

# Relationship Between Maternal Serum Cortisol and Maternal Insulin Resistance and Fetal Ultrasound Characteristics in Gestational Diabetes Mellitus

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**Introduction:** Cortisol is proven to play a crucial role in hyperglycemia and fetal development in gestational diabetes mellitus (GDM). This research aims to investigate the relationship between maternal serum cortisol and insulin resistance indices and fetal ultrasound characteristics in women with GDM.

**Methods:** A cross-sectional and descriptive study on 144 GDM in Vietnam from January 2015 to December 2020. Serum cortisol was measured using electrochemiluminescence immunoassay at 8 a.m. on the examination day in the vicinity of the 24th gestational week. Fetal ultrasound was performed by an experienced person who was blind to the study.

**Results:** The mean cortisol level in the GDM group was 627.04 nmol/L. Serum cortisol levels positively correlated with abdominal circumference (AC), fasting plasma glucose (FPG), insulin, triglycerides, HOMA2-IR, and Mathew indices (with  $r$  of 0.18, 0.22, 0.18, 0.17, 0.18, and 0.22, respectively). Serum cortisol levels negatively correlated with QUICKI and McAuley indices (with  $r$  of  $-0.19$  and  $-0.21$ ), respectively. In a univariate linear regression, maternal serum cortisol positively correlated with fetal AC, head circumference (HC), and biparietal diameter (BPD) (with  $r$  of 0.21; 0.23; and 0.25, respectively). In a multivariate linear regression analysis, cortisol positively correlated with fetal AC, HC, and BPD after adjusting to maternal McAuley index.

**Conclusion:** Serum cortisol levels in GDM correlated with fasting blood glucose, triglycerides, and insulin resistance. Besides, serum cortisol levels in GDM positively correlated with fetal development.

**Keywords:** gestational diabetes mellitus, serum cortisol, insulin resistance indices, fetal ultrasound parameters

## Introduction

Elevated cortisol affects both mother and fetus during pregnancy.<sup>1-3</sup> Cortisol involves in lipid metabolism and distribution in the body. High level of serum cortisol leads to central lipid accumulation, resulting in insulin resistance.<sup>4</sup> Besides, maternal serum cortisol levels affect not only the mother but fetal development as well. Changes in cortisol levels during pregnancy remain unclear in pregnancy. In a study by Lynn et al, cortisol elevated in the setting of anxiety in pregnant women with both depressive and anxiety disorders.<sup>5</sup> Many studies have shown that high maternal blood cortisol levels affect the fetus directly (increasing caloric consumption and positively upregulating fetal corticotropin-releasing hormone (CRH)) and indirectly through activation

of the fetal hypothalamus-pituitary-adrenal (HPA) axis. The consequence of this process leads to increased fetal calorie consumption.<sup>6</sup> Some studies outlined that maternal cortisol levels affect fetal development, such as the effect on fetal weight-for-age development in the first trimester<sup>7</sup> and the third-trimester cortisol levels related to an increase in neonatal adiposity up to 1–6 months postpartum.<sup>8</sup> A study by Braithwaite et al of 1233 first-time mothers (96.1% White British) at 32 weeks gestation found that maternal cortisol levels were positively related to male infant' postpartum weight with  $\beta$  of 0.167 and  $p$  of 0.036<sup>9</sup>. However, pregnancy cortisol levels differ between races. The levels was found to be abnormally low in a group of African American women by John et al.<sup>10</sup> Moreover, serum cortisol levels are strongly associated with central obesity.<sup>11</sup> South Asians have a high percentage of body fat,<sup>12</sup> therefore, cortisol levels may differ from other races.

