

Gestational diabetes mellitus increases the baseline level of procalcitonin in maternal blood but not in umbilical cord blood in late pregnancy

A retrospective case-controlled study

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Abstract

To study the effects of gestational diabetes mellitus (GDM) on the level of procalcitonin (PCT) in maternal blood and umbilical cord blood in late-pregnant women.

We retrospectively analyzed 37 pregnant women in late pregnancy who had GDM and compared with those of 97 age-matched normal glucose-tolerant (NGT) pregnant women. The PCT level was converted to a value with normal distribution (LG-PCT) by taking the logarithm of each value to the base 10 (log₁₀).

The body mass index (BMI) before delivery, family history of diabetes mellitus (DM), and postpartum blood loss within 24 hours were markedly higher in GDM group than in NGT group, while the gestational age was smaller in GDM group than in NGT group. The maternal blood LG-PCT was significantly higher in GDM group than in NGT group, while the umbilical cord blood LG-PCT was not significantly different between the 2 groups. Multivariate analysis showed that family history of DM, gestational age, and maternal blood LG-PCT were independent risk factors of GDM after adjusting for BMI and postpartum blood loss within 24 hours.

GDM increases the baseline level of maternal blood PCT but has little effect on umbilical cord blood PCT.

Abbreviations: BMI = body mass index, CI = confidence interval, CRP = C-reactive protein, DM = diabetes mellitus, GDM = gestational diabetes mellitus, Hb = hemoglobin, N% = neutrophil percentage, NGT = normal glucose tolerance, OGTT = oral glucose tolerance test, OR = odds ratio, PCT = procalcitonin, TC = total cholesterol, TG = triglyceride, WBC = white blood cell count.

Keywords: gestational diabetes mellitus, maternal blood, pregnancy, procalcitonin, umbilical cord blood

1. Introduction

Gestational diabetes mellitus (GDM) is a common metabolic disease that occurs or is initially diagnosed during pregnancy.^[1] Up to 14% of pregnant women worldwide will develop GDM during pregnancy.^[2] The incidence of GDM depends on race and ethnicity, as well as diagnostic and screening criteria.^[3]

According to the data from multicenter clinical trials, the incidence of GDM in China has reached 17.5%.^[4] GDM is associated with increased risk of adverse maternal and perinatal outcomes, including pre-eclampsia, preterm birth, cesarean section, macrosomia, and respiratory distress syndrome.^[5] The main pathological mechanism of GDM involves biochemical pathways of insulin resistance and chronic subclinical inflammation.^[6]

The role of pro-inflammatory cytokines in GDM is controversial. Recent reviews and meta-analyses have shown that women with GDM have a higher pro-inflammatory state.^[7] A study carried out in Southeast Asian women showed that women with increased white blood cell count (WBC) in early pregnancy had a significantly higher incidence of GDM than women with normal WBC.^[8] Zhu et al^[9] found that women with GDM showed significantly increased neutrophil counts and WBC in both fasting and 1-hour oral glucose tolerance test (OGTT). During pregnancy, elevated level of C-reactive protein (CRP) is associated with insulin resistance, maternal blood glucose abnormality, and GDM.^[10] Since CRP level is associated with body mass index (BMI) during pregnancy, the association between CRP and GDM can be attenuated or eliminated by correcting BMI.^[11] However, CRP seems unlikely to provide additional information on the risk factors of GDM except BMI. Many studies have suggested that elevated level of high-sensitive CRP in early pregnancy is associated with an increased risk of GDM.^[12] In addition, recent studies have shown that pro-inflammatory cytokines such as CRP, interleukin-6, and tumor necrosis factor- α are increased in the plasma of women with late-onset GDM.^[13]

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Procalcitonin (PCT) has high sensitivity and specificity in the diagnosis of infection and has become a promising biochemical marker for early detection of infection, inflammation estimation, and prognosis.^[14] Some researchers have used maternal serum PCT and neonatal cord blood PCT in intrauterine infection studies.^[15] So far, few studies have focused on the correlation between PCT and GDM. In this study, we compared the inflammation indicators in maternal blood and umbilical cord blood of women with GDM in late pregnancy with those of normal glucose-tolerance (NGT) control and explored the role of PCT in GDM.

