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Hs-CRP and TNF-α Effects on Postnatal Umbilical Coiling: Impact Assessment of the Gestational Diabetes Mellitus

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Abstract

Background: No study has been conducted to specifically demonstrate the relationship between gestational diabetes mellitus (GDM) status, inflammatory factors, and postnatal umbilical coiling index (pUCI). Understanding this relationship could help select the best interventions to save the fetus. To evaluate the effects of maternal venous and umbilical cord blood levels of high sensitivity C-reactive protein (hs-CRP) and tumor necrosis factor-alpha (TNF-alpha) on pUCI in GDM and non-GDM groups.

Methods: This prospective observational study included 40 participants in each of the GDM and non-GDM groups, matched for maternal age, ethnicity, and parity. The GDM diagnosis was confirmed by 24 to 28 weeks of gestation (WOG) and a 2-step strategy. The covariates of interest were maternal hs-CRP and TNF-α, measured at 37 to 40 WOG, and their UC analogous was measured during delivery. The gross morphologies were assessed immediately after delivery. The UC coiling was quantitatively assessed by the pUCI. To compare the GDM and non-GDM groups, the t test and the Mann-Whitney test were used for normal and non-normal variables, respectively.

Results: There was not a significant difference in hs-CRP and TNF-a levels in maternal venous blood or UC blood between the GDM and non-GDM groups. The mean (SD) of pUCI in the GDM and non-GDM groups were 0.28 (0.15) and 0.24 (0.21) (P = 0.441), respectively. In the GDM group, none of the 4 covariates of interest had significant effects on the UCI. Among the non-GDM participants, merely the UC hs-CRP had a direct association with the pUCI, with a Pearson correlation of 0.54 (P = 0.001). Impacts of hs-CRP and TNF-α on the pUCI were assessed using Poisson regression models and no significant findings were detected (95% CI, 0.999-1.001, for all parameters).

Conclusion: In the GDM group, no apparent association was observed between inflammatory factors and pUCI, although a direct association was detected between UC hs-CRP and pUCI in the non-GDM.

Keywords: Gestational Diabetes Mellitus, Hs-CRP, TNF-α, Postnatal Umbilical Coiling Index

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Introduction

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance presenting in variable severity of hyperglycemia first diagnosed during pregnancy, which is associated with an increased risk of fetal morbidity and mortality (1). The metabolic impairments in GDM status create an abnormal environment in peripheral blood, and subsequently, vascular structure alterations may occur that affect the function and development of the placenta (2). GDM persuades excessive chronic hypoxia stress and

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↑What is "already known" in this topic:
GDM generates inflammatory changes in maternal and umbilical cord samples, which could affect the pUCI value.

→What this article adds:
Understanding the relationship between GDM status, inflammatory factors, and pUCI could help select the best interventions to save the fetus. The present study found that umbilical cord hs-CRP is directly correlated with the pUCI.

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inflammatory response in the placenta (2), and this inflammatory cascade and vascular endothelial dysfunction play an important role in the progression and pathogenesis of GDM (3).

Conversely, mild but significant inflammatory activity is involved in the development of normal pregnancy, which might have important physiological roles (4), and pregnancy is a proinflammatory and anti-inflammatory condition, depending on the stage of gestation (5).

Accordingly, genetics, maternal characteristics, placental, and umbilical cord structure and functions are the most important health factors that influence the fetus. We could observe coiling in the umbilical cord, which serves as the fetus's active lifeline (6), and the umbilical coiling index (UCI) can be used to measure it (7). Postnatal UCI (pUCI) is calculated by dividing the total number of complete vascular coils by the umbilical cord length in centimeters after delivery (7, 8). The changes in the UCI are individualized (9).

The mechanisms underlying the changes in cord coiling are not fully understood (10). Unfavorable fetal outcomes brought on by aberrant umbilical cord flow, constriction, or thrombosis could explain the significance of UCI anomalies (10). Negative perinatal outcomes in UCI abnormalities specifically reflect diabetes-complicated pregnancies (7, 10, 11).

GDM is one of the most important risk factors for abnormal coiling (12), which has an injurious effect on umbilical vessels and connective tissue(13). The augmented perinatal fatality and morbidity associated with GDM may be the result of a vascular etiology (13).

Vascular endothelial dysfunction and elevated serum levels of inflammatory and endothelial markers have also been observed in women with GDM (3).

