Original Article

First-Trimester Interleukin-6 Outperforms C-Reactive Protein as an Independent Pathophysiological Driver of Gestational Diabetes Mellitus

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Abstract

Background: Gestational diabetes mellitus (GDM) is a major pregnancy complication associated with subclinical inflammation. The relative predictive value of first-trimester interleukin-6 (IL-6) compared with C-reactive protein (CRP) remains unclear. This study evaluated their association with subsequent risk of GDM.

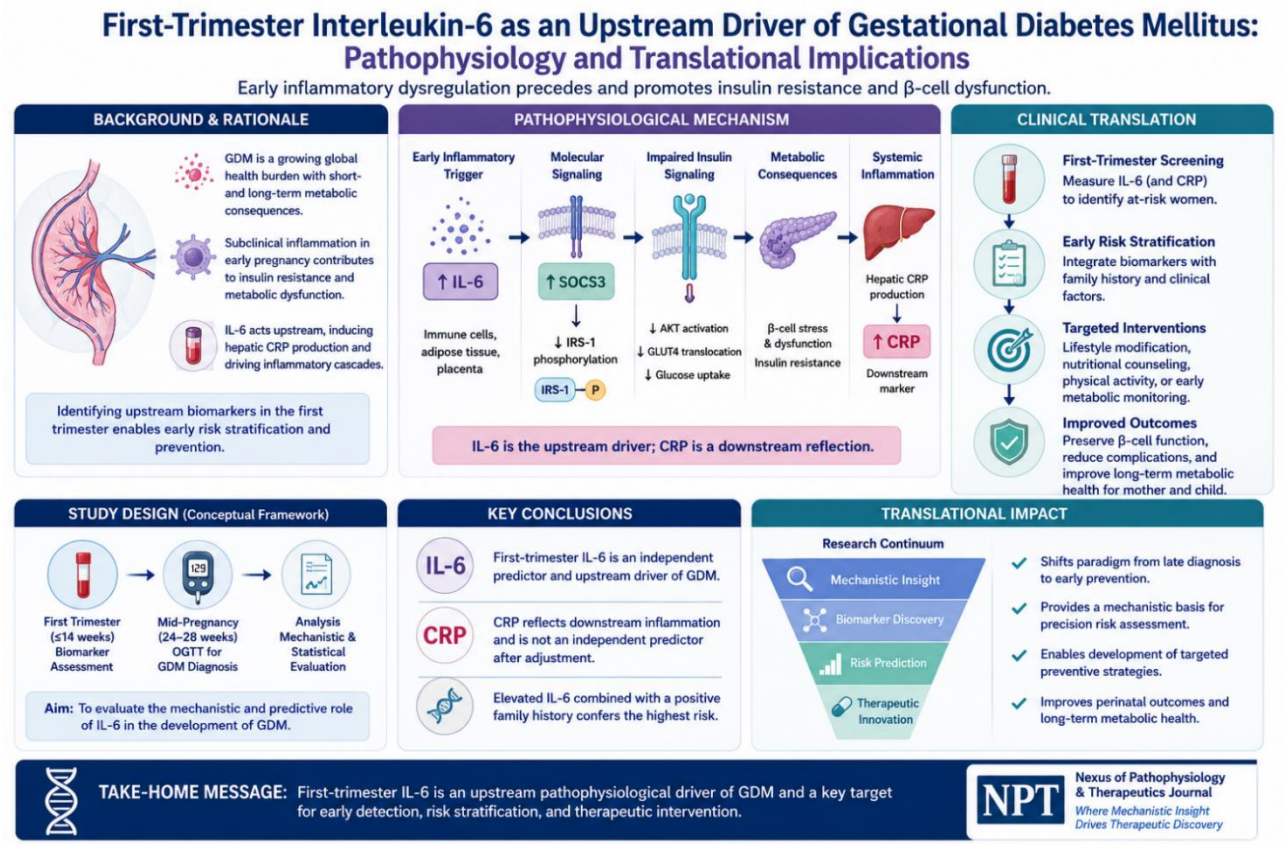
Methods: This prospective study included 300 pregnant women (<14 weeks of gestation) in Khorramabad, Iran. Serum IL-6 and CRP were measured at baseline using automated assays. Participants were followed until 24–28 weeks of gestation, when GDM was diagnosed using a standard 75-g oral glucose tolerance test. Multivariable logistic regression was performed adjusting for maternal age and body mass index (BMI), along with other clinical covariates.

