Role of Serum Irisin During Early Pregnancy to Predict The Development of Gestational Diabetes Mellitus at 24–28 Weeks of Pregnancy in high-risk patients

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Abstract

Aims: The aim of this prospective study was to investigate the role of serum irisin during early pregnancy to predict the development of GDM at 24–28 weeks in high-risk patients. **Methodology:** This study was conducted among the pregnant women attending the Department of Endocrinology and antenatal clinic of Department of Obstetrics and Gynecology of MKCG Medical College for a period of one year with at least one risk factor for the development of gestational diabetes mellitus (GDM). Blood samples were collected for measurement of fasting plasma glucose, serum insulin, serum irisin, lipids (TC, LDL, HDL, TG), and HbA1c. Oral glucose tolerance test was performed using 75 g of glucose during the first trimester and between 24–28 weeks of pregnancy. Patients were diagnosed as GDM based upon IADPSG criteria at 24–28 weeks. Serum irisin, glycemic parameters, and homeostatic model assessment of insulin resistance during first trimester were analyzed for predicting GDM between 24–28 weeks. **Results:** Sixty-five patients were included in the study, out of which 20 (30.8%) patients developed GDM and the rest 45 patients had normal glucose tolerance (NGT). The first trimester mean serum irisin concentration was significantly lower in women who later developed GDM compared with women who had NGT (111.65 ± 25.43 μg/L vs 185.89 ± 28.89 μg/L). Serum irisin concentration was the best predictor with an optimal threshold value of 149 μg/L, which had sensitivity, specificity, positive predictive value, and negative predictive value of 90%, 91.1%, 81.8%, 95.3%, respectively, for predicting GDM at 24–28 weeks of pregnancy. **Conclusion:** We suggest the utility of serum irisin as an early biomarker to predict the development of GDM later in pregnancy in high-risk patients.

Keywords: Early predictor, Irisin, GDM

Introduction

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance, which is first diagnosed in the second or third trimester of pregnancy and is not clearly either preexisting type 1 or type 2 diabetes.[1]

GDM is found to be associated with various maternal and perinatal adverse outcomes.[2,3] Thus, early diagnosis of GDM is crucial in preventing maternal and neonatal complications. Bio-markers predicting GDM during first trimester are not well validated. Serum irisin in first trimester has been proposed as a bio-marker to be associated with the later development of GDM during 24–28 weeks of pregnancy.

Irisin is a polypeptide, which is secreted from muscle and adipose tissue, and is derived by proteolytic cleavage of fibronectin type III domain containing protein 5 (FNDC5).[4]

It is shown to have insulin-sensitizing properties by increasing glucose uptake in skeletal muscle and adipose tissue and it also improves pancreatic β cell function.[5,6] Earlier studies mostly concentrated on serum irisin during second trimester of pregnancy with varied results.[7,8] There are only few studies on serum irisin in early pregnancy for predicting GDM.[9,10] Therefore, the aim of the present study is to assess serum irisin as an early bio-marker during first trimester for predicting

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Access this article online

Quick Response Code:

Website:
www.ijem.in

DOI:
10.4103/ijem.ijem_466_21

GDM between 24th–28th week of pregnancy and to find its correlation with fasting plasma glucose (FPG), oral glucose tolerance test (OGTT) values, insulin, and homeostatic model assessment of insulin resistance (HOMA-IR) during early pregnancy.

MATERIAL AND METHODS

This was a prospective single center study, conducted among the pregnant women attending the Endocrinology Department and antenatal clinic of Department of Obstetrics and Gynecology of MKCG Medical College for a period of one year. Patients were recruited consecutively after satisfying the inclusion and exclusion criteria. Patient recruitment started from October 2019 till end of March 2020. All the patients who were enrolled, were followed up till the end of their pregnancy and in the post-partum period. The last patient follow-up was on September 28, 2020. The study was approved by institutional ethics committee. All participants were informed about the study protocol and written informed consent was obtained before inclusion. This trial is registered under Clinical Trial Registry India (CTRI/2019/09/021379).

