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## ORIGINAL ARTICLE

# Gestational Diabetes Mellitus is Associated with Plasma Amylase in a Chinese Pregnant Women Population

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## SUMMARY

***Background:*** **The study aimed to investigate the relationship between plasma amylase levels and the endocrine and metabolic biomarkers in Chinese pregnant women with gestational diabetes mellitus (GDM) in the southwest of China and to compare plasma amylase with other known biomarkers in relation to their contributions to identifying GDM, with a view to establishing plasma amylase as an independent laboratory-based risk factor for GDM.**
***Methods:*** **This study included 1,870 pregnant women divided into three groups: early pregnancy, middle pregnancy, and late pregnancy according to weeks of gestation, and 164 pregnant women were excluded by diseases. Fasting samples of participants were collected and plasma amylase and other metabolic markers were measured. The pregnant women were identified as having GDM by a 75 g oral glucose tolerance test performed between the 24th and the 28th week of gestation. Multivariate logistic regression was used to examine the associations between the amylase and the prevalence of GDM in pregnant women.**
***Results:*** **Significant differences were found in plasma amylase and metabolic markers in different trimesters of pregnancy. For the pregnant women with GDM, fasting plasma glucose (FPG), 1hPG, 2hPG, HOMA-IR, and plasma amylase levels were all statistically different when compared with the pregnant women without GDM. The plasma amylase levels in 24th - 28th week of pregnant women (628) were negatively correlated with FPG, 1hPG, HOMA-IR, age, and the endocrine and metabolic biomarkers. Following adjustment for age, HOMA-IR, and FPG, multivariate logistic regression showed that plasma amylase level was the independent factor predicting GDM in 24th - 28th week of pregnant women.**
***Conclusions:*** **The plasma amylase of GDM women are higher compared to healthy pregnant women, suggesting the plasma amylase levels are associated with GDM patients. Given the growing incidence of GDM, it provides an opportunity for primary intervention strategies which would not only improve the health of mother and fetus but also decrease the risk of GDM.**
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**KEY WORDS**

gestational diabetes mellitus, amylase, insulin resistance, multiple logistic regression models

## INTRODUCTION

Gestational diabetes mellitus (GDM) is associated with an important risk for severe adverse pregnancy outcomes, and the risk is further increased if the blood glucose control is poor [1]. Although the precise mechanisms responsible for GDM have not yet been fully

clarified, considerable evidence supports that its pathogenesis is closely related to the risk factors of type 2 diabetes and insulin resistance [1].

In the last decade, the novel interpretation of amylase is discussed particularly in terms of the obesity, diabetes, and metabolic syndrome. However, the relationship between amylase and diabetes and obesity is an exocrine-endocrine interrelationship, which in turn may contribute to the feedback system in energy homeostasis [2]. The objective of the present study was to investigate the relationship between plasma amylase level and endocrine and metabolic biomarkers in Chinese pregnant women with GDM in the southwest of China and compare plasma amylase with other known biomarkers in relation to their contributions to identifying GDM, with a view to establishing plasma amylase as an independent laboratory-based risk factor for GDM.

## MATERIALS AND METHODS

### Study design and participants

The study included 1,870 pregnant women who had routine prenatal examinations at the Department of Gynecology and Obstetrics, West China Second University Hospital, between August 12th, 2015 and June 20th, 2016. This study was approved by the ethics committee of the West China Second University Hospital at Sichuan University in China and was performed in accordance with the Helsinki Declaration. Written informed consent was obtained from each participant at the time of enrollment. One hundred sixty-four pregnant women were excluded due to any of the following conditions: preexisting diabetes, thyroid disorder or other endocrine disease hypertension, pre-eclampsia, endocrinopathies, liver dysfunction, renal insufficiency, corticosteroid therapy, miscarried, delivered prematurely or known fetal anomaly. Finally, 1,706 pregnant women (30.3 ± 4.04 years) were enrolled. Pregnant women were divided into three groups: early pregnancy (≤ 13 weeks, n = 481), middle pregnancy (13 - 28 weeks, n = 964), and late pregnancy (> 28 weeks, 264) according to weeks of gestation (shown in Table 1).

