Original Article

Preconception Lifestyle Intervention could Reduce the Incidence of Recurrent or New GDM: An Interventional Body Mass Index-Based Study

Basma Sakr

Department of Obstetrics and Gynecology, Faculty of Medicine, Benha University, Egypt

ABSTRACT

Aim: Evaluation of effects of 4-m preconception lifestyle intervention (LSI) on preconception body mass index (BMI), insulin resistance (IR) and glucose homeostasis and on the frequency and severity of gestational diabetes mellitus (GDM) during the oncoming pregnancy in women had (Group A)/not (Group B) GDM during previous pregnancy.

Patients and Methods: 498 women; 147 in group A and 351 in group B completed the applied LSI consisted of high-fiber and low-calorie diet with mild-moderate aerobic exercise for at least 4-m pre-pregnancy. Pre-LSI (T1) and Post-LSI (T2) evaluations included determination of body mass index (BMI) and determination of variables of glucose homeostasis. Study outcomes included the effect of the applied LSI on the incidence of newly developed or recurrent IR and of GDM, the success rate of the applied LSI as defined as the T2-number of new Av women in comparison to their T1-number.

Results: The success rate of the applied LSI was 19.3% and 10.5% among women of groups A and B, respectively for a total success rate of 12.8%. Mean T2-BMI of all LSI participants was significantly decreased in comparison to their T1-BMI with significantly higher median value of change in both groups. Moreover, all the glucose homeostasis variables were significantly reduced. During pregnancy all variables of glucose homeostasis were significantly elevated in comparison to T2-levels. However, the total incidence of new IR and GDM was significantly ($p=0.011$ & <0.0001, respectively) higher in women of group A than women of group B, irrespective of BMI.

Conclusion: 4-m preconception LSI could decrease the frequency and severity of new or recurrent GDM mostly through reduction of BMI and minimization of its associated metabolic and hormonal disturbances.

Key Words: Gestational diabetes mellitus, glucose homeostasis, insulin resistance, lifestyle intervention, preconception.

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Corresponding Author: Basma Sakr, Department of Obstetrics & Gynecology, Faculty of Medicine, Benha University, Egypt, **Tel.:** +20 1069493010, **E-mail:** sakrbasma807@gmail.com

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INTRODUCTION

Obesity has become widespread in the world and has attracted attention not only for being a cause of diabetes mellitus (DM)[1], hypertension and atherosclerotic diseases[2], but also as a factor in carcinogenesis[3] and for being associated with increased risk of mortality[4,5]. Moreover, overweight (OV) and obesity (Ob) present health risks for pregnant women and their children[6].

Diabetes is prevalent in general population and in hospitalized cases, but all may underscore the high morbidity associated with DM[7]. In diabetics, raised variability in glycosylated hemoglobin A1c and lipid parameters are associated with an elevated risk for diabetic complications and all-cause mortality[5].

Diabetes mellitus was ranked by the Center for Disease Control and Prevention as the seventh leading cause of death and its most prevalent forms are Type 2 DM (T2D), T1D, and gestational diabetes mellitus (GDM)[4]. GDM is defined as diabetes with onset or first recognition during gestation and is a common complication of pregnancy that has become more prevalent over the past few decades[8].

Understanding the association between maternal metabolic conditions during pregnancy and pregnancy-induced disorders and the fetal risks is a growing concern[9] and abnormalities in fetal growth, either large- or small-for-gestational age suggest placental dysfunction[8].

GDM is highly associated with obesity that independently increases the risk of both pregnancy-related complications and future impaired glycemic control and risk factors for both the mother and child[10]. Moreover, women with GDM have high risk of GDM recurrence at their next pregnancy and inter-pregnancy weight gain is a strong predictor of recurrent GDM, so, strategies to help women lose weight postpartum may be invaluable[11]. One of the ten questions to establish priorities for future research in DM and GDM is diet and lifestyle interventions (LSI) for diabetes management during pregnancy[12] and

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reaching women during preconception stage is an ideal opportunity to enable health behavior change[6].

OBJECTIVES

Determination of the effect of preconception lifestyle intervention (LSI) consisted of dieting regimen with aerobic exercise on preconception body mass index (BMI), insulin resistance (IR) and glucose homeostasis and to evaluate the reflection of this intervention on the frequency and severity of gestational diabetes mellitus (GDM) during the oncoming pregnancy in women had/not GDM during previous pregnancy.

Design

Prospective interventional study

Setting

Department of Obstetrics & Gynecology, Faculty of Medicine, Benha University, Egypt

PATIENTS AND METHODS

Through the duration of the study since Jan 2018, all women attending the outpatient clinic of obstetrics seeking for stoppage of contraception to get pregnant were eligible for evaluation. History taking included the following items: age, number of previous pregnancies, development of pregnancy-induced morbidities especially GDM, preeclampsia, renal diseases, anemia, and mode of delivery, outcome of pregnancy and number of living offspring. All women were clinically evaluated for presence of manifest DM, hypertension, renal or hepatic diseases, body weight, height, and underwent full investigations for renal and liver function.

Exclusion criteria

Exclusion criteria included previous gestational or manifest hypertension, renal or hepatic affection; endocrinopathy especially that induces obesity, BMI of >30 kg/m2, inability to follow dieting or exercise regimen or to use the mode of contraception that would be described. Also, women who refused to sign the written informed consent to participate in the study or got pregnant before completion of 4-m lifestyle change were also excluded from the study.