2. Materials and methods

We retrospectively analyzed the PCT levels in maternal blood and cord blood of 37 women with GDM who delivered in the Department of Obstetrics, Third Affiliated Hospital of Suzhou University from March 2018 to September 2018. The patients were 22 to 39 years old and their gestational ages were 37 to 40⁺² weeks. This study was approved by the Ethics Review Committee/Institutional Review Board. GDM was diagnosed according to the guidelines for the diagnosis and treatment of pregnancy-related diabetes issued by the Obstetrics and Gynecology Section of the Chinese Medical Association Obstetrics and Gynecology Branch in 2014.^[16] Another 97 age-matched healthy pregnant women with NGT who were 20 to 42 years old, with gestational age of 37⁺² to 41⁺² weeks served as the control group.

The demographics of the patients, including age at admission, family history of diabetes, number of pregnancies, number of deliveries, blood pressure, body weight, and vital signs at admission (body temperature, heart rate, and respiratory rate), were recorded. Patients received routine blood tests, including WBC ($5.8\text{--}20 \times 10^9/\text{L}$), percentage of neutrophils (N%, 64–89%), red blood cell count ($2.9\text{--}4.5 \times 10^{12}/\text{L}$), hemoglobin (83–136 g/L), and platelet count ($96\text{--}297 \times 10^9/\text{L}$) before delivery using Sysmex XN9000 (Hyogo, Japan). The maternal serum PCT level was detected using a Roche cobas 8000 system (Indianapolis, IN) ranging 0.020 to 100.00 ng/mL. The umbilical cord blood PCT was extracted from 5 mL umbilical vein blood drawn within 5 minutes after the delivery of the fetus and was processed the same as the maternal blood. CRP (0–10.0 mg/L) and other biochemical indexes such as alanine aminotransferase (6–32 U/L), aspartate aminotransferase (9–45 U/L), serum creatinine (41–77 $\mu\text{mol}/\text{L}$), blood urea nitrogen (1.25–5.29 mmol/L), total cholesterol (4.09–8.63 mmol/L), and triglyceride (1.34–4.03 mmol/L) were measured using Beckman Coulter AU5800 (Brea, CA). The delivery methods, neonatal gender, neonatal weight, 1-minute and 5-minute Apgar score, amniotic fluid volume, amniotic fluid status, and postpartum blood loss within 24 hours were recorded. The values of the above blood indexes referred to the normal reference intervals in normal late-pregnant women.^[17]

2.1. All babies were born alive

The pregnant women who had the following conditions were excluded from the study: hypertension, pre-eclampsia, twin pregnancy, chronic diseases, liver disease or endocrine disease, history of other genetic diseases, abnormalities in the structures of the heart, liver, lung, and kidney detected by ultrasound or electrocardiogram, and viral infections (i.e., HIV, hepatitis B, or C). The NGT group did not contain any GDM patient.

2.2. The oral glucose tolerance test

All pregnant women received the OGTT (75 g OGTT) routinely for GDM screening between 24 and 28 gestational weeks. The procedure of 75 g OGTT^[16]: The patients received normal diet for 3 consecutive days before the test to ensure that the daily intake of carbohydrates was not less than 150 g, and fasted for at least 8 hours before OGTT test. During the test, the patients were required to sit quietly with no smoking. Each patient received 300 mL liquid containing 75 g of glucose orally within 5 minutes. The venous blood samples were collected individually before the test, and 1 and 2 hours after taking glucose (calculated when the patient started to drink glucose containing liquid) in test tubes containing sodium fluoride. The blood glucose levels of the patients were determined using the glucose oxidase method. Diagnostic criteria for 75 g OGTT: Fasting serum glucose level and the serum glucose levels 1 and 2 hours after taking glucose should be lower than 5.1, 10.0, and 8.5 mmol/L (92, 180, and 153 mg/dL), respectively. Patients with any of the glucose levels meeting or exceeding the above criteria were diagnosed as GDM.

