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Plasma sFRP4 Levels and Their Relationship with HOMA IR in Women with Gestational Diabetes Mellitus

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Abstract

Background: Secreted Frizzled Related Protein 4 (sFRP4) is an inflammatory mediator and an antagonist of Wnt signalling, which has been implicated in the pathogenesis of T2DM by causing reduced insulin exocytosis. However, its association with gestational diabetes mellitus (GDM), has not been elucidated extensively.

We measured and compared sFRP4 in pregnant women with and without GDM and evaluated the association between sFRP4 and insulin sensitivity indices.

Methods: We conducted a cross-sectional case–control study of 42 women with IADPSG-defined GDM and 36 normoglycaemic controls at 24–28 weeks' gestation. Plasma sFRP4 was quantified by ELISA, insulin on an automated analyser, and HOMA-IR/HOMA-β were calculated. Group differences were tested with t/Mann–Whitney U and χ^2 tests, and multivariable logistic and linear regressions (adjusted for age and BMI) assessed the association of sFRP4 with GDM risk and HOMA-IR (SPSS IBM 20, Stata 17; two-tailed $P < 0.05$)

Results: Median (IQR) sFRP4 concentrations were higher in women with GDM than in controls (287.2 (225–416) vs 230.8 (165–299) ng/mL; $P = 0.018$). Plasma sFRP4 was not significantly correlated with HOMA-IR or HOMA-β (r = 0.145 and 0.068, respectively). On multivariable logistic regression, each 1 kg/m² increase in BMI raised the odds of GDM by 27 % (OR = 1.27, 95 % CI 1.07–1.50; $P = 0.006$), and each 1 ng/mL increase in sFRP4 raised the odds by 0.4 % (OR = 1.004, 95 % CI 1.000–1.010; $P = 0.033$).

Conclusion: Women with GDM have significantly higher sFRP4 levels as compared to healthy pregnant controls.

Keywords: sFRP4, Secreted frizzled related protein, Gestational diabetes mellitus (GDM), Wnt, Insulin, HOMA IR

Conflicts of Interest: *None declared*
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Introduction

Secreted Frizzled Related Protein 4 (sFRP4), an inflammatory mediator, belongs to a family of secreted proteins exhibiting sequence similarity to the extracellular domain of frizzled proteins, which function as Wnt receptors (1–3). Wnt signalling pathway components, including β-catenin, are part of the glucose and lipid metabolism, influencing

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↑What is "already known" in this topic:

- Circulating secreted frizzled-related protein-4 (sFRP4), a Wnt-signalling antagonist, has been linked to obesity, insulin resistance, and type 2 diabetes.
- Evidence for its role in gestational diabetes mellitus (GDM) is scant and inconsistent; few studies have adjusted for maternal body-mass index (BMI).

→What this article adds:

- In a cross-sectional case-control sample of Indian women at 24–28 weeks' gestation, higher plasma sFRP4 independently increased the odds of GDM even after controlling for BMI and age (OR = 1.004 per ng/mL; 95 % CI 1.000–1.010).
- BMI remained the strongest modifiable predictor (OR = 1.27 per kg/m²), whereas sFRP4 showed no independent association with HOMA-IR once confounders were considered.
- These findings suggest sFRP4 may serve as an early biochemical signal of GDM risk rather than a driver of insulin resistance, pointing clinicians toward combined weight-management and biomarker-based screening strategies.

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the evolution of diabetes (4). Demonstrated to be induced by oestrogen in the endometrium, Wnt signalling is involved in pregnancy as well, specifically in blastocyst formation & activation, endometrial receptivity and decidualisation, implantation, placentation (trophoblast differentiation and invasion) & later on in developmental processes including embryogenesis as well as mammary development postnatally (5–11). Multiple Wnt proteins secreted by the blastocyst may also be responsible for activating Wnt/ B-catenin signalling in the uterus (12, 13).

Aberrant Wnt signalling in the uterus is associated with infertility, endometriosis, endometrial cancer, and many other gestational diseases (14).

The sFRP family encompasses domains for Wnt-binding and functions as soluble regulators of Wnt signalling pathways (15, 16). sFRP4 has been linked to Type 2 Diabetes Mellitus (T2DM) in several studies (17–22).

