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The Association between Resolvin D1 Levels and Gestational Diabetes Mellitus: Implications for Perinatal Outcomes

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ABSTRACT

OBJECTIVE: To evaluate maternal Resolvin D1 levels in women with gestational diabetes mellitus (GDM) and investigate the association between perinatal outcomes.

STUDY DESIGN: This case-control study included 88 singleton pregnancies, conducted from August 2023 to January 2024, at a tertiary care center. Participants were divided into two groups: 44 pregnant women diagnosed with GDM comprised the study group, and 44 healthy pregnant women served as the control group. Additionally, the GDM group was categorized based on management approach into 21 women managed with diet alone and 23 women requiring insulin therapy. Maternal plasma Resolvin D1 levels and maternal-neonatal outcomes were then compared between groups. The analysis involved determining the optimal Resolvin D1 cut-off levels for predicting composite adverse neonatal outcomes in GDM using receiver operating characteristic curve (ROC) analysis.

RESULTS: The plasma Resolvin D1 level in pregnant women with GDM was significantly higher compared to the control group (337±74.1 vs. 297±56.7, p<0.001). Furthermore, maternal plasma Resolvin D1 levels were associated with composite adverse neonatal outcomes [presence of at least one of the following conditions: preterm birth (<37 weeks), low birth weight (LBW) (<2500 grams), neonatal hypoglycemia, hyperbilirubinemia, APGAR score at 5th minute <7, respiratory distress syndrome (RDS), and admission to the neonatal intensive care unit (NICU)], with a cut-off of >338.75, showing a sensitivity of 56.3%, a specificity of 79.2%, and an AUC of 0.675 (95% CI: 0.567-0.771, p=0.024).

CONCLUSIONS: This study demonstrated that pregnancies affected by GDM exhibit elevated levels of Resolvin D1, which is associated with a higher incidence of composite adverse neonatal outcomes.

Keywords: Gestational diabetes mellitus; Perinatal outcomes; Resolvin D1

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Introduction

Gestational diabetes mellitus (GDM), which is one of the most common complications of pregnancy, manifests with the presence of peripheral insulin resistance, carbohydrate intolerance, low-grade inflammation, inadequate insulin secretion or activity, and hyperglycemia that occurs after the second trimester (1). In 2021, the International Diabetes Federation reported a standardized global prevalence of GDM of 14% (2). Over the last twenty years, the prevalence of GDM has disturbingly increased by over 30% in multiple countries (3). In addition to the increase in screening methods, the prevalence of GDM is expected to rise further due to sedentary lifestyles, advanced maternal age, and obesity (4). GDM is a global public health problem that poses short- and long-term adverse effects for the mother and fetus. The condition is linked to various adverse perinatal consequences, including macrosomia, preterm delivery, birth injury for the fetus, neonatal hypoglycemia, respiratory distress syndrome (RDS), admission to the neonatal intensive care unit (NICU), metabolic complications, gestational hypertension, preeclampsia, and the need for a cesarean section (CS) (5,6). Pregnant women with

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GDM face a heightened susceptibility to developing type 2 diabetes, significant cardiovascular risk, and early atherosclerosis (7). While the incidence of GDM is increasing, the exact factors contributing to its pathophysiology are not yet fully understood. A comprehensive understanding of the pathophysiology, predisposing factors, and consequences of gestational diabetes is necessary to facilitate efficacious preventive measures, timely identification, and appropriate treatment (8).

Resolvin D1, a key molecule within the specialized pro-resolving mediators (SPMs) category, is synthesized from docosahexaenoic acid (DHA), an omega-3 polyunsaturated fatty acid (9). Resolvins, identified for their significant pro-resolving and anti-inflammatory properties, play a crucial role in the body's response to inflammation (10,11). Resolvin D1 exerts anti-inflammatory effects by inhibiting the migration of polymorphonuclear neutrophils (PMN), promoting the release of macrophages, reducing pro-inflammatory cytokines, and enhancing anti-inflammatory pathways. It also acts as an antioxidant by suppressing the synthesis of oxides and increasing the expression of antioxidants (11). The placenta, affected by increased inflammation and oxidative stress, has been linked to GDM. Consequently, changing inflammatory responses are an important pathophysiological element in the development of GDM (12).

Considering the limited research on the role of lipid mediators such as Resolvin D1 in GDM, our study aims to examine plasma levels of Resolvin D1 in pregnancies affected by GDM and its association with composite adverse neonatal outcomes.

Material and Method

This case-control study was carried out in the Perinatology Department of Ankara Etlik City Hospital, a tertiary care center in Turkey, between August 2023 and January 2024. The study received ethical approval from the Hospital's Ethics Committee (Approval number: AESH-EK1-2023-481). The informed consent of all patients was documented and signed before participants were included in the study. The study was carried out in accordance with the guidelines stated in the Declaration of Helsinki.

