Diabetes & Metabolic Syndrome: Clinical Research & Reviews 13 (2019) 1463–1468

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Original Article

Serum irisin levels in polycystic ovary syndrome after ovarian drilling

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ARTICLE INFO

Article history:
Received 25 January 2019
Accepted 12 February 2019

Keywords:
Irisin
PCOS
Ovarian drilling

ABSTRACT

Background: Many cases of Poly-Cystic Ovary Syndrome (PCOS) are overweight and presenting with insulin resistance.
Main objective: was to evaluate the effects of ovarian drilling on the serum levels of Irisin in women with polycystic ovaries.
Study design and setting: Serum Irisin levels were investigated in 100 cases with PCOS before ovarian drilling and 3 months after drilling, and in 80 control cases. Serum Irisin, hormonal profile and HOMA-IR were estimated in PCOS cases before and after ovarian drilling. Statistical analysis was performed by using Statistical Package for Social Scientists (SPSS).
Results: The serum irisin levels in overweight and in normal weight PCOS cases before ovarian drilling were significantly higher as compared with the corresponding control cases. Fasting serum Irisin levels were found to be significantly elevated in PCOS patients before ovarian drilling as compared to the levels after drilling. The serum irisin levels in overweight and in normal weight PCOS cases before ovarian drilling were found to be significantly positively correlated with BMI, insulin levels, and HOMA-IR.
Conclusion: Elevated serum Irisin levels in PCOS may contribute to the development of insulin resistance. Ovarian drilling for polycystic ovaries results in a significant decrease in the serum Irisin levels. The analysis of ROC curves may suggest that serum Irisin may be a valuable biomarker for diagnosis and for monitoring cases with PCOS during treatment.

1. Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder of reproductive-aged women. It is associated with reproductive problems, and with metabolic disorders including insulin resistance [1]. (see Fig. 1)

It was suggested that impaired regulation of some adipomyokine hormones may play a role in the development of PCOS, because most PCOS patients have a tendency to become overweight or obese and insulin resistant.

Irisin is a newly identified muscle-derived myokine that acts as a messenger from skeletal muscle to other parts of the body. Irisin is named for Iris, the Greek Goddess who served as a messenger between Gods [2]. The circulating factor Irisin, cleaved from fibronectin type III domain containing 5 (FNDC5) activates thermogenic programs (browning) in white adipose tissue (WAT) leading to weight loss [2].

Skeletal muscle is not the main source of irisin; it is produced by many tissues as testis, pancreas, liver, spleen, stomach, brain, cardiac tissues, and fetal skeletal muscle cells as evidenced by Irisin staining [3].

Irisin may have a role in the pathophysiology of a number of diseases characterized by insulin resistance such as type-2 diabetes and metabolic syndrome [4]. Higher irisin levels are reported to be associated with body mass index (BMI), muscle mass and adipose tissue mass [5]. It was reported that plasma irisin concentration in PCOS cases and in healthy subjects is related to the adipose content [6].

2. Objectives

The aim of this study was to determine the serum levels of

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https://doi.org/10.1016/j.dsx.2019.02.019
1871-4021/

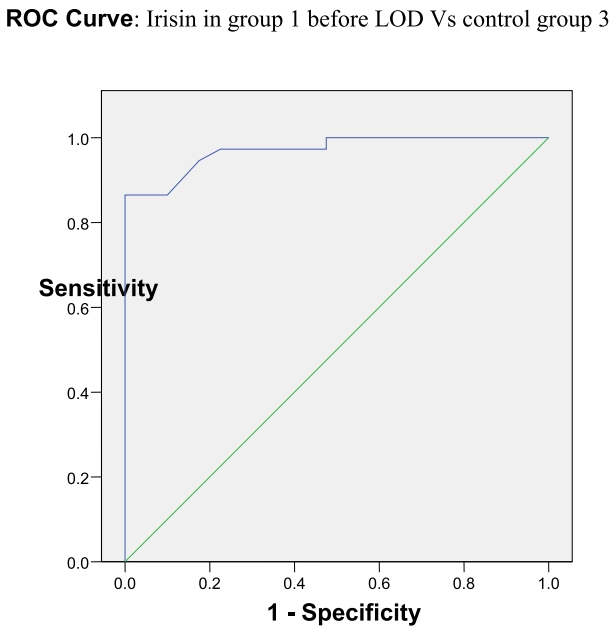

Fig. 1.