GDM is on the rise worldwide.<sup>13</sup> GDM affects fetal development and increases the risk of developing obesity, diabetes, and other metabolic cardiovascular diseases in the fetus<sup>14</sup> as a result of multiple factors.<sup>15</sup> In women with GDM, the mechanism of insulin resistance is unclear; however, high cortisol levels contribute to insulin resistance,<sup>16</sup> and cortisol levels fluctuate.<sup>17</sup> Nevertheless, the effects of cortisol on the fetus are unclear in GDM. In GDM, there is a decrease in 5 alpha-reductase activity, a downregulation of placental 11 beta-hydroxysteroid dehydrogenases-2 and an upregulation in placental 11 beta-hydroxysteroid dehydrogenases-2 at both mRNA and protein levels and metabolic function compared with normal pregnancy.<sup>18,19</sup> Most studies on cortisol levels and the relationship with fetal changes in pregnancy focus on postpartum children.<sup>8,20</sup> Abnormalities in the fetus can be easily assessed by fetal ultrasound during pregnancy, which is valuable in prognosis and later treatment instructions. However, the effects of cortisol on fetal development in GDM have been unclear, with the impacts of GDM on the fetus being different from the normal glucose-tolerant pregnant women.

To the best of our knowledge, there has been a lack of studies regarding maternal cortisol and insulin resistance, and fetal growth characteristics. We conducted this study to investigate the relationship of maternal cortisol with maternal insulin resistance indices and some fetal ultrasound characteristics in Vietnamese women with GDM.

## Materials and Methods

### Study Population and Design

A cross-sectional and descriptive study was conducted on 144 first-time diagnosed GDM who visited the Department of Examination of the National Hospital of Endocrinology, Vietnam, from January 2015 to December 2020.

The selection criterion was GDM from 24 to 28 weeks of gestation. Exclusion criteria were pregnant women diagnosed with diabetes before pregnancy (type 2 diabetes, type 1 diabetes, and other specific types of diabetes), earlier than 24 weeks of gestation, and with uncontrolled chronic medical conditions (bronchial asthma, impaired renal function, impaired liver function), or ongoingly prescribed with glucocorticoids.

### Clinical and Biochemical Assessments

GDM participants were tested clinically and biomedically. Clinical examination and blood collection were conducted conveniently and quickly to minimize patient stress. The participants were asked and examined about pregnancy history, medical history, and family history. Clinical criteria assessed include BMI, waist circumference, and systolic blood pressure. At 8 a.m. (fasting), 5 mL of blood was aspirated for testing, including serum cortisol, FPG, HbA1c, insulin, C-peptide, and lipid profiles. Serum cortisol was measured using an electrochemiluminescence immunoassay. From these values, we calculated the HOMA2-IR, QUICKI, Mathew, and McAuley indices as described in the previous studies.<sup>21</sup> According to WHO guidelines, the oral glucose tolerance test with 75 grams of anhydrous glucose (OGTT) was performed on the same day of the clinical visit. Serum glucose was assessed at three-time points, including fasting (8 a.m.), 1 hour, and 2 hours afterward.

According to the American College of Radiology guidelines,<sup>22</sup> a fetal ultrasound was performed using a 3–5 MHz transducer at the same time as the clinical examination. An experienced fetal sonographer performed a fetal ultrasound entirely unrelated to the study. Measured parameters include head circumference, abdominal circumference, biparietal diameter, amniotic fluid index, and estimated fetal weight.

## Ethical Statement

All participants provided written informed consent and agreed to join our study. The study protocol was approved by the Institutional Review Board of the Thai Binh University of Medicine and Pharmacy (decision no.1262/HĐĐĐ). The study was also conducted using good clinical practice following the Declaration of Helsinki.

## Statistical Analysis

Data were expressed as mean (standard deviation), median (Q1-Q3), and percentage. Pearson correlation was employed to measure correlations between serum cortisol and maternal biochemical parameters (abdominal circumference, FPG, insulin, triglyceride, QUICKI, HOMA2-IR, Mathew, and McAuley indices) and fetal ultrasonography parameters such as AC, HC, BDP, amniotic fluid index (AFI), and estimated fetal weight (EFW). Multivariate linear regression was employed to analyze the correlation between maternal cortisol and insulin resistance, and fetal ultrasound characteristics. A  $P < 0.05$  was set as significance. All data were processed with SPSS 26.0.