Two hundred thirty women were screened and 65 women were included for final analysis according to inclusion and exclusion criteria [Figure 1].

Inclusion criteria
(i)   Pregnant women of age 18–40 years
(ii) Gestational age < 12 completed weeks at 1st assessment
(iii) Having at least any one of the following risk factors for the development of GDM: overweight (BMI ≥ 23 kg/m^2), family history of type 2 diabetes, polycystic ovary syndrome, previous history of macrosomic (≥4 kg) or large for gestational age infant (weight > 90 percentile for gestational age), and previous history of GDM.

Exclusion criteria
Patients with any of the following features will be excluded from the study.

(i)   Diagnosis of overt DM by any value above the cut off given by ADA; FPG ≥ 126 mg/dL, HbA1c ≥ 6.5%, random plasma glucose or 2 h post 75 g OGTT glucose value ≥ 200 mg/dL
(ii) Patient having multi-fetal gestation
(iii) Patients with heart disease, chronic hypertension or preeclampsia, autoimmune disease, hematological disease, liver disease, chronic kidney disease, alcohol and/or drug addiction, immunosuppressive treatment, and malignant diseases.

At the first antenatal visit (before 12 weeks of gestational age), a detailed history regarding risk factors like family history of diabetes, history of PCOS, previous history of macrosomic or large for gestational age (LGA) baby was taken. Then, a thorough physical examination was performed including weight, height and body mass index (BMI) was calculated as weight in kg/height in m^2 (Kg/m^2). Overweight
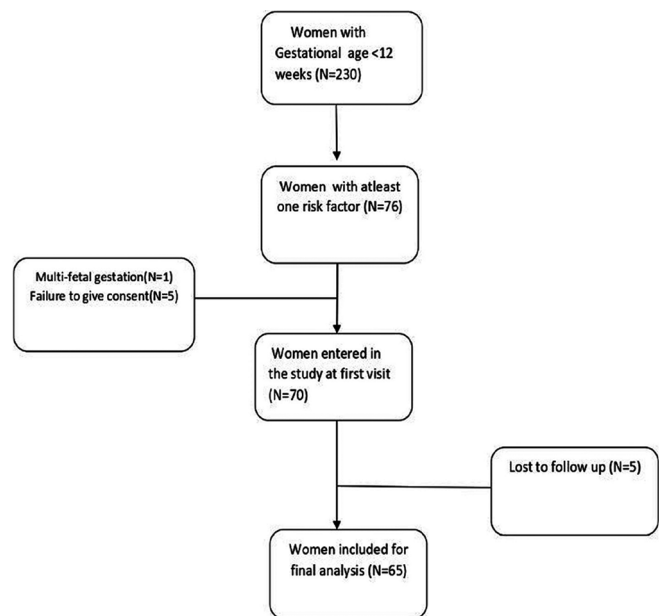
Figure 1: Flowchart depicting the selection of study population

was classified as BMI of ≥ 23 Kg/m^2 to < 27.5 Kg/m^2 and obesity was classified as BMI ≥ 27.5 Kg/m^2, according to Asian ethnic-specific criteria.[11]

Patients were included if at least one risk factor for GDM was present. In all the patients, fasting samples were collected for plasma glucose, insulin, irisin, and lipids (TC, LDL, HDL, TG). For irisin assay, all samples were stored at room temperature for at least 30 min to allow the blood to clot, followed by centrifugation (2500 rpm, 5 min). Serum specimens were aliquoted and stored at − 80°C until irisin levels were analyzed. Serum irisin levels were measured by enzyme-linked immunosorbent assay (ELISA) KIT (Cusabio) in accordance with manufacturer's instructions using the sandwich enzyme immunoassay technique. The detection range of the kit was 7.8 ug/L–500 ug/L. It was highly specific for the detection of human FNDC5. Intra-assay CV% was < 8% and inter-assay CV% <10%. EDTA blood was collected for HbA1c assay using Biorad 10 by HPLC method. HOMA-IR was calculated as: Fasting serum insulin (mIU/L) × fasting plasma Glucose (mmol/L)/22.5.

