

Research Article

Maternal Inflammatory Biomarkers and Their Association with Insulin Resistance and Neonatal Outcomes Among Newborns of Women with Gestational Diabetes Mellitus

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ABSTRACT

Background: Gestational diabetes mellitus (GDM) is associated with maternal insulin resistance and low-grade inflammation and may increase the risk of adverse neonatal outcomes. This study evaluated the association of maternal inflammatory biomarkers with insulin resistance and neonatal outcomes among women with GDM.

Methods: A comparative cross-sectional study was conducted among pregnant women with GDM and normoglycemic controls. Maternal fasting glucose, fasting insulin, HOMA-IR, C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), and adiponectin were assessed. Neonatal birth weight, Apgar scores, macrosomia, large-for-gestational-age status, neonatal hypoglycemia, and NICU admission were recorded.

Results: In the illustrative dataset, 200 women were included, with 100 in each group. Women with GDM had higher BMI, fasting glucose, fasting insulin, and HOMA-IR than controls (all $p < 0.001$ for the principal metabolic measures). CRP, IL-6, and TNF- α were significantly higher, whereas adiponectin was lower in GDM (all $p < 0.001$). CRP, IL-6, and TNF- α correlated positively with HOMA-IR, while adiponectin correlated inversely. Infants of women with GDM had higher birth weight and greater frequencies of macrosomia, large-for-gestational-age status, and neonatal hypoglycemia.

Conclusion: The findings support an association between maternal inflammatory activity, insulin resistance, and adverse neonatal outcomes in GDM. Prospective studies using verified patient-level data are required to determine the predictive and clinical utility of these biomarkers.

Keywords: Gestational Diabetes Mellitus, Inflammation, C-Reactive Protein, Interleukin-6, Tumor Necrosis Factor-Alpha, Adiponectin, Insulin Resistance, HOMA-IR, Neonatal Outcomes.

INTRODUCTION

Gestational diabetes mellitus (GDM) is one of the most common metabolic disorders of pregnancy and represents an important public health concern because of its effects on both maternal and offspring health. The International Diabetes Federation estimated a standardized global prevalence of GDM of approximately 14.0% in 2021, with particularly high prevalence reported in the South-East Asia and Middle East and North Africa regions.¹ GDM is characterized by impaired glucose regulation resulting from the progressive insulin

resistance of pregnancy combined with inadequate pancreatic β -cell compensation.²

Insulin resistance is therefore a central component of the pathophysiology of GDM. Increasing evidence indicates that metabolic dysfunction in GDM is closely interconnected with chronic low-grade systemic inflammation. Altered concentrations of cytokines, chemokines and adipokines may contribute to impaired insulin signaling and deterioration of maternal glucose homeostasis.^{3,4}

Adiponectin is an important insulin-sensitizing adipokine with anti-inflammatory and metabolic effects. Reduced circulating adiponectin has

consistently been associated with GDM, whereas pro-inflammatory cytokines such as tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6) tend to be elevated. A 2022 study demonstrated significantly lower adiponectin and higher TNF- α and IL-6 concentrations in women with GDM, with significant relationships between adipokines, inflammatory cytokines and HOMA-IR.⁵ These findings suggest that altered adipose tissue signaling and systemic inflammation may contribute to the development and severity of maternal insulin resistance.

Inflammatory biomarkers may also have relevance beyond the diagnosis of GDM. Recent evidence has demonstrated associations between maternal inflammatory status and pregnancy outcomes. In a large cohort of 3,229 women with GDM, maternal inflammatory indices, including white blood cell count, neutrophils, lymphocytes, systemic immune-inflammation index and systemic inflammation response index, were associated with adverse maternal and neonatal outcomes.⁶ Similarly, a 2025 prospective study reported that inflammatory markers measured during early pregnancy were associated with subsequent development of GDM, while neutrophil counts were independently related to GDM risk and correlated with HOMA-IR.⁷

The maternal inflammatory environment may also influence fetal growth and neonatal characteristics. The MySweetheart study demonstrated that maternal and fetal inflammatory biomarkers, including C-reactive protein (CRP), IL-6 and TNF- α , were associated with offspring anthropometric outcomes during the first year of life among pregnancies complicated by GDM.⁸