There is a correlation between gestational diabetes mellitus (GDM) status, coiling abnormalities, and poor perinatal outcomes. The causes of this correlation include simple differences in the mechanical properties of the cord, growth response of the cord to metabolic and pharmacological abnormalities, intrinsic vascular structural changes, and variations in placental morphology affecting placental blood flow and maternal-fetal gas exchange (14).

Thus far, no study has been conducted to specifically demonstrate the relationship between GDM status, inflammatory factors, and pUCI. However, understanding this association could help select the best interventions to save the fetus. The inflammatory biomarkers were therefore evaluated in this study as potential indicators of coiling abnormalities, which appears to help identify pregnancies that should get more intensive fetal monitoring.

We hypothesized that GDM generates inflammatory changes in the maternal and umbilical cord (UC) samples, which could affect the pUCI value. The current study evaluated the impact of maternal venous blood and umbilical cord blood (UC blood) levels of tumor necrosis factor-alpha (TNF-alpha) and high-sensitivity C-reactive protein (hs-CRP) on postnatal umbilical coiling in pregnant women with and without gestational diabetes.

Methods

Participants

This prospective observational study recruited 80 singleton pregnant women (mother-infant pairs), from April 2018 to September 2019. This study was performed in Sayad Shirazi hospital (tertiary perinatal center), located in Gorgan, Golestan, Iran.

The pregnant women were recruited at the 37th week of gestation (WOG) (determined by the first day of the last menstrual period or the first-trimester ultrasound scan using crown-rump length) and observed until delivery and the postpartum period. Using G Power software Version 3.1, the sample size was computed with a power of 90%, a level of 5%, a d of 0.15, a prevalence macrosomia of 7%, and a probable drop rate of 10% (6). The participants were selected through a convenience sampling design.

These patients, who were divided into 2 groups according to whether they had gestational diabetes mellitus (GDM) or not (each group had 40 participants), were matched for maternal age, ethnicity, and parity.

The exclusion criteria were unavailable demographic, maternal, laboratory, neonatal, and gross morphological data, or being afflicted by overt diabetes, presence of gross fetal anomalies, history of chronic hypertension, smoking or substance abuse, systemic disease, use of medications other than routine pregnancy supplements, single-artery UC, chorioamnionitis, placenta previa, placenta abruption, fever, and multifetal pregnancy.

Face-to-face interviews were performed in the first and the following prenatal visits by a single trained physician. Maternal and fetal detailed history, anthropometric variables, obstetrical, physical examination, and paraclinical parameters were collected from the participants' files.

GDM was diagnosed according to the American Diabetes Association criteria at 24 to 28 WOG using a 2-step strategy (100 grams oral glucose tolerance test [100-g OGTT]) (15). The non-GDM group included pregnant women who were not complicated by GDM.

Medical nutrition therapy was prescribed for all GDM pregnant women, and after 2 weeks, insulin therapies were assigned due to ethical considerations. Because the pregnant women self-monitored their blood sugar levels and were of lower socioeconomic status, appropriate insulin therapy was selected for them.

After 5 minutes of relaxing, while seated, without using tobacco, drinking coffee or tea, and without eating for at least 30 minutes, participants had their blood pressure (BP) taken in accordance with standard procedures.

Blood glucose was measured by the enzymatic calorimeter method using a standard kit (EliTech kit) supplied by the EliTech Group (France).

In the laboratory of the aforementioned hospital, maternal serum samples were collected and assessed according to hs-CRP and TNF-a, and the same tests were performed immediately for the UC blood samples of 80 neonates. The hs-CRP and TNF-α were analyzed by the ELISA method, using the Monobind kit (Germany) (ng/mL) and the Manual kit (USA) (ng/L), respectively.

Then, infantile evaluation was performed and entered into the checklist. All of the gross morphologic assessments

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were performed for all the pregnant women immediately after delivery. To avoid diagnostic error, all evaluations were performed in the same physical conditions and by the same instruments and procedures.

Definition of Terms

The umbilical cord coiling is quantitatively assessed by the UCI. The pUCI was determined by dividing the total number of complete UC twists by the total UC length in cm after delivery, resulting in range variability (0-1) (16). One coil was defined as complete 360 degrees of umbilical artery around the umbilical vein (7, 10, 12, 17).