Inclusion criteria & Grouping

All women attended the clinic and accepted to participate in the study and free of exclusion criteria and had GDM previously or not were included in the study. Women who had GDM during previous pregnancies were collected as group A and those who had previous pregnancies free of GDM were collected as group B. Within each group women were re-categorized according to BMI grades as Av or OV-Ob subgroups.

Clinical evaluations

1. BMI determination & grading: BMI (kg/m^2) was calculated as weight (kg)/ height (m^2)[13] and was graded according to WHO guidelines as Av weight (BMI<24.9 kg/m2), OV (BMI=25-<30 kg/m^2) and Ob women (BMI=30-<35 kg/m^2) and morbid Ob (BMI>35 kg/m^2)[14].

2. Glucose tolerance was evaluated using the 75-oral glucose tolerance test (75-OGTT), which entails obtaining three blood samples; a fasting sample and two samples 1-hr and 2-hrs after taking an oral snack containing 75 gm of glucose for estimation of postprandial blood glucose (PPBG). The results of the 75-OGTT were interpreted according to the recommendations of the International association of diabetes and pregnancy study groups[15] as follows: FBG ≥92 mg/dl, 1-h PPBG ≥180 mg/dl and 2-h PPBG ≥153 mg/dl.

3. Homeostasis model assessment of insulin resistance (HOMA-IR) score for diagnosis of IR using the following formula: fasting serum insulin (μU/ml) x [FBG (mg/ml)/18])/22.5; HOMA-IR score of >2 is considered abnormal[16].

4. Control of glucose homeostasis was evaluated using estimation of glycosylated hemoglobin A1c (HbA1c) levels that were interpreted as follows HbA1c at range of 4-6% indicates non-diabetic state, 6-6.5% indicates controlled glucose homeostasis, 6.5-8% indicates good diabetic control and >8% indicates need for interference to achieve control[17].

Study protocol

1. Method of contraception: all women who were maintained on pills were asked to stop this method and to shift to other mechanical methods; as IUD, condom, coitus interrupts, or safe period

2. Lifestyle intervention:

    a. Dieting regimen was advised for all enrolled women for 4-m duration pre-conception and consisted of diet rich in fiber, fruit and vegetables with dietary fiber at rate of 14 g/1000 kcal, lean proteins in amount of 0.8–1.0 g/kg of acceptable bodyweight and complex carbohydrates with restriction of simple carbohydrates to 10–12% of the total calorie intake. The intake of saturated fat must be <7% of the total calories, the intake of unsaturated fat should be minimized, and the cholesterol intake must be <300 mg/day. Obese women were advised to take 5 mg of folic acid supplementation every day, starting at least 1 month before conception[18,19].

b. Exercise regimen consisted of 30–45 min of aerobic exercise daily, such as walking, stair climbing or swimming, for 3–5 days a week to allow weight loss, improve cardiorespiratory fitness and reduces blood pressure and plasma lipid levels[18].

Follow-up

At the end of 4-m lifestyle intervention women who did not get pregnant were enrolled in follow-up program, which consisted of the following items:

1. Re-evaluation of BMI, glucose tolerance, HOMA-IR score and glycemic control to determine the success of the lifestyle intervention

2. All women were allowed to get intercourse freely so as to get pregnant and were asked to attend the gynecology outpatient clinic when they had missed period.

3. After chemical and clinical assurance of pregnancy, all women were asked to attend the antenatal care unit at the start of the 2nd and 3rd trimester for re-evaluation of 75-OGTT to diagnose GDM

Study outcome

1. The primary outcome is the effect of the applied preconception LSI on the incidence of newly developed IR and of GDM at the end of 4-m LSI (T2).

2. The secondary outcomes include:

   - The success rate of the applied LSI as defined as the T2-number of new Av women in comparison to number of enrolled women at time of start of the LSI (T1).

   - The effect of the applied preconception LSI on BMI, IR and glucose homeostasis parameters

Statistical analysis

The obtained data were presented as mean, standard deviation (SD), numbers, percentages, median and interquartile ranges (IQR). The percentage of change was calculated as the value determined after LSI minus the value determined before LSI and the difference was divided by the value determined before LSI and multiplied by 100. Parametric data were compared using paired t-test and Mann-Whitney test. Non-parametric data were compared using Chi-square test. Statistical analysis was performed using SPSS software package, 2015. *P value* of <0.05 was considered significant.

RESULTS

Throughout the duration of the study 643 women were eligible for evaluation; 72 women were excluded for not fulfilling the inclusion criteria and 571 women were included. There were 169 women had GDM during a previous pregnancy (Group A); 37 were Av women and 132 were OV-Ob women, and 402 women had previous pregnancies free of GDM (Group B); 275 were OV-Ob and 127 were Av women. All women, irrespective of their BMI, underwent change of their contraception method and underwent the study LSI. Unfortunately, 73 women were excluded for either getting pregnant or lost during follow-up and 498 women; 147 in group A and 351 in group B completed the intervention (Figure 1). The enrolment data of studied patients showed non-significant (p>0.05) differences between both groups (Table 1).