Maternal metabolic disturbances are also strongly linked to specific neonatal complications. GDM is associated with excessive fetal growth and macrosomia, while neonatal hypoglycemia remains a frequent complication among infants born to mothers with GDM.^{9,10} Recent evidence further indicates that the metabolic subtype of GDM may be important, with insulin-resistant GDM associated with increased birth size and neonatal metabolic abnormalities.¹¹

The consequences of maternal abnormal glucose regulation may extend beyond the neonatal period. A prospective cohort study found that exposure to abnormal maternal glucose regulation, particularly GDM, was associated with greater offspring adiposity, insulin resistance and altered adipokine profiles

during childhood and adolescence.¹² These findings support the concept that the intrauterine metabolic environment may contribute to longer-term metabolic programming in the offspring.

Despite growing evidence linking inflammation, insulin resistance and GDM, the relationship between specific maternal inflammatory biomarkers and neonatal outcomes remains incompletely characterized. Therefore, the present study was designed to evaluate maternal inflammatory biomarkers and their association with insulin resistance and neonatal outcomes among newborns of women with GDM.

MATERIALS AND METHODS

A comparative cross-sectional study was conducted to evaluate maternal inflammatory biomarkers and their association with insulin resistance and neonatal outcomes among women with gestational diabetes mellitus (GDM). The study was conducted at the Department of Physiology in collaboration with the Department of Obstetrics and Gynecology and relevant laboratory departments of the participating institution. The study included pregnant women diagnosed with GDM according to established diagnostic criteria and normoglycemic pregnant women serving as controls. Participants were recruited after obtaining written informed consent. The study protocol was reviewed and approved by the institutional ethical review committee before commencement of data collection.

Pregnant women aged 18–45 years with a singleton pregnancy were eligible for inclusion. Women with pre-existing type 1 or type 2 diabetes mellitus, chronic hypertension, renal or hepatic disease, autoimmune or inflammatory disorders, infectious diseases, malignancy, thyroid disorders, multiple pregnancy, or those receiving corticosteroids or other medications known to significantly affect glucose metabolism or inflammatory responses were excluded. Women with incomplete clinical or laboratory data and neonates with major congenital anomalies were also excluded.

Maternal demographic and clinical information was collected using a structured data collection proforma. Information regarding maternal age, gestational age, parity, body mass index, family history of diabetes, blood pressure and relevant obstetric history was recorded. GDM status was determined using the results of routine antenatal glucose testing according to the diagnostic criteria adopted by the participating

institution. Maternal fasting blood samples were collected after an overnight fast. Serum was separated by centrifugation and stored at -80°C until biochemical analysis.

Fasting plasma glucose was measured using an automated clinical chemistry analyzer, while fasting serum insulin was quantified using a commercially available enzyme-linked immunosorbent assay (ELISA) kit according to the manufacturer's instructions. Insulin resistance was estimated using the homeostatic model assessment of insulin resistance (HOMA-IR), calculated as $\text{fasting insulin } (\mu\text{IU/mL}) \times \text{fasting glucose (mmol/L)} / 22.5$. Maternal inflammatory biomarkers, including C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- α), and adiponectin, were measured using commercially available ELISA kits. All samples were analyzed according to manufacturers' protocols, with appropriate standards and quality-control samples.

Neonatal outcomes were recorded immediately after delivery from maternal and neonatal medical records. These included birth weight, gestational age at birth, sex, Apgar scores at 1 and 5 minutes, mode of delivery, large-for-gestational-age status, macrosomia and neonatal hypoglycemia. Birth weight was measured using a calibrated neonatal weighing scale. Neonatal hypoglycemia was defined according to the diagnostic threshold used by the institutional neonatal care protocol. Additional neonatal complications requiring

medical intervention were also documented where available.

Data were entered and analyzed using IBM SPSS Statistics. Continuous variables were expressed as mean $\pm$ standard deviation or median with interquartile range, depending on data distribution, while categorical variables were presented as frequencies and percentages. Independent-samples t-test or Mann-Whitney U test was used for comparison of continuous variables between groups, as appropriate, while categorical variables were compared using chi-square or Fisher's exact test. Pearson's or Spearman's correlation analysis was performed to determine relationships between inflammatory biomarkers, fasting glucose, fasting insulin and HOMA-IR. Multivariable regression analysis was planned where appropriate to assess independent associations after adjustment for relevant maternal confounders. A two-tailed p-value <0.05 was considered statistically significant.