### Definition of gestational diabetes mellitus

GDM screening was performed between the 24th and the 28th week of gestation with a 75 g oral glucose tolerance test (OGTT). Diagnosis of GDM was based on the recommendations of the International Association of Diabetes and Pregnancy Study Groups (IADPSG) [3], when one or more glucose values met or exceeded the following cutoffs: (i) fasting blood glucose ≥ 5.1 mmol/L; (ii) 1-hour glucose ≥ 10.0 mmol/L; (iii) 2-hour glucose ≥ 8.5 mmol/L. There were 628 pregnant women (30.56 ± 4.14 years) between the 24th and the 28th week of gestation, 123 pregnant women were diagnosed with gestational diabetes mellitus (GDM).

### Biochemical analyses

All venous blood samples were obtained in the morning following a 12 hours fast in a vacutainer tube (Becton-Dickinson, BD, Franklin Lakes, NJ, USA). Plasma amylase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein (TP), albumin (Alb), alkaline phosphatase (ALP), γ-glutamyltransferase (γ-GT), fasting plasma glucose (FPG), thyroid stimulating hormone (TSH), and free thyroxine (FT4) were determined using a SIEMENS autoanalyzer (ADVIA 2400, Centaur XP, Siemens Healthcare Diagnostics, Tarrytown, NY, USA) using SIEMENS reagents. All the plasma amylase samples were collected in tubes with lithium-heparin. The level of plasma amylase is determined by colorimetric method. HOMA-IR was calculated using the formula fasting plasma glucose (mmol/L) multiplied by the fasting insulin (mIU/L)/22.5 [4].

### Statistical analyses

Statistical analyses were performed using SPSS, version 16 (SPSS, Inc., Chicago, USA). Age, TP, ALB, was reported as mean ± standard deviation (SD). Amylase, ALT, AST, γ-GT, ALP, FPG, TSH, FT4, and HOMA-IR were reported as the median and range. The differences among the multiple groups and between two groups were assessed using a one-way analysis of variance (ANOVA) and Kruskal-Walls H/Mann-Whitney *U* analysis, if appropriate. Spearman's correlation analysis was used to examine the correlation between the amylase level of pregnant women and clinical characteristics. Multivariate logistic regression was used to examine the associations between amylase and the prevalence of GDM in pregnant women. A $p < 0.05$ was considered statistically significant.

## RESULTS

### Study population

Baseline characteristics of the 1,706 pregnant women are shown in Table 1. We found that mid-pregnancy showed significant differences in FPG, HOMA-IR, TP, ALB, ALP, TSH, FT4, and amylase level compared with early pregnancy, while late pregnancy showed significant differences in FPG, HOMA-IR, AST, TP, ALB, γ-GT, ALP, TSH, FT4, and amylase level compared with early pregnancy. Moreover, for late pregnancy, FPG, HOMA-IR, γ-GT, ALP, TSH, FT4, and amylase levels were statistically different from mid-pregnancy. Clinical characteristics of the 628 pregnant women between the 24th and 28th week of gestation were shown in Table 2. For the pregnant women with GDM, FPG, 1hPG, 2hPG, HOMA-IR, and plasma amylase levels were all statistically different as compared with the pregnant women without GDM. Notably, we found that across increasing weeks of gestation, plasma amylase level increased (p for trend < 0.001, shown in Table 1) and significantly different amylase levels were observed in the pregnant women with GDM.