Gross morphology Assessment

In this study, the presence of UC coiling, the number of vascular coils, UC length, UC diameter, and existing complete vascular coils by 5 cm cord length (UCI) were all evaluated. Macroscopic examination of the placenta and UC was carried out following previously published protocols (18). A trained single physician who was blinded to the participant's clinical characteristics, laboratory results, and pregnancy outcomes handled the specimen with extreme caution to prevent lacerations and performed a gross evaluation of a true pUCI within 24 hours of delivery and cord clamping in the fresh state. The cord was clamped and cut straight at 5 cm from the fetal insertion right after birth, being careful not to milk or stretch the chord, which could impair the UCI (19). Five cm was added to the length of each cord to account for the portion of the cord that remained attached to the fetal umbilicus (20). From its insertion into the placenta up to the neonatal clamp, the UC's length and diameter were measured against a non-elastic tape graduated in cm. The placenta was allowed to separate spontaneously. Immediately after delivery, the placenta and the UC were preserved in a labeled, clean, and dry plastic container full of normal saline (21) with an airtight lid. They were kept in a dry, clean laboratory with a constant temperature maintained at 5℃ and were washed clean of blood before the examination.

Intrapartum and Neonatal Outcomes

Intrapartum outcomes included gestational age (GA) at delivery, emergency cesarean delivery, preeclampsia, premature rupture of membranes (PROM), polyhydramnios, and meconium-stained amniotic fluid. Neonatal outcomes were inspected by a blinded pediatrician after delivery. Neonatal outcomes included fetal complications, large for GA (LGA), small for GA (SGA), and preterm delivery. They also included neonatal sex, height, weight, and head circumference, first- and fifth-minute Apgar scores, respiratory distress syndrome, cardiopulmonary resuscitation (CPR), and oxygen consumption after CPR.

Statistical Analysis

For continuous variables with normal distributions, the independent sample t test was used to compare the GDM and non-GDM groups, and for non-normal continuous variables, the non-parametric Mann-Whitney U test was applied. Moreover, for comparing the discrete variables between the 2 groups, the chi-squared test was used.

Since the response variable (pUCI) was a rate, the Poisson regression model was used. Multivariate models with adjustments for systolic blood pressure, body mass index (BMI), family history of diabetes, and a binary indicator for those with GDM versus those without GDM were fitted to analyze the impact of each of the variables of interest, maternal hs-CRP, UC hs-CRP, maternal TNF-, and UC TNF-a on the pUCI. As an inferential metric, the models offered incidence-rate ratios.

Statistical analysis was performed using Stata Version 13. The significance level was set at $P < 0.05$.

Results

In this study, the mean GA at the delivery time was 37.8 (1.1) versus 37.8 (1.4) weeks ($P = 0.090$) for the GDM and non-GDM groups, respectively. The demographic and reproductive characteristics of participants are summarized in Table 1.

The mean (SD) of GA of GDM diagnosis was 22.3(9.3), and the mean (SD) of GDM duration was 15.4 (9.3) weeks. All the GDM group received insulin therapy, and the type of insulin therapy was a combination of short and long-acting insulin in 52.5% of cases—25% long-acting and 22.5% short-acting insulin. The mean (SD) of insulin duration was 13.3 (8.9) weeks.

The laboratory findings are compared between GDM and non-GDM groups in Table 2, implying no significant differences in hs-CRP and TNF-α (maternal or UC) between

Table 1. Demographic and Reproductive Characteristics of Participants

Variable	GDM (N = 40)	Non-GDM (N = 40)	*P* Value
Maternal age (yrs., mean(SD))	29.9 (5.5)	28.7 (5.6)	0.327
Relativity (n (%))	6 (15.0)	6 (15.4)	0.962
Gravidity (median (IQ))	2 (1-3)	2 (1-3)	0.694
Parity (median (IQ))	0 (0-1)	1 (0-2)	0.080
History of Abortion (n (%))	2 (1-3)	1 (0-2)	0.041
History of stillbirth (n (%))	1 (2.5)	3 (7.5)	0.615
History of macrosomia (n (%))	0 (0.0)	1 (2.5)	0.506
History of GDM (n (%))	5 (12.5)	1 (2.5)	0.201
Family history of DM (n (%))	17 (42.5)	3 (7.5)	0.001
Pre-pregnancy BMI (mean(SD))	29.5 (5.1)	25.6 (4.7)	<0.001
Maternal systolic BP (mean(SD))	117.9 (11.7)	109.5 (10.0)	0.001
Maternal diastolic BP (mean(SD))	74.9 (6.8)	71.4 (9.5)	0.066

GDM: Gestational diabetes mellitus. DM: Diabetes mellitus, BMI: Body mass index. BP: Blood Pressure.

