Bariatric Surgery versus Dieting Regimen and Lifestyle change as a modality to improve Ovarian Function in Clomiphene-resistant PCOS Women

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Abstract

Background: Obesity is worldwide spreading epidemic and deleteriously affects the metabolic and reproductive functions of females. The results of therapeutic lines provided for obese citrate-resistant women with polycystic ovary syndrome (CCR-POCS) were variable and discrepant.

Objectives: Evaluation of the effects of weight reduction programs on the ovulatory function of obese CCR-POCS women in comparison to bariatric surgery

Patients and Methods: 135 obese CCR-PCOS women were randomly divided into group I assigned for bariatric surgery, and groups II and III that followed dieting regimen, and lifestyle change with or without insulin sensitizer, respectively. Body mass index (BMI), Homeostasis Model Assessment of Insulin resistance (HOMA-IR) score and serum levels of testosterone and Ferriman-Gallwey (FG) hirsutism score were determined at enrolment (Pre-intervention) and 6-m later (Post-intervention). The study outcome is the frequency of post-intervention ovulation and regular menstrual cycles.

Results: Post-intervention BMI, HOMA-IR, estimated serum levels of testosterone, and FG score were significantly decreased in all patients than pre-intervention data with significantly higher change in women of group I compared to other groups. During 6-m follow-up after the intervention, 43 women (31.9%) got a regular menstrual cycle with significantly higher frequency among women of group I compared to other groups.

Conclusion: Weight reduction interventions might ameliorate the deleterious effects of obesity and insulin resistance on ovarian functions. Bariatric surgery allowed significant weight reduction, decreased hyperandrogenemia, and improved ovarian function. Weight reduction regimens, lifestyle changes, and insulin sensitizers are effective alternatives whenever surgery is contraindicated or refused by patients.

Keywords: Clomiphene resistance; PCOS; Ovulation; Bariatric surgery; Weight reduction programs.

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Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder that affects women of childbearing age and is responsible for many adverse effects with increased social burden **(Davinelli et al., 2020)**. PCOS is characterized by the presence of many areas of uncertainty, with subsequent under-or over-diagnosis **(Copp et al., 2020)**. However, its main diagnostic criteria include ovulatory disturbance with concomitant infertility or disturbed menstrual cycle **(Zhang et al., 2021)**, hyperandrogenemia, and the presence of enlarged ovaries or multiple ovarian cysts **(Zhang et al., 2020)**.

Clomiphene citrate (CC) is widely used for ovulation induction; however, some PCOS women may show CC resistance that meant failure to achieve ovulation after gradual dose increment up to 150 or 250 mg/day for at least three consecutive cycles **(Ege et al., 2021)**.

There is an interrelation between PCOS and obesity with its concomitant insulin resistance that deleteriously affects ovarian functions leading to menstrual disturbances and/or infertility leading to multiple psychological problems that per se may induce obesity, and thus a vicious circle was established **(Moran et al., 2010)**.

Lack of definite treatment of PCOS allowed multiple trials to be conducted for breaking this vicious circle using insulin sensitizers to minimize the effect of IR on ovarian functions **(Notaro et al., 2022)**, dieting regimen with or without exercise to promote weight loss **(Zhao et al., 2022)**, laparoscopic drilling of ovarian cysts was found to improve the ovarian function **(Sun et al., 2022)**, and lastly, the bariatric surgeries to achieve long-term control on eating behavior and loss of weight **(Bhandari et al., 2022)**.This clinical trial was provided to compare the effect of weight reduction and lifestyle changes with or without insulin sensitizers versus bariatric surgery on the ovulatory function of CC-resistant PCOS (CCR-PCOS) women.

Patients and methods

Study design and participants

A Prospective multicenter randomized clinical trial conducted at Department of General Surgery at Benha Teaching Hospital, in association with Departments of Obstetrics and Gynecology and Community at Faculty of Medicine, Benha University in conjunction with multiple private centers. Obese CCR-PCOS women, free of exclusion criteria and accepted to sign the informed consent were enrolled in the study. The exclusion criteria included the presence of obesity-inducing endocrinopathy, current or previous pregnancy within 1 year of enrollment or the use of hormonal contraception within the last 6 months before inclusion in the study, presence of peptic ulcer disease, previous abdominal surgery especially for gastric or intestinal pathologies, contraindication for general anesthesia, extensive exercise, severe symptomatizing hypovitaminosis, and coagulopathy.