Expressed in several embryonic and adult cells as well as tissues, the association of SFRP4 with β-cell dysfunction in diabetes is closely related to expression in pancreatic islets (23, 24). It has been found to regulate insulin exocytosis in murine and human islet cells by downregulating the expression of L and P/Q-type Ca2+ channels, and has been observed to be increased several years before the diagnosis of diabetes is made clinically, possibly useful as an early diabetes marker (4, 17, 18, 25). In early pregnancy, SFRP4 was found to have diminished expression (21-fold) in the uterus (15).

Studies assessing sFRPs in GDM are scarce. Few studies reported serum sFRP4 to be significantly elevated in GDM patients when compared to the healthy control group (26–28).

In the present study, plasma levels of sFRP4 and insulin were measured, and homeostasis model assessment of insulin resistance (HOMA IR) was calculated in the second trimester of pregnancy (24-28 weeks of gestation) in pregnant women with and without GDM applying the International Association of the Diabetes and Pregnancy Study Group (IADPSG) criteria. sFRP4 levels were compared in cases and controls and correlated with HOMA-IR. We hypothesized that since a large percentage of GDM-diagnosed women have been found to develop T2DM later in life, sFRP4 blood levels may be increased in women diagnosed with GDM too.

Methods

Study participants

For this cross-sectional, observational, and non-interventional case-control study, blood samples sent to the clinical laboratory of pregnant women at the second trimester (24-28 weeks of gestation), who attended the Obstetrics and Gynecology department, Kasturba Medical College, Manipal, for a 75g oral Glucose tolerance test (OGTT) for routine antenatal screening were utilized. At the time, the pregnant women were informed about the study & informed consent was taken with the help of the treating Obstetrician. The blood samples were collected for a period of 8 months.

Ethics approval- The study with biological samples was carried out after obtaining approval from the Institutional Ethics Committee & informed consent was taken with the help of a consulting obstetrician. This study was performed in line with the principles of the Declaration of Helsinki (IEC no. 440/2015).

The process of participant selection and group allocation is illustrated in Figure 1.

Following the OGTT, GDM was defined based on newly diagnosed diabetes according to the guidelines of IADPSG (29). Based on these thresholds and inclusion exclusion criteria (as listed in the flowchart), 42 pregnant subjects were grouped as GDM patients between the age group of 18-45 years. Pregnant women diagnosed with pre-existing Diabetes mellitus before pregnancy were not considered for the study. Furthermore, 36 pregnant women with normal OGTT served as controls. Pregnant women suffering from any major medical or surgical illness or on any medications were excluded from the study. BMI was determined at 24-28 weeks of gestation as weight divided by squared height and categorized into four major categories applying the WHO criteria (kg/m^2), (I – Underweight (<18.5), II- Normal (18.5-24.9), III- Overweight (25-29.9), IV-Obese (≥30)) (30). Routine analysis data available of total and differential WBC count was used to calculate the neutrophil to lymphocyte ratio (NLR) as a measure of a simple inflammatory marker (31, 32). Furthermore, insulin sensitivity index, HOMA-IR, and HOMA-β (beta cell function) (%B) were determined as described by Matthews et al. (33) and modified for accommodating glucose in mg/dl as follows: HOMA-IR= (I0 x G0) / 405. Where I0 is fasting plasma glucose in mg/dL, G0 is fasting plasma insulin in μIU/mL (mU/L), and 405 is a constant. HOMA-β = 360 × I0/(G0–63), where 360 and 63 are constants (34). An increase in HOMA-IR and a decrease in HOMA-β are associated with an increased incidence of diabetes. Data recording for a proforma containing routine clinical details was filled through the treating obstetrician.

Assays

All blood samples, namely fasting, 1 hr, and 2 hr, were obtained from pregnant women undergoing OGTT tests in grey capped evacuation tubes (BD Vacutainer) coated with sodium fluoride and EDTA. Centrifugation of the blood sample was done at 2500 rpm for 5 minutes in the REMI centrifuge. Plasma was separated from the samples, aliquoted, and stored at -80°C in Eppendorf tubes until use for a maximum of 18 months. Glucose levels (mg/dL), namely Fasting plasma glucose (FPG), 1hrPG (1 hr plasma glucose), 2hrPG (2 hr plasma glucose), measured using the hexokinase method (Roche Diagnostics, USA) in COBAS 6000 c501 for routine OGTT test, were retrieved via electronic laboratory records. sFRP4 (USCNK Life Science Inc., Cloud-clone Corp, TX, USA) plasma concentrations were determined according to the manufacturer's instructions by ELISA. Appropriate dilutions and multiplication factors were applied as instructed by the manufacturer. Fasting plasma insulin (FPI) (μIU/mL) (Roche Diagnostics, USA) in the stored samples was determined with the Sandwich principle by electrochemiluminescence immunoassay (ECLIA) in the COBAS 6000 e601 automated analyzer. sFRP4 and FPI levels were estimated only in fasting plasma samples.