Results: Among 300 participants, 129 (43.0%) developed GDM. These women had significantly higher first-trimester CRP (10.5 vs. 6.1 mg/L, $p = 0.004$) and IL-6 (3.8 vs. 2.9 pg/mL, $p = 0.010$) compared with controls. In multivariable analysis, IL-6 remained significantly associated with GDM (OR = 1.10, $p < 0.001$), whereas CRP, maternal age, and BMI were not statistically significant after adjustment. A positive family history of diabetes was strongly associated with GDM in univariate analysis (79.4% vs. 25.6%, $p < 0.001$).

Conclusion: First-trimester maternal serum IL-6 is independently associated with subsequent development of GDM, whereas CRP and conventional clinical risk factors were not significant after adjustment. These findings suggest that early inflammatory activation, particularly IL-6–related pathways, may contribute to gestational glucose dysregulation, especially in women with underlying genetic susceptibility such as a family history of diabetes.

Mechanistic and Translational Relevance: IL-6 may promote insulin resistance through impaired insulin receptor substrate signaling and downstream PI3K/Akt pathway activity. These findings indicate that inflammatory changes precede clinical GDM diagnosis, typically made in mid-pregnancy, and support early pregnancy risk stratification to enable preventive interventions.

Keywords: Gestational diabetes mellitus, Interleukin-6, C-reactive protein, First-trimester biomarker, Pathophysiology.



Graphical Abstract. First-Trimester Interleukin-6 as an Upstream Driver of Gestational Diabetes Mellitus. The figure illustrates the mechanistic interplay between early gestational inflammation and the development of gestational diabetes mellitus (GDM). Elevated first-trimester interleukin-6 (IL-6), derived from immune activation, adipose tissue, and placental stress, promotes systemic insulin resistance through SOCS3-mediated disruption of insulin receptor substrate-1 (IRS-1) signaling and impaired AKT-dependent glucose uptake. Concurrent hepatic stimulation induces C-reactive protein (CRP) production as a downstream inflammatory response. These interconnected inflammatory and metabolic disturbances contribute to beta-cell dysfunction and progressive glucose intolerance before overt hyperglycemia becomes clinically evident. Collectively, the findings position IL-6 as a mechanistically relevant upstream biomarker with translational potential for early risk stratification, preventive intervention, and precision metabolic monitoring during pregnancy.

Introduction

Gestational diabetes mellitus (GDM) is the most common medical complication of pregnancy (1). It is characterized by varying degrees of glucose intolerance first recognized during pregnancy (2). Depending on the population and diagnostic criteria, the prevalence of GDM varies considerably, with a global prevalence estimated at approximately 14%, affecting nearly one in seven pregnancies worldwide (3). GDM is associated with adverse maternal and neonatal outcomes, including preeclampsia, polyhydramnios, large-for-gestational-age (LGA) neonates/macrosomia, neonatal hypoglycemia, jaundice (hyperbilirubinemia), and respiratory distress syndrome (4).

Beyond pregnancy, GDM elevates the child's risk of metabolic syndrome, glucose intolerance, and obesity (5). It may also increase the mother's long-term risk of type 2 diabetes and cardiovascular disease (6). Emerging evidence suggests that metabolically induced low-grade inflammation contributes to immune dysregulation, insulin resistance, and the pathogenesis of GDM (7). Proinflammatory cytokines like interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), secreted

by immune cells, adipose tissue, and the developing placenta, can directly impair insulin signaling (8). Specifically, these mediators disrupt insulin receptor substrate (IRS) phosphorylation (9). This disruption inhibits the intracellular cascade required for glucose uptake, driving insulin resistance and triggering acute-phase inflammatory responses (10). Additionally, IL-6 stimulates hepatic synthesis of acute-phase proteins, including C-reactive protein (CRP), a sensitive marker of systemic inflammation (11). Since elevated CRP and IL-6 levels are well-documented in obesity and type 2 diabetes, they likely play a similar mechanistic role in gestational metabolic dysregulation (12). Several studies have investigated how maternal IL-6 and CRP levels associate with GDM. While some report significant correlations, suggesting early inflammatory changes can predict GD, others show no clear relationship (13). Overall, the evidence remains limited and inconsistent, especially regarding the first trimester. This gap is critical because GDM is conventionally diagnosed late in pregnancy, typically between the 24th and 28th weeks using an oral glucose tolerance test (OGTT) (14). Identifying reliable biomarkers offers a vital window for early risk stratification, allowing timely lifestyle or therapeutic interventions before clinical symptoms appear (15). Therefore, this study evaluated the association between first-trimester maternal serum IL-6 and CRP levels and the subsequent development of GDM among women attending Shahid Rahimi Hospital in Khorramabad. These insights could help clarify early pathogenic processes and highlight potential targets for preventive strategies.