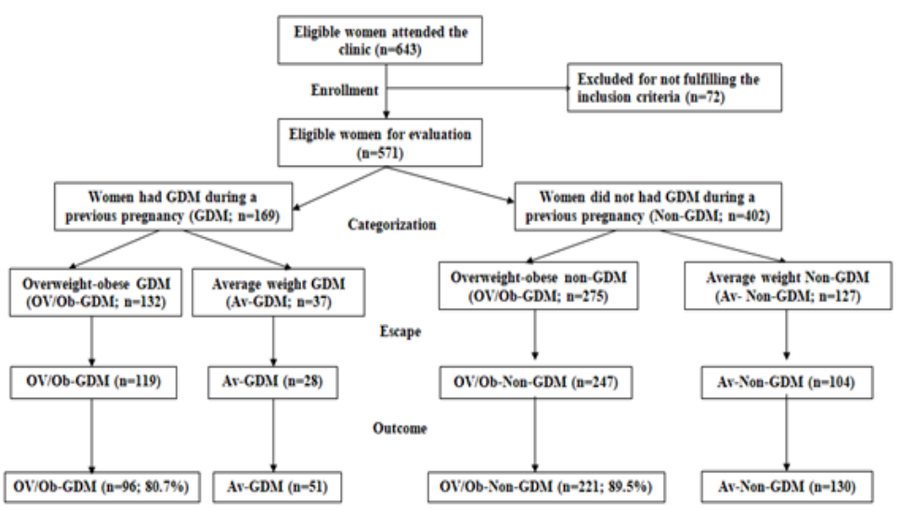

Fig. (1): Flow chart for lifestyle intervention

Table 1: Enrolment data of patients of both groups

Data	Group A (n=169)	Group B (n=402)	*P value*
Age (years)	28.2 (3.5)	27.9 (2.9)	0.265
Gravidity	2 [1-2]	2 [1-2]	0.142
Parity	1 [1-2]	2 [1-2]	0.134
Systolic blood pressure (mmHg)	118.9 (5.4)	118 (6.2)	0.141
Diastolic blood pressure (mmHg)	78.8 (5.2)	77.9 (4.4)	0.058
Random blood glucose (mg/dl)	89 (7.7)	89.2 (9.3)	0.809

Data are presented as mean; standard deviation (SD); median; interquartile range [IQR]; P value indicates the significance of difference between both groups; *P*<0.05 indicates significant difference; *P*>0.05 indicates non-significant difference

The success rate of the applied LSI was 19.3% and 10.5% among women of groups A (n= 23) and B (n= 26), respectively for a total success rate of 12.8%. Moreover, the T2-frequency of Av women was significantly (p=0.0008) increased (181 vs. 132) in comparison to T1-frequency of AV women. Despite of the decreased number of OV-Ob women in both groups, it was still significantly higher (p=0.003 & 0.037, respectively) in comparison to number of Av women. Moreover, the difference of the T1-frequency of Av women was significantly (p=0.015) higher in group B, but became non-significantly (p=0.619) higher at T2. The T2-frequency of IR Av-women was non-significantly (p=0.193 & 0.063) decreased in groups A and B, respectively in comparison to T1-frequency. Also, the T2-frequency of IR OV-Ob women was non-significantly (p=0.202) decreased among women of group B, but was decreased significantly (p=0.0031) among women of group A in comparison to T1-frequency. Total number of IR women at T2 was significantly decreased in groups A (p=0.0013) and B (p=0.029) in comparison to T1-number. However, the differences between both groups regarding T1 and T2 numbers of IR women were non-significant (p=0.081 & 0.636), respectively, (Table 2, Figure 2).

Table 2: Pre- & Post-LSI distribution of women of both groups according to the frequency of BMI grades and IR

Items	Sub-group		Pre-LSI (T1)	Post-LSI (T2)	*P value*
BMI					
Group A	Av		28 (15.8%)	51 (34.7%)	0.003
	OV-Ob		119 (84.2%)	96 (65.3%)	
	Total		147	147	
Group B	Av		104 (29.6%)	130 (37%)	0.037
	OV-Ob		247 (70.4%)	221 (63%)	
	Total		351	351	
P1 value			0.015	0.619	
Insulin resistance					
Group A	Av	Yes	8 (28.6%)	4 (14.3%)	0.193
		No	20 (71.4%)	24 (85.7%)	
	OV-Ob	Yes	41 (34.5%)	21 (17.6%)	0.0031
		No	78 (65.5%)	98 (82.4%)	
	Total	Yes	49 (33.3%)	25 (17%)	0.0013
		No	98 (66.7%)	122 (83%)	
Group B	Av	Yes	18 (17.3%)	9 (8.7%)	0.063
		No	86 (82.7%)	95 (91.3%)	
	OV-Ob	Yes	72 (29.1%)	57 (23.1%)	0.202
		No	175 (70.9%)	190 (76.9%)	
	Total	Yes	90 (25.6%)	66 (18.8%)	0.029
		No	261 (74.4%)	285 (81.2%)	
P1 value			0.081	0.636	

Data are presented as numbers; percentages; LSI: Lifestyle intervention; Av: Average weight; OV: Overweight; Ob: Obese; P value indicates the significance of difference between Pre- & Post-LSI; P1 indicates the significance of difference between both groups; *p*<0.05: indicates significant differences; *p*>0.05: indicates non-significant differences

