STUDY ON THE RELATIONSHIP OF MATERNAL SERUM CORTISOL AND LOW-GRADE INFLAMMATION INDICES WITH SOME PREECLAMPSIA RISKS AND FETAL GROWTH INDICES BY ULTRASOUND IN FIRST-TIME DIAGNOSED GESTATIONAL DIABETES MELLITUS

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Abstract

Objectives: To describe serum cortisol and low-grade inflammation (LGI) in first-time diagnosed gestational diabetes mellitus (GDM) and investigate the relationship of maternal serum cortisol and LGI with maternal preeclampsia risks and fetal growth indices by ultrasound in first-time diagnosed GDM. ***Methods:*** A cross-sectional, descriptive study was conducted on 248 first-time diagnosed GDM in Military Hospital 103 and National Hospital of Endocrinology from 2015 to 2024. ***Results:*** Serum cortisol, platelet-to-lymphocyte ratio (PLR), and neutrophil-to-lymphocyte ratio (NLR) were significantly higher in GDM compared with the normal glucose-tolerant (NGT) group. LGI but not cortisol levels were associated with percentage of age > 35, systolic blood pressure, and BMI. While maternal cortisol positively correlated with abdominal circumference - AC (r = 5.5) and estimated fetal weight - EFW (r = 85.3) of the fetus, NLR negatively correlated with EFW (B = -64.4) after adjusting for maternal BMI and FPG. PLR negatively correlated with fetal biparietal diameter - BPD (B = -0.02), AC (B = -0.06), EFW (B = -1.1), and head circumference - HC (B = -0.06), with $p < 0.05$. ***Conclusion:*** Serum cortisol, LGI, and fetal growth indices in GDM were higher than those in NGT pregnancy.

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LGI, but not serum cortisol, was related to risk factors for preeclampsia (SBP, BMI). Maternal cortisol positively correlated with fetal AC and EFW. LGI indices correlated negatively with fetal AC, EFW, BDP, and HC.

Keywords: Gestational diabetes mellitus; Cortisol; Low-grade inflammation; Fetal ultrasound index; Preeclampsia risk.

INTRODUCTION

Gestational diabetes mellitus is a condition of insulin resistance that causes high blood glucose levels to first appear during pregnancy, affecting the health of the mother and the development of the fetus. Among the complications caused by GDM for mothers and pregnant women, preeclampsia and gestational diabetes are common complications [1]. Chronic LGI is a persistent inflammatory condition that contributes to insulin resistance in GDM. Clinically, LGI is often assessed through C-reactive protein (CRP), NLR, and PLR [2]. Preeclampsia is characterized by a systemic inflammatory response, where the body's immune system is activated and releases inflammatory substances. Studies suggest that preeclampsia may be related to an overactive immune system, where the body's inflammatory response is heightened. While optimal levels of maternal cortisol can benefit neurodevelopment, excessive or prolonged exposure to high cortisol levels during pregnancy can negatively impact the developing fetus, potentially leading to long-term health issues, such as lower birth weight, lower weight for length [3], and an increased risk of postpartum depressive symptoms [4]. However, pregnancy cortisol levels differ between races. To the best of our knowledge, there has been a lack of studies regarding maternal cortisol, LGI and insulin resistance, and fetal growth characteristics. Therefore, we conducted this study to: *Describe serum cortisol and LGI in first-time diagnosed GDM and investigate the relationship of maternal serum cortisol and LGI with maternal preeclampsia risks and fetal growth indices by ultrasound in first-time diagnosed GDM.*

MATERIALS AND METHODS

1. Subjects

Including 248 first-time diagnosed GDM according to the American Diabetes Association (ADA) 2014 criteria and a control group of 48 NGT pregnant women at 24 - 28 weeks of gestation at two major hospitals in Northern Vietnam: Military Hospital 103 and National Hospital of Endocrinology, from January 2015 to December 2024.