The included patients underwent 75 g OGTT for estimation of 1 h and 2 h plasma glucose values. Patients were excluded if they were diabetic by ADA criteria. They were classified as "Dysglycemia" if they fulfill IADPSG criteria during the first trimester. In the present study, OGTT was performed in first trimester, as we have included only high-risk patients.

Patients were reassessed between 24–28 weeks and fasting blood samples were collected for plasma glucose, HbA1c, insulin, irisin, and lipids (TC, LDL, HDL, TG). Then, they underwent 75 g OGTT. They were diagnosed as GDM or NGT based upon International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria. All women were followed for pregnancy outcomes and neonatal complications.

According to IADPSG, diagnosis of GDM is made when any one of the following plasma glucose values are fulfilled.[12]

- Fasting: ≥ 92 mg/dL

- 1 h: ≥ 180 mg/dL

- 2 h: ≥ 153 mg/dL

Statistical analysis

Data distribution normality was assessed using the Kolmogorov-Smirnov test. Categorical variables are presented as percentages, and continuous variables as mean ± standard deviations. The statistical significance of any intergroup difference was assessed using Fisher's exact test for categorical variables, and Student's t-test t for continuous variables. Correlations between irisin levels and other variables were evaluated using Pearson's correlation (continuous variables) or Spearman's rank test (categorical variables). The area under the curve (AUC) and 95% confidence interval (CI) for the irisin threshold level to predict GDM were evaluated by receiver operating curve (ROC) analysis. All sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and relative risk (RR) were calculated based on cut-off points obtained by the ROC curve. A two-sided $P < 0.05$ was considered to indicate statistical significance. All statistical analyses were performed using the SPSS software (ver. 26).

RESULTS

The present study included sixty-five patients for final analysis according to the inclusion and exclusion criteria.

GDM developed in twenty patients (30.8%) out of sixty-five patients between 24–28 weeks by using IADPSG criteria. The rest forty-five patients were classified as normal glucose tolerance group (NGT). All the patients had at least one risk factor. Two, three, four, and five risk factors were present in 21.5%, 6.2%, 3.1%, and 1.5% of patients, respectively.

The baseline characteristics of GDM group and NGT group are shown in Table 1, which compares various variables between GDM group and NGT group. There was no significant difference regarding age, parity, FPG, and HbA1c between the two groups. However, BMI, fasting insulin, and HOMA-IR were significantly higher in the GDM group compared to NGT group both at first visit and during 24–28 weeks [Table 1].

The mean BMI was 29.58 ± 2.67 kg/m² in the GDM group compared to 24.50 ± 2.07 kg/m2 in NGT group at first visit. The BMI remained significantly higher even during 24–28 weeks in the GDM group (33.29 ± 2.81 kg/m²) compared to NGT group (29.08 ± 2.37 kg/m²) [$P < 0.001$].

Mean fasting insulin levels were significantly higher in the GDM group (9.85 ± 2.32 mIU/L) compared to NGT group (6.64 ± 1.94 mIU/L) at first visit, which remained significantly higher even during 24–28 weeks in the GDM group (15.5 ± 1.85 mIU/L) compared to NGT