Methods

Study Design and Institutional Approval

This prospective observational study was conducted in 2023 at Shahid Rahimi Hospital in Khorramabad, Iran. The institutional protocol received official ethical approval from the Ethics Committee of Lorestan University of Medical Sciences (NO: IR.LUMS.REC.1402.164). All participating women provided written informed consent prior to enrollment, following a comprehensive explanation of the study objectives. The investigation adhered strictly to the ethical tenets of the Declaration of Helsinki, ensuring absolute participant confidentiality and voluntary cooperation.

Participant Selection and Criteria

Pregnant women presenting for routine prenatal care were screened for eligibility. The inclusion criteria required a gestational age below 14 weeks, Iranian nationality, residency in Khorramabad, a singleton pregnancy, and adherence to a standard dietary regimen. Conversely, individuals with pre-existing type 1 or type 2 diabetes, chronic systemic illnesses, or an active COVID-19 infection at baseline were excluded. Additionally, participants who chose to withdraw from the study at any stage, experienced pregnancy termination before 14 weeks, or contracted COVID-19 during the follow-up period were excluded from the final analysis.

Data Collection and Laboratory Assays

A total of 300 eligible women were enrolled using consecutive sampling, with recruitment proceeding sequentially until the target sample size was achieved. Baseline demographic and clinical characteristics, including maternal age, family history of diabetes, education level, monthly income, employment status, and body mass index (BMI), were systematically recorded using a standardized, researcher-designed checklist. At enrollment during the first trimester, maternal venous blood samples were collected from all participants. Serum IL-6 and CRP concentrations were quantified using a Cobas Integra autoanalyzer (Roche, Germany) with CFAS protein calibration. Serum IL-6 levels were expressed in picograms per

milliliter (pg/mL), while CRP concentrations were reported in milligrams per liter (mg/L). All laboratory assays were performed in a single, centralized facility to ensure diagnostic consistency and technical quality.

Gestational Diabetes Assessment

All enrolled participants were prospectively followed until 24 to 28 weeks of gestation, at which point they underwent a one-step 75-g oral glucose tolerance test (OGTT) for GDM screening (16). Following standard international thresholds, GDM was diagnosed if at least one of the following glycemic parameters was met: a fasting plasma glucose level ≥ 92 mg/dL, a 1-hour post-load glucose level ≥ 180 mg/dL, or a 2-hour post-load glucose level ≥ 153 mg/dL (17).

Statistical Analysis

Statistical analyses were conducted using SPSS software, version 22.0, with the significance level set at $p < 0.05$. Data normality was assessed using the Kolmogorov–Smirnov test. Quantitative variables were expressed as mean ± standard deviation for normally distributed data, while non-normally distributed variables (IL-6 and CRP) were reported as median (interquartile range). Comparisons between groups were performed using the Mann–Whitney U test for skewed variables. Spearman rank correlation was used to evaluate the relationship between IL-6 and CRP. A multivariable logistic regression model with backward elimination was applied to identify independent predictors of GDM, adjusting for maternal age and BMI. Sample size was determined based on the number of eligible pregnant women attending Shahid Rahimi Hospital during the study period. A total of 300 participants were consecutively enrolled to ensure adequate statistical power for multivariable logistic regression analysis and reliable estimation of associations between inflammatory biomarkers and GDM.

Results

1. Age of Participants

Table 1 summarizes the age distribution of the 300 pregnant women enrolled in this study. The largest proportion of participants fell within the 25–30 age range (25.3%), followed closely by those aged 20–25 years (24.0%). Overall, more than half of the women (59.3%) were under 30 years old, whereas those over 40 years accounted for only 8.0% of the sample. This baseline distribution aligns with the typical reproductive age profile of the region. Because advanced maternal age is an established risk factor for metabolic complications, these age data were critical for control purposes and were utilized to adjust for potential confounding in subsequent multivariable statistical models.