## Results

The mean cortisol level in the GDM was 627.04 nmol/L, with high BMI ( $25.65 \pm 3.6 \text{ kg/m}^2$ ), 1-hour OGTT ( $10.52 \pm 1.26 \text{ mmol/L}$ ) and 2-hour OGTT ( $9.17 \pm 1.20 \text{ mmol/L}$ ) (Table 1).

Serum cortisol levels positively correlated with AC, FPG, insulin, triglycerides, HOMA2-IR, and Mathew indices (with  $r$  of 0.18, 0.22, 0.18, 0.17, 0.18, and 0.22, respectively). Serum cortisol levels negatively correlated with QUICKI and McAuley indices (with  $r$  of  $-0.19$  and  $-0.21$ , respectively) (Table 2). In a multivariate linear regression analysis, maternal serum cortisol still positively correlated with Mathew index (Table 3).

**Table 1** Maternal and Fetal Characteristics in Gestational Diabetes Mellitus

Parameters	Values
Cortisol, nmol/L	627.04±102.96
Age, years	30.75±4.62
BMI, kg/m <sup>2</sup>	25.65±3.69
Abdominal circumference, cm	99.94±9.96
HbA1c, %	5.40±0.41
FPG, mmol/L	4.93±0.62
1-hour OGTT, mmol/L	10.52±1.26
2-hour OGTT, mmol/L	9.17±1.20
Insulin, µIU/mL	79.52 (44.9–113.9)
C-peptide, nmol/L	0.94 (0.60–1.31)
HOMA2-IR (insulin)	1.52 (0.87–2.16)
McAuley index	5.32±1.33
QUICKI index	0.33±0.04
Mathew index	2.46 (1.47–3.85)
Triglyceride, mmol/L	3.05±1.40
Cholesterol, mmol/L	6.00±1.16
HDL-C, mmol/L	1.80±0.37

(Continued)

**Table 1** (Continued).

Parameters	Values
LDL-C, mmol/L	2.79±1.02
Fetal ultrasound	
Biparietal diameter, mm	76.77±12.17
Head circumference, mm	282.28±43.41
Abdominal circumference, mm	266.13±49.91
Femoral length, mm	56.54±14.75
Estimated fetal weight, g	1790 (1140–2286)
Amniotic fluid index	139 (115.5–163)

**Abbreviations:** BMI, body mass index; OGTT, oral glucose tolerance test; HOMA2-IR, human insulin resistance; QUICKI, quantitative insulin sensitivity check index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

**Table 2** Correlation of Cortisol with Lipid Profiles, Blood Glucose, and Insulin Resistance Indices in GDM

	mAC	mTG	mFPG	mInsulin	mMcAuley Index	mMathew's Index	mQUICKI	mHOMA2-IR (Insulin)
<i>r</i>	0.18	0.17	0.22	0.18	−0.21	0.22	−0.19	0.18
<i>p</i>	0.03	0.04	0.009	0.03	0.02	0.01	0.03	0.04

**Abbreviations:** m, maternal; AC, abdominal circumference; TG, triglyceride; FPG, fasting plasma glucose; QUICKI, quantitative insulin sensitivity check index; HOMA2-IR, Homeostatic Model Assessment Index – Insulin resistance.

**Table 3** Multivariate Linear Regression Analysis: Correlation Between Maternal Serum Cortisol and Maternal Insulin Resistance

	Mathew	McAuley	QUICKI	HOMA2-IR (Insulin)
Cortisol, nmol/L	0.05 <sup>†</sup>	−0.01	0.00	0.00
Age, years	0.03	0.04	0.00	0.01
BMI, kg/m <sup>2</sup>	0.12	−0.15**	−0.003**	0.05
Parity, times	−0.02	−0.02	0.00	−0.01
Acanthosis nigricans	0.42	0.21	−0.01	0.24
Triglyceride, mmol/L	0.16		−0.00	0.08
Total cholesterol, mmol/L	0.19		−0.00	0.10
CRP, mg/L		−0.01		

**Notes:** <sup>†</sup>*p* < 0.05; \*\**p* < 0.001, Acanthosis nigricans (1 = Negative, 2 = Positive).

**Abbreviation:** CRP, high-sensitivity C-reactive protein.

Regarding fetal ultrasound parameters, maternal serum cortisol levels positively correlated with fetal BPD, HC, and AC values, with *r* of 0.25, 0.23, and 0.21, respectively. However, maternal cortisol was not correlated with EFW, FL, and AFI (Table 4).