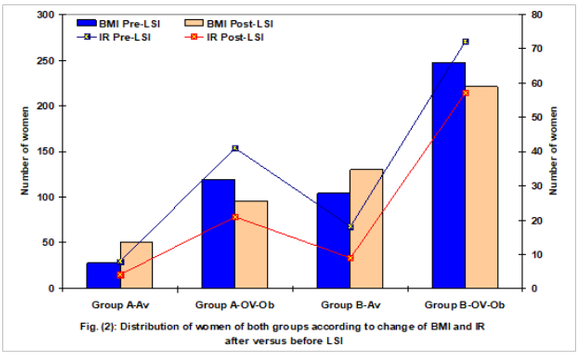

Fig 2: Distribution of women of both groups according to change of BMI and R after versus before LSI

The mean T2-BMI of all LSI participants was significantly decreased in comparison to their T1-BMI, irrespective of their grade of BMI. Interestingly, the median value of change in BMI was significantly (p=0.0015) higher among Av women of group A (3.94; IQR: 3.16-6) in comparison to those of group B (3.67; 2.57-4.8). Moreover, OV-Ob women of group A had median value of BMI change (3.17; 2.07-4.4) that was significantly (p<0.0001) higher in comparison to that of OV-Ob women of group B (2.13; 1.7-2.8) (Table 3; Figure 3).

Table 3: Mean Pre- & Post-LSI values of BMI of women of both groups

Group	Sub-group	Pre-LSI (T1)	Post-LSI (T2)	*P value*	% of change
Group A	Av-Av (n=28)	24.2 (0.79)	23.78 (0.9)	0.084	1.5 [1.2-1.74]
	OV-Av (n=23)	25.86 (0.55)	24.65 (0.27)	<0.0001	4.11 [3.1-6.5]
	Total Av (n=51)	24.94 (1.09)	24.17 (0.81)	0.0001	3.94 [3.16-6]
	OV-OV (n=26)	28.9 (0.83)	28.2 (0.9)	0.0058	2.4 [1.7-2.8]
	Ob-OV (n=7)	31.1 (0.4)	29.5 (0.33)	<0.0001	5.3 [4.4-5.5]
	Ob-Ob (n=63)	33.5 (1.1)	32.3 (1.1)	<0.0001	3.75 [2.5-4.5]
	Total OV-Ob (n=96)	32.1 (2.3)	31 (2.1)	0.0006	3.17 [2.07-4.4]
Group B	Av-Av (n=104)	24.2 (0.77)	23.2 (0.8)	<0.0001	3.9 [2.44-5.2]
	OV-Av (n=26)	25.2 (0.65)	24.3 (0.7)	0.00003	3.5 [2.84-3.72]
	Total Av (n=130)	24.4 (0.85)	23.5 (0.92)	<0.0001	3.67 [2.57-4.8]
	P value	0.0003	<0.0001		0.0015
	OV-OV (n=33)	27.6 (1)	26.9 (1.1)	0.008	2.13 [2.1-3.07]
	Ob-OV (n=13)	30.4 (0.31)	29.6 (0.25)	<0.0001	2.58 [1.68-3.4]
	Ob-Ob (n=175)	32.8 (1.26)	32.08 (1.19)	<0.0001	2.05 [1.63-2.8]
	Total OV-Ob (n=221)	31.9 (2.22)	31.16 (2.19)	0.0005	2.13 [1.7-2.8]
	P value	0.508	0.445		<0.0001

Data are shown as mean, standard deviation (SD), median, interquartile range (IQR); LSI: Lifestyle intervention; % of change: percentage of change of Post-LSI in relation to Pre-LSI value; BMI: Body mass index; Av: Average weight; OV: Overweight; Ob: Obese; *P value* indicates the significance of difference between Pre- & Post-LSI; P1 indicates the significance of difference between both groups; $p<0.05$: indicates significant differences; $p>0.05$: indicates non-significant differences

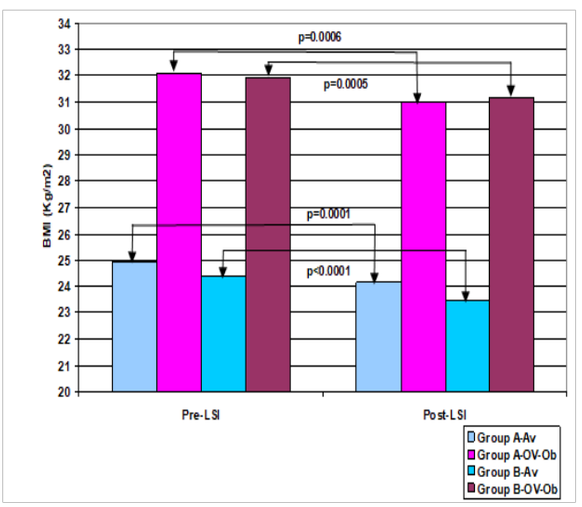

Fig. 3: Pre. & Post-LSI BMI of women of both groups

The applied LSI significantly reduced the values of all the glucose homeostasis variables. However, 2hr-PPBG levels were significantly higher among OV-Ob women in comparison to Av women in both T1 and T2 samples, while the other variables showed non-significant differences between both subgroups of women of group A. On contrary, both T1 and T2 levels of FBG, 2hr PPBG and HOMA-IR score of OV-Ob women of group B were significantly higher in comparison to corresponding values of Av women of group B (Table 4). The percentage of change of levels of FBG and HOMA-IR scores at T2 were significantly higher among all women of group A in comparison to those of group B. Moreover, the percentage of change of 2hr PPBG (p=0.159) and HbA1c (p=0.067) levels were significantly higher among OV-Ob women of group A in comparison to OV-Ob women of group B, while the differences were non-significant between Av women of both groups (Figure 4).