Table 1: Comparison between GDM group and NGT group			
Variables	**GDM (N = 20) (Mean ± SD)**	**NGT (N = 45) (Mean ± SD)**	**P- Value**
Age (years)	27.7 ± 3.9	27.2 ± 3.4	0.635
Multigravida *n* (%)	8 (40)	18 (40)	0.612
PCOS *n* (%)	4 (20)	1 (2.2)	<0.001*
Family H/O Diabetes *n* (%)	12 (60)	12 (26.6)	<0.001*
Previous H/O GDM *n* (%)	4 (20)	0	<0.001*
Previous H/O macrosomic baby *n* (%)	4 (20)	0	<0.001*
BMI (Kg/m²)			
V1	29.58 ± 2.67	24.50 ± 2.07	<0.001*
V2	33.29 ± 2.81	29.08 ± 2.37	<0.001*
Fasting insulin (mIU/L)			
V1	9.85 ± 2.32	6.64 ± 1.94	<0.001*
V2	15.5 ± 1.85	9.71 ± 1.84	<0.001*
HOMA-IR			
V1	2.08 ± 0.69	1.38 ± 0.41	<0.001*
V2	3.64 ± 0.53	2.02 ± 0.37	<0.001*
FPG (mg/dL)			
V1	84.40 ± 7.52	84.29 ± 3.90	<0.938
V2	95.20 ± 7.22	84.55 ± 3.58	<0.001*
OGTT 1 h (mg/dL)			
V1	163.15 ± 17.69	155.64 ± 13.50	0.045*
V2	186.20 ± 7.39	154.40 ± 12.56	<0.001*
OGTT 2 h (mg/dL)			
V1	142.70 ± 16.75	128.13 ± 14.45	<0.001*
V2	156.70 ± 7.74	123.50 ± 11.20	<0.001*
HbA1C (%)			
V1	5.51 ± 0.27	5.43 ± 0.29	0.375
V2	5.89 ± 0.40	5.47 ± 0.24	<0.001*
TC (mg/dL)			
V1	177.70 ± 11.68	175.21 ± 7.47	0.305
V2	199.20 ± 10.69	196.97 ± 8.03	0.357
LDL (mg/dL)			
V1	95.60 ± 11.90	95.64 ± 7.10	0.985
V2	116.80 ± 10.23	115.64 ± 7.10	0.601
TG (mg/dL)			
V1	176.25 ± 9.14	150.73 ± 4.37	<0.001*
V2	208.11 ± 11.89	187.89 ± 7.21	<0.001*
HDL (mg/dL)			
V1	46.85 ± 1.91	49.42 ± 4.00	0.008*
V2	40.80 ± 1.24	43.76 ± 1.49	<0.001*
Irisin (µg/L)			
V1	111.65 ± 25.43	185.89 ± 28.89	<0.001*
V2	206.30 ± 20.10	355.44 ± 60.73	<0.001*
Neonatal hypoglycemia *n* (%)	4 (20)	2 (4.4)	0.046*
LGA>90th Centile *n* (%)	5 (25)	2 (4.4)	0.013*
Macrosomic baby *n* (%)	2 (4.4)	0	0.031*
LSCS *n* (%)	15 (75)	19 (42.2)	0.014*
Preeclampsia n (%)	2 (10)	0	0.031*

*Data are in mean ± SD or n (%) unless otherwise specified. †P-value<0.05 is considered as significant. ‡V1-Visit 1 (<12 weeks). §V2-Visit 2 (24–28 weeks) HOMA: Homeostatic model assessment, FPG: Fasting plasma glucose, OGTT: Oral glucose tolerance test, TC: Total cholesterol, LDL: Low-density cholesterol, TG: Triglycerides, HDL: High-density cholesterol, PCOS: Polycystic ovary syndrome, LGA: Large for gestational age, LSCS: Lower segment cesarean section, H/O: History of.

group (9.71 ± 1.84 mIU/L) [$P < 0.001$]. At first visit, GDM group had a HOMA-IR of 2.08 ± 0.69 and NGT group had a HOMA-IR of 1.38 ± 0.41. At second visit, it increased in both the groups but the rise was more in GDM group (3.64 ± 0.53) than the NGT group (2.02 ± 0.37). GDM group had significantly higher TG and lower HDL compared to NGT group at both the visits.