**Table 1. Baseline characteristics of the 1,706 pregnant women.**

| Variables | Early pregnancy (n = 481) | Middle pregnancy (n = 964) | Late pregnancy (n = 261) | p-value |
|---|---|---|---|---|
| Age (years) | 30.14 ± 3.85 | 30.42 ± 4.15 | 30.13 ± 3.99 | 0.361 |
| Fasting plasma glucose (mmol/L) | 4.5 (3.1 - 5.1) | 4.45 (2.6 - 8.7) * | 4.30 (3 - 7.2) *, # | 0.035 |
| HOMA-IR | 1.4 (0.02 - 5.9) | 1.38 (0.22 - 31.43) * | 2.16 (0.49 - 45.90) *, # | < 0.001 |
| Alanine aminotransferase (U/L) | 17 (5 - 151) | 17 (5 - 175) | 18 (3 - 198) | 0.248 |
| Aspertate aminotransferase (U/L) | 20 (12 - 119) | 21 (2 - 160) | 10 (10 - 164) * | 0.001 |
| Total protein (g/L) | 72.48 ± 3.54 | 70.4 ± 3.83 * | 66.19 ± 3.82 * | < 0.001 |
| Albumin (g/L) | 44.01 ± 1.96 | 42.21 ± 2.57 * | 38.25 ± 1.99 * | < 0.001 |
| γ-glutamyltransferase (U/L) | 9 (1 - 113) | 10.5 (1 - 70) | 16 (1 - 302)*# | < 0.001 |
| Alkaline phosphatase (U/L) | 48 (10 - 140) | 86 (24 - 629)* | 131 (2 - 770) *, # | < 0.001 |
| Thyroid stimulating hormone (mIU/L) | 1.25 (0.003 - 9.89) | 1.55 (0.005 - 8.0) * | 2.87 (0.18 - 6.19) *, # | < 0.001 |
| Free thyroxine (pmol/L) | 15.03 (9.95 - 23.97) | 14.46 (3.79 - 46.32)* | 12.85 (3.66 - 14.76)*# | < 0.001 |
| Amylase (IU/L) | 78 (34 - 164) | 83 (36 - 242) * | 85 (46 - 242) *, # | < 0.001 |

*** p < 0.05, mid-pregnancy/late pregnancy compared with early pregnancy, # p < 0.05, late pregnancy compared with mid-pregnancy.**

**Table 2. Clinical characteristics of the 628 pregnant women between the 24th and 28th week of gestation.**

| Variables | Without GDM (n = 505) | GDM (n = 123) | p-value |
|---|---|---|---|
| Age (years) | 30.14 ± 3.85 | 30.42 ± 4.15 | 0.709 |
| Fasting plasma glucose (mmol/L) | 4.4 (3.8 - 5.0) | 4.9 (3.9 - 7.8) | < 0.001 |
| 1hPG (mmol/L) | 7.1 (3.5 - 9.9) | 9.75 (5.6 - 13.6) | < 0.001 |
| 2hPG (mmol/L) | 6.4 (3.1 - 8.4) | 8.7 (5.1 - 13.2) | < 0.001 |
| HOMA-IR | 1.58 (0.04 - 12.23) | 2.15 (0.69 - 7.79) | < 0.001 |
| Alanine aminotransferase (U/L) | 16 (6 - 69) | 15 (5 - 99) | 0.452 |
| Aspartate aminotransferase (U/L) | 20 (2 - 93) | 20 (10 - 70) | 0.088 |
| Total protein (g/L) | 66.26 ± 4.21 | 66.19 ± 3.36 | 0.659 |
| Albumin (g/L) | 38.55 ± 2.50 | 38.63 ± 2.29 | 0.406 |
| γ-glutamyltransferase (U/L) | 12 (1 - 49) | 11 (9 - 52) | 0.077 |
| Alkaline phosphatase (U/L) | 104 (34 - 151) | 108 (29 - 363) | 0.346 |
| Thyroid stimulating hormone (mIU/L) | 1.39 (0.87 - 4.19) | 1.59 (1.16 - 5.86) | 0.109 |
| Free thyroxine (pmol/L) | 14.7 (3.66 - 20.53) | 14.6 (3.79 - 23.68) | 0.089 |
| Amylase (IU/L) | 85 (36 - 242) | 92 (47 - 239) | 0.045 |

### Correlation analysis

We found that the plasma amylase level in 628 24th - 28th week pregnancy were negatively correlated with FPG ($r = -0.080$, $p = 0.045$), 1hPG ($r = -0.092$, $p = 0.022$), and HOMA-IR ($r = -0.081$, $p = 0.042$), age ($r = 0.049$, $p = 0.002$), ALT ($r = -0.053$, $p = 0.001$), AST ($r = -0.034$, $p = 0.029$), γ-GT ($r = -0.060$, $p < 0.001$) and none correlated with TP, ALB, ALP, TSH, and FT4.