* *Exclusion criteria:* Previously diagnosed diabetes, insomnia, chronic or acute stress; history of drug treatment or comorbidities affecting the results of complete blood count, including infection, hematologic malignancy, use of leukocyte-activating drugs, corticosteroids, and allergies.

2. Methods

* *Study design:* A cross-sectional, descriptive study was conducted.

* *Research process:*

Pregnant women with all 3 blood glucose record times, including fasting blood glucose, 1-hour, and 2-hour post-oral tolerance test blood glucose with 75 grams of anhydrous glucose below the diagnostic threshold according to ADA 2014, are classified into the NGT group.

GDM participants were clinically examined, including BMI, weight increment, and systolic blood pressure (SBP), and had blood tests and fetal ultrasounds performed at the time of the regular check-up visit.

The examination and testing are performed under the guidance of caring medical staff to minimize stress for GDM. GDM with CRP levels of 3 - 10 mg/L is considered to have LGI [5]. High age (> 35 years), weight increment > 12kg, and SBP are selected preeclampsia risk factors used in this study [6]. 5mL of blood was drawn from GDM participants at 8 a.m. on the day of the examination while fasting to measure study parameters and cortisol. Fetal ultrasound was performed after GDM participants collected venous blood 1 hour after the oral glucose tolerance test to save time and avoid maternal fatigue. Ultrasound evaluation indicators included HC, AC, BPD, and EFW according to the guidelines of the American College of Radiology. Serum cortisol levels of GDM were assigned as “high” if those values were greater than the Mean + 1SD of the control group.

* *Statistical analysis:* Data were analyzed using SPSS 26.0 software. Data were presented as Mean (Standard Deviation) or Median (Interquartile Range). Multivariate regression analysis between cortisol, LGI assessment indices, and fetal growth indices, NLR adjusted with maternal BMI and maternal FPG; PLR adjusted with maternal BMI, maternal FPG, maternal age, and maternal parities, CRP adjusted with maternal BMI, maternal FPG, maternal age, and maternal parity. A $p < 0.05$ was set as significance.

3. Ethics

The study protocol was approved by the Institutional Review Board of the Military Hospital 103 (Decision No. 99A/2022.CNChT-HĐĐĐ, September 8th, 2022). Data were used and published with permission of Military Hospital 103 and National Hospital of Endocrinology. The authors declare to have no conflicts of interest in the study.

RESULTS

Table 1. Comparison of maternal serum cortisol between GDM and normal glucose tolerance pregnancy.

Parameters	GDM (n = 248)	NGT pregnancy (n = 48)	p
Cortisol, nmol/L	767.32 ± 189.04	552.33 ± 148.84	< 0.001
Increased, n (%)	144 (58.1)		
Within control range, n (%)	104 (41.9)		

The mean cortisol concentration in GDM was 767.32 nmol/L, which was statistically significantly higher than that in the NGT group, with $p < 0.001$. The percentage of high cortisol levels in GDM was 58.1%.

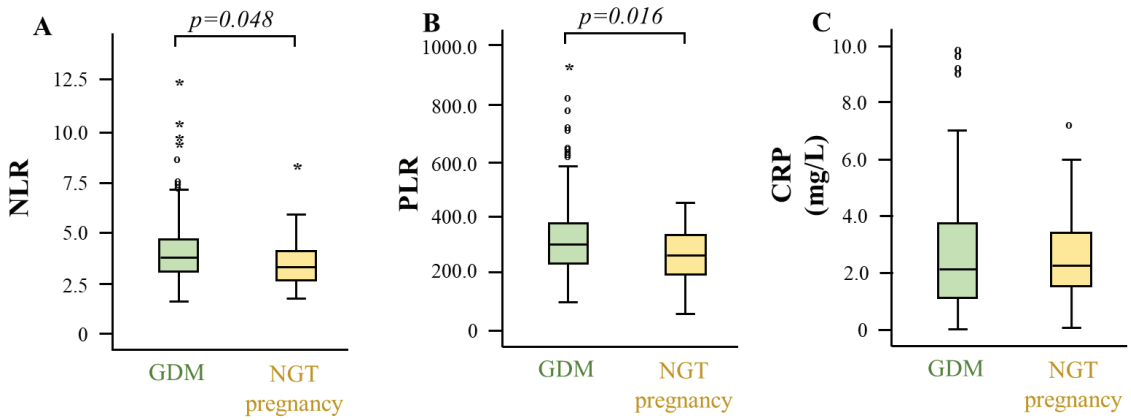

Figure 1. Chronic LGI indices between GDM and NGT groups.