All women eligible for evaluation were notified by the study protocol, mode of randomization and

period of follow-up and the possible outcomes of the study. Women who accepted to participate in the study were asked to sign written fully informed consents. The study protocol was approved by The Local Ethical Committee at Benha Faculty of Medicine by approval number: RC: 3/8/2022.

The included participants were categorized into three groups:

1. Group I: Laparoscopic sleeve gastrectomy was performed under general anesthesia and abdominal inflation to 14mmHg, and using the 5-port technique as previously described **(Ramos et al., 2015)**. The main steps are shown in **(Fig.1A,B, and C).**
2. Groups II and III received a weight reduction regimen with diet calories were provided as protein, carbohydrates and fat as 30%, 40% and 30%, respectively. Lifestyle change program included initial training as walking/jogging program comprising five weekly sessions and treadmill training with gradually increased duration till 45 min by end of the study. Additionally, patients of group II received insulin sensitizer.

Evaluation tools

1. Diagnosis of PCOS using the Rotterdam criteria **(Chen et al., 2007)**, a woman was diagnosed to have PCOS must had at least two of these criteria and those were refined to include only women had CCR, which is diagnosed as previously documented **(Ege et al., 2021)**.
2. Body mass index (BMI) was calculated as weight divided by the square of the height and expressed as kg/m2 **(Bray 1992)**. BMI was determined before and at 6-m after the intervention (Pre- and Post-intervention) to calculate the percentage of change in Post-intervention BMI in relation to the pre-intervention BMI.
3. The Matthews Homeostasis Model Assessment of Insulin resistance (HOMA-IR) score **(Matthews et al., 1985)** was used to detect the presence of IR at cutoff point of score >2 **(Ascaso et al., 2001)**. Pre- and post-intervention HOMA-IR scores were determined for calculation of the percentage of change.
4. Ferriman-Gallwey (FG) hirsutism visual scoring **(Ferriman and Gallwey 1961)** that evaluates eleven body parts with a 0-4 score was applied and FG score of ≥ 8 indicates hirsutism **(Brodell and Mercurio 2010)**.
5. Pre- and post-intervention estimation of serum levels of testosterone and sex-hormone binding protein (SHBP) levels and the extent of change were calculated.

Sample size calculation

Non-comparative studies to evaluate the effect of bariatric surgery on PCOS-associated metabolic and hormonal disturbances included 14 **(Eid et al., 2014)** and 29 **(Chiofalo et al., 2017)** obese PCOS women. The current study, as a randomized comparative study, suggested that 6-m Post-intervention the difference in the frequency of patients who will have significant changes in their BMI, HOMA-IR, and hormonal changes

must be significant in favor of bariatric surgery. Thus, to achieve a significant difference with α value of 0.05 and β value of 0.2 to get a study power of 80%, the calculated sample size was 42 patients per group, but to guard against dropout during the randomization or during follow-up, the number of participants was 50/group.

Randomization and Grouping

The randomization sequence was conducted using Excel 2007 (Microsoft, Redmond, WA, USA) by random block sizes and the generated sequence was translated as labels I, II and III and the labels were written on cards that were put in dark envelopes to be chosen by patients who were divided as bariatric surgery, insulin sensitizer plus the dieting regimen and lifestyle change protocol and lifestyle change with a weight reduction regimen without insulin sensitizer, respectively.

Outcome evaluation

1. The ovulation success rate is the primary outcome and was judged by serum progesterone level ≥25 nmol/l on Day 21 of the menstrual cycle and was assured by detection of a dominant follicle size of >16 mm at day 10 of the cycle using TVU.
2. The percentage of change in BMI and HOMA-IR scores, hyperandrogenemia, and FG scores are the secondary outcomes.

Statistical analysis

Results were analyzed using the paired t-test, One-way ANOVA and Chi-square tests, while the correlation between the outcomes was evaluated using Pearson's correlation analysis with r as coefficient of correlation. Statistical analysis was conducted using IBM® SPSS® Statistics (Version 22, 2015; Armonk, USA) with P value <0.05 indicated significant difference.