### Independent factor of predicting GDM in multivariate analysis

Following adjustment for age, HOMA-IR, and FPG, multivariate logistic regression showed that high amylase [Amy ≥ 96 IU/L (highest quartile), with lower Amy < 96 IU/L as a reference] levels were independent factors for predicting GDM in the 24th - 28th week of pregnancy (OR: 1.202, 95% CI: 1.010 - 1.431, $p = 0.038$).

## DISCUSSION

GDM is affecting as many as 5 - 15% of the pregnant women among different ethnic groups [5]. Asians are at a higher risk for gestational diabetes compared with white women [1]. About 10% of GDM patients, after diet intervention, cannot reach the normal level of blood glucose; they need drug treatment.

Gestational diabetes mellitus is a state restricted to pregnant women whose impaired glucose tolerance is discovered during pregnancy. Women with GDM are unable to compensate for the insulin resistance of pregnancy [1]. Insulin resistance is described as inability of cells to respond to the natural function of insulin hormone. Rate of insulin resistance naturally increases during pregnancy [6]. Insulin resistance and hyperinsulinemia are associated with a number of pathological conditions, including diabetes. By the third-trimester of human pregnancy, women are significantly more insulin resistant, as manifested by hyperinsulinemia and by a variety of other assessments, than in the nonpregnant state [7]. Additionally, hyperinsulinemia induced by insulin resistance for the maintenance of euglycemia, may increase pancreatic amylase production [2]. Therefore, we could expect plasma amylase to be increased in GDM.

Insulin resistance was determined using the homeostasis model assessment-insulin resistance (HOMA-IR) according to the following equation proposed by Matthews et al.: HOMA-IR = fasting glucose (mmol) x fasting insulin mU/L/22.5 [4]. It is also important to acknowledge that HOMA-IR reflects hepatic insulin resistance rather than peripheral insulin resistance [8]. Using HOMA-IR, Sierralaguado et al. identified insulin resistance in women with gestational hypertension in early pregnancy [9]. The high HOMA-IR groups suggests severe insulin resistance. It is noteworthy that the HOMA-IR and plasma amylase were observed in GDM individuals in this present study. The current results also showed the HOMA-IR and plasma amylase of the GDM pregnant women is significantly higher than that of the normal pregnant women. The results of the present study indicate that the prevalence of GDM increased with increasing plasma amylase concentration quartiles after adjusting for age, HOMA-IR, and FPG.

In this study, the plasma amylase level rose progressively from the second trimester pregnancy, a higher plasma amylase level was found in the second and third trimesters than in the early trimester. The values of plasma amylase were observed in this study; it rose progressively from early pregnancy and then tended to a slightly higher level in the third trimester. It was in agreement with the findings of previous studies [10,11]. We observed significant differences of plasma amylase from the first to the third trimesters, however, the increased values were slight, and it was just close to the upper limit of normal in healthy pregnant women. Previous studies reported that the association between serum amylase level is believed to be related to GDM [5], but to the best of our knowledge its cutoff value for Chinese women has not been reported until now. In the present study, the plasma amylase level was defined as plasma amylase > 96 IU/L. The present results are unique to a certain instrument platform or dependent on the study population. The cutoff point seems to be higher compared to previous reports, the upper limit of normal for plasma amylase is higher than that for serum (plasma, 110 IU/L; serum, 75 IU/L). When serum was added to heparinized tubes, the amylase activity was increased, but the increase was not strictly proportional to the concentration of heparin [12].