irisin in overweight and normal weight PCOS patients before and after laparoscopic ovarian drilling, and to correlate the irisin levels with hormonal profile and with insulin resistance (IR) parameters.

3. Materials and methods

3.1. Participants

The present study was a case-control study carried on *100 cases with PCOS and 80 control cases*. The cases were selected from cases seen for infertility at the Department of Obstetrics and Gynecology, Faculty of Medicine, Mansoura University, during the period between September 2016 and November 2018, in accordance with the following inclusion/exclusion criteria. The cases were not under medical or hormonal treatment for at least 3 months.

3.1.1. Inclusion criteria

Diagnosis of PCOS was based on the revised Rotterdam criteria [7], which require two of the following three manifestations: (1) oligo-ovulation and/or anovulation, (2) clinical and/or biochemical hyperandrogenism, and (3) polycystic ovaries on ultrasound.

The control cases consisted of healthy women who had regular menstrual cycles, normal findings on pelvic ultrasound scan, and no clinical hyperandrogenism (hirsutism/acne).

3.1.2. Exclusion criteria

For the study included age >40 years, known cardiovascular disease, thyroid disease, other endocrinopathies, neoplasms, endometriosis, current smoking, diabetes, renal impairment, hypertension, oral contraceptives users, hormonal or anti-hypertensive medication for at least 3 months before the study.

The final clinical study involved the following groups of cases:

Group 1-before (group 1-B) laparoscopic ovarian drilling (LOD): consisted of 50 overweight PCOS cases (with BMI ≥25 - < 30 kg/m^2) before LOD.

Group 1-after LOD (group 1-A): consisted of 37 overweight PCOS cases three months after ovarian drilling. Thirteen cases withdrew during the second visit due to pregnancy.

Group 2-before LOD (group 2-B): consisted of 50 normal weight PCOS cases (with BMI < 25 kg/m^2) before laparoscopic ovarian drilling.

Group 2-after LOD (group 2-A): consisted of 35 normal weight PCOS cases three months after ovarian drilling. Fifteen cases withdrew due to pregnancy.

Group 3: consisted 40 overweight cases (BMI ≥ 25 - <30 kg/m^2) as a control.

Group 4: consisted 40 normal weight cases (BMI <25 kg/m^2) as a control.

BMI (kg/m^2) was calculated by dividing weight (kg) by height squared (m^2). Overweight is considered if BMI ≥25 - < 30 kg/m^2 (according to the WHO criteria).

3.2. Ethical approval

The study was approved by the IRB committee of Faculty of Medicine, Mansoura University, Egypt. *[Code number; R/15.08.61, date: 1/9/2015].*

Informed written consents were taken from the cases

3.3. Sampling

All samples were obtained in the morning (at 9–10 a.m.) after an overnight fast (10–12 h) and complete bed rest, during the early follicular phase (days 2–4 of the cycle). Five ml of maternal venous blood were withdrawn from anti-cubital vein under complete aseptic conditions.

All samples were collected in a vacutainer tube with gel, and the serum was separated by centrifugation and divided into two parts: one part was used for assessment of fasting blood glucose, insulin levels and hormonal profile (FSH, LH, free testosterone, total testosterone & DHEA-S), and the second part was stored at −80 °C until the time of assay of Irisn.

3.4. Methods of assay

- **Serum levels of glucose** were measured by the enzyme-calorimetric methods.
- **Serum levels of Insulin:** was measured by electro-chemiluminescence immunoassay method.
- **Homeostasis Model of Assessment-Insulin Resistance (HOMA-IR) index** for the assessment of insulin resistance was measured by calculation by using the equation of **Matthews et al.,** [8].

