

Serum SFRP-4 And Ficolin-3 as Early Predictors of Gestational Diabetes Mellitus in the First Trimester: A Study from Himachal Pradesh

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Abstract

Objective: Secreted frizzled-related protein-4 (SFRP-4) and Ficolin-3 have separately been linked to insulin resistance and low-grade inflammation underlying type 2 diabetes mellitus. This study was aimed to estimate serum SFRP-4 and Ficolin-3 levels in the first trimester of pregnancy and to examine their relationship, if any, with oral glucose tolerance test (OGTT) outcomes, body mass index (BMI) and gestational period.

Methods: A total of 100 pregnant women attending their first prenatal visit between 6 and 13 weeks of gestation at MMMCH Solan were enrolled. Serum SFRP-4 and Ficolin-3 were estimated by enzyme-linked immunosorbent assay (ELISA) and plasma glucose was measured hexokinase method.

Results: Mean SFRP-4 and Ficolin-3 levels were 1.86 ± 1.33 ng/mL and 16.85 ± 14.92 ng/mL, respectively. OGTT, SFRP-4, and Ficolin-3 did not differ significantly across gestational-period subgroups (6-8, 9-11, and ≥ 12 weeks; $p=0.949$, 0.697 , and 0.906). All three parameters rose progressively and significantly across BMI categories and OGTT categories.

Conclusion: Serum SFRP-4 and Ficolin-3 are already detectable and rise in proportion to maternal BMI and glycemic status as early as the first trimester, while remaining stable across small differences in early gestational period.

Keywords: GDM, SFRP-4, Ficolin-3, IR, BMI, OGTT.

Introduction

Gestational diabetes mellitus (GDM), defined as glucose intolerance first recognized during pregnancy, has become a major public health concern in India and globally [1]. In India, nearly four million pregnancies have been affected annually, carrying significant maternal and fetal risk [1]. A national survey stated the prevalence of GDM in Himachal Pradesh at less than 1% [2]. Secreted frizzled-related protein-4 (SFRP-4) has been implicated in insulin resistance and the pathogenesis of T2DM through antagonism of Wnt signaling and direct suppression of insulin secretion from pancreatic β -cells [3]. SFRP-4 also induces apoptosis in pancreatic endothelial cells by enhancing reactive oxygen species, to which β -cells are sensitive.

Ficolin-3 (H-ficolin/Hakata antigen) activates the lectin complement pathway, driving the chronic low-grade inflammation increasingly implicated in insulin resistance. SFRP-4 and Ficolin-3 acting in two mechanistically distinct pathways; metabolic/adipokine-driven and inflammatory/innate-immune, become potent predictor of GDM as early as first trimester [4].

Objectives

- To estimate the levels of SFRP-4 during the first trimester of pregnancy.
- To estimate the levels of Ficolin-3 during the first trimester of pregnancy.

Materials And Methods

This study was conducted in the Department of Biochemistry in collaboration with the Department of Obstetrics and Gynecology, Maharishi Markandeshwar Medical College and Hospital (MMMCH), Solan, Himachal Pradesh.

Inclusion and exclusion criteria

A total of 100 pregnant women attending their first prenatal examination (first screening) between 6 and 13 weeks of gestation at MMMCH Solan Hospital were study participants. Women on extensive medical treatment or lipid-lowering drugs, smokers, and alcoholics were excluded. Written informed consent was obtained from all participants prior to inclusion.

Ethical approval

The study was approved by the Institutional Ethics Committee of MMMCH Solan (Approval No. MMMCH/IEC/24/958).

Anthropometric and biochemical assessment

Anthropometric measurements were taken for calculation of body mass index (BMI). Serum SFRP-4 and Ficolin-3 levels were estimated by enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions (BT-LAB). Plasma glucose was measured on a Cobas c311 fully automated analyzer.