Mean serum irisin levels at first visit were significantly lower in women who later developed GDM than the NGT group. Mean irisin levels at first visit in the GDM group were 111.65 ± 25.43 μg/L and in NGT group were 185.89 ± 28.89 μg/L ($P < 0.001$). The levels remained low in the GDM group compared to NGT group during 24–28 weeks of pregnancy also. They were 206.30 ± 20.10 μg/L in the GDM group compared to 355.44 ± 60 μg/L in the NGT group ($P < 0.001$) during 24–28 weeks of pregnancy.

Maternal and neonatal complications were significantly higher in the GDM group. Women in the GDM group had a higher lower segment cesarean section (LSCS) rate (75% vs 42.2%), more preeclampsia (10% vs 0%), neonatal hypoglycemia (20% vs 4.4%), LGA (25% vs 4.4%), and macrosomic (4.4% vs 0) babies as compared to NGT group.

At first visit, five patients in the GDM group had post-OGTT glucose values, which were fulfilling the IADPSG criteria to qualify for "Dysglycemia." All the five patients later developed GDM at 24–28 weeks by 75 g OGTT. BMI, fasting insulin, and HOMA-IR were significantly more in these five patients compared to rest fifteen patients in the GDM group. Mean serum irisin levels remained significantly lower in the GDM group compared to NGT group even after exclusion of these five dysglycemic patients at first visit (118.20 ± 26.26 μg/L vs 185.80 ± 28.89 μg/L).

Correlation of serum irisin with other variables
During first visit, serum irisin had a nonsignificant correlation with age, parity, BMI, FPG, OGTT 1 h, OGTT 2 h glucose values, HbA1c, and lipids, but it was significantly negatively correlated with fasting insulin (r= −0.46) and HOMA-IR (r =−0.45) in the GDM group [Table 2]. Irisin at first visit was also significantly negatively correlated with fasting insulin and HOMA-IR between 24–28 weeks of pregnancy in the GDM group. However, there was no significant correlation of irisin levels (< 12 weeks) with maternal and neonatal complications.

Variables at first visit (< 12 weeks) predicting GDM between 24–28 weeks
Comparison of various variables during the first trimester for predicting the development of GDM between 24–28 weeks was done using the ROC curves and calculating the AUROC [Table 3].

FPG, OGTT 1 h glucose values, and HbA1c at first visit had an AUROC of 0.41 (95% CI: 0.25–0.57), 0.64 (95% CI: 0.49–0.80), and 0.58 (95% CI: 0.43–0.73), respectively, for

Table 2: Correlation between irisin levels at first visit (<12 weeks) and other variables in the study population				
Variables	GDM ($N = 20$) r	P-value	NGT ($N = 45$) r	P-value
Age	0.10	0.670	0.28	0.061
Gravida	0.20	0.392	0.23	0.119
BMI (Kg/m²)				
V1	−0.19	0.408	−0.07	0.604
V2	−0.17	0.470	0.11	0.473
Fasting Insulin (mIU/L)				
V1	−0.46	0.038*	−0.35	0.017*
V2	−0.47	0.035*	0.41	0.004*
HOMA-IR				
V1	−0.45	0.043*	−0.36	0.015*
V2	−0.56	0.009*	0.38	0.010*
FPG (mg/dL)				
V1	−0.07	0.744	−0.09	0.542
V2	−0.36	0.112	−0.22	0.140
OGTT 1 h (mg/dL)				
V1	−0.12	0.600	−0.02	0.892
V2	−0.17	0.463	−0.07	0.606
OGTT 2 h (mg/dL)				
V1	−0.28	0.218	−0.06	0.665
V2	−0.07	0.744	−0.02	0.888
HbA1C (%)				
V1	0.01	0.976	0.08	0.586
V2	0.06	0.798	0.01	0.928
TC (mg/dL)				
V1	−0.13	0.566	0.09	0.529
V2	−0.19	0.419	0.17	0.255
LDL (mg/dL)				
V1	−0.06	0.797	0.15	0.300
V2	−0.14	0.547	0.15	0.222
TG (mg/dL)				
V1	−0.32	0.165	−0.11	0.448
V2	−0.34	0.141	0.20	0.189
HDL (mg/dL)				
V1	0.34	0.142	−0.07	0.624
V2	0.18	0.440	−0.01	0.931
Irisin (μg/L)				
V2	0.32	0.154	0.57	<0.001*

