

Dose Weight Gain in Lean Patients with Polycystic Ovary Syndrome Improves Ovulation and Pregnancy Rates?

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ABSTRACT

Background & Objective: To evaluate the effect of weight gain in lean patients with polycystic ovary syndrome (PCOS) on ovulation and pregnancy rates.

Materials & Methods: Lean patients with PCOS seeking fertility were invited to participate in the study. Weight gain was commenced by dietary modifications. Patients were classified later into responder and non-responder. All patients were stimulated with Letrozole 2.5 mg twice daily for five days for six cycles. Ovulation and pregnancy rates were assessed.

Results: From 84 patients who were enrolled in our study, 33 patients were allocated into non responder group and 28 patients were allocated to the responder group, and it was found that despite there was statistical difference between both groups as regard weight gain, weight after six months and BMI after six months, there was no significant difference between both groups as regard the ovulation rate, pregnancy rate and complications to ovulation induction ovarian hyperstimulation syndrome (OHSS).

Conclusion: weight gain in lean PCOS patients - although non-significant- but it may improve the reproductive outcomes (ovulation rate and pregnancy rate) and the need of further study with larger number and longer duration of follow up for confirmation of these results.

Keywords: Weight Gain, Polycystic Ovarian Syndrome, Infertility, Ovulation, Pregnancy

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrinological disorder affecting 5-10 % of women in childbearing age. PCOS is a cause of normogonadotrophic anovulation and a manageable cause of infertility. Beside the hormonal imbalance caused by PCOS, it also causes or associated with metabolic problems that may affect the overall health and appearance (1).

Women with PCOS are mostly overweight or obese and also the weight gain in PCOS appears to be higher and this was attributed to higher genetic susceptibility to obesity. On the other hand, lean patients with PCOS are a unique group requiring a special management plan different from the obese patients (2).

Weight loss is one of major important lines in management of PCOS as reduction of body weight improves insulin resistance, reduces hyperandrogenemia and yields better ovulation and pregnancy rates (2). Many authors suggest that the caloric restriction rather than macronutrient effect had a better effect on weight control; however, the oral medications for weight loss have a minor effect.

Exercise also had an important effect and could be used with dietary regimen to intensify the weight loss (3).

In the case of lean patients, this line of management (weight loss) couldn't be employed, and a lot of debates are present regarding those patients' management. European Society of Human Reproduction and Embryology (ESHRE) guidelines stated that nutritional management in PCOS is controversial, where modifications of macronutrients were not beneficial for obese patients (4).

The role of a dietitian in the management of PCOS is very important and should be put in consideration, especially for the long-term follow-up. There is now a raise in the awareness among dietitians about the dietary and lifestyle management of PCOS patient as a very important step in controlling the symptoms and prevention of health hazards (5).

To our knowledge, there are no studies addressing the nutritional modification for lean patients with PCOS to gain weight till optimization of BMI. This study was designed to address this issue.

Methods

Study design and settings

This study was a prospective observational study conducted at Tanta University Hospitals in the period from June, 1, 2017 to August 31, 2021.

Patients

patients were selected according to inclusion and exclusion criteria. The inclusion criteria were: (a) infertile patients whether primary or secondary, (b) lean patients with BMI < 18.5, (c) PCOS according to Rotterdam's criteria 2003. The exclusion criteria were: (a) infertile patients with other causes of infertility as male factor or endometriosis or previous surgery, (b) patients with previous ovarian surgery as drilling or endometrioma, (c) patients with one ovary, (d) patients with chronic medical disorders as diabetes, renal disease or malabsorption syndrome. (e) any other associated endocrine disorders like thyroid abnormalities or adrenal abnormalities.

Sample size calculation: The sample size was calculated using Epi-Info 7 (CDC, USA) specific programs. H₀ was postulated as the prevalence of PCOS in lean women 5.5% prevalence in Spain (which is a Mediterranean country with the same ethnic criteria as Egypt) and we considered the prevalence of lean females in reproductive age in Egypt to be about 60% (according to Nermine et al. Sixty-eight percent of the students were within normal weight, 3.3% were underweight) (6). The calculated sample size was 75 (7).

Interventions and allocations: After initial assessment, eligible patients were investigated to exclude other factors of infertility. Hormonal profiles and ultrasound examinations were done. Height, weight and BMI were taken.

Strict dietary regimen: All patients were subjected to both macronutrient and micronutrient modifications. The modified macronutrient diet was composed of high protein, high carbohydrate and low-fat diet. The micronutrients were supplemented in the form of chocolate like powder (ZENO formula® Bio-Pharma, Egypt) to be taken twice daily with milk or yoghurt. The dietary modifications were tailored by a specialized nutritionist. The duration of dietary regimen modifications was six months. During this period, the dietary regimen was strictly monitored by

the nutritionist and the patient's weight was assessed every two weeks.

Non-followers of the strict dietary regimens were excluded from participation. At the end of the dietary regimen period, all patients were allocated to either respondents or non-respondents to weight gain. The response was estimated by normalization of BMI.