HOMA-IR = [glucose (mg/dl) × insulin (mIU/ml)] ÷ 405.

Insulin resistance (IR) was accepted as HOMA-IR ≥ 2.5 [8].

- **Hormonal parameters** [LH, FSH, free testosterone, total testosterone, and dehydro-epi-androsterone-sulfate (DHEA-S)] were analyzed by immune chemiluminescence method.
- **Serum irisin** concentrations were measured with enzyme-linked immunosorbent assay (ELISA) by using Human Irisin ELISA Kit (Cat No RAGO18R, Lot No ×14-369) supplied by Bio-Vendor, according to the methods recommended by the manufacturer**.**

3.4.1. Principle of Irisin assay

This assay is a specific competitive Enzyme Linked-Immuno-Sorbent Assay (ELISA) for quantitative determination of Irisin in human biological fluids. A polyclonal antibody recognizing native Irisin reacts with a series of predetermined recombinant Irisin standard proteins In the irisin coated plate. Their relative reactivity is plotted with that of the standard proteins. The color was measured at OD 450 in an ELISA reader within 30 min. Generate the standard curve by plotting the average absorbance obtained by each standard concentration on vertical (Y) axis vs the corresponding irisin concentration on the horizontal axis. Calculate the irisin concentrations by interpolation of the regression curve formula. If the test samples were diluted, multiply the interpolated values by the dilution factor to calculate the concentration of irisin in the sample.

3.5. Statistical analysis:

Normality of the distribution of the variables was confirmed by the Shapiro-Wilk test. Mean and standard deviation were used to describe data.

Paired *t*-test was used to compare the means of normally distributed variables studied between the groups before and after LOD.

Unpaired *t*-test and Mann-Whitney U tests were used to compare the means of variables with normal and not-normal distribution between two groups, respectively.

Pearson's product moment correlation was used to determine the correlation between irisin levels and other studied parameters in the same group. P value was considered significant if less than 0.05.

Statistical analysis of the results was performed by using Statistical Package for Social scientists (SPSS) for Windows (SPSS Inc., Chicago, IL, USA).

4. Results

Table 1 represents the clinical outcomes after LOD.

After **LOD, the menstrual cycles** were found to be regular in 64.86% of group 1-after **LOD cases (p = 0.0055)**, while it was regular in 77.14% in group 2-after **LOD cases** (***p* = 0.006).** As regard oligomenorrhea, there was a significant decrease after LOD in group 1 ($p = 0.028$) and in group 2 ($p = 0.021$). There was no significant improvement in hirsutism or acne after LOD in group 1 or in group 2 ($p > 0.434$).

In the overweight group 1-after **LOD,** 13 cases withdrew due to pregnancy (26%). In these pregnant cases, the LH levels were >10 mIU/ml (range 10–11 mIU/ml) and the LH/FSH ratios were >2.08 (range 1.9–2.14). The BMI and HOMA-IR changes were not associated with pregnancy.

In normal weight PCOS cases of group 2-after **LOD**, 15 cases were missed after three months due to pregnancy (30%). In 12 of these cases, the LH levels were >10 mIU/ml (range 9.7–11 U/L), and the LH/FSH ratio was >2.32 (range 2.06–2.65 U/L). There was no association between pregnancy and BMI or HOMA-IR changes.

Table 2 represents the effects of LOD on the studied variables in group 1 before LOD versus group 1 after LOD and in group 2 before LOD versus group 2 after LOD.

In overweight PCOS cases (group 1) after LOD, there were significantly ($p = 0.001$) decreased values of BMI (25.554 ± 0.85) as compared with the value before LOD (27.646 ± 1.01). Also, WHR was significantly decreased ($p < 0.001$) after LOD (0.783 ± 0.015 versus 0.834 ± 0.04).