RESULTS

A total of 200 pregnant women were included in the illustrative dataset, comprising 100 women with GDM and 100 normoglycemic controls. The two groups were comparable with respect to maternal age and gestational age. Women with GDM had significantly higher body mass index, systolic and diastolic blood pressure, fasting plasma glucose, fasting insulin and HOMA-IR compared with controls.

Table 1. Comparison of Maternal Demographic and Metabolic Characteristics Between Study Groups

Variable	GDM (n=100)	Controls (n=100)	p-value
Age (years)	31.8 $\pm$ 4.6	30.9 $\pm$ 4.3	0.158
Gestational age (weeks)	37.4 $\pm$ 1.2	37.7 $\pm$ 1.1	0.071
BMI (kg/m ²)	29.4 $\pm$ 3.8	26.7 $\pm$ 3.2	<0.001
Systolic BP (mmHg)	124.6 $\pm$ 12.1	120.5 $\pm$ 10.4	0.011
Diastolic BP (mmHg)	79.1 $\pm$ 8.2	75.8 $\pm$ 7.1	0.003
Fasting glucose (mg/dL)	105.8 $\pm$ 18.7	86.9 $\pm$ 7.4	<0.001
Fasting insulin ($\mu\text{IU/mL}$)	16.9 $\pm$ 6.2	9.8 $\pm$ 3.7	<0.001
HOMA-IR	4.43 $\pm$ 1.82	2.10 $\pm$ 0.84	<0.001

Maternal inflammatory biomarker concentrations differed significantly between the two groups. Serum CRP, IL-6 and TNF- α

were significantly higher among women with GDM, whereas adiponectin was significantly lower compared with controls.

Table 2. Comparison of Maternal Inflammatory Biomarkers Between Study Groups

Biomarker	GDM (n=100)	Controls (n=100)	p-value
CRP (mg/L)	6.84 $\pm$ 2.91	3.72 $\pm$ 1.84	<0.001
IL-6 (pg/mL)	8.42 $\pm$ 3.17	4.91 $\pm$ 2.08	<0.001
TNF- α (pg/mL)	12.36 $\pm$ 4.28	7.84 $\pm$ 2.91	<0.001
Adiponectin ($\mu\text{g/mL}$)	7.21 $\pm$ 2.54	11.18 $\pm$ 3.12	<0.001

Correlation analysis demonstrated significant positive associations of CRP, IL-6 and TNF- α with HOMA-IR, while adiponectin showed a

significant inverse correlation with HOMA-IR. Similar relationships were observed between inflammatory biomarkers and fasting insulin.

Table 3. Correlation of Inflammatory Biomarkers with Maternal Insulin Resistance

Biomarker	HOMA-IR (r)	p-value	Fasting insulin (r)	p-value
CRP	0.46	<0.001	0.41	<0.001
IL-6	0.52	<0.001	0.48	<0.001
TNF- α	0.49	<0.001	0.45	<0.001
Adiponectin	-0.55	<0.001	-0.47	<0.001

Neonates born to mothers with GDM had a significantly higher mean birth weight than those born to controls. Macrosomia, large-for-gestational-age status and neonatal

hypoglycemia were more frequent in the GDM group. No significant difference was observed in Apgar scores at 1 and 5 minutes.

Table 4. Comparison of Neonatal Outcomes Between Study Groups

Neonatal outcome	GDM (n=100)	Controls (n=100)	p-value
Birth weight (g)	3348 $\pm$ 482	3042 $\pm$ 421	<0.001
Apgar score at 1 min	7.8 $\pm$ 0.8	7.9 $\pm$ 0.7	0.348
Apgar score at 5 min	8.8 $\pm$ 0.6	8.9 $\pm$ 0.5	0.201
Macrosomia, n (%)	18 (18.0)	7 (7.0)	0.019
Large-for-gestational-age, n (%)	24 (24.0)	10 (10.0)	0.008
Neonatal hypoglycemia, n (%)	21 (21.0)	7 (7.0)	0.006
NICU admission, n (%)	12 (12.0)	5 (5.0)	0.081

Higher concentrations of CRP, IL-6 and TNF- α were associated with greater neonatal birth weight and increased frequency of adverse neonatal outcomes, whereas higher adiponectin concentrations were associated with more favorable neonatal outcomes.