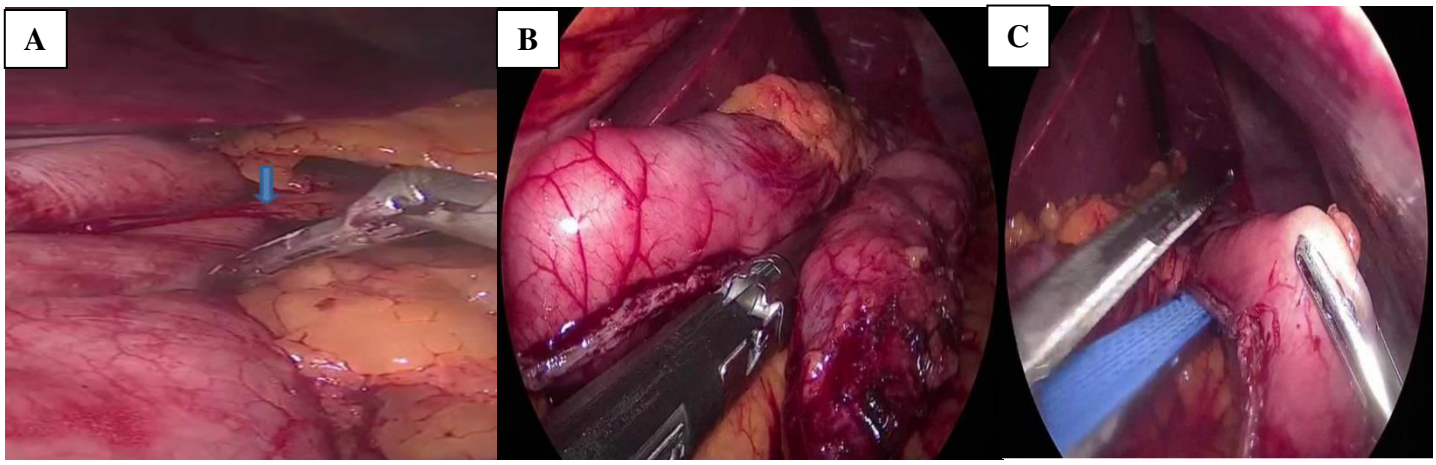

Fig.1. A: Dissection of the gastrosplenic ligament ; B: Initiation of a vertical cut of greater curvature ; C: Firing of endo-GIA stapler over greater curvature.

Results

During the study duration from Oct 2019 to Oct 2021, 135 obese CCR-PCOS women completed the study protocol as shown in (**Fig.2).** All surgeries performed for patients of group I were completed uneventfully