Table 4: Mean Pre- & Post-LSI values of variable of glucose homeostasis of women of both groups

			Time	Pre-LSI (T1)	Post-LSI (T2)	*P1 value*	% of change
Group A							
Av women (n=28)	75-OGTT	FBG		96.4 (8.4)	91.3 (8.7)	0.0296	5.15 [3.675-6.75]
		2hr PPBG		120.8 (6.4)	115.5 (5.6)	0.0018	3.85 [3.18-5.425]
	HbA1c			4.58 (0.53)	4.12 (0.48)	<0.0001	9.3 [7.15-10.6]
	HOMA-IR score		Frequency	8 (28.6%)	4 (14.3%)	0.193	
			Level	1.44 (0.55)	1.18 (0.5)	0.058	19.565 [14-24.2]
OV-Ob women (n=119)	FBG		Level	98.4 (7.7)	93.8 (7.2)	<0.0001	4.44 [3.32-5.5]
			P2	0.239	0.094		
	2hr PPBG		Level	133.5 (16.5)	125.5 (12.9)	0.00004	5 [3.95-6.92]
			P2	0.0001	0.0001		
	HbA1c		Level	4.63 (0.39)	4.15 (0.32)	<0.0001	9.8 [8.89-11.22]
			P2	0.693	0.719		
	HOMA-IR score		Frequency	41 (34.5%)	21 (17.6%)	0.003	
			Level	1.46 (0.53)	1.17 (0.72)	0.008	16.9 [11.6-21.3]
			P2	0.927	0.986		
Group B							
Av women (n=104)	75-OGTT	FBG		96.1 (5.3)	92.5 (4.9)	<0.0001	3.35 [2.9-4.4]
		2hr PPBG		120 (9.2)	113.8 (7.7)	<0.0001	4.6 [3.6-5.85]
	HbA1c			4.37 (4)	4 (0.38)	<0.0001	8.5 [6.67-9.5]
	HOMA-IR score		Frequency	0	0		
			Level	1 (0.33)	0.9 (0.3)	0.010	11.9 [9.9-14.6]
OV-Ob women (n=247)	75-OGTT	FBG	Level	100.5 (8.6)	97.6 (8.1)	0.0002	2.5 [2-3.2]
			P2	<0.0001	<0.0001		
		2hr PPBG	Level	140.8 (7.7)	131.9 (7.4)	<0.0001	6.16 [4.75-7.96]
			P2	<0.0001	<0.0001		
	HbA1c		Level	4.43 (0.45)	4.09 (0.5)	<0.0001	7.14 [5.2-8.89]
			P2	0.303	0.132		
	HOMA-IR score		Frequency	70 (28.8%)	43 (17.4%)	0.0038	
			Level	1.62 (0.58)	1.47 (0.5)	0.0016	8.81 [6.72-11.25]
			P2	<0.0001	<0.0001		

Data are shown as mean, standard deviation (SD), median, interquartile range (IQR); LSI: Lifestyle intervention; % of change: percentage of change of Post-LSI in relation to Pre-LSI value; Av: Average weight; OV: Overweight; Ob: Obese; 75-OGTT: 75-gm oral glucose tolerance test; HbA1c: Glycosylated hemoglobin A1c; HOMA-IR: Homeostasis model assessment of insulin resistance; P1 value indicates the significance of difference between Pre- & Post-LSI; P2 indicates the significance of difference between Av women and OV-Ob women of the same groups; $p<0.05$: indicates significant differences; $p>0.05$: indicates non-significant differences

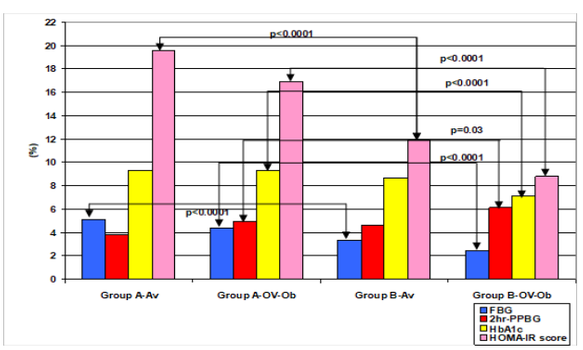

Fig. 4: Median of percentage of change after the applied LSI in comparison to Pre-LSI levels

During pregnancy, FBG and HOMA-IR score were significantly higher at the 6th gestational week (GW) among Av women, while 2hr PPBG and HbA1c levels were non-significantly higher in comparison to levels estimated T2-levels. However, at the start of the 2nd and 3rd trimesters, all variables of glucose homeostasis were significantly elevated in comparison to T2-levels. On the other hand, all women of group B, both Av women and OV-Ob women showed significant elevations of levels of parameters of glucose homeostasis in comparison to their T2-levels (Table 5).