*r –Correlation co-efficient
†P-value<0.05 is considered as significant
‡V1-Visit 1 (<12 weeks)
§V2-Visit 2 (24–28 weeks)
HOMA: Homeostatic model assessment, FPG: Fasting plasma glucose, OGTT: Oral glucose tolerance test, TC: Total cholesterol, LDL: Low-density cholesterol, TG: Triglycerides, HDL: High-density cholesterol.

predicting GDM at 24–28 weeks, which were statistically nonsignificant. Fasting insulin, HOMA-IR, and OGTT 2 h glucose values at first visit had a significant AUROC of 0.88 (95% CI: 0.80–0.96), 0.86 (95% CI: 0.77–0.94), and 0.74 (95% CI: 0.62–0.87), respectively, for predicting GDM

Table 3: Area under ROC curve of various variables at first visit (<12 weeks) to predict GDM at 24–28 weeks

| Variables	AUROC	*P*-value	95% CI	
			UB	LB
FPG V1	0.41	0.258	0.25	0.57
OGTT 1 h V1	0.64	0.080	0.49	0.80
OGTT 2 h V1	0.74	<0.001*	0.62	0.87
HbA1C V1	0.58	0.280	0.43	0.73
Fasting Insulin V1	0.88	<0.001*	0.80	0.96
HOMA-IR V1	0.86	<0.001*	0.77	0.94
Irisin V1	0.94	<0.001*	0.88	0.99

*UB-Upper bound, LB-Lower bound
†P-value<0.05 is considered as significant
‡V1-Visit 1 (<12 weeks)
§V2-Visit 2 (24–28 weeks)
HOMA: Homeostatic model assessment, FPG: Fasting plasma glucose, OGTT: Oral glucose tolerance test.
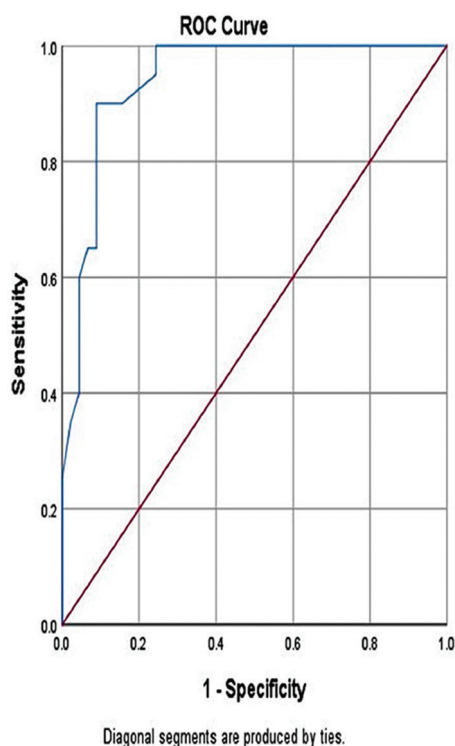
Figure 2: ROC curve of irisin level at first visit (< 12 weeks) for predicting GDM at 24–28 weeks.
*AUROC: 0.94 ; 95% CI: 0.88–0.99
†*P* < 0.001

at 24–28 weeks. Serum irisin at first visit had the highest AUROC of 0.94 with 95% CI: 0.88–0.99 for predicting GDM at 24–28 weeks [Figure 2].