and operative and postoperative (PO) data are shown in (**Table 1).**

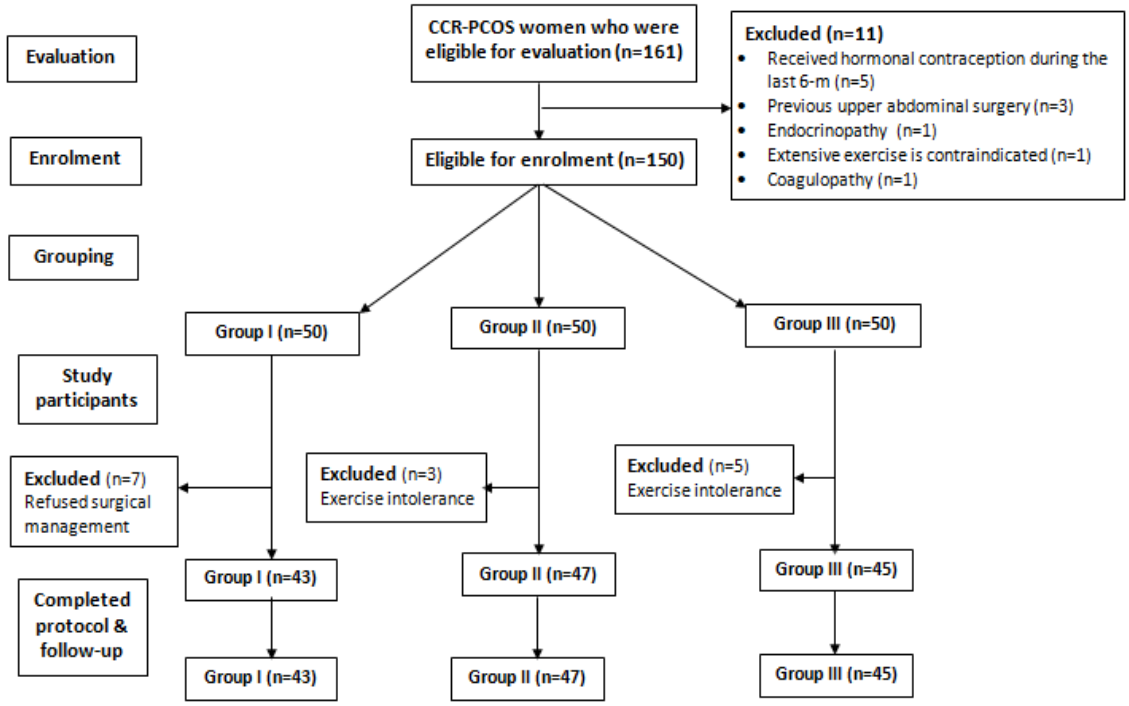

Fig.2. Consort flow sheet

Table 1. Operative and Postoperative data of patients who underwent surgery

Variables	Findings
Operative time (min)	65.6±9.1 (50-90)
The frequency of shift to open procedure	0
The frequency of cancellation due to surgical difficulties	0
PO duration till 1st ambulation (h)	5.6±1.4 (3-8)
PO duration till 1st oral intake (h)	7.3±1.4 (4.5-10.5)
PO hospital stay (h)	19.8±2.5 (16-24)

Data are presented as mean; standard deviation

At 6-m Post-intervention BMI and HOMA-IR data of all patients significantly decreased compared to their pre-intervention data, but the change was more superior in group I than in other groups **(Table 2).**

Serum levels of testosterone and sex-hormone binding-globulin, and free androgen index were significantly decreased at the end of intervention in all patients with non-significant differences between groups, while the percentage of change was significantly lower in patients of group III compared to patients of other groups with significantly higher percentage of change in patients of group I than those of group II **(Table 3).**

Table 2. Pre- and Post-intervention BMI and HOMA-IR scores of the studied patients

Variables			Group I	Group II	Group III	P1	P2	P3
BMI (kg/m^2)	Pre		37.3±2.3	38.2±3.3	38.5±2.1	0.102	0.218	0.918
	Post		30.8±1.8	33.8±2.5	34.2±2	<0.001	<0.001	0.496
	P4		<0.001	<0.001	<0.001			
	BMIL%		17.4±3.1	11.4±4.1	11±2.3	<0.001	<0.001	0.809
BMI grade	Pre (No.; %)	Overweight	0	0	0	0.193	0.121	0.747
		Obese-I	7 (16.3%)	4 (8.5%)	3 (6.7%)			
		Obese-II	31 (72.1%)	30 (63.8%)	32 (71.1%)			
		Obese-III	5 (11.6%)	13 (27.7%)	10 (22.2%)			
	Post (No.; %)	Overweight	12 (27.9%)	2 (4.2%)	2 (4.4%)	0.0001	0.002	0.456
		Obese-I	30 (69.8%)	35 (74.6%)	29 (64.5%)			
		Obese-II	1 (2.3%)	9 (19.1%)	14 (31.1%)			
		Obese-III	0	1 (2.1%)	0			
	P4		<0.001	<0.001	<0.001			
HOMA-IR grade	Pre (No.; %)	Score <2	26 (60.5%)	26 (55.3%)	22 (48.9%)	0.622	0.377	0.537
		Score ≥2	17 (39.4%)	21 (44.7%)	23 (51.1%)			
	Post (No.; %)	Score <2	37 (86%)	37 (78.7%)	32 (71.1%)	0.364	0.089	0.399
		Score ≥2	6 (14%)	10 (21.3%)	13 (28.9%)			
	P4		0.0037	0.016	0.031			
Mean HOMA-IR score	Pre		1.7±0.5	1.82±0.5	1.85±0.54	0.468	0.315	0.958
	Post		1.32±0.4	1.5±0.44	1.57±0.5	0.169	<0.001	0.001
	P4		0.0002	0.0006	0.01			
	% of change		22.4±7.8	18.8±6.9	15.2±4.6	0.029	<0.001	0.028

Data are presented as mean (±SD); numbers (%); BMIL: BMI loss; HOMA-IR: Homeostasis Model Assessment of Insulin resistance; P1 indicates the significance of the difference between groups I and group II; P2 indicates the significance of the difference between groups I and III; P3 indicates the significance of the difference between groups II and III; P4 indicates the significance of the difference between pre-and post-intervention data for each group; P<0.05 indicates the significant difference

Post-intervention FG scores were significantly lower in all patients compared to pre-intervention scores with non-significant differences between groups, while the percentage of change was significantly lower in patients of group III than in other groups **(Table 3).**

Table 3. Pre- and Post-intervention androgenic hormonal and FG scores of the studied patients