2.3. Statistical analysis

All data were analyzed using SPSS 18.0 statistical software (Chicago, IL). The normally distributed measurement data were expressed as the mean \pm SD, the measurement data with non-normal distribution were expressed as the median (range), and the count data were expressed in numbers or percentages. Comparison between 2 groups of normally distributed data was performed using the 2-sample *t* test, and comparison between 2 groups of non-normally distributed data was carried out using the Mann–Whitney *U* test. PCT and CRP contents were converted to normally distributed data by taking the logarithm of each value to the base 10 (log₁₀) (LG-PCT and LG-CRP) and analyzed using *t* test. The rates were compared using the Chi-squared test. Non-normally distributed data and grade data were analyzed using Spearman correlation analysis. The categorical variable correlation analysis was performed using univariate and multivariate logistic regression analysis to calculate the odds ratio (OR) and 95% confidence interval. *P* < .05 was considered statistically significant.

3. Results

A total of 37 women with GDM aged 22 to 39 years (mean, 30.3 \pm 4.0 years) were enrolled in this study. All of them were in the third trimester, with the median gestational age of 38 weeks (range, 37–40⁺² weeks). Among these patients, 26 cases (70.3%) terminated pregnancy at 37 to 39 gestational weeks because of middle cerebral artery decline (9 cases), poor glycemic control (8 cases), acute fetal sputum (1 case), social factors (4 cases), and natural labor (4 cases). Another 97 age-matched NGT pregnant women aged 20 to 42 years (mean, 28.9 \pm 4.8 years), with the median gestational age of 39 weeks (range, 37⁺²–41⁺² weeks) were enrolled as the control group. In these patients, 37 cases (38.1%) terminated the pregnancy at 37 to 39 gestational weeks because of middle cerebral artery decline (20 cases), social factors (11 cases), and natural labor (6 cases).

The general information of GDM and NGT groups was compared in Table 1. The BMI before delivery, family history of diabetes mellitus (DM), and postpartum blood loss within 24 hours were higher in GDM group than in NGT group (*P* < .05), while the gestational age in GDM group was smaller than that of NGT group (*P* = .001).

Table 1
Comparison of general data between gestational diabetes mellitus and normal glucose-tolerant groups.

| Characteristics | GDM (n=37) | NGT (n=97) | P |
|---|---------------------------|--|------|
| Age (years) | 30.3±4.0 | 28.9±4.8 | .123 |
| BMI before delivery (kg/m ²) | 28.2±3.9 | 26.9±2.9 | .030 |
| Family history of DM (%) | 9 (24.3%) | 1 (1.0%) | .000 |
| Gestational week (weeks) | 38 (37~40 ⁺²) | 39 (37 ⁺² ~41 ⁺²) | .001 |
| Number of pregnancies | 2 (1~6) | 2 (1~5) | .763 |
| Number of deliveries | 0 (0~2) | 0 (0~2) | .719 |
| Systolic blood pressure (mm Hg) | 121±14 | 117±10 | .077 |
| Diastolic blood pressure (mm Hg) | 77±12 | 75±9 | .319 |
| Hb (g/L) | 120±15 | 119±13 | .779 |
| TC (mmol/L) | 6.48±1.07 | 6.32±1.08 | .546 |
| TG (mmol/L) | 4.24±2.03 | 3.77±1.60 | .244 |
| Caesarean section rate (%) | 22 (59.5%) | 43 (44.3%) | .117 |
| Percentage of boys (%) | 16 (43.2%) | 45 (46.4%) | .744 |
| Fetal weight (g) | 3431±485 | 3298±359 | .078 |
| 1-minute Apgar score | 9 (8-9) | 9 (6-9) | .075 |
| 5-minute Apgar score | 9 (8-9) | 9 (8-9) | .127 |
| Amniotic fluid volume (mL) | 520±315 | 492±160 | .498 |
| Amniotic fluid status (0-3) | 0 (0-3) | 0 (0-3) | .844 |
| Postpartum blood loss within 24hours (mL) | 430 (250-2070) | 370 (200-1340) | .004 |

Normally, distributed data are expressed as the mean±SD, and the data that were not normally distributed are expressed as the median (range).
 BMI=body mass index, DM=diabetes mellitus, GDM=gestational diabetes mellitus, Hb=hemoglobin, NGT=normal glucose tolerant, TC=total cholesterol, TG=triglyceride.
 P<.05 indicates that the difference is statistically significant.