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Table 3. Laboratory Findings of 2 GDM and non-GDM Groups

Variable	GDM[†](N = 40)	Non-GDM(N = 40)	*P* Value
Maternal Hs-CRP (median [IQR])	4633.5 (2277.6-8519.3)	6579.2 (2409.1-13235.1)	0.400
UC Hs-CRP (median [IQR])	27.1 (7.3-55.2)	13.5 (0-89.6)	0.500
Maternal TNF-α (median [IQR])	105.3 (85.1-277.9)	130.4 (93.9-226.3)	0.310
UC TNF-α (median [IQR])	163.3 (140.7-297.9)	186.1 (158.3-373.9)	0.100

GDM: Gestational diabetes mellitus; Hs-CRP: high-sensitivity C-reactive protein; UC: Umbilical Cord; TNF-α: tumor necrosis factor-alpha.

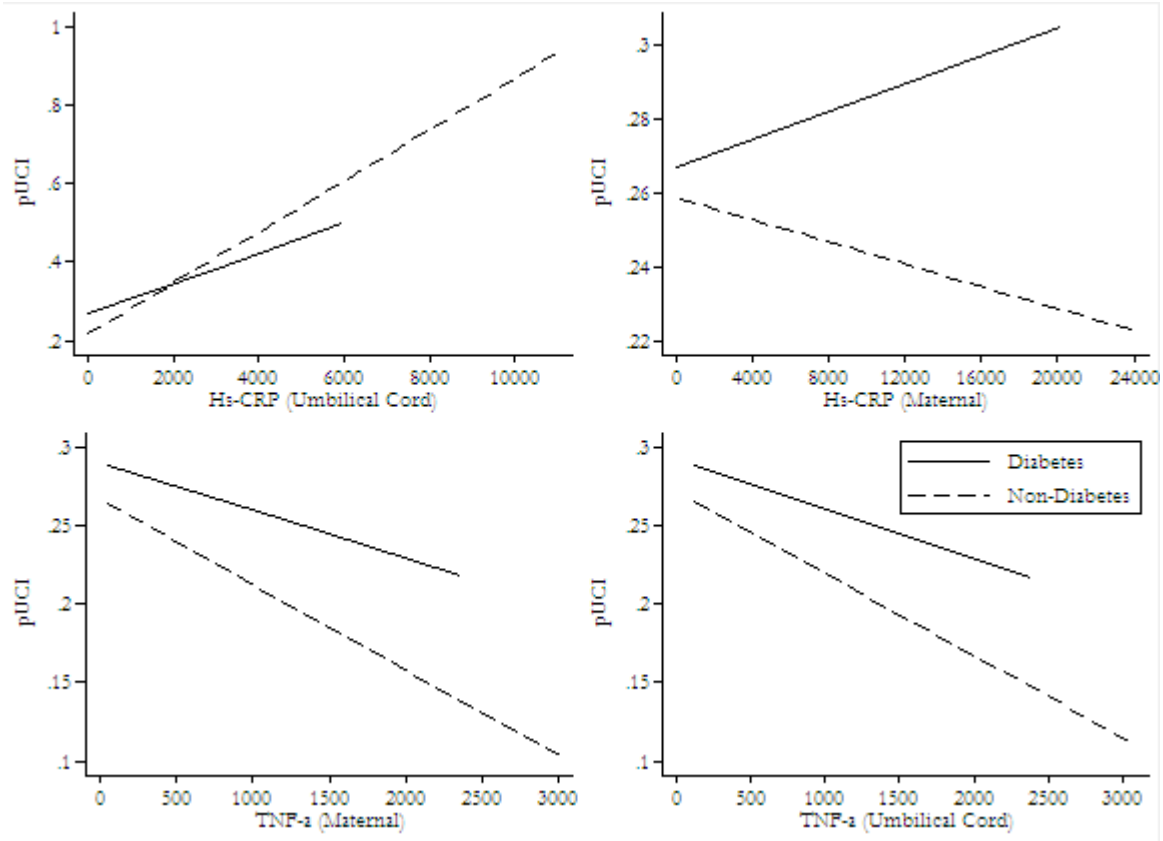

Figure 1. The correlation between high sensitivity C-reactive protein (hs-CRP) and tumor necrosis factor-Alfa (TNF-α) (in maternal venous blood and umbilical cord blood) and pUCI, in GDM and non-GDM groups.

the 2 groups.