Variables		Group I	Group II	Group III	P1	P2	P3
Testosterone (nmol/L)	Pre	2.46±0.51	2.44±0.55	2.48±0.46	0.861	0.838	0.905
	Post	2.03±0.41	2.09±0.49	2.15±0.4	0.525	0.153	0.508
	P4	0.00005	0.0022	0.0004			
	% of change	17.24±6.1	14.43±2.6	13.15±3	0.0055	0.0001	0.031
Sex-hormone binding-globulin (nmol/L)	Pre	21±5.7	20.88±6.5	21.7±7.55	0.927	0.623	0.578
	Post	28.8±5.5	27.3±7.6	27.2±8.1	0.307	0.294	0.949
	P4	<0.001	0.00004	0.0009			
	% of change	7.8±3.3	6.5±2.4	5.5±1.9	0.032	0.0001	0.045
Free androgen index	Pre	0.127±0.05	0.13±0.05	0.13±0.06	0.862	0.800	0.939
	Post	0.073±0.02	0.083±0.03	0.086±0.03	0.113	0.017	0.476
	P4	<0.001	<0.001	0.00002			
	% of change	0.054±0.03	0.047±0.02	0.044±0.03	0.215	0.086	0.566
FG score	Pre	8.6±3.7	9.4±4.6	8.1±3.7	0.39	0.564	0.162
	Post	5.44±2.31	6.51±4.4	5.74±3	0.159	0.598	0.329
	P4	<0.001	0.0033	0.001			
	% of change	3.16±2.2	2.87±0.94	2.4±1	0.407	0.033	0.023

Data are presented as mean (±SD); numbers (%); P1 indicates the significance of the difference between groups I and group II; P2 indicates the significance of the difference between groups I and III; P3 indicates the significance of the difference between groups II and III; P4 indicates the significance of the difference between pre-and post-intervention data for each group; P<0.05 indicates the significant difference

Correlation analysis showed a positive significant correlation between the application of bariatric surgery and the extent of improvement of BMI (r=0.661, p<0.001), HOMA-IR score (r=0.350, p<0.001), and hyperandrogenemia (r=0.368, p<0.001). Moreover, there was a positive significant correlation between the percentage of change in BMI and percentage of change in HOMA-IR score (r=0.465, p<0.001) and serum testosterone level (r=0.484, p<0.001) at 6-m post-intervention (**Fig.3A and B**). Further, the incidence of getting regular menstruation was positively (r=0.530, p<0.001) related to the extent change of serum testosterone.