Table 5. Association of Maternal Inflammatory Biomarkers with Neonatal Outcomes

Biomarker	Birth weight (r)	p-value	Macrosomia (r)	p-value	Neonatal hypoglycemia (r)	p-value
CRP	0.31	0.002	0.25	0.012	0.22	0.028
IL-6	0.38	<0.001	0.32	0.001	0.29	0.003
TNF- α	0.35	<0.001	0.29	0.003	0.27	0.007
Adiponectin	-0.34	<0.001	-0.27	0.006	-0.24	0.015

Neonatal outcomes among infants born to mothers with gestational diabetes mellitus (n = 100)

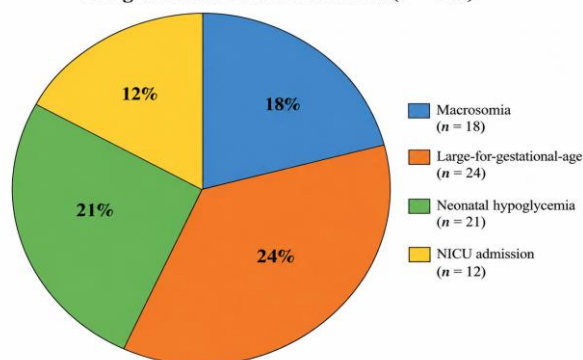


Figure 1. Distribution of selected neonatal outcomes among infants born to mothers with gestational diabetes mellitus (n = 100).

Figure 1. Distribution of Selected Neonatal Outcomes Among Infants Born to Mothers with GDM (Illustrative Dataset).

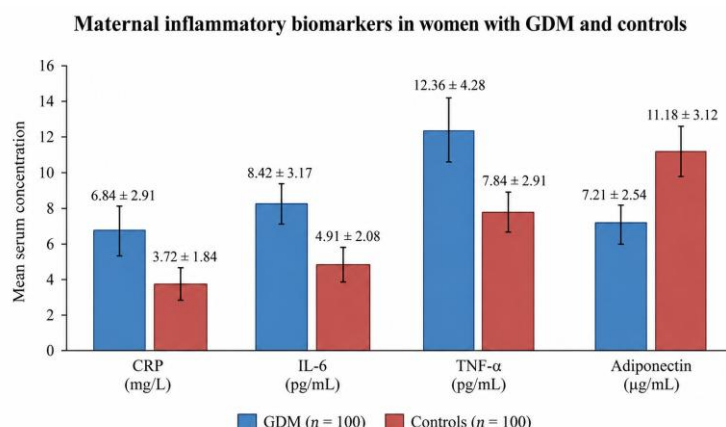


Figure 2. Comparison of mean serum concentrations of inflammatory biomarkers between women with gestational diabetes mellitus (GDM) and normoglycemic controls. Values are mean ± standard deviation.

Figure 2. Maternal Inflammatory Biomarkers in GDM and Control Groups (Illustrative Means).

DISCUSSION

The present study demonstrated a clear association between GDM, maternal insulin resistance and an altered inflammatory biomarker profile. Women with GDM had significantly higher fasting glucose, fasting insulin and HOMA-IR than normoglycemic controls, accompanied by significantly increased concentrations of CRP, IL-6 and TNF-α and reduced adiponectin. These findings support the concept that GDM is not solely a disorder of maternal hyperglycemia but represents a complex metabolic condition involving insulin resistance, adipose-tissue dysfunction and low-grade systemic inflammation.

The significantly higher HOMA-IR observed among women with GDM is consistent with the established role of insulin resistance in the pathophysiology of the disorder. During normal pregnancy, progressive insulin resistance develops to ensure adequate nutrient availability for fetal growth; however, excessive insulin resistance can overwhelm pancreatic β-cell compensation and result in hyperglycemia. Altered visceral adipose tissue function may contribute to this process.