Statistical analysis

Data were expressed as mean±standard deviation (SD) and analyzed using one-way analysis of variance (ANOVA) for comparison across gestational age, BMI, and OGTT categories, and Pearson's correlation was used to assess the relationship of SFRP-4 and Ficolin-3 with OGTT within each stratum. A p-value <0.05 was considered statistically significant.

Results

Of the 100 participants, the majority (63%) were of normal weight, while 34% were overweight or obese (Table 1). Most women were enrolled before 12 weeks of gestation, and the majority had OGTT values within the normal range (≤ 120 mg/dL). The mean age, gestational age at enrolment, BMI, OGTT, SFRP-4, and Ficolin-3 values are summarized in Table 1.

Table 1: Baseline characteristics of study participants (n=100)

Variable	Category	n / Mean±SD
BMI (kg/m ²)	Underweight (≤ 18.5)	8
	Normal weight (18.5-22.9)	63
	Overweight (23-27.49)	29
	Obese (≥ 27.5)	4
Period of gestation (POG)	6-8 weeks	42
	9-11 weeks	36
	Above 12 weeks	22
OGTT (mg/dl)	≤ 120	53
	121-139	36
	≥ 140	11
Age (years)	—	28.94±5.11
Gestational weeks (POG)	—	9.19±2.3
BMI (kg/m ²)	—	23.35±3.47
OGTT (mg/dl)	—	118.36±17.80
SFRP-4 (ng/ml)	—	1.86±1.33

Ficolin-3 (ng/ml)	—	16.85±14.92
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Values are presented as number (n) or mean±SD.

The baseline profile indicates that although the majority of participants were of normal weight, a substantial proportion (34%) fell into the overweight or obese categories a recognized risk factor for impaired glucose tolerance in pregnancy. Biomarker analysis showed that SFRP-4 concentrations increased with rising BMI, supporting its candidacy as a marker of insulin resistance and metabolic stress, whereas the relationship of Ficolin-3 with BMI followed the same upward pattern, consistent with its role in obesity-associated inflammation (Table 3).

Table 2: Comparison of OGTT, SFRP-4, and Ficolin-3 across period of gestation (POG)

Parameter	6-8 weeks	9-11 weeks	≥12 weeks	F	p-value
OGTT (mg/dl)	117.75±20.64	118.52±18.42	119.26±16.01	0.0527	0.9487
SFRP-4 (ng/ml)	1.75±1.66	1.86±1.35	2.05±1.12	0.3625	0.6969
Ficolin-3 (ng/ml)	16.14±16.71	17.66±15.78	16.89±13.45	0.0991	0.9057

Significance level: $p < 0.05$ (one-way ANOVA). No significant differences were observed across POG groups for any parameter.

Table 3: Comparison of OGTT, SFRP-4, and Ficolin-3 across BMI categories

Parameters	<18.5	18.5-22.9	23-27.49	≥27.5	F	p-value
OGTT (mg/dl)	97.30±21.86	114.93±16.31	130.53±8.83	138.5±4.5	14.1363	<0.001
SFRP-4 (ng/ml)	0.97±1.28	1.55±1.21	2.61±1.13	3.76±0.3	9.7479	<0.001
Ficolin-3 (ng/ml)	9.09±12.64	13.03±12.59	25.32±15.57	39.67±1	10.0740	<0.001

Significance level: $p < 0.05$ (one-way ANOVA).

Table 4: Comparison of SFRP-4 and Ficolin-3 across OGTT categories

Parameters	OGTT ≤120	OGTT 121-139	OGTT ≥140	F	p-value
SFRP-4 (ng/ml)	1.01±0.6	2.30±0.76	4.49±1.24	107.0735	<0.001
Ficolin-3 (ng/ml)	7.59±2.85	21.11±11.28	47.56±12.64	116.5995	<0.001

Significance level: $p < 0.05$ (one-way ANOVA)

Pearson's correlation analysis further reinforced these associations. Within every gestational age category, OGTT showed a strong, statistically significant positive correlation with both SFRP-4 ($r=0.76-0.90$) and Ficolin-3 ($r=0.81-0.86$), all $p < 0.001$ (Table 5).