Table 5: Mean Pre- & Post-LSI values of variables of glucose homeostasis in women of both groups

Time		Post-SLI (T2)	6th GW			Start of 2nd trimester			Start of 3rd trimester		
Group	Variable		level	% of change	*P*	level	% of change	*P*	level	% of change	*P*
Group A (Av women; n=28)											
75-OGTT	FBG	91.3 (8.7)	94.8 (9.8)	2.55 [2-4.2]	0.146	99.4 (10.6)	7.7 [6-10.2]	0.0024	109.3 (11.2)	18.8 [15.2-23]	<0.0001
	2hr PPBG	115.5 (5.6)	121.5 (5.8)	4.5 [4-5.3]	0.0007	132.2 (17)	10 [8.6-13.8]	<0.0001	143.8 (18.5)	20.4 [16.8-27]	<0.0001
Frequency of GDM		0	0			3 (10.7%)			4 (14.3%)		
HBA1c		4.12 (0.48)	4.41 (0.39)	4.8 [3-6.4]	0.009	5 (1)	12.4 [9.5-26.8]	0.00004	5.8 (1.3)	25 [20.5-62.6]	<0.0001
HOMA-IR score	Frequency	4 (14.3%)	4 (14.3%)			5 (17.9%)		0.716	9 (32.1%)		0.114
	Level	1.18 (0.5)	1.29 (0.53)	9.6 [7.5-11.3]	0.407	1.46 (0.58)	23.1 [19.4-30]	0.043	1.8 (0.67)	51 [43-64.4]	0.0002
Group A (OV-Ob women; n=119)											
75-OGTT	FBG	93.8 (7.2)	101 (7.5)	7.1 [5-9.6]	<0.0001	105.7 (8)	12.1 [10.1-15]	<0.0001	109.2 (8.1)	16.2 [14-18.6]	<0.0001
	2hr PPBG	125.5 (12.9)	130.9 (13.8)	3.6 [3-4.7]	0.002	136.2 (15)	7.8 [6.6-9.6]	<0.0001	145.3 (17.4)	14.6 [12-18.8]	<0.0001
Frequency of GDM		0	4(3.4%)			13 (11%)	0.0235*		32 (26.9%)	<0.0001*	
HBA1c		4.15 (0.32)	4.66 (0.6)	11.4 [8-16]	<0.0001	5.13 (0.83)	20 [15.8-28.3]	<0.0001	5.85 (1.22)	33.3 [24.4-51]	<0.0001
HOMA-IR score	Frequency	21 (17.6%)	40 (33.6%)		0.0047	43 (36%)	0.0013		48 (40.3%)		0.0001
	Level	1.17 (0.72)	1.48 (0.8)	23.8 [17.6-34]	0.002	1.66 (0.89)	39.6 [31-52.5]	<0.0001	1.84 (0.92)	53.7 [43-78]	<0.0001
Group B (Av women; n=104)											
75-OGTT	FBG	92.5 (4.9)	96.9 (6.4)	3.3 [3-4.1]	<0.0001	99.3 (6.4)	5.7 [5.3-7.1]	<0.0001	103.5 (6.3)	10.5 [9-12.6]	<0.0001
	2hr PPBG	113.8 (7.7)	124.4 (10.4)	7.8 [6-11]	<0.0001	134.2 (10.9)	17.4 [13.2-21.8]	<0.0001	142.8 (11.6)	24.1 [20.5-29]	<0.0001
Frequency of GDM		0	0			3 (2.9%)			9 (8.7%)**		0.074
HBA1c		4 (0.38)	4.48 (0.43)	11.4 [7-14]	<0.0001	5.15 (0.76)	25 [19.5-28.9]	<0.0001	5.65 (0.9)	35.3 [29-42.1]	<0.0001
HOMA-IR score	Frequency	0	9 (8.7%)			13 (12.5%)	0.367*		15 (14.4%)		0.193*
	Level	0.9 (0.3)	1.08 (0.5)	10.9 [9-16]	0.0013	1.17 (0.5)	20.9 [17.2-28.6]	<0.0001	1.3 (0.5)	36.6 [30.2-46]	<0.0001
Group B (OV-Ob women; n=247)											
75-OGTT	FBG	97.6 (8.1)	102.6 (8.9)	4.3 [3-6.5]	<0.0001	106 (1.8)	8 [6.2-10.1]	<0.0001	110.2 (9.4)	12.5 [10-14.6]	<0.0001
	2hr PPBG	131.9 (7.4)	139.8 (7.1)	4.3 [3.1-6.5]	<0.0001	144.1 (7.8)	8.6 [6.5-11.4]	<0.0001	149.4 (8.5)	12.5 [10.7-15]	<0.0001
Frequency of GDM		0	2 (0.8%)			8 (3.2%)	0.055*		20 (8.1%)		0.00001*
HBA1c		4.09 (0.47)	4.41 (0.51)	7.3 [5-8.8]	<0.0001	5.33 (0.7)	27 [19.6-38.1]	<0.0001	5.85 (0.8)	40 [30.7-51.6]	<0.0001
HOMA-IR score	Frequency	43 (17.4%)	64 (25.9%)		0.0218	67 (27.1%)		0.0094	74 (30%)		0.001
	Level	1.47 (0.5)	1.65 (0.59)	11.6 [4-16]	0.0003	1.8 (0.6)	21.6 [17.1-28.7]	<0.0001	1.98 (0.67)	34 [27.1-42.2]	<0.0001