A total of 88 pregnant women aged 18-45 years who were between 34 and 37 weeks pregnant were included in this study. Patients were selected from pregnant women who came for routine control. These participants were categorized into two main groups: 44 pregnant women diagnosed with GDM and 44 healthy pregnant women in the control group. Furthermore, the GDM group was subdivided based on their management strategy into 21 women who managed through diet alone and 23 women who required insulin therapy. GDM screening and diagnosis were performed with a 75-gram (g) oral glucose tolerance test (OGTT) between 24 and 28 weeks of gestation, according to the guidelines set by the International Diabetes in Gestational Study Groups (IADPSG). Gestational diabetes was diagnosed if at least one value was positive in the 75-g OGTT: Fasting plasma glucose level ≥92 mg/dl (5.1 mmol/L) and/or 1-hour glucose level ≥180 mg/dl (10.0 mmol/L), and/or 2-hour glucose level ≥153 mg/dl (8.5 mmol/L) (13).

Exclusion criteria included multiple pregnancies, known type 1 or type 2 diabetes mellitus (DM), essential hypertension or hypertensive diseases of pregnancy, intrahepatic cholestasis of pregnancy, maternal nutritional disorders, maternal comorbidities such as liver or kidney disease, thyroid dysfunction, smoking, substance abuse, and fetal structural or cytogenetic abnormalities.

Maternal age, gravidity, parity, weight gain during pregnancy, body mass index (BMI) at the test, HbA1c levels (for the GDM groups), mode of delivery, and gestational age at delivery were documented. The study evaluated various neonatal outcomes, including preterm birth (<37 weeks), birth weight (grams), neonatal hematocrit level, neonatal hypoglycemia, hyperbilirubinemia, APGAR scores at the 1st and 5th minutes, RDS, and admission to the NICU. The composite adverse neonatal outcome was defined as the occurrence of at least one of the following situations: preterm birth (<37 weeks), low birth weight (<2500 grams), neonatal hypoglycemia, hyperbilirubinemia, APGAR score at the 5th minute <7, RDS, and admission to the NICU.

Gestational diabetes management protocol: All pregnant women diagnosed with gestational diabetes are first consulted by a dietitian and a diabetic diet is started. Then, peripheral blood sugars are measured at morning fasting and post-prandial (one hour after meal), and post-prandial lunch and dinner peripheral blood sugars are measured. The target blood glucose concentrations align with the recommendations of the American Diabetes Association (ADA) and the American College of Obstetricians and Gynecologists (ACOG): fasting blood glucose concentration should be <95 mg/dL (5.3 mmol/L) and one-hour post-prandial concentration should be <140 mg/dL (7.8 mmol/L) (1,14).

If the desired blood glucose targets cannot be achieved through dietary measures alone, insulin therapy is initiated after consultation with Internal Medicine to calculate the initial dosage. Subsequent adjustments to insulin doses are made based on blood glucose monitoring. The primary goals are to maintain normoglycemia, prevent ketosis, and facilitate controlled weight gain.

Sample collection: A volume of 4 ml of venous blood was collected from pregnant women between the gestational ages of 34 and 37 weeks. This blood was drawn using an ethylenediaminetetraacetic acid (EDTA) anticoagulant tube and centrifuged at 3000 revolutions per minute (rpm) for 15 minutes within 30 minutes of collection. The resulting plasma was then collected and stored at a temperature of -80°C for further analysis. The concentration of Resolvin D1 was measured in picograms per milliliter (pg/ml) using a Human Resolvin D1

ELISA Kit provided by Shanghai Coon Koon Biotech Co., Ltd. (Shanghai, China). Comparisons were made between the levels of maternal plasma Resolvin D1 in pregnant women with GDM and those in the control group. Additionally, a cut-off value for Resolvin D1 was established to predict the occurrence of composite adverse neonatal outcomes.