The inflammation indexes in maternal blood and cord blood were compared between the 2 groups (Table 2). We found that the maternal blood LG-PCT in the GDM group was significantly higher than that in the NGT group (P=.008). However, there were no significant differences in maternal blood LG-CRP, WBC, and N% between the 2 groups (P>.05). Besides, the cord blood LG-PCT was also not significantly different between the 2 groups (P=.917).

Univariate logistic analysis results showed that the BMI before delivery, family history of DM, postpartum blood loss within 24 hours, and maternal blood LG-PCT were positively correlated with GDM (OR=1.135, 30.857, 1.002, and 78.939, respectively; P<.05 for all); whereas gestational age was negatively correlated with GDM (OR=0.463, P=.002) (Table 3). Correlation analysis revealed that maternal blood LG-PCT had no significant correlation with maternal BMI and systolic blood pressure before delivery, fetal weight, 1-minute Apgar score, 5-minute Apgar score, and postpartum blood loss within 24hours (P>.05). However, it had a slightly negative correlation with gestational age (r=-0.234, P=.017). After multivariate logistic

analysis, we found that the family history of DM, gestational age, and maternal blood LG-PCT were independent risk factors of GDM (OR=29.666, 0.498, and 87.936, respectively; all P<.05) after adjusting for BMI and postpartum blood loss within 24 hours (Table 3).

4. Discussion

A study on 200,000 cases of GDM in the United States identified that there was no difference in stillbirth rate and infant mortality rate when the baby was delivered between 36 and 38 weeks; however, if the delivery was at 39 weeks and beyond, the relative risk of expectation management exceeded the risk of delivery.^[18] Coustan et al^[19] suggested that delivery can be at 39 to 40 weeks depending on the patient's preference. When the blood glucose control of GDM patients is poor, the preferred delivery time usually is between 34 and 39 weeks, depending on the condition of the patient. In this study, the timing of delivery in GDM group was determined based on the 2014 Diagnostic and Therapeutic Guidelines for Pregnant Women with GDM in China.^[16] Because of GDM-related complications, 70.3% of pregnant women in GDM group gave birth before 39 weeks, which is in agreement with the principle that the time of pregnancy termination should be individualized.

Infants of GDM mothers have a greater incidence of large for gestational age and macrosomia (birth weight over 4000-4500 g).^[20] We found that the average weight of neonates in GDM group was slightly greater than that in NGT group, but the difference was not statistically significant.

Studies have suggested that the risk factors of GDM include advanced maternal age, obesity, ethnics, family history of DM, previous GDM history, macrosomia, and unexplained still-birth.^[21] Consistent with these findings, we found that the incidence of GDM in a family with DM history is about 30 times of that in a family without DM history.

Maternal BMI and age can affect levels of inflammatory markers and cause glucose intolerance in pregnant women.^[22]

Table 2
Comparison of maternal blood and cord blood inflammation indexes between gestational diabetes mellitus and normal glucose-tolerant groups.

| Characteristics | GDM (n=37) | NGT (n=97) | P |
|--|------------|------------|------|
| Maternal blood indexes before delivery | | | |
| LG-PCT | -1.53±0.15 | -1.61±0.12 | .008 |
| LG-CRP | 0.71±0.31 | 0.64±0.15 | .205 |
| WBC (×10 ⁹ /L) | 8.66±2.34 | 8.58±2.03 | .840 |
| N% (%) | 74.9±7.3 | 74.9±5.8 | .995 |
| LG-Cord blood PCT | -1.12±0.21 | -1.13±0.19 | .917 |

Normally distributed data are expressed as the mean±SD.
 CRP=C-reactive protein, GDM=gestational diabetes mellitus, N%=neutrophil percentage, NGT=normal glucose tolerant, PCT=procalcitonin, WBC=white blood cell count.
 P<.05 indicates that the difference is statistically significant.