In group 1 after LOD, there were a significantly decreased insulin ($p = 0.027$), & **HOMA-IR** ($p = 0.0001$), LH ($p = 0.0001$), LH/FSH ratio ($p = 0.0001$), free testosterone ($p = 0.016$), total testosterone ($p = 0.011$) and Irisin ($p = 0.004$) as compared with the values before LOD. The FSH level significantly increased after LOD ($p = 0.015$).

In normal weight PCOS cases after LOD (group 2), there were a significantly decreased ($p < 0.001$) values of BMI (24.22 ± 0.361) as compared with the value before LOD (24.71 ± 1.01). Also, WHR was significantly decreased ($p < 0.001$) after LOD (0.797 ± 0.014 versus 0.813 ± 0.01).

In normal weight PCOS cases (group 2) after LOD, **there were a** significant decrease in insulin ($p = 0.003$), & **HOMA-IR** ($p = 0.002$), LH ($p = 0.0001$), LH/FSH ratio ($p = 0.0001$), free testosterone ($p = 0.023$), total testosterone ($p = 0.013$) and Irisin ($p = 0.002$) values as compared with group 2 values before LOD. The FSH level significantly increased after LOD ($p < 0.0001$).

Table 3 represents the studied variables in group 1 before LOD versus control group 3, and group 2 before LOD versus control group 4.

In group 1-before LOD, there were a significantly increased values of insulin, LH, LH/FSH, free testosterone, & total testosterone as compared with overweight group 3 control cases ($p < 0.011$). This represents the effects of PCOS in the overweight cases on the variables as compared with corresponding overweight control group.

The group 2 before LOD had a significantly increased values of fasting glucose, insulin, HOMA-IR, LH, LH/FSH, free testosterone, total testosterone & Irisin as compared with normal weight group 4

Table 1
p value using the Chi square test for clinical features before and after LOD.

	Group 1 [number (%)]			Group 2 [number (%)]		
	Before LOD (50 cases)	After LOD (37 cases)	P value	Before LOD (50 cases)	After LOD (35 cases)	P value
Regular cycles	10/50 (20%)	24/37 (64.86%)	= 0.0055	13/50 (26%)	27/35 (77.14%)	= 0.006
Oligomenorrhea	40/50 (80%)	11/37 (29.73%)	= 0.028	37/50 (74%)	10/35 (28.57%)	= 0.021
Acne	28/50 (56%)	13/37 (35.14%)	= 0.242 (NS)	25/50 (50%)	9/35 (25.71%)	= 0.133 (NS)
Hirsutism	34/50 (68%)	19/37 (51.35%)	0.434 (NS)	32/50 (64%)	12/35 (34.29%)	0.119 (NS)
Pregnancy	0/50 (0%)	13/50 (26%)	= 0.0001	0/50 (0%)	15/50 (30%)	= 0.0001

(NS): p value > 0.05 & is not significant.

Table 2
Metabolic, hormonal and irisin values (mean ± SD) in group 1 before LOD versus group 1 after LOD, and in group 2 before LOD versus group 2 after LOD.