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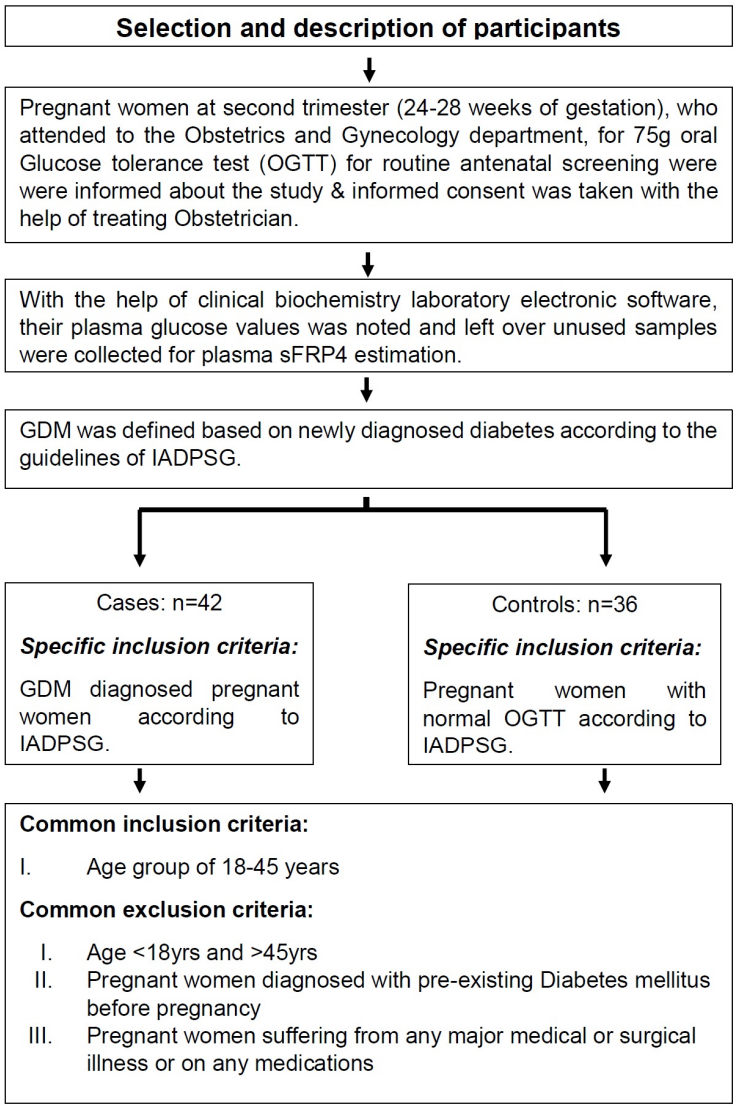

Figure 1. Flowchart of participant recruitment, eligibility screening, and group allocation

Statistical analysis

SPSS Software version 20.0 (IBM, USA) and Stata 17.0 (StataCorp, College Station, TX, USA) were used in all statistical analyses. Continuous variables were screened for outliers, tested for normality with the Shapiro–Wilk test, and summarised as mean ± SD if normally distributed or median (interquartile range) if skewed. Categorical variables are presented as counts and percentages. Group comparisons between GDM cases and controls employed Student's t-test or the Mann–Whitney U test, and χ^2 tests for proportions.

Spearman's rank correlation assessed crude associations between circulating sFRP4 and metabolic indices (HOMA-IR, HOMA-β). Two multivariable models were then fitted. First, a logistic-regression model estimated the odds of GDM with sFRP4, body-mass index (BMI), and maternal age entered simultaneously; results are expressed as adjusted odds ratios (ORs) with 95 % confidence intervals (CIs). Second, a multiple-linear regression model examined predictors of HOMA-IR, reporting unstandardised coefficients, standard errors, standardised β-coefficients, and p-values. Variance-inflation factors confirmed the absence of multicollinearity (all VIF < 2). Model adequacy was checked with the likelihood-ratio test for the logistic model and adjusted R^2 plus residual plots for the linear model. Statistical significance was set at a two-tailed $P < 0.05$.