All neonates were alive and delivered by cesarean section in 85% of GDM and 39.5% of non-GDM pregnant women ($P \leq 0.001$). Comparing the intrapartum and neonatal outcomes, no significant statistical difference was detected. No PROM, SGA, and preterm delivery were reported. However, polyhydramnios and neonatal intestinal atresia were detected in 1 GDM pregnant woman and 1 LGA neonate.

The gross morphology findings were compared between the GDM and non-GDM groups, implying no significant difference regarding the presence of UC coiling, number of vascular coils, UC length, and diameter. The mean (SD) of the pUCI in the GDM and non-GDM groups was 0.28 (0.15) and 0.24 (0.21) ($P = 0.441$), respectively.

Figure 1 shows that only the UC hs-CRP was directly correlated with the pUCI in the non-GDM participants, while none of the 4 covariates of interest—hs-CRP and TNF-a—found in maternal venous blood and UC blood among the GDM pregnant women appeared to have any relationship with the pUCI. It was further supported by the Pearson correlation analysis, where the only highly significant correlation was found between the UC hs-CRP and

Table 2. Multivariate Poisson Regression Models Evaluate the Effects of hs-CRP and TNF-α (maternal and UC forms) on pUCI, Adjusted for Confounders

Variable	IRR	*P* value	95% CI	
Maternal hs-CRP	1.000001	0.980	0.99992	1.00007
UC hs-CRP	1.0001	0.180	0.99993	1.0003
Maternal TNF-α	0.9998	0.630	0.9989	1.0006
UC TNF-α	0.9998	0.640	0.9989	1.0006

IRR: Incidence-rate ratio, pUCI: Postnatal umbilical coiling index
Hs-CRP: high-sensitivity C-reactive protein. UC: Umbilical Cord.
TNF-α: tumor necrosis factor-alpha.
Adjusted for the confounders; systolic blood pressure, BMI, family history of diabetes, and GDM/non-GDM status.

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the pUCI (r = 0.54; *P* = 0.001). Although no statistically significant correlations were found, both GDM and non-GDM groups appeared to have inverse relationships between (maternal and UC) the TNF- and the pUCI.

The pUCI was used as the dependent variable in the multivariate regression models, along with the confounder's systolic blood pressure, BMI, family history of diabetes, and GDM/non-GDM status. The variables of interest were hs-CRP and TNF-a in both forms of maternal venous blood and umbilical cord blood. The findings are reported in Table 3. None of the 4 assessed variables showed any significant effect on the pUCI.

Discussion

This prospective observational study investigated the effect of hs-CRP and TNF-α (maternal and UC) on postnatal umbilical coiling in GDM and non-GDM pregnancy.

The present study was unable to find any prior studies that connected the inflammatory variables, postnatal umbilical coiling, or GDM status.

We found no significant difference between hs-CRP and TNF-α in maternal venous blood or UC blood between the 2 groups. The same result was detected by Gomes et al for TNF-α between the GDM and non-GDM groups (22). The same nonsignificant difference in UC hs-CRP was demonstrated between the GDM and non-GDM groups in other studies (23, 24). In addition, no significant difference in pUCI in the 2 groups was detected, the same as in other studies (6, 16, 25).

The maternal and UC hs-CRP had no discernible influence on the pUCI in the GDM group. Despite the lack of a statistically significant link, there appeared to be a direct relationship. Among the non-GDM participants, merely the UC hs-CRP had a direct and significant association with pUCI, in contrast with maternal hs-CRP.

No statistically significant correlations were detected between maternal/UC TNF-α and pUCI in the 2 groups, although there seemed to be reverse relations.

In the multivariate regression models, adjusted for the confounders, including systolic BP, BMI, and family history of diabetes, none of the 4 assessed covariates showed any significant effect on the pUCI.

Important inflammatory activity that may play crucial physiological roles is required for optimal pregnancy development (4).