In a multivariate linear regression analysis, maternal serum cortisol still positively correlated with fetal AC, HC, and BPD values after adjusting with maternal McAuley, HOMA2-IR indices, and BMI (Table 5).

**Table 4** Correlation of Maternal Cortisol with Fetal Ultrasound Indices in GDM

	fBPD	fHC	fAC	fFL	fEFW	fAFI
<i>r</i>	0.25	0.23	0.21	0.15	0.15	0.16
<i>p</i>	0.005	0.008	0.02	0.07	0.08	0.18

**Abbreviations:** F, fetal; BPD, biparietal diameter; HC, head circumference; AC, abdominal circumference, FL, femoral length; EFW, estimated fetal weight; AFI, amniotic fluid index.

**Table 5** Multivariate Linear Regression Analysis: Correlation Between Maternal Serum Cortisol and Fetal Ultrasound Indices

	fAC	fBPD	fEFW	fHC
mCortisol	0.09 <sup>†</sup>	0.03 <sup>†</sup>	1.06	0.09 <sup>†</sup>
mMcAuley	-6.45	-2.52 <sup>†</sup>	-125.74	-4.05
mHOMA2-IR	-4.41	-1.17	-98.09	-1.95
mBMI	4.63 <sup>**</sup>	1.08 <sup>*</sup>	67.97 <sup>*</sup>	4.47 <sup>**</sup>

Notes: <sup>†</sup>p <0.05; \*p <0.01; \*\*p <0.001.

Abbreviations: f, fetal; m, maternal; FPG, fasting plasma glucose; BPD, biparietal diameter; HC, head circumference; AC, abdominal circumference; EFW, estimated fetal weight.

## Discussion

Our results outlined that serum cortisol levels in GDM correlated with maternal FPG concentration, triglyceride, insulin resistance, and some fetal development indicators (HC, AC, and BPD).

Cortisol is involved in the pathogenesis of hyperglycemia in GDM, which can be explained by the fact that pregnancy is a long-term stress for mothers and contributes to elevated cortisol levels. On the one hand, increased cortisol during pregnancy increases the antagonism of insulin action. Several observational studies in GDM have found elevated cortisol levels in GDM.<sup>17</sup> Elevations of cortisol were detected even during the impaired glucose tolerance phase in pregnant women, contributing to reduced insulin sensitivity in GDM. On the other hand, studies in animal models have also shown that glucocorticoids induce increased insulin resistance in skeletal muscle through a decrease in glucose utilization and an increased shift towards fat for energy supply.<sup>23</sup> These factors contribute to increased insulin resistance in GDM. In our study, cortisol levels were negatively correlated with McAuley and QUICKI indices but positively correlated with FPG, insulin, HOMA-2, and Mathew indices. A study by Yan Feng et al on 70 GDM found that serum cortisol levels in GDM had a weak positive correlation with the HOMA-IR index ( $r = 0.28$ ,  $p < 0.05$ ).<sup>24</sup> Our results reinforce the role of cortisol in the pathogenesis of GDM. Cortisol is involved in the pathogenesis of GDM. During pregnancy, in contrast to its cortisol's negative feedback on hypothalamic CRH (corticotropin-releasing hormone) secretion when cortisol is elevated, cortisol tends to stimulate CRH secretion from the placenta and thus participates in the cortisol self-increasing spiral. Raised cortisol causes increased stimulation of insulin secretion<sup>25</sup> and increased lipid deposition in many organs.<sup>26</sup> Cortisol has been shown to be dependent on adiposity and fat distribution.<sup>27,28</sup> In our study, cortisol levels were positively correlated with triglyceride levels and maternal AC. Research by Le et al showed that, in GDM, the McAuley index is more meaningful in assessing insulin resistance and fetal abnormalities than other common insulin resistance indices built based on a healthy population and solely on serum glucose and insulin or C-peptide.<sup>21</sup> The results above confirm the difference in insulin resistance in GDM with the role of cortisol and serum lipids.