Statistical analysis

The RStudio integrated development environment for statistical computation (Affero General Public License v3; published 2011) was utilized to conduct all statistical analyses. To ascertain whether the variables followed a normal distribution, both visual (histograms, probability plots) and analytic techniques (Kolmogrov-Simirnov/Shapiro-Wilk's test) methodologies were applied. Utilizing the Levene test, the homogeneity of the variance was evaluated. In the case of variables that followed a normal distribution, descriptive analyses were expressed as means and standard deviations. An Independent Samples T-test was used to compare these parameters between groups. Numerical data that were not normally distributed were displayed using medians and quartiles (Q1-Q3). Mann-Whitney U tests were applied to compare these parameters between groups. Descriptive analyses were performed on categorical variables using frequency and percentage measurements. Associations between categorical variables were examined using the Chi-square test or Fisher's exact test. To predict composite adverse neonatal outcomes, the Receiver Operating Characteristics (ROC) curve analysis was employed to assess the capability of Resolvin D1. If a significant cut-off value was detected, sensitivity, specificity, and Area Under the Curve (AUC) were displayed. Correlation coefficients and their significance were calculated using Pearson and Spearman tests. A p-value below 0.05 was deemed to indicate a statistically significant result. A power analysis was conducted using G*Power 3.1.9.6 to determine the required sample size for the study. The analysis aimed to ensure the study has sufficient power to detect a medium effect size (Cohen's d=0.5) with an 80% probability (1-β=0.80). Accordingly, it was found that there should be at least 34 participants in each group.

Results

The comparison of maternal and perinatal outcomes between GDM and the control group is analyzed in Table I.

Table I: *Comparison of maternal and perinatal outcomes in GDM cases versus control group*

	GDM (n=44)	Control (n=44)	p
Maternal age (year)	33±5.7	31±4.4	0.070
Gravidity	3 (2-4)	2 (1-3)	**0.006**
Parity	1 (1-2)	1 (0-2)	0.077
Weight gain (kilograms)	10 (7-13)	10 (9-14)	0.562
BMI at during test (kg/m^2)	32.9±4.74	31.8±3.95	0.247
HbA1c (%)	5.5±0.49	-	N/A
Mode of delivery			
Total CS	31 (70.5%)	17 (38.6%)	**0.005**
VD	13 (29.5%)	27 (61.4%)	**0.005**
Primer CS	12 (27.3%)	17 (38.6%)	0.614
Gestational age at delivery (weeks)	39 (38-39)	39 (38-40)	0.642
Preterm birth (<37 weeks)	3 (6.8%)	0 (0%)	0.240
Blood sample collection time (weeks)	36 (36-37)	35 (34-37)	0.071
Resolvin D1 (pg/mL)	337±74.1	297±56.7	**<0.001**
Gender			0.522
Male	23 (52.3%)	19 (43.2%)	
Female	21 (47.7%)	25 (56.8%)	
Birth weight (grams)	3270 (2968-3710)	3175 (2923-3388)	0.170
Low birth weight (<2500 grams)	3 (2.3%)	1 (2.3%)	0.616
Neonatal hematocrit (%)	53.7±5.81	55.8±5.91	0.895
Neonatal hypoglycemia	5 (11.4%)	0 (0%)	0.055
Hyperbilirubinemia	2 (4.5%)	0 (0%)	0.494
APGAR Score at 1st minute	9 (8-9)	9 (9-9)	**0.021**
APGAR Score at 5th minute	10 (10-10)	10 (10-10)	0.143
Apgar score at 5th minute <7	1 (2.3%)	0 (0%)	0.998
RDS	4 (9.1%)	1 (2.3%)	0.202
NICU admission	5 (11.4%)	0 (0%)	0.055
Composite adverse neonatal outcomes*	14 (31.8%)	2 (4.5%)	**0.002**

*BMI: Body mass index, HbA1c: Hemoglobin A1C, CS: Cesarean section, VD: Vaginal delivery, RDS: Respiratory distress syndrome, NICU: Neonatal intensive care unit. Data are expressed as mean±SD, median, and quartiles (Q1–Q3), or number (percentage) where appropriate. A p-value of <0.05 indicates a significant difference. Statistically significant p-values are in bold. * The composite adverse neonatal outcome was defined as the occurrence of at least one of the following situations: preterm birth (<37 weeks), low birth weight (<2500 grams), neonatal hypoglycemia, hyperbilirubinemia, APGAR Score at 5th minute <7, respiratory distress syndrome (RDS), and admission to neonatal intensive care unit (NICU)*

Maternal age and parity were similar between the two groups, and gravidity was higher in the GDM group (p=0.006). Pregnancy weight gain and BMI at the time of testing did not differ significantly between groups. While blood sample collection time was similar in both groups, the maternal plasma Resolvin D1 level in the GDM group was significantly higher than the control group (337±74.1 vs. 297±56.7, p<0.001). There was a higher CS rate in the GDM group (70.5%) compared to the control group (38.6%) (p=0.005). However, gestational age at delivery, preterm birth rates, newborn weights, and the incidence of LBW were similar between the groups. There was no significant difference in the frequency of neonatal hypoglycemia and hyperbilirubinemia between groups. Although the 1st-minute APGAR score was significantly lower in the GDM group (p=0.021), the 5th-minute APGAR score and Apgar score at the 5th minute <7 were similar between the groups. Both groups were similar in terms of RDS and NICU admissions. However, composite adverse outcomes were significantly higher in the GDM group (31.8% vs. 4.5%, p=0.002), underscoring the broader impact of GDM on neonatal health. Maternal plasma Resolvin D1 levels were associated with composite adverse neonatal outcomes, with a cut-off of >338.75, showing a sensitivity of 56.3%, a specificity of 79.2%, and an AUC of 0.675 (95% CI: 0.567-0.771, p=0.024). (Table I, Figure 1).