In the prepartum period, the metabolic and immunological disorders in addition to the inflammatory status alterations could affect the fetal developing environment (4). The inflammation is an important determinant of adverse fetal and perinatal outcomes (26). The fetal response to inflammation is considered by increased levels of proinflammatory cytokines in the amniotic fluid and UC blood (26), which induces inflammation of the chorionic plate, placental, and UC vessels (fetal vasculitis) (27). However, the association between perinatal inflammation and biochemical inflammatory indicators in UC blood and maternal circulation is not completely understood. TNF-α and CRP have been mentioned for their role in the inflammatory process and are most commonly assessed concerning insulin resistance and obesity (28, 29). The TNF-α has been recognized as being responsible for the hepatic production of acute-phase reactants, such as cytokines and CRP (30). Hs-CRP is an acute phase reactant biomarker and is produced by the liver in response to proinflammatory cytokines, which may be used as an adjunctive test in the diagnosis of inflammation (26). The plasma levels of hs-CRP will rise within a day of the initiation of inflammation and tissue injury, when diagnostic clinical signs and other laboratory tests may be nonspecific, and will stay elevated until the stimulus has subsided (31). Given that very little hs-CRP crosses the placenta, the increased serum and UC hs-CRP in the newborn is caused by endogenous hepatic synthesis (26). Perinatal inflammation is associated with increased UC inflammatory cytokines, including hs-CRP (32), but the impact on inflammatory markers in the early neonatal period is less well described (26).

The TNF-α is mainly produced by activated macrophages and monocytes (33). It affects insulin secretion and sensitivity by influencing B-cell function and insulin signaling pathways, which possibly induces GDM (34). Its level is controversial in that no differences between pregnancy and postpartum were seen (4), in contrast to Germain's (35) study, which showed greater TNF-α level in a typical pregnancy, and vice versa. According to Graham, the majority of proinflammatory cytokine expression, including TNF-a, was decreased during a typical pregnancy (36).

Pregnancy duration (37), the number of analyzed trimesters (5), the severity of comorbidities (38), and the style of delivery (38), among other factors, all influence the prepartum proinflammatory and anti-inflammatory states.

Hs-CRP, TNF-α, and other adipokines were found to be highly correlated with obesity, which contributes to insulin resistance and this correlation leads to many diseases, notably GDM and preeclampsia during pregnancy (39). The TNF-α and hs-CRP are mostly raised at the end of pregnancy (29).

GDM diagnosis was made during the second trimester, which may expose the infant to intrauterine metabolic changes, inflammatory process, and epigenetic programming for nearly 24 to 28 WOG, which predisposes infants to long-term abnormality (40). Hyperglycemia is contributed to produce reactive oxygen species, which concluded oxidative tresses, and thus proinflammatory cytokines and TNF-α are produced (41). Vascular endothelial dysfunction and placental angiogenesis are noted in GDM, which is characterized by the rise of serum inflammatory biomarkers and endothelial markers (3, 41). According to a different theory, the metabolic problems associated with GDM status lead to changes in vascular structure, which have an impact on the morphology, development, and function of the placenta and UC (2, 41). GDM induces chronic hypoxia and inflammatory response in placental and UC vascular endothelial cells (2). A hypoxic placenta may release cytokines and inflammatory factors (TNF-α and CRP), which could induce vascular endothelial dysfunction (42). This inflammatory cascade and vascular endothelial dysfunction play an important role in the progression and pathogenesis of GDM (3).

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Critic et al and other researchers demonstrated greater expression of TNF-a in the placenta in GDM pregnant women (43) in contrast to UC, where a low level of TNF-a was observed (41, 43). Increased oxidative stress and an imbalance in the expression of pro- and anti-inflammatory cytokines may contribute to elevated TNF-a levels in GDM, which may then affect glucose metabolism (43).

In the prepartum period, hs-CRP is correlated with maternal serum glucose of GDM pregnant women, when measured in the third trimester as a standard screening time (44), which is similar to the present study. According to the adverse perinatal outcomes in GDM pregnant women, vascular etiology is deemed as an important cause (13, 45) and also metabolic and pharmacological abnormalities are the other causes. Additionally, the fetal morbidities mentioned above are particularly prevalent in pregnancies complicated by GDM (7, 10, 11, 46, 47). GDM as one of the most important causes of coiling abnormalities (12) has a deleterious effect on umbilical vessels and connective tissues (13).