2. Family History of Diabetes

A positive family history of diabetes was reported by 97 participants (32.3%), while 203 women (67.7%) had no familial history of the disease (Table 2). This distribution indicates that nearly one-third of the study population possessed a potential genetic or shared environmental predisposition to metabolic dysregulation. Because family history of diabetes is an established risk factor for gestational diabetes, it was recorded and evaluated as an important baseline clinical characteristic during the statistical analysis.

3. Education Level of Participants

Participant educational attainment ranged from illiteracy to doctoral degrees (Table 3). The largest proportions of women held either a high school diploma (29.0%) or a bachelor's degree (28.7%), while only 0.7% of the sample had earned a doctoral degree or higher. Overall, the majority of the study

population possessed at least a moderate level of education. This baseline socioeconomic variable was collected to control for potential variations in health literacy and to evaluate its independent or interactive effects on GDM risk in subsequent multivariable analyses.

Age Range (years)	Frequency (n)	Percentage (%)	Cumulative Percentage (%)
<20	30	10.0	10.0
20–25	72	24.0	34.0
25–30	76	25.3	59.3
30–35	54	18.0	77.3
35–40	44	14.7	92.0
>40	24	8.0	100.0
Total	**300**	**100.0**	–

Table 1. Frequency distribution of participants by age. The table demonstrates that the majority of participants were under 30 years, consistent with regional reproductive age patterns. This distribution provides context for analyzing gestational diabetes risk and highlights the potential need for age-adjusted analyses in subsequent models.

Family History	Frequency (n)	Percentage (%)
No	203	67.7
Yes	97	32.3
Total	**300**	**100.0**

Table 2. Frequency distribution of participants by family history of diabetes. Nearly one in three participants reported a family history of diabetes. This finding underscores the relevance of genetic predisposition in gestational diabetes risk and supports its inclusion in subsequent analytical models.

4. Income Level of Participants

The income distribution of the participants is presented in Table 4. Over half of the women (51.3%) were within the middle-income bracket, while the lower- and higher-income groups showed representation at 24.0% and 24.7%, respectively.

This baseline socioeconomic characteristic was recorded to characterize the study population and was evaluated as a potential confounding factor in subsequent multivariable regression models assessing GDM risk.

Education Level	Frequency (n)	Percentage (%)	Cumulative Percentage (%)
Illiterate	14	4.7	4.7
Below Diploma	58	19.3	24.0
Diploma	87	29.0	53.0
Associate Degree	27	9.0	62.0
Bachelor's Degree	86	28.7	90.7
Master's Degree	26	8.6	99.3
Doctorate or Higher	2	0.7	100.0
Total	**300**	**100.0**	–

Table 3. Frequency distribution of participants by education level. This pattern reflects a generally moderate to high educational background, which may influence health literacy, pregnancy-related knowledge, and adherence to lifestyle recommendations. Considering education in subsequent analyses helps contextualize potential behavioral and metabolic risk factors for gestational diabetes.

Income Level	Frequency (n)	Percentage (%)
Low (Class 1)	72	24.0
Middle (Class 2)	154	51.3
High (Class 3)	74	24.7
Total	**300**	**100.0**

Table 4. Frequency distribution of participants by income level. The data show that the majority of participants belonged to the middle-income group. This socioeconomic profile helps contextualize risk factors and may inform targeted interventions for gestational diabetes prevention and management in populations with varying economic backgrounds.

5. Employment Status of Participants

Regarding employment status, the majority of the participants (69.3%) were unemployed, while 30.7% were employed (Table 5). This baseline socioeconomic characteristic was recorded as a potential proxy for variations in daily physical activity and maternal stress exposure. To ensure a rigorous evaluation of the inflammatory biomarkers, employment status was included as a covariate in the final multivariable regression models to adjust for its potential confounding effects on GDM risk.

Employment Status	Frequency	Percentage
Unemployed	208	69.3
Employed	92	30.7
Total	300	100

Table 5. Frequency distribution of participants by employment status. Most participants were unemployed, reflecting a high proportion of non-working mothers in the study population. This socioeconomic context provides insight into lifestyle patterns, physical activity, and access to healthcare, all of which may influence gestational diabetes risk.