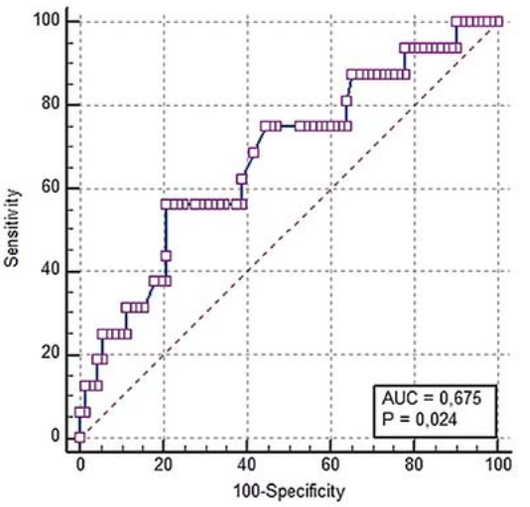

Figure 1: *Maternal plasma Resolvin D1 levels were associated with composite adverse neonatal outcomes, with a cut-off of >338.75, showing a sensitivity of 56.3%, a specificity of 79.2%, and an AUC: 0.675 (95% CI: 0.567-0.771, p=0.024)*

Table II reviews the analysis of maternal and perinatal outcomes based on the required treatment for GDM, distinguishing between diet-regulated and insulin-regulated groups. HbA1c levels, blood sample collection timing, and maternal serum Resolvin D1 levels showed no significant variation be-

Table II: *Analysis of maternal and perinatal outcomes according to required medical interventions in the GDM group*

	Dietary Regulation in GDM (n=21)	Insulin requirement in GDM (n=23)	p
HbA1c (%)	5.5±0.44	5.5±0.55	0.991
Mode of delivery			
Total CS	14 (66.7%)	17 (73.9%)	0.845
VD	7 (33.3%)	6 (26.1%)	0.845
Primer CS	5 (23.8%)	7 (30.4%)	0.835
Gestational age at delivery (weeks)	39 (39-39)	38 (38-39)	**0.012**
Preterm birth (<37 weeks)	1 (4.8%)	2 (8.7%)	0.605
Blood sample collection time (weeks)	36 (36-37)	36 (35-37)	0.234
Resolvin D1 (pg/mL)	335±57.1	338±88.2	0.347
Gender (n,%)			0.127
Male	14 (66.7%)	9 (39.1%)	
Female	7 (33.3%)	14 (60.9%)	
Birth weight (grams)	3423±572.5	3260±540.4	0.337
Low birth weight (<2500 grams)	1 (4.7%)	2 (8.7%)	0.998
Neonatal hematocrit (%)	53.5±5.96	53.9±5.67	0.792
Neonatal hypoglycemia	2 (9.5%)	3 (13%)	0.713
Hyperbilirubinemia	2 (9.5%)	0 (0%)	0.222
APGAR Score at 1st minute	9 (8-9)	9 (9-9)	0.419
APGAR Score at 5th minute	10 (10-10)	10 (10-10)	0.663
Apgar score at 5th minute <7	0 (0%)	1 (4.3%)	0.998
RDS	1 (4.8%)	3 (13%)	0.609
NICU admission	1 (4.8%)	4 (17.4%)	0.348
Composite adverse neonatal outcomes *	5 (23.8%)	9 (39.1%)	0.444

HbA1c: Hemoglobin A1C, CS: Cesarean section, VD: Vaginal delivery, RDS: Respiratory distress syndrome, NICU: Neonatal intensive care unit
*Data are expressed as mean±SD, median, and quartiles (Q1–Q3), or number (percentage) where appropriate. A p-value of <0.05 indicates a significant difference. Statistically significant p-values are in bold. * The composite adverse neonatal outcome was defined as the occurrence of at least one of the following situations: preterm birth (<37 weeks), low birth weight (<2500 grams), neonatal hypoglycemia, hyperbilirubinemia, APGAR Score at 5th minute <7, respiratory distress syndrome (RDS), and admission to neonatal intensive care unit (NICU).*

tween the groups. Gestational age at birth was higher in the diet-regulated GDM group (p=0.012). Delivery methods, preterm birth rates, newborn weights, LBW incidence, neonatal hematocrit levels, and 1st and 5th-minute APGAR scores were similar between the two groups. Furthermore, the frequency of other adverse neonatal outcomes (neonatal hypoglycemia, hyperbilirubinemia, APGAR score at 5th minute <7, RDS, and NICU admission), and composite adverse neonatal outcomes were similar between the two groups (Table II).