Ovulation induction protocol: All patients were given Letrozole 2.5mg twice daily for five days starting from the third day of menstrual cycle. Ovulation was monitored by transvaginal ultrasound to detect rupture of leading follicle (18-22mm) with free fluid in Douglas pouch. Pregnancy was detected by positive β-HCG in serum plus presence of gestational sac in utero. Ovulation induction is continued till six cycles or pregnancy, which is the nearest.

Study outcomes:

These were normalization of BMI, ovulation and pregnancy rates.

Ethical approval:

This study was conducted after approval from the local ethical committee of Tanta University, faculty of medicine. All patients were informed about study design and outcomes and consented to participate.

Statistical methods:

The data were analyzed by SPSS, version 18 (USA, Chicago). The tests used were mean, standard deviation, paired-t test. The P value was considered significant for 0.05.

Results

84 patients were enrolled in the study after following of strict inclusion and exclusion criteria, 14 of them were excluded as they didn't follow the strict nutritional regimen, while 70 of them followed the strict nutritional regimen, they allocated into non responder group (of 40 patients, seven were lost in follow up) and responder group (of 30 patients, two were lost in follow up), both groups took the same treatment and follow-up plan ([Figure 1](#)).

After proper statistical analysis, there was no statistical difference between both groups as regard to age, duration of infertility, type of infertility, height, weight and BMI before joining of study ([Table 1](#)).

Assessed for eligibility (n=91)
Excluded (n= 7) <ul style="list-style-type: none"> • Not meeting inclusion criteria (n=5) • Declined to participate (n=2)
Lost in follow up (n=2)
Responders group (n=30)
Non-responders' group (n=40)
Lost in follow up (n=7)
Allocation
Enrollment
Strict nutritional regimen plus ZENO formula supplementations for 6 months (n=84)
Excluded (n= 14) not following the strict dietary regimen
Ovulation induction (Letrozole 2.5mg twice daily for 5 days / cycle) for 6 months (n=66)
Follow up
Analysis
Analyzed (n=33)
Analyzed (n=28)

Figure 1. Flow chart of enrolled patients during the study

Table 1. Characteristics of all patients after 6 months of strict dietary regimen (n=37)

	Responders group (n=28)	Non-responders group (n=33)	T.test	P.value
Age (years) (Mean±SD)	25.54±2.22	24.10±2.49	-1.842	0.074
Duration of infertility (years) (Mean±SD)	3.82±1.47	3.60±1.54	-0.442	0.661
Type of infertility (n, %)				
Primary	22(78.57%)	23 (69.70%)	0.606	0.436
Secondary	6 (21.43%)	10 (30.30%)		
Height (cm) (Mean±SD)	169.18±4.76	170.80±3.36	1.209	0.234
Weight at joining of study (kg) (Mean±SD)	50.74±2.81	51.30±2.25	0.673	0.505
BMI at joining of study	17.72±0.28	17.58±0.42	-1.170	0.250
Weight after 6 months	57.03±3.87	52.79±2.13	-4.213	0.002*

There was a statistical difference between both groups as regard weight gain (6.41±2.32, 1.49±0.80 in responder and non-responder group respectively) with P value < 0.001, also there was a statistical difference

between both groups as regard weight after six months (57.03±3.87, 52.79±2.13 in responder and non-responder group respectively) with P value 0.002, and so there was statistical difference between both group

as regard BMI after six months (19.90 ± 0.86 , 18.08 ± 0.29 in responder and non-responder group respectively) with P. value < 0.001 (Table 1).

Despite that The number of cases with ovulation in the responder group (15 -53.57%) was higher than the non-responder group (10 -30.30%), there was no statistical significance between both groups with P

value 0.067, also that the number of cases with pregnancy rate in responder group (10 -35.71%) was much higher than non-responder group (5 -15.15%), but there was no statistical significance between both groups with P value 0.065, at last there was similarity in both groups as regard the number of cases complicated by OHSS (two in both groups) with P. value 0.866 (Table 2).

Table 2. Outcomes of study

	Responders group (n=28)	Non-responders' group (n=33)	X ²	P.value
Ovulation rate	15 (53.57%)	10 (30.30%)	3.336	0.067
Pregnancy rate	10 (35.71%)	5 (15.15%)	3.397	0.065
OHSS	2 (7.14%)	2 (6.06%)	0.028	0.866

Discussion

Overweight and obesity is one of the common features of PCOs patients, it is uncommon to encounter PCO patient with low BMI, so lean PCO patients are difficult to diagnose and easy to be missed, also till now there is no universal consensus about their line of management (4).

As weight manipulation in obese PCOS could improve many aspects in PCOS patients, also weight manipulation in lean PCOS could improve the pathological condition, so we aimed to evaluate the effect of weight gain on lean PCOs patients on the ovulation rate and pregnancy rate mainly.

From 84 patients who were enrolled in our study after following of strict inclusion and exclusion criteria, 33 patients were allocated into non responder group and 28 patients were allocated to the responder group then both groups took the same treatment and follow-up plan.

It was found that despite there was statistical difference between both groups as regard weight gain, weight after six months and BMI after six months, there was no significant difference between both groups as regard the ovulation rate, pregnancy rate and complications to ovulation induction (OHSS).