Both NLR and PLR were significantly higher in GDM than in the NGT group ($p < 0.05$). However, CRP concentration did not differ between the two groups.

Table 2. Preeclampsia risks among the cortisol and LGI groups.

Criteria	Cortisol		LGI	
	Normal (n = 104)	Increased (n = 144)	LGI (n = 96)	Non-LGI (n = 152)
Age (year)	4.9 ± 0.6	5.0 ± 0.6	31 (28 - 35)	30 (27 - 34)
Age				
≤ 35, n (%)	70 (67.3)	107 (74.3)	58 (60.4)*	119 (78.3)*
> 35, n (%)	34 (32.7)	37 (25.7)	38 (39.6)*	33 (21.7)*
BMI (kg/m^2)	25.3 ± 3.3	25.6 ± 3.5	26.4 ± 3.6*	25.0 ± 3.0*
Weight increment				
≤ 12kg, n (%)	35 (33.7)	53 (36.8)	36 (37.5)	52 (34.2)
> 12kg, n (%)	69 (66.3)	91 (63.2)	60 (62.5)	100 (65.8)
SBP (mmHg)	108.5 ± 8.5	110.1 ± 10.9	110 (106 - 120)*	110 (100 - 120)*
Parity (time)	2 (1 - 3)	2 (1 - 4)	2 (1 - 3)	2 (1 - 4)

(: Significant difference between two groups with p < 0.05)*

In GDM, LGI, but not cortisol levels, was associated with percentage of age > 35, SBP, and BMI. In particular, GDM women with LGI exhibited significantly higher percentages of age > 35, SBP, and BMI compared with the non-LGI group. No differences in age, weight increment, and parity were observed.

Table 3. The relationships between maternal cortisol and LGI, fetal indices in gestational diabetes.

	Cortisol		LGI		
	Normal (n = 104)	Increased (n = 144)	LGI (n = 96)	Non-LGI (n = 152)	p
BPD (mm)	73.4 ± 12.2	76.5 ± 12.5	79.5 (75.0 - 83.5)	80.5 (74.0 - 85.0)	< 0.05
AC (mm)	249.8 ± 54.3	266.1 ± 50.9	261 (242.8 - 294.8)	276.0 (242.8 - 305.3)	< 0.05
EFW (g)	731.6 ± 61.4	758.9 ± 77.5	1577.0 (1303.8 - 2191.0)	1766.5 (1197.8 - 2306.3)	< 0.05
HC (mm)	271.1 ± 41.5	281.0 ± 45.4	286.5 (265.3 - 310.5)	294.5 (270.0 - 316.0)	< 0.05

LGI groups witnessed significantly lower BPD, AC, EFW, and HC compared with the non-LGI group. The high cortisol group exhibited higher BPD, AC,

EFW, and HC than the normal cortisol group. No differences in the classification of EFW between these groups were observed.

Table 4. Univariate and multivariate linear correlations between maternal NLR, PLR, CRP, serum cortisol and fetal indices.