Serum Resolvin D1 levels according to maternal BMI were examined in Table III. The analysis revealed that serum Resolvin D1 levels did not significantly differ based on maternal BMI (Table III).

Table IV explores the correlation between maternal serum Resolvin D1 levels and various maternal-perinatal characteristics. It was found that maternal serum Resolvin D1 level was not significantly influenced by maternal age, parity, weight gain, BMI, gestational age at delivery, blood sample collection time, birth weight, or APGAR scores at the 1st and 5th minutes (Table IV).

Discussion

This study found that the serum levels of Resolvin D1 were significantly higher in mothers in the GDM group compared to those in the control group. Furthermore, an association was observed between the level of serum Resolvin D1 and composite adverse neonatal outcomes. Specifically, maternal plasma Resolvin D1 levels were associated with composite adverse neonatal outcomes, with a cut-off of >338.75, showing a sensitivity of 56.3%, a specificity of 79.2%, and an AUC of 0.675 (95% CI: 0.567-0.771, p=0.024). These findings indicate that Resolvin D1 could play a physiological role during pregnancies complicated by GDM.

The inflammatory response of an organism is sustained by a delicate equilibrium between the induction and cessation of inflammation; moreover, chronic inflammation results from the overexpression of inflammatory signals or the dysfunction of pro-resolving/anti-inflammatory pathways (15). During the progression of the inflammatory response, there is a process of switching between different classes of lipid mediators in the production of SPMs, such as lipoxins, resolvins, protectins, and maresins (16). Resolvin D1, which works as an anti-inflammatory and antioxidant, has been studied in the context of a variety of organ and systemic pathologies (15-17). In the study comparing women with polycystic ovary syndrome (PCOS), including increased insulin resistance, and healthy women, Resolvin D1 levels were found to be higher in the PCOS group, which is characterized by increased inflammation such as obesity (17). The relationship between Resolvin D1 level and preeclampsia was investigated. Perucci et al. found that Resolvin D1 plasma concentrations were higher in preeclamptic pregnant women at 12–19 weeks of gestation compared to normotensive pregnant women. They found that it decreased during the gestational weeks (18). However, the relationship between Resolvin D1 and GDM has not yet been investigated in the literature. Pregnant women with GDM display higher levels of inflammatory markers than those with normal pregnancies (19). This inflammation can lead to pancreatic β-cell damage and promote the pathogenesis of GDM by contributing to the development of insulin resistance (20). Inflammation is considered to be one of the fundamental pathogenic processes that trigger GDM. An animal study by Bathina et al. showed that Resolvin D1 has anti-diabetic and

Table III: *Serum resolvin D1 levels according to maternal BMI*

	GDM (n=44)	Control (n=44)	p
BMI at during test healthy weight range ≥18.5-25 (kg/m^2) n=2	15 (34.1%)	15 (34.1%)	0.965
BMI at during test overweight range ≥25-30 (kg/m^2) n=25	13 (29.6%)	12 (27.3%)	
BMI at during test obesity ≥30 (kg/m^2) n=61	16 (36.3%)	17 (38.6%)	

BMI: Body mass index

Table IV: *Correlation between maternal serum resolvin D1 levels and maternal-perinatal characteristics*

	r	p
Maternal age	0.102	0.343
Parity	0.120	0.266
Weight gain (kilograms)	0.079	0.598
BMI	0.043	0.693
Gestational age at delivery	-0.077	0.475
Blood sample collection time	0.167	0.121
Birth weight	0.007	0.949
APGAR Score at 1st minute	-0.017	0.874
APGAR Score at 5th minute	-0.039	0.717

BMI: Body mass index

anti-inflammatory actions and enhances cell regeneration (21). In contrast, at the population level, higher concentrations of Resolvin D1 and Resolvin D2 were associated with an increased risk of type 2 DM, according to the research of Sun et al (22). Moreover, a study has demonstrated that chronic low-grade activation of the immune system may contribute to the development of type 2 diabetes mellitus in healthy, normal glucose-tolerant individuals by reducing insulin sensitivity (23). This background suggests that women with GDM might experience increased inflammation, potentially leading to an upregulation of SPMs synthesis as a compensatory mechanism. Our study observed a significant increase in Resolvin D1 levels among pregnant women with GDM, supporting this hypothesis. Given the relatively short duration of GDM as a disease, it may not progress to chronic inflammation, thereby possibly explaining the observed increase in anti-inflammatory and pro-resolving lipid mediators in response to acute inflammation. Future research could further elucidate the concentrations of these mediators and assess the risk of these patients developing diabetes mellitus, enhancing our understanding of the inflammatory processes in GDM and their implications.