6. Gestational Diabetes Status of Participants

Among the 300 participants, 129 women (43.0%) were diagnosed with GDM based on the oral glucose tolerance test (OGTT) criteria, while 171 (57.0%) remained normoglycemic throughout pregnancy (Table 6). This clinical outcome served as the primary dependent variable for all subsequent comparative assessments and predictive statistical modeling.

Gestational Diabetes Status	Frequency	Percentage
No GDM	171	57.0
GDM	129	43.0
Total	300	100

Table 6. Frequency distribution of participants by gestational diabetes status. A total of 43.0% of participants were diagnosed with GDM. This prevalence is higher than many published estimates and may reflect differences in population characteristics, metabolic risk profiles, and diagnostic criteria.

7. Descriptive Statistics for Quantitative Variables

Table 7 summarizes the baseline clinical and biochemical characteristics of the study population. Quantitative variables were expressed as mean ± standard deviation for normally distributed data and as median (interquartile range) for non-normally distributed variables (IL-6 and CRP). These baseline metrics delineate the metabolic and inflammatory profile of the cohort prior to stratification into GDM and normoglycemic groups.

8. Association Between Family History of Diabetes and Gestational Diabetes

A strong association was observed between a maternal family history of diabetes and the incidence of GDM (Table 8). Among women with a positive family history, 79.4% developed GDM. In contrast, only 25.6% of those without a familial history of the disease developed the condition. These data indicate a significantly higher distribution of GDM among participants with a genetic or shared environmental predisposition.

Variable	Measure
Interleukin-6 (pg/mL)	3.8 (2.4–5.6)
CRP (mg/L)	8.9 (5.1–12.7)
Fasting Blood Glucose (mg/dL)	105.96 ± 35.30
1-hour post-Glucose (mg/dL)	164.80 ± 18.60
2-hour post-Glucose (mg/dL)	133.70 ± 15.30
Body Mass Index (kg/m²)	28.20 ± 3.03

Table 7. Baseline distribution of quantitative clinical and biochemical parameters. IL-6 and CRP are presented as median (interquartile range), while other variables are expressed as mean ± standard deviation.

Family History of Diabetes	No GDM (n=171)	GDM (n=129)	p-value	Interpretation
Absent	151	52	<0.001	Significant association
Present	20	77		

Table 8. Family History of Diabetes and GDM. Women with a family history of diabetes exhibited a markedly higher likelihood of developing GDM, underscoring the importance of genetic and familial factors in identifying high-risk pregnancies early.

9. Association Between Income Level and Gestational Diabetes

No significant association was observed between maternal income level and the development of GDM ($p = 0.576$). The distribution of GDM cases was similar across low, middle, and high-income groups (Table 9).

10. Association Between Employment Status and Gestational Diabetes

No significant association was found between maternal employment status and GDM development ($p = 0.462$). The proportion of GDM cases was comparable between employed and unemployed participants (Table 10).

Income Level	No GDM (n = 171)	GDM (n = 129)	P-value	Interpretation
Level 1	45	27	0.576	No significant association
Level 2	84	70		
Level 3	42	32		
Total	**171**	**129**		

Table 9. Income Level and GDM. No significant association was found between income level and gestational diabetes. This indicates that, in this population, socioeconomic status alone may not strongly influence GDM risk.

Employment Status	No GDM (n=171)	GDM (n=129)	p-value	Interpretation
Unemployed	116	92	0.462	No significant association
Employed	55	37		

Table 10. Employment Status and GDM. No significant association was found between employment status and gestational diabetes. This indicates that occupational activity alone does not appear to meaningfully influence GDM risk in this population.

11. Comparison of CRP and IL-6 Levels Between GDM and Non-GDM Groups

Median serum concentrations of both CRP and IL-6 were significantly higher in participants diagnosed with GDM compared to those who remained normoglycemic (Table 11). This significant divergence demonstrates a heightened baseline inflammatory state during the first trimester in women who subsequently developed the condition. These elevated biomarker profiles reflect active subclinical systemic inflammation prior to the clinical manifestation of hyperglycemia.