Results

Baseline characteristics of case and controls

The clinical laboratory-related data of pregnant women diagnosed with and without GDM by applying IADPSG are given in Table 1. A total of 78 pregnant women were included in the current study, of which 42 were diagnosed

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with GDM and 36 were healthy pregnant women with normal glucose levels.

BMI, FPG, 1hrPG, 2hrPG, HOMA-IR, and FPI were significantly elevated in GDM-diagnosed women when compared to controls (Table 1).

Median (IQR) plasma fasting sFRP4 levels were higher in women with GDM when compared to pregnant controls without GDM (287.17 (225-416) vs 230.75 (165-299) ng/mL (P = 0.018)) (Figure 2).

Figure 3 demonstrates sFRP4 levels in women with and without GDM across different categories of WHO-based BMI criteria.

Comparison of sFRP4 levels in pregnant women diagnosed by applying the Carpenter-Coustan (CC) criteria was also done (35). Median levels of 259.3 ng/mL and 253.73 ng/mL for cases and controls, respectively, showed no statistically significant differences.

Power analysis (G*Power 3.1; two-tailed independent-samples t-test) indicated that, with 42 GDM cases and 36 controls (total n = 78), α = 0.05, and an expected effect size of d = 0.60, the study achieved 74 % power to detect the specified difference in plasma sFRP4 concentrations.

sFRP4 levels in women with a current or previous history of adverse pregnancy outcomes

Women with previous or current pregnancy culminating in LSCS (Lower segment caesarean section), IUGR (Intrauterine growth restriction), small for gestational age baby, preterm birth, PPROM (Premature preterm rupture of membranes), h/o threatened preterm abortion, decreased fetal movements, gestational hypertension) were included in the adverse pregnancy outcome group. Women with previous or current pregnancy culminating in full-term normal vaginal delivery were grouped as uneventful pregnancies.

Among women with a previous or current history of adverse pregnancies, sFRP4 (ng/mL) concentrations were significantly higher in women with GDM than those with normal OGTT values (P = 0.016) (Table 2).

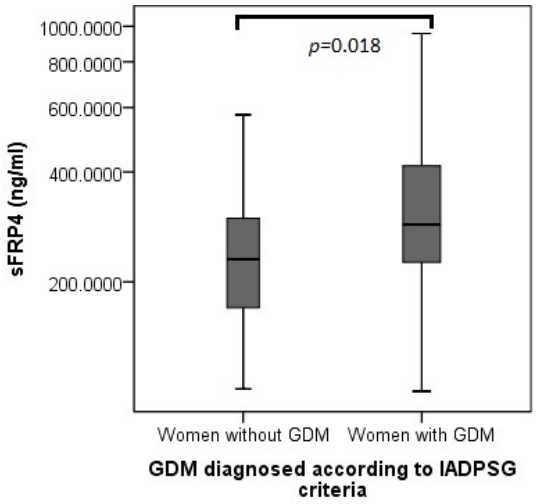

Figure 2. Boxplot showing sFRP4 median levels and Inter-quartile range (IQR) in women with and without GDM

Correlation of SFRP4 with other parameters

Spearman correlation of sFRP4 with various parameters, including HOMA-IR, within cases and controls was not found statistically significant (Table 3).

Multiple linear regression

In the multiple-linear regression (Table 4), plasma sFRP4 (ng/mL), fasting insulin (μIU/mL), and BMI (kg/m^2) together accounted for roughly one-third of the variability in fasting-plasma glucose (mg/dL). After all predictors were standardised, sFRP4 remained the strongest positive determinant of glucose, followed by BMI and fasting insulin; age did not contribute independently. Multicollinearity was negligible (all VIF < 1.5), and residual diagnostics showed no violation of model assumptions. These findings indicate that higher circulating sFRP4, greater adiposity, and insulin resistance each drive fasting hyperglycaemia during pregnancy, whereas chronological age has little impact once

Table 1. Demographic and clinical laboratory data of women diagnosed with and without GDM by applying International Association of the Diabetes and Pregnancy Study Group (IADPSG) criteria