From ROC analysis, the optimal threshold value of serum irisin was 149 μg/L, which had sensitivity, specificity, PPV, and NPV of 90%, 91.1%, 81.8%, and 95.3%, respectively, for predicting GDM at 24–28 weeks. When the value of 128 ug/L (−2 SD of NGT) is taken as cut-off for predicting GDM,

the sensitivity, specificity, PPV, and NPV were 85%, 91.1%, 80.9%, and 93.1%, respectively.

Discussion

Early diagnosis and appropriate treatment of GDM is helpful in reducing the adverse maternal and fetal outcomes and also in protecting mothers and infants from long-term complications. Previous studies have tried to determine the predictive value of maternal biomarkers before the development of GDM.[13-16] To our knowledge, this is the first study in the Indian population to investigate serum irisin levels in early pregnancy as a predictive marker for the development of GDM.

The prevalence of GDM in our study is 30.8%, which is higher than previous studies as we have included only pregnant women with at least one risk factor and IADPSG criteria was used where one value is sufficient for the diagnosis of GDM. Meta-analysis by Li. *et al*.[17] reported a prevalence of 19.19% in India using IADPSG criteria and the prevalence of GDM has been found to be 18.9% in the study by Seshiah *et al*.[18]

OGTT during first trimester is not routinely recommended except by National Institute for Health and Care Excellence (NICE) guidelines, where patients with previous history of GDM were recommended to undergo OGTT. The suggested cut-off by NICE during first trimester were 100 mg/dL and 140 mg/dL for FPG and OGTT 2 h glucose values, respectively.[19] IADPSG has loosely coined the term "Early GDM" based on FPG value of ≥ 92 mg/dL in early pregnancy.[12] The present study explored the role of OGTT during first trimester. Five patients were diagnosed as dysglycemia in early pregnancy, where two patients had fasting plasma glucose values and three patients had both fasting plasma glucose and OGTT (1 h and 2 h) glucose values beyond the cut-off of IADPSG criteria. These patients were followed between 24–28 weeks of pregnancy and found to have classical GDM by IADPSG criteria. Future studies are required to assess the role of OGTT during first trimester of pregnancy in high-risk patients.

Irisin levels at first visit

In the present study, the mean irisin level was 111.65 μg/L in the GDM group, which was lower compared to women who had NGT (185.89 ug/L). The median irisin level was also significantly low in GDM group compared to NGT group (104.5 μg/L vs 192 μg/L). Few studies previously looked into the role of serum irisin in early pregnancy for predicting GDM.[9,10] In the study by Wang *et al*.,[9] the median serum irisin was 106.5 μg/L in women with GDM compared to 148.4 μg/L in women without GDM. These results were consistent with the present study. However, the study by Erol *et al*.[10] found median serum irisin level of 453 μg/L in the GDM group and 721 μg/L in the control group, which was higher compared to the present study. The discrepancy in the serum irisin values could be due to the inclusion of all GDM patients in their study compared to the inclusion of only high-risk patients in our study.

Irisin levels at second visit

In our study, the mean irisin level between 24–28 weeks was 206.3 μg/L in the GDM group and 355.4 μg/L in the NGT group. The serum irisin levels were consistently low in the GDM group during first trimester and were maintained low between 24–28 weeks of pregnancy also. Zhao *et al.*[20] similarly found mean serum irisin level of 213.4 μg/L in the GDM group and 289.6 μg/L in the control group at 24–28th week of gestation.