	Group 1 before LOD *(37 cases*	Group 1 after LOD *(37 cases)*	*p1 value (paired t-test)*	Group 2 before LOD *(35 cases)*	Group 2 after LOD *(35 cases)*	*p 2 value (paired t-test)*
FBGL *(mg/dl)*	104.3 ± 4.782	98.7 ± 4.11	0.763 (NS)	108.314 ± 7.108	102.257 ± 5.66	= 0.814 (NS)
Insulin *(IU/L)*	14.85 ± 2.11	12.7 ± 0.829	= 0.027	12.2 ± 2.386	9.83 ± 0.61	= 0.003
HOMA-IR	4.13 ± 0.*73*	2.542 ± 0.22	<0.0001	3.295 ± 0.84	2.47 ± 0.19	= 0.002
FSH *(mIU/ml)*	4.11 ± 0.36	4.72 ± 0.38	= 0.015	3.989 ± 0.292	4.43 ± 0.287	<0.0001
LH *(mIU/ml)*	9.06 ± 0.89	5.18 ± 0.62	<0.0001	8.249 ± 0.613	5.137 ± 0.50	<0.0001
LH/FSH	2.21 ± 0.19	1.12 ± 0.106	<0.0001	2.09 ± 0.048	1.15 ± 0.47	<0.0001
F. testo *(pg/ml)*	4.19 ± 0.79	3.33 ± 0.61	= 0.016	4.08 ± 0.48	3.27 ± 0.47	= 0.023
T. testo *(pg/ml)*	696.514 ± 66.92	532.549 ± 84.64	= 0.011	641.286 ± 109.24	517.29 ± 74.392	<0.013
Irisin *(ng/ml)*	803.24 ± 85.87	667.4 ± 72.79	= 0.004	641.8 ± 55.8	524.114 ± 54.29	= 0.002

p1 & p2 values using the **paired *t*-test**.
(NS): p value > 0.05 & is not significant.

Table 3
Metabolic, hormonal and irisin values (mean ± SD) in group 1 before LOD versus group 3 and in group 2 before LOD versus group 4.

	Gr 1 before LOD *(50 cases)*	Group 3 *(40 cases)*	*p1 value*	Gr 2 before LOD *(50 cases)*	Group 4 *(40 cases)*	*p 2 value*
FBGL *(mg/dl)*	104.78 ± 4.92	93.24 ± 5.67	**= 0.2 (NS)**	107.86 ± 6.93	83.97 ± 7.01	**= 0.015**
Insulin *(IU/L)*	14.91 ± 2.31	10.89 ± 1.*85*	**= 0.003**	12.34 ± 2.4	8.963 ± 0.906	**<0.0001**
HOMA-IR	4.17 ± 0.*78*	2.55 ± 0.56	**= 0.001**	3.345 ± 0.84	*1.763 ± 0.308*	**<0.0001**
FSH *(mIU/ml)*	4.11 ± 0.35	4.058 ± 0.489	**= 0.233 (NS)**	3.96 ± 0.31	4.37 ± 0.77	**= 0.07 (NS)**
LH *(mIU/ml)*	8.92 ± 0.82	4.69 ± 0.559	**<0.0001**	8.17 ± 0.62	4.575 ± 0.416	**<0.0001**
LH/FSH	2.19 ± 0.21	1.198 ± 0.24	**<0.0001**	2.08 ± 0.04	1.13 ± 0.146	**<0.0001**
F. testo *(pg/ml)*	3.63 ± 0.64	2.485 ± 0.45	**= 0.011**	4.03 ± 0.47	2.56 ± 0.53	**= 0.002**
T. testo *(pg/ml)*	664.33 ± 69.25	456.71 ± 59.07	**<0.0001**	647.9 ± 104.63	454.375 ± 59.5	**= 0.002**
Irisin *(ng/ml)*	802.53 ± 95.07	579.525 ± 83.348	**<0.0001**	655.57 ± 51.48	465.225 ± 67.346	**<0.0001**

P value (unpaired *t*-test).
(NS): p value > 0.05 & is not significant.

control cases ($p < 0.015$). This represents the effects of PCOS in normal weight cases on the variables as compared with normal weight control group.

Table 4 represents the correlation between irisin and the studied variables.

In group 1 before LOD the fasting serum irisin levels ***had a significant positive* correlation** with BMI ($p = 0.002$), WHR ($p = 0.017$), the fasting serum insulin levels ($p = 0.014$), HOMA-IR ($p = 0.048$), LH ($p < 0.0001$), LH/FSH ($p = 0.029$), free testosterone ($p = 0.045$), and total testosterone ($p = 0.003$).

In group 1 after LOD drilling **there was a significant positive correlation** with BMI ($p = 0.017$) and with WHR ($p = 0.05$).