Given that obesity is a significant risk factor for GDM, it is plausible to identify underlying molecular mechanisms that are impacted by elevated body fat mass in individuals who are susceptible to GDM. Obesity is associated with chronic low-grade inflammation, and the accumulation of adipose tissue in obese individuals prompts an inflammatory response (24). In research conducted by Szczuko et al., the levels of Resolvin D1 were measured across all three trimesters of pregnancy, revealing a progressive increase in its levels through each trimester. Furthermore, it was observed that overweight or obese women exhibited significantly higher levels of Resolvin D1 in the third trimester compared to those of normal weight (25). Our research focused on assessing Resolvin D1 levels exclusively in the third trimester, with all participants having similar weight gain and BMI values. This approach reduced the potential confounding effects of obesity on Resolvin levels, but we were unable to assess obesity and trimester-based levels.

GDM is associated with significant morbidity and mortality in both the mother and the newborn (26). Neonates born from pregnancies complicated by GDM are more frequently affected by multifactorial morbidities such as hypoglycemia, hyperbilirubinemia, hypocalcemia, hypomagnesemia, polycythemia, respiratory disorders, and cardiomyopathy. Although these conditions are often transient, they occur more commonly in newborns born to mothers with GDM (27,28). However, a universally acknowledged model for predicting the likelihood of adverse perinatal outcomes does not yet exist. Consistent with current literature, our study shows that composite neonatal outcomes are significantly worse in newborns of mothers with GDM compared to non-GDM pregnancies. We also found that maternal plasma Resolvin D1 levels were associated with these adverse outcomes, defining a threshold of >338.75 pg/ml,corresponding to a sensitivity of 56.3%, a specificity of 79.2%, and an AUC of 0.675 (95% CI:0.567-0.771, p=0.024). These results suggest that Resolvin D1 could potentially act as a biomarker for predicting adverse perinatal outcomes in gestational diabetes. Nonetheless, further investigations involving larger cohorts are imperative to substantiate this potential.

This study has some limitations. Firstly, the data were collected from a single center, limiting our ability to assess the impact on various populations. Secondly, we did not examine Resolvin D1 levels in the non-regulated GDM group, missing an opportunity to explore this subgroup. Another limitation of our study is the lack of data on Resolvin D1 levels in the first and second trimesters of pregnancy. This gap prevents a direct comparison with the levels observed in the third trimester, limiting our ability to understand changes across different pregnancy stages. However, this deficiency does not diminish the originality and importance of our findings. On the other hand, the strength of this study lies in the inclusion of well-defined cases and the breadth of parameters investigated. Furthermore, to our knowledge, this study performed the first evaluation of the association between Resolvin D1 levels in women who developed GDM and Resolvin D1 in women who did not. In addition to the biochemical markers investigated, the study also broadly covered maternal and perinatal outcomes, which provide a more comprehensive understanding of the effects of GDM.

In conclusion, our findings indicate that pregnancies complicated by GDM show high levels of Resolvin D1 in maternal plasma and that these high levels are associated with adverse perinatal outcomes. This highlights the potential of Resolvin D1 as a biomarker for predicting the severity and impact of GDM. However, comprehensive studies involving larger, population-based cohorts are essential to precisely define the relationship between Resolvin D1 levels and GDM. Additionally, future research should include studies on Resolvin D1 levels in the non-regulated GDM population to enrich the literature. A deeper understanding of GDM's pathophysiology, informed by such studies, could lead to improved outcomes for both mothers and newborns.

Declarations

Ethics approval and consent to participate: The study received ethical approval from the hospital's Ethics Committee (Approval number: AESH-EK1-2023-481). Informed consent of all patients was documented and signed before participants were included in the study. The study was conducted in compliance with the guidelines outlined in the Declaration of Helsinki.

Availability of data and materials: The data supporting this study is available through the corresponding author upon reasonable request.