The exact reason for low irisin in GDM patients is not known.[21,22] Some of the proposed mechanisms are that it could be due to glucotoxicity and inflammatory damage to adipocytes and muscle, which are not able to further increase irisin production.[23,24] TNF-alpha and IL-6 are the proposed inflammatory markers responsible for the damage.[25-27] Serum irisin levels increased significantly in the second trimester compared with values in the first trimester in both GDM and NGT group. As the pregnancy progresses, an increase in maternal BMI contributes to increased circulating irisin levels, which is an adaptive response to counteract the insulin resistance and maintain the balance of energy storage and expenditure, but it is not adequate in GDM patients.[28,29]

Irisin as a predictive marker in GDM

Irisin levels at first visit (<12 weeks) was a better predictor of GDM at 24–28 weeks than FPG, OGTT 1 h and 2 h glucose values, fasting insulin, and HOMA-IR. Irisin levels at first visit had the highest AUROC of 0.94 with 95% CI: 0.88–0.99 for predicting GDM at 24–28 weeks. When the value of 128 μg/L (-2 SD of NGT) was taken as cut-off for predicting GDM, the sensitivity, specificity, PPV, and NPV were 85%, 91.1%, 80.9%, and 93.1%, respectively.

We found that a threshold value of 149 μg/L had optimal sensitivity, specificity, PPV, and NPV of 90%, 91.1%, 81.8%, and 95.3%, respectively, for predicting GDM at 24–28 weeks. In the study by Erol *et al.*,[10] irisin levels at first trimester had AUROC of 0.77 (95% CI: 0.602–0.938) for predicting GDM with optimal cut-off of 540 μg/L with sensitivity, specificity, PPV, and NPV of 66.7%, 100%, 100%, and 75%, respectively. Wang *et al.*[9] found that irisin level at first visit had AUROC of 0.723 (95% CI: 0.683–0.763) with a threshold value of 155 μg/L for predicting GDM, which had a sensitivity and specificity of 67.6% and 70.7%, respectively. The sensitivity and specificity varied across the studies depending upon the cut-off taken. The lower irisin cut-off value in the present study could be due to the inclusion of high-risk patients.

From the present study, two observations can be made. First, low irisin levels in early pregnancy consistently predict the development of GDM and threshold of 149 μg/L had optimal sensitivity (90%) and specificity (91.1%) for predicting GDM between 24–28 weeks. Future studies are required to further explore the role of serum irisin in early pregnancy.

In our study, a significant negative correlation of irisin with insulin and HOMA-IR was found in GDM group at both the visits, but it was not significant for BMI, suggesting that fasting insulin and HOMA-IR are the better surrogate markers of insulin resistance and have good correlation with irisin levels than BMI in GDM patients. It also suggests the role of other adipokines associated with insulin resistance and irisin production. No significant correlation was found between irisin levels (<12 weeks) and maternal and neonatal complications. This could be due to small number of study participants in the GDM group and fewer maternal and neonatal complications in the present study. Studies involving large number of GDM patients are required to arrive at any conclusion.

Irisin is an adipomyokine that decreases insulin resistance. Some of the other actions of irisin are: browning of white adipocytes by overexpression of UCP1 (uncoupler protein1), which leads to an increase in energy expenditure and thermogenesis, thus improving insulin sensitivity, reducing body weight, and improving glucose tolerance[30]; increase in GLUT4 expression in human mature adipocytes[31]; enhancement of lipolysis via cAMP–protein kinase A–hormone-sensitive lipase/perilipin pathway, and regeneration of beta cells by peroxisome proliferator-activated receptor-gamma coactivator (PGC) 1α–irisin–betatrophin axis.[32,33] Irisin secretion is physiologically increased by exercise and reduced by hyperglycemia and high fatty acid concentrations. Drugs like fenofibrate and metformin also modulate serum irisin levels.[5]

Our study had few limitations. It had a relatively small sample size as it was a pilot study. It included high-risk patients so these findings cannot be extrapolated to patients without any risk factor and further studies are needed in GDM patients without risk factors.

We consider serum irisin as a biomarker for GDM in early pregnancy as it had shown a significantly greater ability to predict GDM early as compared to other parameters.

Hence, the current study demonstrated that serum irisin can be used as an early biomarker during first trimester of pregnancy for predicting GDM between 24–28 weeks of pregnancy in high-risk patients.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Conflicts of interest

There are no conflicts of interest.

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