	GDM status		
Variable	Yes	No	*P* value
N	42	36	
Age (yrs)	29.02 ± 4.4	28.66 ± 4.03	0.600
BMI (Kg/m^2)	24.2 ± 5.9	21.7 ± 2.8	0.001
FPG (mg/dL)	95 ±12	81 ± 6	<0.001
1hrPG (mg/dL)	167 ± 35	136 ± 23	<0.001
2hrPG (mg/dL)	152 ± 40	112 ± 20	<0.001
FPI (μIU/mL)	11 (7.3-17)	6.09 (4.4-7.3)	0.028
HOMA-IR (glucose in mg/dL)	2.54 (1.6-4.3)	1.2 (0.9-1.5)	<0.001
HOMA-β % (glucose in mg/dL)	144.32 (99.9-194.6)	117.35 (90-166)	0.360
sFRP4 (ng/mL)	287.17 (225-416)	230.75 (165-299)	0.018
Total WBC (cells/μl)	12.5 (10.1-15.5)	10.6 (8.9-12.6)	0.010
Neutrophil (cells/μl)	74.8 (64.1-79.4)	68.1 (14.1-74.7)	0.027
Lymphocytes (cells/μl)	17.6 (13.7-21.7)	19.3 (17.-22.3)	0.155
NLR	3.9 (2.4-5.7)	3.1 (0.58-4.1)	0.050

BMI- Body mass index, FPG-Fasting plasma glucose, 1hrPG- 1 hr plasma glucose, 2hrPG -2 hr plasma glucose, FPI- Fasting plasma insulin, HOMA-IR homeostasis model assessment of insulin resistance, HOMA-β (beta cell function), sFRP4-Secreted Frizzled Related Protein 4, NLR- Neutrophil/Leukocyte ratio, WBC- White blood cells.
Data presented as mean +- SD unless specified otherwise.
P-value <0.05 was considered significant.

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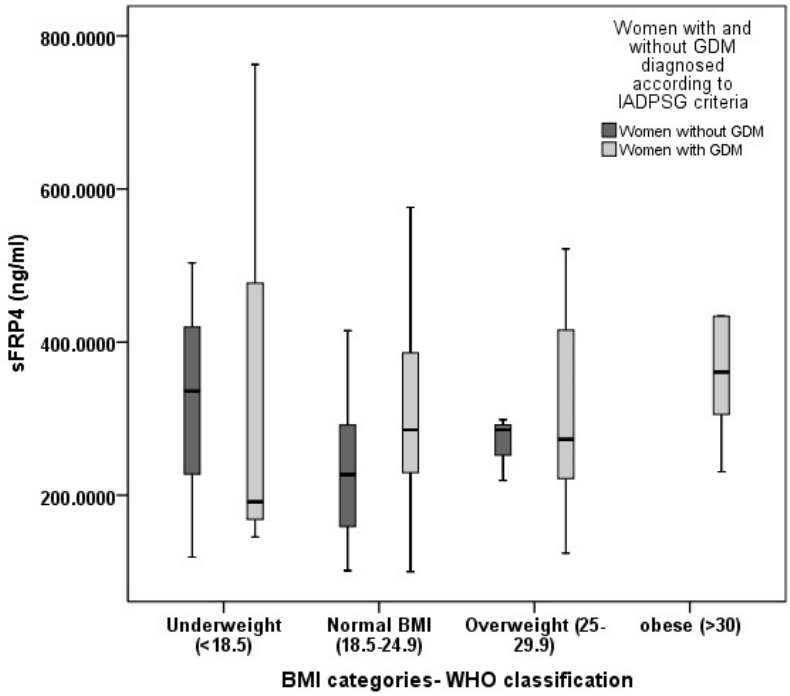

Figure 3. Boxplot showing sFRP4 median levels and Inter-quartile range (IQR) in women with and without GDM across different categories of WHO-based BMI criteria

Table 2. Comparison of plasma sFRP4 concentrations (ng/mL) in women with and without adverse pregnancy outcomes, stratified by GDM status

Pregnancy		N	sFRP4 (ng/ml)	*P* value
Adverse pregnancy out-come	Women with GDM	34	302.73 [231.27–416.85]	0.016
	Pregnant women with normal OGTT	28	227.11 [175.74–303.17]	
Uneventful pregnancy	Women with GDM	8	246.77 [217.61–307.21]	0.768
	Pregnant women with normal OGTT	8	240.38 [181.24–293.61]	

Independent samples Mann-Whitney U test.
sFRP4 (ng/mL) Median (IQR)
P-value <0.05 was considered significant.