In normal weight PCOS cases before drilling (group 2 before), the fasting serum irisin levels had a significant positive correlation with the fasting serum glucose ($p = 0.047$), with insulin levels ($p = 0.009$), with HOMA-IR ($p < 0.0001$), with LH ($p = 0.026$), with LH/FSH ($p = 0.001$), with free testosterone ($p < 0.0001$), and with total testosterone ($p < 0.0001$).

In group 2-after LOD, irisin levels were significantly correlated with the free testosterone ($p = 0.046$) and with total testosterone ($p = 0.047$).

ROC curve analysis of irisin data for discriminating cases with PCOS from group 3 healthy controls (group 1 before LOD versus the control group 3) revealed that the area under the curve, sensitivity, and specificity were 0.971, 86.3% & 100%, respectively. The cut-off value of serum Irisin was 742 ng/ml.

By using ROC curve analysis for irisin in group 2 versus control group 4, the area under the curve was 0.992, sensitivity was 97%, and specificity was 95%. The cut-off value of serum Irisin was 556 ng/ml.

Table 4
Correlation between Irisin levels and studied variables.

	Gr 1 before LOD		Gr-1 after LOD		Gr 2 before LOD		Gr 2 after LOD	
	r	p	r	p	r	p	r	p
BMI	0.634	0.002*	0.482	0.017*	0.072	0.683	0.033	0.853
WHR	0.486	0.017*	0.514	0.05*	0.165	0.343	0.221	0.202
Glucose	0.011	0.948	0.076	0.076	0.338	0.047*	0.015	0.931
Insulin	0.530	0.014*	0.177	0.177	0.438	0.009*	0.285	0.097
HOMA-IR	0.399	0.048*	0.112	0.508	0.77	0.001*	0.054	0.758
FSH	0.017	0.315	0.145	0.393	0.209	0.228	0.176	0.312
LH	0.737	0.001*	0.102	0.550	0.375	0.026*	0.385	0.022*
LH/FSH	0.359	0.029*	0.116	0.496	0.523	0.001*	0.143	0.413
Free Testost.	0.392	0.045*	0.033	0.847	0.674	0.001*	0.389	0.046*
Total Testo.	0.625	0.003*	0.098	0.563	0.771	0.001*	0.378	0.047*

F. testo.: free testosterone.
T. testo.: total testosterone.
*p < 0.05 is statistically significant.

5. Discussion

The results of the present study showed that PCOS patients have an elevated fasting Irisin levels when compared with the normal control cases ($p = 0.000$), and these changes are associated with insulin resistance (high HOMA-IR).

It was found that Irisin levels increased in patients with metabolic syndrome (MS) compared to those of patients without the syndrome, and the Irisin level has been associated with BMI and muscle mass [9].

The high levels of Irisin in PCOS patients can be explained as an Irisin resistance state [10,11] similar to insulin resistance [12] or by the suggestion that it acts as a protective mechanism to counteract excess energy inflow, because Irisin normally increases energy expenditure in brown and beige adipose tissues [2].

In the present study, the serum Irisin levels were significantly higher in PCOS cases before ovarian drilling as compared with the control cases [p = 0.0001], and this may be attributed to differences in BMI between the two groups. The present results are in

agreement with the previous findings [6,13,14].

In the present study, fasting insulin levels as well as HOMA-IR were significantly decreased after ovarian drilling. This can be explained by an improvement of insulin sensitivity due to reduced androgen secretion from the ovaries after LOD, because androgens act directly on peripheral tissues to promote insulin resistance [15].

It was suggested that normal ovarian physiology is maintained by interactions between endocrine factors from muscle, gut, and ovarian tissues. The abnormal regulation of Irisin may contribute to the metabolic manifestations of PCOS and may represent early events in PCOS development [13,14]. The elevated serum Irisin level was suggested to be a protection in the pre-diabetic state of PCOS before development of diabetes mellitus [15].