The influence of UCI on perfusion pressure is unknown, and it is hypothesized that the pressure reduction is caused by a weaker stimulus to angiogenesis with failure to form vascular-syncytial membranes (11). Diabetes results in an increase in the pressure in the coiling anomalies, which causes terminal villi congestion and angiogenesis to increase (11). In addition to the effect of insulin on placental vascularity, other factors such as angiogenic factors and inflammatory/oxidative stress factors also induce angiogenesis (48, 49). Adverse fetal outcomes were attributed to abnormal UCI (50), which predisposed the vessels of the umbilical to stenosis, thrombosis, constriction, occlusion, torsion of umbilical vessels, and cord entanglement (10). These abnormal mechanisms lead to compress fetoplacental blood flow, maternal-fetal gas exchange abnormality, and fetal hypoxia (7, 14, 51), which may strengthen and exaggerate in GDM pregnant women because of the reduction of the Wharton's jelly content, decrement of mucopolysaccharide synthesis, and the collagen molecules changes (13). Fetal hypoxia leads to more oxidative and nitrative stresses (52). In conclusion, all of these circumstances led to a decrease in the placental blood supply (14, 51), which may have an impact on the number of coils and was a significant cause of all the problems listed (12).

All the above-mentioned changes were noticed in nearly one-third of diabetic pregnant women and it seems that poor glycemic control is significantly related to these changes; these changes are prominently described in pregestational diabetes, not in GDM and occult form (11).

Similarly, Mayhew et al defined normal vascular function in GDM pregnant women with good glycemic control (53) in contrast with Leach who described vascular insufficiency with appropriate glycemic control (54). According to ethical considerations, a reduction in the severity of the GDM, prompt diagnosis, and proper follow-ups in the GDM group, and the described inflammatory activity may affect intrapartum GDM treatment with lifestyle changes, medical nutrition therapy, and glycemic management. We propose the aforementioned aspects as confounding factors that influence our findings. In the literature review, no study has been conducted to specifically demonstrate the relationship between biochemical inflammatory biomarkers and pUCI in pregnant women whose conditions were complicated by GDM.

The strengths of this study were that all evaluations were demonstrated in a referral obstetric hospital (tertiary perinatal center). In this prospective observational study, the authors could follow the late prenatal, perinatal, and postnatal periods. GDM and normal pregnancies made up the study population, allowing for a reliable comparison between the 2. To avoid immediate blood draining, the cord's entire length was taken into account for the UCI calculation, and a quick bilateral clamping procedure was used. To avoid overdiagnosis by a "1-step strategy," only a "2-step strategy" (100-g OGTT) should be used for all instances with GDM.

Conclusion

These are the first findings to demonstrate that, in the GDM group, there was no apparent association between inflammatory biomarkers and pUCI, despite a direct correlation between UC hs-CRP and pUCI in the non-GDM group.

The present study's limitation may be the limited sample size, which prevented an impact assessment of some variables. Therefore, additional studies in larger populations with the serial and early evaluation of inflammatory biomarkers are needed to understand the associations between the aforementioned and other inflammatory indicators (adiponectin) and UCI; these studies could also serve as screening tests for the detection of coiling abnormalities and prediction of the pUCI in various comorbidities such as GDM, preeclampsia, and other conditions.

Ethical Approval

The ethics committee of Golestan University of Medical Sciences approved the study protocol (IR.GOUMS.REC.1397.273, IR.GOUMS.REC.1397.272), and all participants signed the written informed consent. In studies involving human subjects, all procedures were carried out in accordance with the 1964 Helsinki Statement and its later revisions or comparable ethical standards, as well as the ethical requirements of the institutional and/or national research committee.

List of Abbreviations

BMI: Body mass index
BP: Blood pressure
CPR: Cardiopulmonary resuscitation
DM: Diabetes mellitus
GA: Gestational Age
GDM: Gestational Diabetes Mellitus
Hs-CRP: High-sensitivity C-reactive
LGA: Large for gestational age
OGTT: Oral glucose tolerance test
PROM: Premature rupture of membranes
SGA: Small for gestational age
TNF-α: Tumor necrosis factor- Alpha
pUCI: Postnatal Umbilical Coiling Index
UC: Umbilical cord
UCI: Umbilical Coiling Index

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WOG: Weeks of gestation

Contribution to Authorship

H.A. and L.N. designed the study. L.N. and A.K. contributed to the analysis and interpretation of data. L.N. and A.K. drafted the manuscript. F.M., A.N., and F.A. critically revised the manuscript. All authors approved the final draft.

Conflict of Interests

The authors declare that they have no competing interests.

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