Table 5: Pearson's correlation of OGTT with SFRP-4 and Ficolin-3, categorized by POG

	OGTT	SFRP-4	r value	p-value
6-8 weeks	117.75±20.64	1.75±1.66	0.8814	< 0.001
9-11 weeks	118.51±18.42	1.85±1.35	0.8994	< 0.001
≥12 weeks	119.25±16.01	2.05±1.12	0.7634	< 0.001
	OGTT	Ficolin-3	r value	p-value
6-8 weeks	117.75±20.64	16.13±16.71	0.8148	< 0.001

9-11 weeks	118.51±	17.66±15.78	0.8432	< 0.001
≥12 weeks	119.25±	16.88±13.45	0.8629	< 0.001

At the <0.05 significance level.

Correlation between OGTT and both biomarkers remained strong and significant within every BMI category, with the strongest correlations observed in overweight and obese women (Table 6), and within every OGTT category, with correlation strength increasing markedly at higher OGTT values (Table 7).

Table 6: Pearson's correlation of OGTT with SFRP-4 and Ficolin-3 under BMI categories

BMI	OGTT	SFRP-4	r value	p-value
<18.5	97.3±21.86	0.97±1.28	0.8688	0.005
18.5-22.9	114.92±16.306	1.54±1.21	0.8018	< 0.001
23-27.49	130.52±8.83	2.61±1.13	0.9697	< 0.001
≥27.5	138.50±4.5	3.76±0.3	0.9982	0.001
BMI	OGTT	Ficolin-3	r value	p-value
<18.5	97.3±21.86	9.09±12.64	0.8562	0.006
18.5-22.9	114.92±16.306	13.02±12.59	0.8404	< 0.001
23-27.49	130.52±8.83	25.32±15.57	0.9507	< 0.001
≥27.5	138.50±4.5	39.67±1	0.9709	0.029

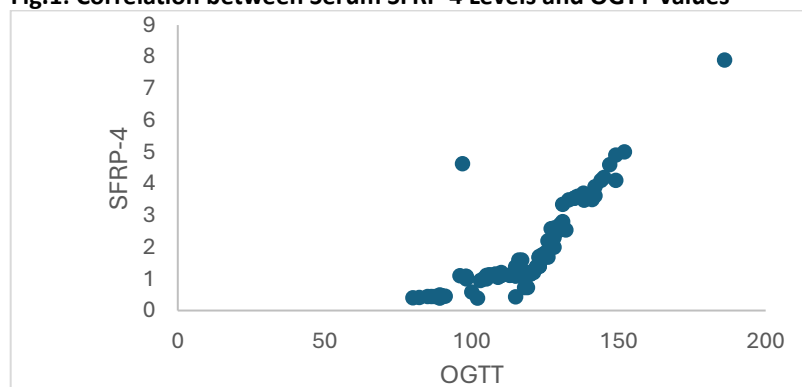
At the <0.05 significance level.

Table 7: Pearson's correlation of OGTT with SFRP-4 and Ficolin-3

	OGTT	SFRP-4	r value	p-value
<120	105.67±11.62	1.01±0.60	0.3219	0.019
121-139	127.72±4.77	2.29±0.76	0.9597	< 0.001
≥140	148.81±12.90	4.49±1.24	0.9807	< 0.001
	OGTT	Ficolin-3	r value	p-value
<120	105.67±11.62	7.58±2.85	0.4647	< 0.001
121-139	127.72±4.77	21.10±11.28	0.9415	< 0.001
≥140	148.81±12.90	47.56±12.64	0.9365	< 0.001