In the present study, Irisin was positively correlated with insulin resistance marker (HOMA-IR) in PCOS cases ($P < 0.05$). The increased irisin levels may be due to an Irisin resistance resulting in a compensatory increased Irisin levels, or due to increased Irisin secretion from the fat tissue in PCOS. The findings in the present study are in agreement with the results of Park et al. [9]. The development of risk factors resulting in increased morbidities such as insulin resistance in PCOS patients may be due to abnormal Irisin metabolism [12].

There were contradictory reports as regards the association of BMI with Irisin levels. Some studies observed a positive correlation of Irisin levels with BMI [12,13], while no correlation was reported by Park et al. [9], or even a negative correlation by others [15]. In the present study, there was a significant correlation between the Irisin levels and BMI in PCOS cases, and this is in agreements with previous reports [12,13].

Pregnancy occurred in 30% of normal weight PCOS cases after **LOD,** and this can be explained by destruction of ovarian follicles and a part of the ovarian stroma after LOD leading to a reduction of serum androgens and inhibin levels, resulting in an increase of FSH restoring the ovulation function [16]. This is in agreement with the previous results by Fernandez et al. [17].

In the present study, there were a significant decrease in luteinizing hormone (LH), increase in follicle-stimulating hormone (FSH) and LH/FSH levels in the 3 months after LOD. This is in agreement with the findings of Wu et al. [16]. The reduction of luteinizing hormone concentrations after LOD leads to an increase in the secretion of FSH leading to effective follicular maturation and ovulation [17].

In the present study, the significant increase in FSH levels three months after ovarian drilling in group 1 and group 2 is in agreement with Fernandez et al. [17].

In the present study, the free testosterone & total testosterone levels were significantly higher in PCOS cases as compared with the control group. After LOD, the levels of testosterone were significantly reduced. These findings are in agreement with [16,18]. However, there were contradictory reports as regards the influence of BMI, insulin resistance, and testosterone concentrations on the fertility following LOD [17,19].

The clinical and endocrine response of patients to LOD depends on the pretreatment LH levels and on the period of infertility, it is better if the basal LH is high (>10 IU/L), and if < 3 years of infertility [17,19], *In the present study*, the LH levels before LOD in the cases that become pregnant were >10 U/L, and this finding is in agreement with previous reports [17,19].

Fernandez et al. [17] concluded that ovarian drilling leads to spontaneous ovulation in 20–64% of women with PCOS who had previously been infertile as a result of anovulation and CC resistance.

In the present study, lower pregnancy rate are reported in overweight PCOS compared to normal weight PCOS cases (23.64% versus 27.27%) and this finding is in agreement with Baghdadi et al. [19], but this is contradictory to a previous study [20].

In the present study, there was improvement in hormonal profiles and HOMA-IR in cases after LOD as compared with the values before LOD. This improvement is in agreement with the findings of Wu et al. [16], but this is not in agreement with previous studies that reported that improvement in hormonal profiles was not associated with improvement of insulin sensitivity [21,22].

To assess the performance of serum Irisin as a biomarker, ROC curves were used to calculate the sensitivity of this marker for discriminating cases with PCOS from healthy controls. The analysis of ROC curves may suggest that serum Irisin may be a valuable biomarker for diagnosis and for monitoring cases with PCOS during treatment.

6. Conclusion

The serum Irisin levels were significantly higher before ovarian drilling in PCOS cases as compared with the cases after ovarian drilling and with the control cases.

The increased Irisin levels in PCOS cases may be due to over-expression from the ovarian tissues or from the adipose tissue. Changes in Irisin serum levels after LOD may be due decreased secretion from the ovaries.

By using the ROC curve, Irisin may be considered as a biomarker for detection polycystic ovarian syndrome, and it may be used as a marker to follow the disease after medical or surgical treatments.

Conflicts of interest

None.

Acknowledgements

We acknowledge all our patients for their cooperation, and all the laboratory technicians for their help and effort.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2019.02.019.

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