Marker	GDM Median	Non-GDM Median	U Statistic	p-value	Interpretation
CRP (mg/L)	10.5	6.1	8784	0.004	Significant difference
IL-6 (pg/mL)	3.8	2.9	8990	0.01	Significant difference

Table 11. Median CRP and IL-6 Levels by GDM Status. Women with GDM exhibited significantly higher median CRP and IL-6 levels, indicating that systemic inflammation may contribute to the early development of gestational diabetes.

12. Correlation Between CRP and IL-6

A significant positive correlation was observed between maternal serum CRP and IL-6 levels (Table 12), indicating that higher IL-6 concentrations are associated with higher CRP levels during early pregnancy. This finding suggests a coordinated activation of systemic inflammatory pathways in the first trimester.

13. Logistic Regression Analysis for Predictors of GDM

A multivariable logistic regression analysis using a stepwise selection method was performed to identify independent predictors of GDM. Interleukin-6 (IL-6) remained the only significant independent predictor of GDM ($p < 0.001$), whereas CRP, maternal age, and BMI were not significantly associated with the outcome after adjustment (Table 13).

Variables	Spearman's rho	p-value
CRP vs IL-6	0.426	<0.001

Table 12. Spearman Correlation Between CRP and IL-6. A moderate positive correlation was found between CRP and IL-6 levels, suggesting that elevated systemic inflammation is reflected by higher IL-6 in early pregnancy. This finding supports the role of inflammatory mechanisms in the development of GDM.

Variable	Regression Coefficient (B)	Odds Ratio (Exp B)	p-value	Status in Model
Interleukin-6 (IL-6)	0.096	1.10	<0.001	Retained
Age (Years)	—	—	0.114	Not retained
CRP (mg/L)	—	—	0.767	Not retained
BMI (kg/m²)	—	—	0.761	Not retained

Table 13. Multivariable logistic regression analysis of predictors of GDM. In the final adjusted model, interleukin-6 (IL-6) was the only variable that remained significantly associated with the development of GDM, while CRP, maternal age, and BMI were not statistically significant predictors. The multivariable logistic regression model was built using a backward elimination approach, initially including maternal age, BMI, CRP, and IL-6 as candidate variables.

Discussion

Our findings suggest that higher first-trimester maternal IL-6 levels are associated with an increased risk of subsequent development of GDM. In contrast, CRP, maternal age, and BMI were not independently associated with GDM after adjustment in this cohort. These results support a potential role of inflammatory processes in the early pathophysiology of gestational glucose dysregulation; however, the observed associations should be interpreted within the context of an observational study design. The prevalence of GDM in our cohort was 43%, which is higher than many international and regional estimates. Several factors may explain this finding, including differences in population characteristics, the use of the one-step 75-g OGTT diagnostic approach, the relatively high prevalence of overweight participants, and the referral nature of the study center. Variations in diagnostic criteria, ethnic background, and baseline metabolic risk profiles across populations may also contribute to differences in reported GDM prevalence. Conversely, socioeconomic indicators such as income and employment status did not significantly influence disease development in this study population. This finding suggests that metabolic and biological pathways, rather than socioeconomic determinants, primarily drive GDM pathogenesis in these patients. Reflecting this biological etiology, biochemical assessments revealed significantly higher first-trimester CRP and IL-6 levels in women who developed GDM, pointing to active subclinical systemic inflammation.

Furthermore, the observed positive correlation between CRP and IL-6 supports a close mechanistic link between these inflammatory pathways, with IL-6 acting as an upstream regulator of CRP, reflecting interconnected systemic inflammatory activity in diabetes (18).