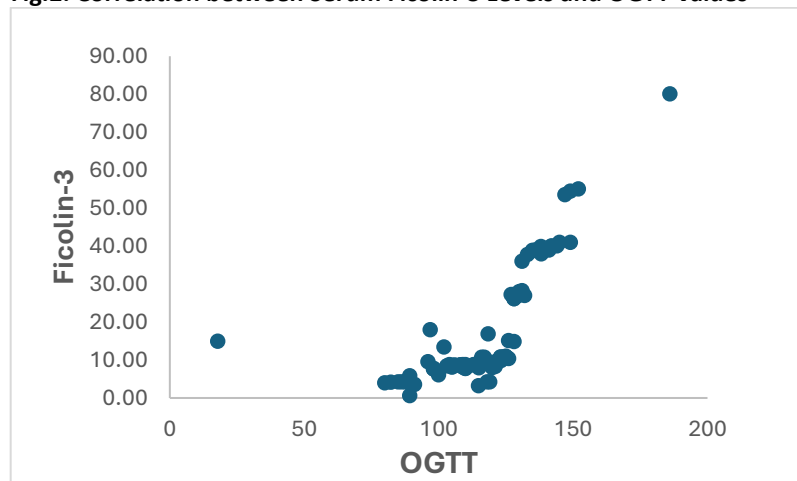
At the <0.05 significance level.

Fig.1: Correlation between Serum SFRP-4 Levels and OGTT Values



Scatter plot showing the relationship between Secreted Frizzled-Related Protein 4 (SFRP-4) concentrations and Oral Glucose Tolerance Test (OGTT) results. A positive association is observed, with SFRP-4 levels rising sharply as OGTT values exceed 130 mg/dL, suggesting a potential link between SFRP-4 and impaired glucose regulation.

Fig.2: Correlation between Serum Ficolin-3 Levels and OGTT Values



Scatter plot illustrating the association between Ficolin-3 concentrations and OGTT results. Ficolin-3 levels show a general upward trend with increasing OGTT values, most notably beyond the 130 mg/dL threshold, indicating a possible relationship between Ficolin-3 and glycemic status.

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of serum SFRP-4 and Ficolin-3 in predicting GDM. The area under the curve (AUC) for SFRP-4 was 0.810 ($p < 0.001$), indicating good discriminative ability. For Ficolin-3, the AUC was 0.790, indicating fair-to-good discriminative performance, marginally lower than that of SFRP-4 (Figs. 3 and 4).

Fig.3: ROC curve for serum SFRP-4 in predicting gestational diabetes mellitus. AUC = [0.810], $p = [<0.001]$.

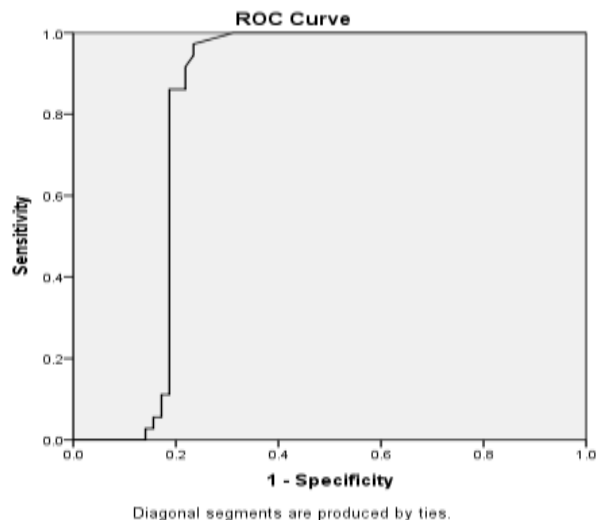
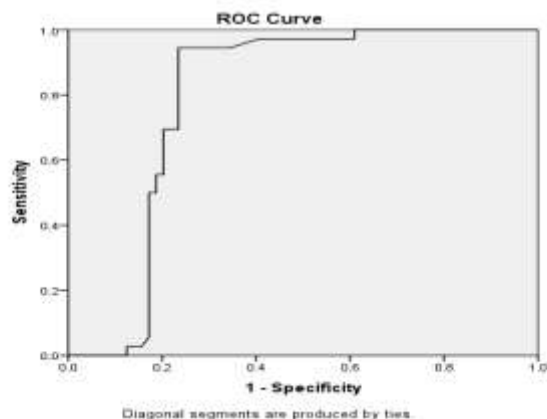


Fig. 4: ROC curve for serum Ficolin-3 in predicting gestational diabetes mellitus. AUC = [0.790], $p = [<0.001]$.