Table 3**Univariate and multivariate analyses of different indexes of gestational diabetes mellitus.**

| Characteristics | Univariate analysis | | Multivariate analysis | |
|---------------------------------------|--------------------------|-------------|--------------------------|-------------|
| | OR (95% CI) | P | OR (95% CI) | P |
| BMI | 1.135 (1.010, 1.276) | .034 | 1.059 (0.884, 1.269) | .534 |
| Family history of DM | 30.857 (3.747, 254.119) | .001 | 29.666 (2.811, 313.063) | .005 |
| Gestational week | 0.463 (0.288, 0.745) | .002 | 0.498 (0.256, 0.968) | .040 |
| Systolic blood pressure | 1.030 (0.997, 1.065) | .079 | 1.025 (0.978, 1.075) | .302 |
| Fetal weight | 1.001 (1.000, 1.002) | .077 | 1.001 (0.999, 1.002) | .473 |
| 1-minute Apgar score | 0.599 (0.232, 1.545) | .289 | 2.440 (0.252, 23.654) | .441 |
| 5-minute Apgar score | 0.182 (0.016, 2.074) | .170 | 0.105 (0.000, 33.620) | .444 |
| Postpartum blood loss within 24 hours | 1.002 (1.000, 1.004) | .024 | 1.001 (0.998, 1.004) | .659 |
| LG-PCT | 78.939 (2.716, 2294.224) | .011 | 87.936 (2.167, 3568.731) | .018 |

BMI = body mass index, CI = confidence interval, DM = diabetes mellitus, GDM = gestational diabetes mellitus, OR = odds ratio, PCT = prolactin. Bold value indicates $P < .05$.

Although BMI is a known clinical risk factor of GDM, it has not been used alone to screen patients with GDM or as an indicator of GDM treatment. In this study, although the BMI was higher in GDM group, BMI and GDM were not independently related, indicating that the relationship between BMI and GDM is weaker than that between GDM and family history of DM/gestational age/maternal blood PCT. We found that the postpartum blood loss within 24 hours in GDM group was higher than that in the control group, which may have certain relationship with fetal weight. The specific mechanism remains to be elucidated.

Pregnancy itself is characterized by altered inflammatory features compared with nonpregnant state. A tight regulatory balance between pro-inflammatory cytokines and anti-inflammatory cytokines may be required for normal implantation, trophoblast invasion, and placental formation.^[23] Aye et al^[24] showed that maternal inflammation in women with GDM may affect fetal development by influencing placental function rather than directly affecting the inflammatory characteristics of the fetus, and the levels of inflammatory markers in umbilical cord blood are unchanged during maternal inflammation. The studies of inflammatory mediators in the maternal, placental, and fetal compartments in GDM patients are not always consistent. No sufficient evidence shows that maternal inflammation is equivalent to the inflammation in fetal serum. Changes in maternal inflammatory markers may not be reflected in fetal circulation.^[23] We found that cord blood PCT was not significantly affected when maternal blood PCT was markedly increased in GDM group, which was consistent with the above finding. A recent study suggests that cord blood PCT originates in the fetus because its molecular weight is too large to pass the placenta.^[25] Our results also indirectly demonstrate that cord blood PCT and maternal blood PCT come from different sources.^[15]

Our study has some limitations. First, we did not have a comprehensive record of the demographic and social characteristics of the patients, such as education, smoking status, physical activity, and diet of the patients. Second, since this study is a retrospective study, it may contain some factors that may potentially affect blood PCT level. Finally, the sample size of the GDM group is relatively small and further study with larger sample size needs to be done to confirm the findings we obtained in this study.

In summary, we conclude that GDM can increase the baseline level of maternal blood PCT, but has little effect on cord blood PCT. Our finding may provide a reference for the diagnosis of infections during pregnancy.

Author contributions

Y.M. and W.Y. researched literature and conceived the study. Y.M. was involved in protocol development, gaining ethical approval, patient recruitment, and data analysis. Y.M. wrote the first draft of the manuscript. W.Y. and Y.T. reviewed and edited the manuscript and approved the final version of the manuscript.

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