Data are shown as mean, standard deviation (SD), median, interquartile range (IQR); % of change: percentage of change of T2 in relation to T1-value; GW: Gestational week; 75-OGTT: 75-gm oral glucose tolerance test; HbA1c: Glycosylated hemoglobin A1c; HOMA-IR: Homeostasis model assessment of insulin resistance; P value indicates the significance of difference in relation to T2-levels; p<0.05: indicates significant differences; p>0.05: indicates non-significant differences; *: significance of difference versus 6th GW; **: significance of difference versus start of the 2nd trimester

Regarding insulin resistance, no Av-woman was IR at T2-evaluation but with the progress of pregnancy, 20 Av-women either returned or newly developed IR; 5 in group A (17.9%) and 15 in group B (12.6%) for a total new IR among Av-women of 13.6% with non-significantly (p=0.466) higher incidence of new IR among women of group A in comparison to women of group B. On the other side, 64 OV-Ob women were IR at T2-evaluation; 21 women (17.6%) of group A and 43 women (17.4%) of group B (p=0.955), and during pregnancy, 27 women of group A (27.6%) and 31 women of group B (15.2%) developed new IR for a total incidence of IR among OV-Ob women of 19.2% with significantly (p=0.0003) higher incidence among OV-Ob women of group A. The total incidence of new IR among women of group A (21.8%) was significantly (p=0.011) higher in comparison to women of group B (15.2%), irrespective of BMI (Figure 5).

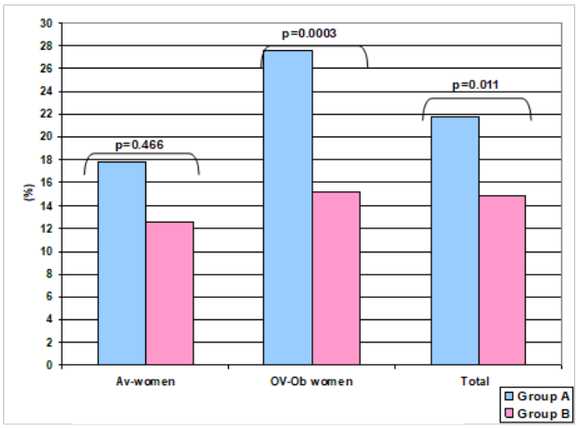

Fig. 5: Incidence of new IR among women of both groups.

Concerning the incidence of GDM, 13 Av-women developed GDM either at the end of the 2nd or 3rd trimester; 4 women of group A (14.3%) and 9 women of group B (8.7%) with non-significantly (p=0.259) higher incidence of GDM among Av women of group A. On the other hand, 52 OV-Ob women developed GDM; 6 at 6th GW evaluation, 15 and 31 at the start of the 2nd and 3rd trimesters, respectively for an incidence of 26.9% and 8.1% among women of groups A and B, respectively, with a significantly (p<0.0001) higher incidence among women of group A. The total incidence of GDM among women of group A (24.5%) was significantly (p<0.0001) higher in comparison to women of group B (8.3%), irrespective of BMI (Figure 6).

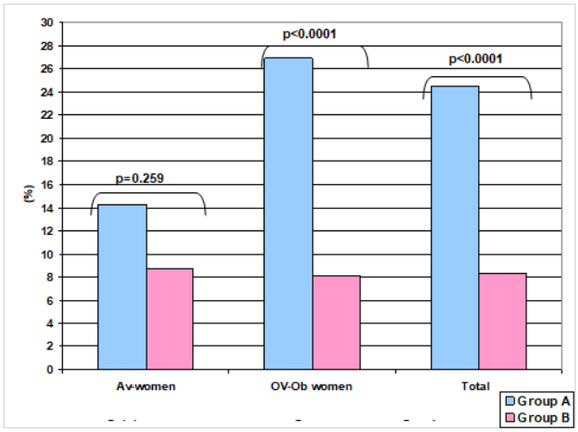

Fig. 6: Incidence of GDM among women of both groups.

DISCUSSION

The hypothesis of the current study was the application of lifestyle intervention (LSI) consisted of high-fiber and low-calorie diet in conjunction with mild-moderate aerobic exercise for at least 4-m pre-pregnancy for overweight (OV women) and obese (Ob women) who had GDM during a previous pregnancy could reduce the frequency and lessen the severity of GDM during upcoming pregnancy. In support of this hypothesis; the use of pre-conception LSI, Cha *et al*.[20] during an integrative literature review detected limited interest in preconception counseling regarding risks of OV/Ob during pregnancy by health care professionals, which may contribute to women's unawareness of these risks on preconception health. Also, Zhu *et al*.[21] found healthy prenatal lifestyle with multiple low-risk modifiable factors, including healthy weight, high-quality diet and low-to-moderate stress during early pregnancy was associated with lower risk of preterm birth. Moreover, Schenkelaars *et al*.[22] reported that preconception weight loss after LSI is effective in reducing risks of hypertensive disorders of pregnancy, and indicates the need to optimize weight in OV/Ob women with a child wish.