Discussion

In this study, serum SFRP-4 and Ficolin-3 were progressively related with OGTT outcomes and BMI ($p < 0.001$ for both) but did not vary across the 6-8, 9-11, and ≥ 12 -weeks POG subgroups ($p = 0.697$). This pattern indicates that both markers track metabolic status rather than gestational period itself within early pregnancy, so a single first-trimester sample is unlikely to be confounded by the exact week of sampling, a practical requirement for any early screening marker. These findings are supported by the study done by Schuitemaker et al [5]. Similar findings were reported by Shrewastwa et al. (2024) among Asian Nepalis at the stage of impaired glucose tolerance proposing that the increased serum SFRP4 may be a good biomarker of decline in β -cell function and insulin resistance [6]. The other supporting studies are done by Brix et al. [7] and by Anand et al. in Tamil Nadu [8]. This is consistent with Schuitemaker et al., who found significantly higher first-trimester sFRP4 (70-90 days) in women who later developed GDM, though sFRP4 alone was not independently predictive in a multivariate adipokine model (AUC 0.699) [9] suggesting SFRP-4 is best combined with complementary markers such as Ficolin-3. The second-trimester observations of Yuan et al., who first reported elevated SFRP-4 and Ficolin-3 in GDM at 16-18 weeks with the two markers correlated across gestation [4], by showing that both are already elevated with rising BMI and glycemia between 6 and 13 weeks. Raised ficolin-3 level was demonstrated by Yaun at al. (2017) among GDM group than normal pregnant women [10] while Halmos et al demonstrated lower level of ficolin-3 among GDM women than healthy women [11]. Dönmez et al. recently showed SFRP-4 acting as a central, correlated node within a Wnt-pathway panel (with WIF-1 and CTNNB1) that outperformed any single marker in GDM [12]. Ficolin-3, acting through the lectin complement pathway, plausibly captures the parallel innate-immune/inflammatory contribution to insulin resistance; together the two markers span complementary metabolic and inflammatory axes [13] and this study extends their first-trimester relevance to a North Indian population not previously represented in this literature. The high discriminative ability of both markers on ROC analysis (Figs.3 and 4) is consistent with their strong positive correlation with OGTT outcomes across BMI and gestational-age strata (Tables 5-7), emphasising their potential role as first-trimester GDM predictor than OGTT alternative.

Limitations: a single-centre design, modest sample size, absence of a formally matched normoglycemic control group, and lack of follow-up to confirmed GDM diagnosis. Larger prospective cohorts with second- and third-trimester follow-up studies are required to establish these markers to be considered for first-trimester GDM screening tool.

Conclusion

Serum SFRP-4 and Ficolin-3 are measurable and vary meaningfully with maternal BMI and glycemic status as early as the first trimester of pregnancy, while remaining stable across small differences in early gestational age. Both biomarkers correlated strongly and consistently with OGTT across BMI and OGTT strata, supporting their potential role as early biomarkers of metabolic stress and gestational dysglycemia. Larger prospective studies are needed to confirm their predictive value for the development of gestational diabetes mellitus and to explore their clinical application in early screening and risk stratification, particularly in North Indian populations where GDM prevalence estimates vary widely.

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Conflict Of Interest

The authors declare no conflict of interest.

Author's Contributions

Miss Samiksha (PhD Scholar) contributed to the initial drafting of the manuscript, literature review, sample collection, sample analysis and data analysis. Dr. Monika Jindal participated in data collection and result interpretation and literature review.