Conflict of interest: The authors declare that they have no competing interests.
Funding: None.
Authors' contributions: ZS, BB, and ATC raised the presented idea. ZS, BB, GK, MB, GK, and GA designed the study. BTC conducted the analyses. ZS, BB, MB, GK, BTC, COU, GA, SOS, and STS developed the first draft of the manuscript. ZS, BB, SOS, and STS participated in data collection and result interpretation. MB, GK, BTC, COU, and GA assisted with data collection and analysis. SC and ATC critically revised the manuscript. All authors contributed to the writing of the article and read and approved the final version of the article.
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References

1. ACOG Practice Bulletin No. 190: Gestational Diabetes Mellitus. Obstet Gynecol. 2018;131(2):e49-e64. Doi: 10.1097/AOG.0000000000002501. PMID: 29370047.
2. Wang H, Li N, Chivese T, Werfalli M, Sun H, Yuen L, et al. IDF Diabetes Atlas: estimation of global and regional gestational diabetes mellitus prevalence for 2021 by International Association of Diabetes in Pregnancy Study Group's Criteria. Diabetes Res Clin Pract. 2022;183: 109050. Doi: 10.1016/j.diabres.2021.109050. PMID: 34883186.
3. Zhu Y, Zhang C. Prevalence of gestational diabetes and risk of progression to type 2 diabetes: a global perspective. Curr Diab Rep. 2016;16(1):7. Doi: 10.1007/s11892-015-0699-x. PMID: 26742932, PMCID: PMC6675405.
4. Teh WT, Teede HJ, Paul E, Harrison CL, Wallace EM, Allan C. Risk factors for gestational diabetes mellitus: implications for the application of screening guidelines. Aust N Z J Obstet Gynaecol. 2011;51(1):26-30. Doi: 10.1111/j.1479-828X.2011.01292.x. PMID: 21299505.
5. Wendland EM, Torloni MR, Falavigna M, Trujillo J, Dode MA, Campos MA, et al. Gestational diabetes and pregnancy outcomes--a systematic review of the World Health Organization (WHO) and the International Association of Diabetes in Pregnancy Study Groups (IADPSG) diagnostic criteria. BMC Pregnancy Childbirth. 2012;12:23. Doi: 10.1186/1471-2393-12-23. PMID: 22462760, PMCID: PMC3352245.
6. Bayraktar B, Balıkoğlu M, Kanmaz AG. Pregnancy outcomes of women with hypoglycemia in the oral glucose tolerance test. J Gynecol Obstet Hum Reprod. 2020;49 (4):101703. Doi: 10.1016/j.jogoh.2020.101703. PMID: 32018048.
7. West NA, Kechris K, Dabelea D. Exposure to maternal diabetes in utero and DNA methylation patterns in the offspring. Immunometabolism. 2013;1:1-9. Doi: 10.2478/immun-2013-0001. PMID: 23741625, PMCID: PMC3670583.
8. Bayraktar B, Balıkoğlu M, Bayraktar MG, Kanmaz AG. The effects of hyperemesis gravidarum on the oral glucose tolerance test values and gestational diabetes. Prague Med Rep. 2021;122(4):285-93. Doi: 10.14712/23362936.2021.26. PMID: 34924106.
9. Chiang N, Serhan CN. Structural elucidation and physiologic functions of specialized pro-resolving mediators and their receptors. Mol Aspects Med. 2017;58:114-29. Doi: 10.1016/j.mam.2017.03.005. PMID: 28336292, PMCID: PMC5623601.
10. Serhan CN, Clish CB, Brannon J, Colgan SP, Chiang N, Gronert K. Novel functional sets of lipid-derived mediators with antiinflammatory actions generated from omega-3 fatty acids via cyclooxygenase 2-nonsteroidal antiinflammatory drugs and transcellular processing. J Exp Med. 2000;192(8):1197-204. Doi: 10.1084/jem.192.8.1197. PMID: 11034610, PMCID: PMC2195872.
11. Serhan CN, Levy BD. Resolvins in inflammation: emergence of the pro-resolving superfamily of mediators. J Clin Invest. 2018;128(7):2657-69. Doi: 10.1172/JCI97943. PMID: 29757195, PMCID: PMC6025982.
12. Bedell S, Hutson J, de Vrijer B, Eastabrook G. Effects of maternal obesity and gestational diabetes mellitus on the placenta: current knowledge and targets for therapeutic interventions. Curr Vasc Pharmacol. 2021;19(2):176-92. Doi: 10.2174/1570161118666200616144512. PMID:32543363.
13. International Association of Diabetes and Pregnancy Study Groups Consensus Panel; Metzger BE, Gabbe SG, Persson B, Buchanan TA, Catalano PA, et al. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care. 2010 Mar;33 (3):676-82. Doi: 10.2337/dc09-1848. PMID: 20190296, PMCID: PMC2827530.
14. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 15. Management of Diabetes in Pregnancy: Standards of Care in Diabetes-2023. Diabetes Care. 2023;46(Suppl 1):S254-S266. Doi: 10.2337/dc23-S015. PMID: 36507645, PMCID: PMC9810465.
15. Leuti A, Fazio D, Fava M, Piccoli A, Oddi S, Maccarrone M. Bioactive lipids, inflammation and chronic diseases. Adv Drug Deliv Rev. 2020;159:133-169. Doi: 10.1016/j.addr.2020.06.028. PMID: 32628989.
16. Levy BD, Clish CB, Schmidt B, Gronert K, Serhan CN. Lipid mediator class switching during acute inflammation: signals in resolution. Nat Immunol. 2001;2(7):612-9. Doi: 10.1038/89759. PMID: 11429545.
17. Morshedzadeh N, Saedisomeolia A, Djalali M, Eshraghian MR, Hantoushzadeh S, Mahmoudi M. Resolvin D1 impacts on insulin resistance in women with polycystic ovary syndrome and healthy women. Diabetes Metab Syndr. 2019;13(1):660-4. Doi: 10.1016/j.dsx.2018.