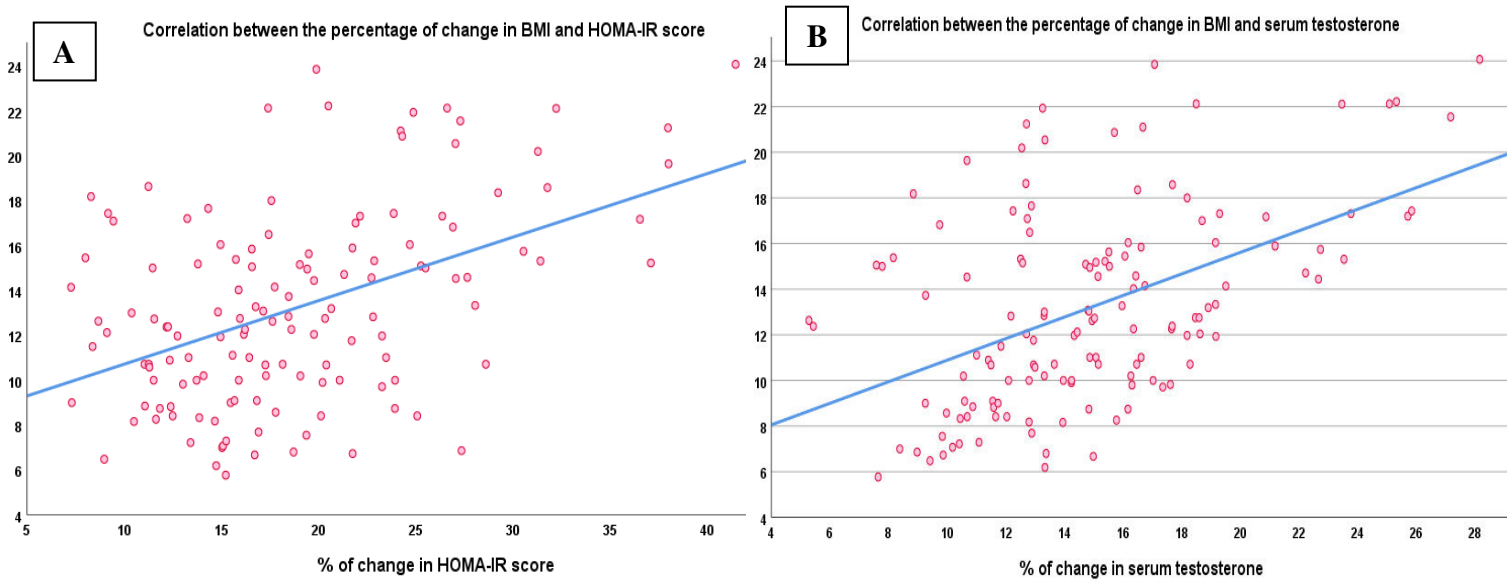

Fig.3.A: the correlation between the percentage of change in BMI and HOMA-IR score at the end of 6-m follow-up; B: the correlation between the percentage of change in BMI and serum testosterone at the end of 6-m follow-up

Discussion

The extent of BMI loss was significantly higher after bariatric surgery compared to other interventions. This finding is coincident with a nonrandomized trial that detected a significant difference in BMI after bariatric surgery for PCOS than after pharmacotherapy and recommended bariatric surgery to be prioritized for these patients **(Hu et al., 2022)**.

Further, the applied protocols significantly improved insulin resistance and this could be explained by the reported decrease in BMI and goes in hand with **Ahmed et al. (2022)** who detected significant reductions in BMI, glycated hemoglobin and blood pressure in diabetic or hypertensive PCOS with improvement quality of life after bariatric surgery. In a comparative study between PCOS and non-PCOS morbidly obese women, **Buyukkaba et al. (2022)** found bariatric surgery significantly decreased HOMA-IR score and serum lipid profile with a significant increase of serum high-density lipoproteins in both groups. Regarding lifestyle change, the reported outcomes supported that reported by **Tan et al. (2021)** who found lifestyle change and insulin sensitizers in non-obese PCOS women significantly decreased BMI and IR with improved hormonal profile and advocated this treatment policy for PCOS women especially the non-obese ones. Also, **Wang and He (2022)** detected improved metabolism on lifestyle modification and insulin sensitizers. The reported results concerning group II and III also coincided with **Chen et al. (2006)** who detected a 5.88% and 11.8% decrease in BMI with the use of metformin alone or in combination with lifestyle change, respectively and with **Rao et al. (2022)** who found 12 weeks of exercise reduced serum testosterone levels and body fat percentage in PCOS.

Moreover, the applied protocols significantly improved the

hormonal milieu of the studied women with subsequent significant decrease of hirsutism scorings. These findings are in line with multiple studies that detected a significantly improved ovarian function and reserve **(Younis et al., 2015)**, higher complete remission rate of PCOS **(Hu et al., 2022)**, and improved fertilization potential **(Buyukkaba et al., 2022)** after bariatric surgery for obese PCOS women. Also, the obtained results coincided with a recent systemic review and meta-analysis that assured the superior outcomes of metabolic surgeries for obese PCOS women and concluded that metabolic surgery could be an option for treatment of PCOS and may improve their reproductive outcomes **(Yue et al.,2022)**.

The reported positive relation between the extent of BMI loss and the extent of change of IR and serum testosterone illustrates the impact of obesity and hyperinsulinism on ovarian function and put it as an important pathogenic factor for induction, maintenance, or even aggravation of disturbed ovarian function in PCOS women. In support of these data, a recent experimental animal model of high-sucrose diet-induced PCOS showed increased adipose tissue accumulation, hyperglycemia with IR and ovaries showed an increased number of atretic antral follicles and cystic follicles, which were correlated with the hypertrophy of periovarian adipocytes **(De Melo et al., 2021)**.

Conclusion

Obesity and its resultant IR deleteriously affected the ovarian functions up to induction of infertility, but weight reduction interventions might ameliorate these effects. Bariatric surgery allowed significant weight reduction and the parallel improvement of hyperandrogenemia and ovarian function. A combined weight reduction regimen, lifestyle change, and insulin sensitizers are an alternative therapeutic plan whenever surgery is contraindicated or refused by patients.

Limitations

The short duration of follow-up did not allow assessing the effect of the applied interventions on fertility for PCOS-associated infertility.

Recommendations

Wider-scale studies are mandatory to assess the long-term outcomes of these interventions with special regard to fertility.

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