Dr. Bharti Kwatra supported data validation, helped refine the study design, and provided critical revisions to improve the manuscript. The overall study supervision at all stages of data analysis and interpretation was under Dr. Bharti Kwatra. All authors reviewed and approved the final version of the manuscript.

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References

1. International Diabetes Federation. IDF Diabetes Atlas. 10th ed. Brussels, Belgium: International Diabetes Federation; 2021.
2. Seshiah V, Balaji V, Balaji MS, Sanjeevi CB, Green A. Gestational diabetes mellitus in India. J Assoc Physicians India. 2004; 52: 707-711.
3. Mahdi T, Hänzelmann S, Salehi A, Muhammed SJ, Reinbothe TM, Tang Y, et al. Secreted frizzled-related protein 4 reduces insulin secretion and is overexpressed in type 2 diabetes. Cell Metab. 2012;16(5):625-633.
4. Yuan XS, Zhang M, Wang HY, Jiang J, Yu B. Increased secreted frizzled-related protein 4 and ficolin-3 levels in gestational diabetes mellitus women. Endocr J. 2018;65(4):499-508.
5. Schuitemaker JHN, Beernink RHJ, Franx A, Cremers TIFH, Koster MPH. First trimester secreted Frizzled-Related Protein 4 and other adipokine serum concentrations in women developing gestational diabetes mellitus. PLoS ONE. 2020; 15(11): e0242423.
6. Shrewastwa MK, Acharya V, Shyam Kumar B, Ray S. A Study to Evaluate the Role of Secreted Frizzled-Related Protein 4 (SFRP4) as a Potential Novel Biomarker of Type 2 Diabetes Mellitus. Med J Dr DY Patil University. 2023;17(3):523-532.
7. Brix JM, Krzizek EC, Hoebaus C, Ludvik B, Schernthaner G, Schernthaner GH. Secreted Frizzled-Related Protein 4 (SFRP4) is Elevated in Patients with Diabetes Mellitus. Horm Metab Res. 2016;48(5):345-8.
8. Anand K, Vidyasagar S, Lasrado I, Pandey GK, Amutha A and Ranjani H et al. Secreted Frizzled-Related Protein 4 (SFRP4): A Novel Biomarker of b-Cell Dysfunction and Insulin Resistance in Individuals with Prediabetes and Type 2 Diabetes. Diabetes Care. 2016; 39 (9): e147-8.
9. Beernink RHJ, Schuitemaker JHN, Faas MM, Poston L, White SL on behalf of the UPBEAT Consortium. Early Pregnancy Serum Concentration of Secreted Frizzled-Related Protein 4, Secreted Frizzled-Related Protein 5, and Chemerin in Obese Women Who Develop Gestational Diabetes Mellitus. Diabetol. 2022; 3(1): 258-65.
10. Yuan XS, Shi H, Wang HY, Yu B, Jiang J. Ficolin-3/adiponectin ratio for the prediction of gestational diabetes mellitus in pregnant women. J Diabetes Investig. 2018; 9(2):403-10.
11. Halmos A, Rigó J Jr, Szijártó J, Füst G, Prohászka Z, Molvarec A. Circulating ficolin-2 and ficolin-3 in normal pregnancy and pre-eclampsia. Clin Exp Immunol. 2012;169(1):49-56.
12. Dönmez YÇ, Keles E, Bağlar İ, Şanlıkan F, Kara SS, Akin ÖD, et al. Wnt signaling-related biomarkers in gestational diabetes mellitus: diagnostic performance and integrated statistical modeling. Diagnostics (Basel). 2026;16(12):1779.
13. Hein E, Honoré C, Skjoedt MO, Munthe-Fog L, Hummelshøj T, Garred P. Functional analysis of Ficolin-3 mediated complement activation. PLoS One. 2010; 5(11): e15443.