Criteria		fAC	fBPD	fEFW	fHC
NLR	M1	-0.06	0.003	-0.15*	-0.09
	M2			-64.4*	
PLR	M1	-0.16*	-0.17*	-0.22**	-0.22**
	M2	-0.06*	-0.02**	-1.1**	-0.06**
Serum cortisol	M1	0.16*	0.13	0.15*	0.16*
	M2	5.5¶		85.3¶	
CRP	M1	0.21*	0.25**	0.15	0.23**
	M2	0.09*	0.03*	1.06	0.09*

*(*p < 0.05; **p < 0.01; ¶p < 0.001; NLR, PLR, and CRP: Model (M)1 = Pearson correlation without any adjustments; M2 = adjusted model)*

While NLR and serum cortisol were negatively correlated with fetal EFW, PLR and CRP negatively correlated with fetal AC, EFW, and HC. Serum cortisol was negatively correlated with AC and HC.

DISCUSSION

Our study outlined that blood cortisol levels, LGI indicators, and ultrasound fetal development indices in GDM were significantly higher than those of NGT pregnancy. Pregnancy is a long-term stressful process for the mother. This increases and changes the circadian rhythm of cortisol. Additionally, cortisol contributes to increased insulin resistance in the pathogenesis of GDM. A study by Yan Feng et al. (2020) on 75 patients with GDM found that blood cortisol levels in GDM (448.2 ± 100.2 nmol/L) were significantly higher than those in the NGT group (395.8 ± 137.1) with p = 0.09 [7]. Many studies have shown that pregnant women with GDM have increased inflammatory factors such as IL-6 and resistin [8]. Clinically, quantifying cytokines and chemokines indicative of LGI is not routinely performed. Clinically, CRP and inflammatory markers calculated from

total blood analysis, such as NLR and PLR, are routinely and rapidly performed. In our study, these LGI markers were statistically significantly higher in the GDM group than in the NGT group. A study by Pace et al. revealed that NLR in the GDM group was 0.58 higher than that in the NGT group, with $p < 0.001$ [2]. In GDM, LGI, but not serum cortisol, was related to some risk factors for preeclampsia (SBP, BMI). Many studies have shown that early pregnancy exposure to LGI is associated with increased risk of hypertensive pregnancy disorders [11], including PE in women with metabolic disorders. Maternal serum proinflammatory cytokine levels seem to be dysregulated during the second trimester, which later develop into hypertension and PE [11]. A study by Prerna et al. revealed that there was a significant increase in serum levels of hs-CRP, TNF-α, and IL-10 in mild and severe preeclamptics compared to controls ($p < 0.001$), and between severe preeclamptics in comparison to the mild group. [11] Regarding fetal development indices, studies have shown that it is the ability of cortisol to easily cross the placenta that leads to disruption of placental CRH secretion and affects fetal development. Our study revealed that maternal serum cortisol positively correlates with fetal EFW and AC after adjusting for maternal insulin resistance and BMI. Our results are similar to those of a Caucasian population study. A study by Crowther et al. showed that maternal cortisol levels were an important predictor of fetal birth weight [9]. Although LGI has been proven for its independent effects on postnatal development, there has been little research on the effects of LGI on the fetus. Our study showed that both PLR and NLR were inversely correlated with fetal growth after adjusting for some maternal characteristics, such as BMI and FPG. Our study results are consistent with other studies. A recent study by Shafiq et al. in Indian pregnant women found that LGI was inversely correlated with fetal growth in weight and length for age (with adjusted B of -0.07 and -0.10, respectively) [10].

This study has some limitations. First, the study was cross-sectional, examining a single point in time, which did not account for postnatal changes. However, fetal abnormalities in the late trimester were well correlated with later developmental velocity and organs. Second, the study sample size was small. Third, the study design was descriptive without follow-ups, making it impossible to assess the influence of the study factors on pregnancy outcomes and the occurrence of preeclampsia in the subjects.

CONCLUSION

At 24th - 28th weeks, serum cortisol levels, indices for LGI and fetal growth indices in GDM were higher than those in NGT pregnancy. LGI, but not serum cortisol, was related to some risk factors for preeclampsia (SBP, BMI). In GDM, maternal cortisol positively correlated with fetal AC and EFW. LGI indices negatively correlated with fetal AC, EFW, BDP and HC.

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