11.018. PMID: 30641785.

18. Perucci LO, de Castro Pinto KM, da Silva SPG, Lage EM, Teixeira PG, Barbosa AS, et al. Longitudinal assessment of leukotriene B4, lipoxin A4, and resolvin D1 plasma levels in pregnant women with risk factors for preeclampsia. Clin Biochem. 2021;98:24-8. Doi: 10.1016/j.clinbiochem.2021.09.002. PMID: 34492288.
19. Briana DD, Malamitsi-Puchner A. Reviews: adipocytokines in normal and complicated pregnancies. Reprod Sci. 2009 Oct;16(10):921-37. Doi: 10.1177/1933719109336614. PMID: 19474287.
20. Donath MY, Böni-Schnetzler M, Ellingsgaard H, Ehses JA. Islet inflammation impairs the pancreatic beta-cell in type 2 diabetes. Physiology (Bethesda). 2009;24:325-31. Doi: 10.1152/physiol.00032.2009. PMID: 19996363.
21. Bathina S, Das UN. Resolvin D1 decreases severity of streptozotocin-induced type 1 diabetes mellitus by enhancing BDNF levels, reducing oxidative stress, and suppressing inflammation. Int J Mol Sci. 2021;22(4):1516. Doi: 10.3390/ijms22041516. PMID: 33546300, PMCID: PMC7913477.
22. Sun Q, Wang J, Jing Y, Liu J, Jin J, Wang S, et al. Influences of resolvin D1 and D2 on the risk of type 2 diabetes mellitus: a Chinese community-based cohort study. Front Immunol. 2023;14:1143456. Doi: 10.3389/fimmu.2023.1143456. PMID: 37334388, PMCID: PMC10272361.
23. Vozarova B, Weyer C, Lindsay RS, Pratley RE, Bogardus C, Tataranni PA. High white blood cell count is associated with a worsening of insulin sensitivity and predicts the development of type 2 diabetes. Diabetes. 2002;51(2):455-61. Doi: 10.2337/diabetes.51.2.455. PMID: 11812755.
24. Makki K, Froguel P, Wolowczuk I. Adipose tissue in obesity-related inflammation and insulin resistance: cells, cytokines, and chemokines. ISRN Inflamm. 2013;2013:139239. Doi: 10.1155/2013/139239. PMID: 24455420, PMCID: PMC3881510.
25. Szczuko M, Szwec-Nadworna N, Palma J, Tomasik M, Ziętek M. Increased demand of obese women for protectins, maresin, and resolvin d1 in the last trimester of pregnancy. Nutrients. 2023;15(20):4340. Doi: 10.3390/nu15204340. PMID: 37892415, PMCID: PMC10609750.
26. Guariguata L, Linnenkamp U, Beagley J, Whiting DR, Cho NH. Global estimates of the prevalence of hyperglycaemia in pregnancy. Diabetes Res Clin Pract. 2014;103(2):176-85. Doi: 10.1016/j.diabres.2013.11.003. PMID: 24300020.
27. Blank A, Grave GD, Metzger BE. Effects of gestational diabetes on perinatal morbidity reassessed. report of the international workshop on adverse perinatal outcomes of gestational diabetes mellitus, December 3-4, 1992. Diabetes Care. 1995;18(1):127-9. Doi: 10.2337/diacare.18.1.127. PMID: 7698033.
28. Hod M, Merlob P, Friedman S, Schoenfeld A, Ovadia J. Gestational diabetes mellitus. A survey of perinatal complications in the 1980s. Diabetes. 1991;40 Suppl 2:74-8. Doi: 10.2337/diab.40.2.s74. PMID: 1748270.