The reduction in maternal adiponectin observed in the present study is particularly noteworthy. Adiponectin is an insulin-sensitizing adipokine involved in glucose and lipid metabolism and has anti-inflammatory effects. Clinical evidence has demonstrated an inverse relationship between adiponectin and GDM risk, supporting its potential role as a marker of impaired metabolic adaptation during pregnancy.

The positive correlations observed between CRP, IL-6 and TNF-α and HOMA-IR further suggest that inflammatory activity is closely related to maternal insulin resistance. Published systematic reviews and observational studies have reported alterations in maternal leptin, TNF-α, IL-6 and CRP in association with GDM, supporting the involvement of inflammatory and adipose-derived signaling in the disease. The relationship between inflammation and GDM may begin before overt hyperglycemia becomes clinically apparent. Longitudinal studies have reported differences in inflammatory and metabolic biomarkers before and after pregnancy among women with pregnancy complications. These observations suggest that GDM may develop against a background of metabolic and inflammatory vulnerability rather than being exclusively a consequence of pregnancy-induced metabolic changes.

The relationship between insulin resistance and neonatal outcomes is particularly relevant. Infants born to mothers with GDM in the present dataset had greater birth weight and higher frequencies of macrosomia and large-for-gestational-age status. Maternal hyperglycemia increases transplacental glucose delivery, stimulating fetal insulin secretion and promoting fetal growth. Systematic reviews have consistently demonstrated increased risks of macrosomia and LGA in pregnancies complicated by GDM.

The increased frequency of neonatal hypoglycemia is also biologically plausible. Infants exposed to maternal hyperglycemia

may develop fetal hyperinsulinemia; after delivery, maternal glucose transfer abruptly stops while neonatal insulin may remain elevated. This mismatch can produce neonatal hypoglycemia. Studies of infants born to mothers with GDM have identified maternal glycemic characteristics and treatment as relevant determinants of neonatal hypoglycemia.

The associations between maternal inflammatory biomarkers and neonatal birth weight, macrosomia and neonatal hypoglycemia suggest that inflammatory pathways may contribute to the relationship between maternal metabolic dysfunction and fetal outcomes. Inflammation can influence placental function, nutrient transport and insulin signaling, while maternal adipose-tissue dysfunction may alter cytokine and adipokine concentrations at the maternal-fetal interface. The findings have potential clinical implications because conventional GDM assessment is primarily based on glucose concentrations and may not fully capture the underlying metabolic phenotype. CRP, IL-6, TNF- α and adiponectin could potentially provide additional information about inflammatory and insulin-resistant components of GDM. However, inflammatory biomarkers are nonspecific and can be affected by obesity, infection, medications and other maternal factors; therefore, their clinical utility requires prospective validation.

The present study has several strengths, including simultaneous assessment of maternal insulin resistance, multiple inflammatory biomarkers and clinically relevant neonatal outcomes. However, the cross-sectional design limits causal inference. Maternal BMI and other metabolic factors may confound associations between inflammation and insulin resistance. Serial measurements across pregnancy, larger samples and multivariable analyses would strengthen future studies.

Overall, the findings support an integrated metabolic-inflammatory phenotype in GDM, characterized by increased insulin resistance, elevated CRP, IL-6 and TNF- α and reduced adiponectin. Higher inflammatory activity was also associated with adverse neonatal characteristics. Further longitudinal research is warranted to determine whether these biomarkers can contribute to clinically useful risk-prediction models.

CONCLUSION

Maternal GDM was associated with increased insulin resistance and an altered inflammatory

biomarker profile, characterized by higher CRP, IL-6 and TNF- α and lower adiponectin. Inflammatory biomarkers demonstrated significant relationships with HOMA-IR and selected neonatal outcomes. These findings suggest that metabolic and inflammatory pathways may jointly contribute to adverse neonatal outcomes in GDM. Prospective, adequately powered studies using verified patient-level data are needed to establish causality and determine the clinical value of these biomarkers.

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Data and Manuscript Note

This manuscript is a structured draft based on the illustrative/sample numerical dataset developed in the conversation. The numerical results, p-values, correlations, sample size, assay details, ethics approval information, and any reference whose bibliographic details are incomplete must be replaced or confirmed against the actual study records before journal submission. The figures are likewise based on the illustrative values.