Our results outlined that maternal serum cortisol positively correlates with some fetal development indicators on ultrasound, such as BPD, HC, and AC. After adjusting for maternal insulin resistance and BMI, maternal cortisol was correlated with fetal AC, BPD, and HC. According to the study by Enteringer et al, serum cortisol level in GDM was not significantly correlated with % body fat in the fetus. However, it was related to lipid deposition and the rate of obesity in the neonate.<sup>8</sup> Maternal cortisol can cross the placenta, which may affect fetal development through dysregulation of placental CRH and directly into the fetus.<sup>29,30</sup> Therefore, in our study, fetal AC, HC, and BPD increased with the increase in maternal cortisol. In normal pregnancy, the correlation between maternal serum cortisol and fetal ultrasound indices is primarily negative or non-sense.<sup>9,31-34</sup> On the contrary, in GDM, our results show a positive correlation. In GDM, macrosomia, with a complex mechanism, is one of the complications for the fetus.<sup>35</sup> Therefore, in GDM, there could be a harmony between insulin resistance and cortisol in the development of a fetus, with an increase in fetal ultrasound indices. However, with the cross-sectional and descriptive design, we could not separate the role of cortisol and insulin resistance in fetal development and could not draw a conclusion.

Nevertheless, our study found no association between maternal cortisol levels and fetal EFW. The relationship between maternal cortisol and EFW is controversial. Whilst, some studies in normal pregnant women have shown that serum cortisol

levels are associated with fetal low birth weight,<sup>10,34</sup> some studies showed the reverse results. In the White population, some studies showed maternal cortisol level is a predicted factor for fetal birth weight.<sup>9,31,32</sup> On the contrary, a study by D'Anna-Hernandez et al also found the same trend as our study in pregnancy.<sup>33</sup> Moreover, a study by Alicia et al in low-income Hispanic pregnancies showed no correlation between maternal serum cortisol and infant birth weight.<sup>34</sup> A study by Fenling Fan et al on Chinese pregnant women showed that although maternal serum cortisol levels inversely correlated with EFW in the first and the second trimesters, no correlation between maternal cortisol and EFW was found in the third trimester.<sup>36</sup> Although EFW is an indirect estimate of actual fetal weight and is generally overestimated in 65% of the cases, EFW is strongly correlated with actual weight at 2 weeks before birth.<sup>37</sup> Therefore, race might contribute to the difference among studies on the correlation between maternal cortisol and fetal development. Besides, the method for collecting and interpreting serum cortisol could lead to the difference. In our study, we measured morning serum cortisol at 8 a.m., associated with lower beta-cell function and higher A1c and FPG in diabetes,<sup>38</sup> to reduce the effects of stressors due to blood sampling and duration of the tests related to cortisol measurement.

This study has some limitations. First, the study was cross-sectional and descriptive at a one-time point that did not consider the postnatal change. However, abnormalities in the fetus are strongly associated with the child's later development. Second, the study sample size was small. Third, we did not employ a control group of healthy pregnant women; therefore, we could not assess whether cortisol levels increased or decreased compared to normal pregnancy. Finally, we did not take the indicators for depression and anxiety in GDM into account. Therefore, we could not separate the effects of stress on maternal cortisol.

## Conclusion

Serum cortisol levels in GDM correlated with FPG, triglycerides, and insulin resistance. Besides, serum cortisol levels in GDM positively correlated with fetal development.

## Abbreviations

GDM, Gestational Diabetes mellitus; FPG, Fasting plasma glucose; PPG, postprandial glucose; OGTT, oral glucose tolerance test; BPD, Biparietal diameter; HC, Head circumference; AC, Abdominal circumference; FL, Femur length; AFI, Amniotic fluid index; HR, fetal Heart rate; EFW, Estimated fetal weight; CRP, high-sensitivity C-reactive protein.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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