Table 3. Spearman correlation analysis of sFRP4 (ng/mL) with other parameters

Variable	sFRP4 (ng/mL)			
	GDM		Controls	
	r	*P*	r	*P*
Age (yrs)	0.049	0.760	0.140	0.416
BMI (Kg/m^2)	0.196	0.214	-0.200	0.243
FPG (mg/dL)	0.192	0.223	-0.155	0.368
1hrPG (mg/dL)	-0.236	0.132	-0.227	0.184
2hrPG (mg/dL)	0.053	0.738	-0.045	0.792
FPI (µIU/mL)	0.231	0.140	-0.256	0.132
HOMA-IR (glucose in mg/dL)	0.229	0.145	-0.276	0.103
HOMA-β % (glucose in mg/dL)	0.066	0.680	0.020	0.907
Total WBC (cells/µl)	0.263	0.093	0.020	0.927
NLR	0.155	0.327	0.075	0.665

BMI- Body mass index, FPG-Fasting plasma glucose, 1hrPG- 1 hr plasma glucose, 2hrPG -2 hr plasma glucose, FPI- Fasting plasma insulin, HOMA-IR homeostasis model assessment of insulin resistance, HOMA-β (beta cell function), sFRP4-Secreted Frizzled Related Protein 4, NLR- Neutrophil Leukocyte ratio, WBC- White blood cells.

these factors are considered.

Multivariate binary logistic regression analysis

A logistic regression analysis was performed to ascertain the effects of sFRP4, age, BMI, and FPI on the probability that pregnant women have GDM (Table 5). The model was statistically significant ($\chi2(4) = 18.36$, $P = 0.001$). The explained variation in GDM based on our model was 28% and we correctly classified 73.1% of cases. sFRP4 levels ($P = 0.033$) and BMI ($P = 0.024$) added significantly to the model prediction, while age and FPI did not add significantly to the model.

Even after accounting for age and fasting insulin, higher sFRP4 and BMI independently increased the odds of GDM, underscoring their usefulness as early-pregnancy biomarkers.

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Table 4. Multiple regression analysis to predict glucose levels from sFRP4, age, FPI, and BMI

				95% CI		*P*	
Variable	β	SE	Std_Beta	Lower	Upper		VIF
sFRP4 (ng/mL)	0.27	0.007	0.389	0.14	0.04	<0.001	1.04
Age (yrs)	-0.263	0.279	-0.093	-0.818	0.293	0.350	1.15
FPI (µIU/mL)	0.218	0.098	0.225	0.024	0.413	0.028	1.2
BMI (Kg/m^2)	0.77	0.303	0.269	0.165	1.375	0.013	1.33

sFRP4-Secreted Frizzled Related Protein 4, FPI- Fasting plasma insulin, BMI- Body mass index. p-value <0.05 was considered significant.

Table 5. Binary-logistic regression evaluating whether circulating sFRP4, BMI, FPI, and age independently predict gestational diabetes mellitus (GDM)

Variable	β	Odds ratio Exp (B)	Adjusted OR (95 % CI)		*P*
			Lower	Upper	
sFRP4 (ng/mL)	0.004	1.004	1.000	1.008	0.033
Age (yrs)	-0.029	0.971	0.854	1.105	0.659
FPI (µIU/mL)	0.027	1.027	0.977	1.080	0.297
BMI (Kg/m^2)	0.204	1.226	1.027	1.464	0.024

sFRP4-Secreted Frizzled Related Protein 4, FPI- Fasting plasma insulin, BMI- Body mass index; p value <0.05 was considered significant, CI = confidence interval for the adjusted odds ratio.

Discussion

In the current study, we analysed plasma circulating levels of sFRP4, which were found to be elevated in women with GDM. sFRP4 levels were also significantly higher than the controls within the cohort of pregnancies with previous and/or current history of adverse outcome events. However, correlation of plasma sFRP4 levels with HOMA-IR and HOMA-β was not statistically significant.