From a mechanistic perspective, IL-6 may contribute to insulin resistance through the induction of suppressor of cytokine signaling 3 (SOCS3), which interferes with insulin receptor signaling by inhibiting IRS-1 phosphorylation and downstream PI3K/Akt pathway activity in insulin-sensitive tissues (19). SOCS3 interferes with insulin signaling by inhibiting IRS-1 activity, which in turn disrupts downstream PI3K/Akt pathway signaling required for normal glucose uptake in metabolic tissues such as skeletal muscle and adipose tissue (20). IL-6, within a pro-inflammatory cytokine network, contributes to sustained activation of NF-κB and MAPK/JNK signalling, thereby promoting oxidative stress–associated signalling cascades and leading to impaired pancreatic β-cell survival and reduced insulin secretory capacity (21). Concurrently, CRP, an acute-phase protein primarily synthesized in hepatocytes in response to IL-6 stimulation, serves as a systemic biomarker of inflammation whose circulating levels correlate with disease severity (22). Elevated CRP may exacerbate endothelial dysfunction, further compromising microvascular insulin kinetics (23). These interconnected molecular pathways contribute to early-pregnancy low-grade inflammation–driven subclinical metabolic dysregulation preceding GDM (24). In our multivariable logistic regression analysis, IL-6 emerged as the sole independent predictor of GDM, whereas CRP, maternal age, and BMI lost statistical significance after adjustment. IL-6 shows a modestly stronger association with type 2 diabetes than CRP, consistent with a potential upstream role in inflammatory pathways, while CRP likely functions as a downstream biomarker of systemic inflammation (25). Because IL-6 lies upstream of hepatic CRP synthesis and represents a more proximal mediator of inflammatory signaling, adjusting for IL-6 may reduce confounding by upstream inflammatory activity and better delineate downstream systemic inflammatory markers such as CRP (26). This independent association highlights the potential utility of first-trimester IL-6 as an early biomarker of gestational diabetes mellitus, reflecting underlying tissue-level insulin resistance and metabolic dysregulation prior to the onset of overt clinical hyperglycemia (27). Nevertheless, these findings are best understood within a broader, multifactorial framework. The coexistence of elevated inflammatory processes and genetic predisposition, such as family history of diabetes, reflects a complex gene–environment interaction contributing to disease pathogenesis (28). In this framework, chronic low-grade systemic inflammation acts as an environmental stressor that, when compounded by baseline familial metabolic vulnerability, cumulatively drives the development of severe gestational insulin resistance (29). Notably, both elevated IL-6 levels and a positive family history of diabetes were associated with an increased risk of GDM, highlighting the potential contribution of both inflammatory and familial factors to disease development. This finding supports a multi-hit pathophysiological model where genetic susceptibility converges with active inflammatory cascades. Genetic predispositions may contribute to lower baseline beta-cell reserve or compensatory capacity, which increases susceptibility to metabolic stressors such as chronic hyperglycemia, oxidative stress, and ER stress, ultimately leading to beta-cell dysfunction and failure (30). While inflammatory pathways have been implicated in the pathophysiology of gestational diabetes mellitus, current evidence from early pregnancy biomarker studies remains limited and heterogeneous. The substantial variability observed across studies is likely attributable to differences in study populations, timing of sample collection during gestation, assay methodologies, diagnostic criteria for GDM, and analytical approaches (31). Identifying these molecular disturbances during early pregnancy may enable timely lifestyle interventions or early therapeutic

strategies aimed at preserving β-cell function and improving glycemic control, thereby optimizing metabolic outcomes for both the mother and the fetus (2).

Conclusion

In conclusion, this study demonstrates that elevated first-trimester maternal serum IL-6 is independently associated with the subsequent development of gestational diabetes mellitus (GDM), whereas CRP, maternal age, and BMI were not independent predictors in the adjusted model. These findings suggest that early inflammatory activation, particularly IL-6–mediated pathways, may play a central role in the pathogenesis of gestational glucose dysregulation, especially in women with underlying genetic susceptibility such as a family history of diabetes. Early pregnancy identification of such high-risk profiles may enable timely risk stratification and preventive interventions before the onset of clinical hyperglycemia.

Mechanistic and Translational Relevance

From a mechanistic perspective, elevated first-trimester interleukin-6 (IL-6) may contribute to insulin resistance through SOCS3-mediated inhibition of insulin receptor signaling, leading to impaired IRS-1 activation and downstream PI3K/Akt pathway disruption in insulin-sensitive tissues, including skeletal muscle and adipose tissue. From a translational perspective, these findings highlight those inflammatory alterations in early pregnancy precede the clinical diagnosis of gestational diabetes, which is typically established between 24 and 28 weeks of gestation. Therefore, early identification of women with elevated IL-6 levels may provide an opportunity for earlier risk stratification and the implementation of preventive strategies such as lifestyle modification and closer metabolic monitoring.

Conflict of Interest

The authors declare that they have no conflict of interest.

Author Contributions

All authors contributed to the conception and design of the study, literature search, data interpretation, drafting of the manuscript, and critical revision of the article. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Ethics Statement

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Data Availability Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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