The applied 4-m preconception LSI allowed significant weight reduction for all women with an increase of the frequency of women with average BMI (Av women), irrespective of having GDM previously or not. This outcome points to an effect of LSI on carbohydrate and lipid metabolism in direction of catabolism with decreased gluconeogenesis and lipogenesis. In support of this assumption, the frequency of women had insulin resistant and/or high glucose intolerance was significantly

decreased with significant decrease of HOMA-IR score on one side and significant increase in the frequency of patients with adjusted glycemic control with normal HbA1c concentration on the other side. In line with these findings, Zhang *et al*.[23], experimentally found 30% caloric restriction significantly attenuated hyperglycemia and dyslipidemia, markedly ameliorated IR as indicated by improved HOMA-IR and thus leading to alleviation of glucolipotoxicity and protection of islet function; and these effects are mostly attributed to upregulation of AKT/AS160/GLUT4 signaling in muscle and reversal of its decrease in white adipose tissue. Clinically, Reynolds *et al*.[24] documented that for diabetic patients higher-fiber diets are an important component of diabetes management resulting in improvements of glycemic control, blood lipids, body weight, and inflammation, as well as a reduction in premature mortality. Thereafter, Shakoor *et al*.[25] found very low-calorie diet (400-800 kcal/day) and ≥ 150 minutes exercise 5 times a week can normalize blood glucose levels, reduce HbA1c and improve insulin sensitivity, so can provide a mechanism for maintaining glucose homeostasis and remission of T2D. Moreover, in a meta-analysis study, Garcia-Hernandez *et al*.[26] reported that adding metformin to hypocaloric diets did not improve serum glucose or insulin concentrations as well as IR in PCOS women and concluded that LSI only can provide the same effect as drug therapies used for improvement of glucose homeostasis in PCOS women. In support of the role of exercise as a part of LSI, Garmendia *et al*.[27] found dietary counseling plus docosahexaenoic acid in a dose of 200 or 800 mg for OV/Ob women at the beginning of pregnancy did not reduce the risk of GDM in mothers or macrosomia and IR in neonates.

At the end of the study, 65 women of those who completed the LSI, developed GDM for a frequency of 13.1%; 36 women had recurrent GDM for a frequency of 24.5% for recurrent GDM, 29 women had new GDM for a frequency of 8.3%. The reported frequency of GDM after 4-m preconception LSI was favorably reduced in comparison to that reported in literature; wherein, Rönö *et al*.[28] found the frequency of new GDM was 13% and 17.6% in the first and second pregnancies and the recurrence rate of GDM was 62.8%. Also, Egan *et al*.[29] identified a GDM recurrence rate of 47.6%, and Morikawa *et al*.[30] found the GDM recurrence rate among women who had GDM in the first and second pregnancies was 66.7%.

The frequency of new GDM after LSI was 4-folds higher among women who still OV/Ob than women who were or became Av women, and the frequency of recurrent GDM was 8-fold higher among women who were still OV/Ob in comparison to Av women. These findings illustrated the impact of obesity on pregnancy outcome, with special regard to development and/or recurrence of GDM. In line with this assumption, Sorbye *et al*.[31] found the relative risk for recurrent GDM in OV/Ob women was 0.8 in women who reduced their BMI by 1-2 points and 0.72 in those who reduced their BMI by >2 points, while was 1.26 if BMI was increased by ≥4 units.

Moreover, the previous development of GDM especially in OV/Ob women endangers the upcoming pregnancy to be associated with recurrence of GDM. However, the applied preconception LSI lessened this effect, similarly, Ali *et al*.[32] found more intensive and long-term LSI might be required early during the pregnancy or the preconception phase to empower pregnant women with a history of GDM to adopt and maintain healthy prenatal behaviors and to minimize the risk of GDM recurrence with its adverse maternal and infant health outcomes. Also, Dieberger *et al*.[33] documented that OV/Ob pregnant women aiming at GDM risk reduction should be advised to reduce time spent in sedentary life and increase time spent in moderate-to-vigorous physical activity early or pre-pregnancy. As another support of the effect of early LSI, Schleger *et al*.[34] found LSI during the third trimester of women who developed GDM showed no influence on the fetal postprandial brain responses and attributed this to relatively late application of LSI and recommended it to be applied as early as possible during gestation, or even prenatally to protect fetal brain responses.

The reported beneficial effect of early application of LSI in relation to the upcoming pregnancy might be attributed to its role in modulation of metabolic and hormonal milieu with weight reduction that allowed minimization of the risk of GDM, both new and recurrent. This assumption goes in hand with Phalen *et al*.[35] who documented that their proposed LSI could allow shifting of current treatment practices towards the inter-conception period and provide evidence-based preconception counseling to optimize reproductive outcomes and prevent GDM and associated health risks.

CONCLUSION

It is possible to assume that once having GDM, always developing GDM if BMI was stable or increased during the inter-pregnancy periods. LSI consisted of dietary regimen and aerobic exercise for four months preconception could break this vicious circle and decrease the frequency and severity of new or recurrent GDM mostly through reduction of BMI and minimization of its associated metabolic and hormonal disturbances.

LIMITATIONS

Evaluation of serum levels of adipocytokines was needed to confirm the mechanism for the reported improvement

RECOMMENDATIONS

Extension of the applied LSI during pregnancy to maintain its effect on the pregnancy-induced weight gain and insulin resistance, and so the maternal and fetal risks secondary to development of pregnancy-induced disorders could be minimized.

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CONFLICT OF INTERESTS

There are no conflicts of interest.

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