The significantly higher distribution of sFRP4 (ng/mL) observed in this study in the GDM cohort (IADPSG) is comparable to several other studies where sFRP4 is found to be elevated (26, 27). The early studies most relevant to this association include those by Mahdi et al. and Hoffman et al., with several later studies reaffirming their observations. In 2012, Mahdi T et al. reported sFRP4 levels in the group without diabetes below the median of 23.7 ng/ml. They found individuals without diabetes who developed T2D later over a period of 15 years (‘‘converters’’) had considerably higher sFRP4 (37%) already at the time of initial visits and prior to developing overt diabetes, with a significant p value (17). In Hoffman’s study, serum sFRP4 levels were positively correlated with FPG, 2hPG, HbA1c, and HOMA-IR and were significantly negatively correlated with HOMA-β (4). In 2015, Liu F et al. reported that serum sFRP4 levels in the T2DM group and IGT (Impaired glucose tolerance test) group were significantly higher than those in the NGT (Normal glucose tolerance) group (21). Similar trends have also been described by a few other studies examining sFRP4 across prediabetic and diabetic populations (21, 22). This was consistent with this study, where increasing levels of plasma sFRP4 were associated with increasing values of HOMA-IR, plasma fasting, as well as 2-hr glucose in GDM diagnosed women, although statistically significant in particular sub-categories of BMI. However, sFRP4 levels negatively correlated in women with normal OGTT levels. This might indicate compensatory mechanisms in women not predisposed to GDM and insulin resistance who have normal downstream insulin signalling. IL-1β stimulation is known to release more SFRP4 in serum. The expression of SFRP4 is also connected with miR-30d, miR-146a, and miR-24, which are elevated in the serum of patients with diabetes. miR-103a and miR-103b lowers sFRP4 levels by acting on its genetic sequence, helping to identify people who are at risk for pre-diabetes with good accuracy. The sFRP4 gene was also identified in a systems genetic study as one of the genes associated with pancreatic islet dysfunction (17, 21, 36-40). These findings highlight sFRP4 as a potential downstream effector of inflammatory and microRNA pathways that compromise β-cell integrity and placental metabolic homeostasis, which may explain its elevation in GDM and related adverse pregnancy outcomes. Recent studies have used gene and miRNA profiles, in predictive models for adverse pregnancy outcomes, improving early identification of high-risk patients (41). Collectively, our results indicate that sFRP4 may help predict subgroups of women at increased risk for adverse pregnancy outcomes, underscoring, the potential of sFRP4 as an integrative marker linking systemic inflammation, β-cell stress, and placental dysfunction in gestational diabetes. This finding extends the utility of sFRP4 beyond GDM diagnosis, suggesting its potential for risk stratification and targeted follow-up in clinical obstetric practice.

Limitations

Limitations of the study- The number of subjects participating could be larger. sFRP4 could have been studied in different trimesters of pregnancy. Blood sFRP4 was measured in plasma and not serum. Due to time constraints, adverse pregnancy outcomes strictly related to the present pregnancy were not available in significant numbers. Pre-pregnancy BMI & glucose levels were not adequately available. Further studies should be undertaken to study Wnt signalling in GDM, as a potential target for medical intervention, diagnosis, or a biomarker.

Conclusion

In conclusion, women with GDM have significantly higher sFRP4 levels as compared to healthy pregnant controls. As an inflammatory mediator, the role of sFRP4 in influencing insulin receptor resistance in GDM patients, which can lead to elevated glucose levels, needs to be further elucidated. sFRP4 could also be associated with damage in the downstream signalling of insulin, resulting in impaired insulin sensitivity, which is subsequently involved in the pathogenesis and development of GDM. Although

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the full mechanisms behind this process are not fully understood, these results suggest a link between GDM and increased sFRP4 levels.

Authors' Contributions

– Neelam M Pawar: Participant recruitment, laboratory assays, statistical analysis, manuscript drafting.

– Pragna Rao: study conception, methodological guidance, data interpretation, critical manuscript revision.

– Muralidhar V Pai: clinical enrolment coordination, obstetric data verification, manuscript revision.

All authors read and approved the final manuscript and agree to be accountable for all aspects of the work.

Ethical Considerations

The study protocol was approved by the Institutional Ethics Committee of Kasturba Medical College, Manipal Academy of Higher Education (IEC no. 440/2015). Written informed consent was obtained from every participant with the help of the Obstetrics department, and the work was conducted in accordance with the Declaration of Helsinki.

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Conflict of Interests

The authors declare that they have no competing interests.

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