This field of research needs more studies and more research work to solve many debates in these topics, also Manu Goyal et al. stated that as they had reviewed lean versus obese Polycystic ovary syndrome patients as many management modalities were found to be not suitable for the lean phenotype of PCOS. They reviewed data for 18 years in relation to hormonal abnormalities and the management of lean PCOS. And they concluded that there is still a debate regarding lean PCOS and the need for Further studies are still required to resolve this debate on the presence of PCOS in lean women (4).

There are many differences in body response and pathology between lean and obese PCOS, Vikrant et al.

had a one-year cross-sectional study which was done in a tertiary care hospital over 50 newly diagnosed PCOS patients. They assessed the clinical characteristics, biochemical, and hormonal profile of those patients. And they found that obese women have a higher risk of insulin resistance, impaired glucose tolerance and increased obesity more than lean PCOS women (8).

Manipulation of diet, and even the simplest way of modulation of the diet like timing of meal may affect weight gain in PCOS patient. Kulshreshtha et al. studied the dietary patterns and its effect on PCOS patients, and they concluded that PCOS women had a significant difference as compared by weight matched controls in the timings of their breakfast and lunch intake rather than the total caloric intake. And they suggested that correction of meal timings and food choices can improve the manifestations of PCOS (9).

Diet and weight manipulation and its effect on reproductive outcome in PCOS patients in general was studied by S. Akshaya et al. who studied the clinical profile of lean PCOS (body mass index (BMI) 23 kg) of over 50 euthyroid PCOS women (15–38 years). And they found that there was no statistically difference in the menstrual irregularities, hyperandrogenism in both lean and obese PCOS. But weight gain, abdominal type obesity with higher waist to hip ratio (0.85) were present in all obese, so they concluded that weight loss through diet interventions and increased physical activity has favorable effects on reproductive outcome in PCOS (10).

The researchers, found that there is a defect in the studies which investigate the weight manipulation in lean PCOS. Most of the studies talked about the effect of weight reduction in obese PCOS and its effect on fertility and metabolic function Hoeger (11) had studied the effect of weight loss and diet control on the reproductive outcome in obese PCOS, they tried modest weight reduction (5% to 10%) as it was difficult

to take the long-term programs, and they found that there were significant improvements in fitness improves ovulatory potential, but also they stated that the need for further research for the long-term sustained weight loss (11).

Also, the same results were found by Moran, Lombard (12) as they found that weight loss in obese PCOS patients was associated with improvement in reproductive outcomes (12).

The debates on the management options of lean PCOS and the lack of strong evidence for its management was proved by Toosy et al. who studied the diagnostic and treatment algorithm for lean PCOS, and they found that there is less hormonal, metabolic and hematological alteration as compared to obese PCOS. And there were promising results for treatment options which included weight maintenance, restoration of ovulation and assisted reproductive technologies in refractory cases, but the evidence on lean PCOS is of low to moderate quality and there are still some uncertainties in the evidence base. So, they concluded that randomized controlled trials are required to confirm findings and to consolidate diagnostic and management (13).

Our result agreed with Barrea et al. who studied the difference of the nutritional approaches between lean and obese PCOS. As the authors reviewed related publications about body configurations and nutritional manipulation for PCOS in lean and obese patients, they found that the dietary manipulation in obese PCOS had an impact on metabolic and fertility health of females, with lower effect and lower focus in research on lean PCO patients (14).

Vitek et al., had studied the effect of different types of ovulation induction on the weight gain in PCOS patients, they randomly divided 750 patients suffering from PCOs and unexplained infertility into clomiphene and Letrozole groups, and they found that PCOs patients had a significant weight gain during ovulation induction, whereas women with unexplained infertility did not have any weight changes. This may open the field of questions if ovulation induction in females with lean PCOs may lead to weight gain and better response to ovulation induction, and also ovulation induction in lean PCOs may be not treatment only for anovulation but also for management of weight balance (15).

Balen et al. assessed the influence of body weight (BMI less than 35 kg/m²) on the outcome of ovulation

induction including ovarian response, ovulation rate and pregnancy rate after one treatment cycle only. They found that with higher body mass index (BMI), a higher dose of gonadotropins was required with more days of stimulation. But there was no difference in the rates of ovulation and clinical pregnancy in relation to body weight. So, they concluded that body weight affects the dose of required gonadotropins but not affect the overall outcome of ovulation induction in women with PCOs, this may explain the valuable effect of weight manipulation on lean PCOs as the dose of ovulation induction required may be changed, and this may open the road for further research (16).

The limitations of our study were the difficulty in diet control and follow up of the patient, and this put limitation in the number of recruited cases, also the patient with lean PCOS is not common and this put also a difficulty on finding patients with motivation to change her dietary style for sake of fertility. At last, there was no comparison between dietary manipulation in obese and lean PCOS patients

So, we concluded that weight gain in lean PCOS patients - although non-significant- but it may improve the reproductive outcomes (ovulation rate and pregnancy rate) and the need of further study with larger number and longer duration of follow up for confirmation of these results.

Conclusion

None.

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Conflict of Interest

There was no conflict of interest.

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