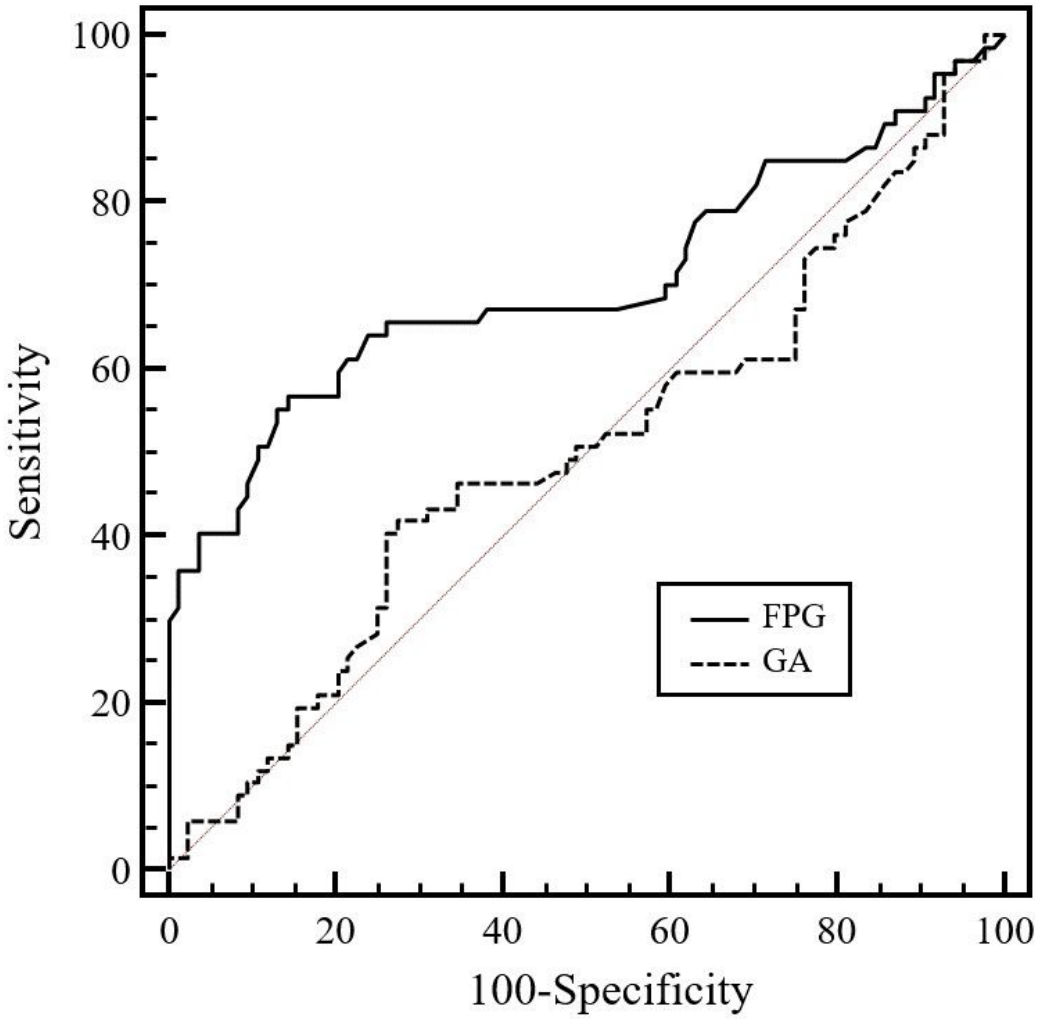

Figure 3

Receiver operating characteristic (ROC) curve analysis of GA and FPG at the 24-28 weeks of gestation for diagnosing GDM. The areas under ROC curve (AUC) values were 0.503 (0.420, 0.585; P=0.957) for GA and 0.705 (0.625, 0.776; P□0.001) for FPG.

Supplementary Files

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