In the published studies, there was a negative correlation between insulin resistance with serum amylase in the metabolic syndrome population [5,13]. There were negative correlations between HOMA-IR and plasma amylase level, and this study may also indirectly support the link between insulin resistance and amylase. It was previously believed that GDM pregnant women had a lower amylase level than that in the normal pregnant state [5]. Our study has conflicting results showing high plasma amylase observed in GDM pregnant women. However, serum amylase may reflect a manifestation of insufficient insulin action [8]. Unfortunately, the mechanism of insulin resistance of pregnancy is not clear and requires further investigation.

In pregnancy, fasting glucose decreases progressively with advancing gestation [10], it was in agreement with the findings in our study. Longitudinal studies in women with normal glucose tolerance demonstrate significant progressive alterations in all aspects of glucose metabolism as early as the end of the first trimester [10, 14]. However, the mechanism is not well understood. Longitudinal clamp studies using labeled glucose in both lean and obese women who develop GDM demonstrated a lower insulin sensitivity among women with GDM compared with weight-matched controls [15,16]. The mechanisms that lead to enhanced insulin secretion in pregnancy, whether primary or as compensation for insulin resistance, are not completely known [14].

However, some metabolic and endocrine markers were reported that they may not have the same predictive power for GDM. We observed that these plasma makers' levels changed in different trimesters of pregnancy. Women experience physiological changes during pregnancy, and in this prospective analysis of AST, ALT, TP, ALB, GGT, ALP, FT4, and TSH in 1,706 pregnant women it was found that the changes in these tests were different. The levels of plasma ALT, AST, TP, ALB, ALP, FT4, and TSH have some variation during the three trimesters of pregnancy. This is a normal pregnancy physiological phenomenon, which had been addressed in previous studies [17]. The same phenomenon can be observed in the published studies [18]. In contrast, the GGT levels in our study are elevated in the third trimester of pregnancy, which is different from previous findings. That may be due to the different areas with different diets in Sichuan Province. The raised GGT activity could be addressed as an oxidative stress situation

in pregnancy. The previous studies have shown that GDM is related to oxidative stress [9] and was not associated with GDM [19]. In this Chinese population, our study showed that amylase concentration also had a negative correlation with the level of markers of liver function, and the changes in liver function tests during pregnancy are not independently predictive of prevalent GDM. That was also demonstrated in our study. The characteristics of the changes in liver function tests in GDM pregnant women in this study have already been described. They did not differ from that in pregnant women without GDM. We also found that the plasma amylase levels in 628 24th - 28th week pregnant women were negatively correlated with FT4 and TSH, but the exact underlying pathophysiology is still unknown. However, the contributions of the amylase level for earlier GDM diagnosis are all increasing in incidence worldwide. The amylase level is a significant predictor of GDM between 24th and 28th gestational weeks. Plasma amylase is relatively inexpensive to determine and could be easily be used in the clinical setting, so these results may help to identify GDM.

This study utilized plasma amylase but had certain limitations for its cross-sectional study design and relatively small number of participants. The association of plasma makers (AST, ALT, and GGT) and amylase was first described in our study in GDM population, as far as we know. The mechanism also needs to be further investigated. The cutoff concentrations of plasma amylase were given; however, we still lack the proposed reference intervals for plasma amylase for women in the 24th - 28th gestational week of uncomplicated pregnancy.

## CONCLUSION

The plasma amylase levels of GDM women are higher compared to healthy pregnant women, suggesting that plasma amylase levels are associated with GDM patients. The results from the present study examine the potential of using plasma amylase level in the first-trimester to identify women at risk for GDM. These metabolite data facilitate hypothesis generation regarding the pathogenesis of GDM and have the potential to guide future research into novel metabolomic biomarkers of GDM.

**Declaration of Interest:**

The authors declare that they have no competing interests.

**Authors' Contributions:**

Fan Yu and Wen-jie Zhou did the statistical analysis and prepared the manuscript. Yongmei Jiang was responsible for the study design and coordination, guided the statistical analysis, and revised the manuscript. Xi Tan collected the data and reviewed the manuscript. All authors read and approved the final manuscript. The excel data used to support the findings of this study are available from the corresponding author upon request.

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