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The change in Sex Hormone Binding Globulin and free androgen index levels after bariatric surgery in obese patients with polycystic ovary syndrome.

Rania S. Ezzat*, Mohamed Elsayed[1], Hend S. Saleh[1], Wael Abdalla[2], Walid A. Abdessalam[1]

[1]Obstetrics and Gynecology, Faculty of Medicine, Zagazig University
[2]General surgery Department, Faculty of medicine, Zagazig University.

***Corresponding author:** Rania S. Ezzat
E-mail: rsezzat@medicine.zu.edu.eg
Telephone: 00201006109904

Abstract

Background: There are limited data about the impact of bariatric procedures on androgen milieu, sex hormone binding globulin (SHBG) and free androgen index (FAI) in obese women with polycystic ovary syndrome. Since the changes in these levels can amenably affect fertility in this group of patients, it is necessary to study such effects.

Objective: to study the impact of bariatric surgery on androgen hormone levels, SHBG and FAI in obese women with polycystic ovary syndrome (PCOS) and infertility.

Study design: A cohort study. Patients and Methods: 36 obese women with PCOS and infertility, attending at Zagazig University Hospitals, outpatient clinic, who underwent bariatric surgery (gastric sleeve or gastric bypass) for excess weight loss. Evaluation of serum free and total testosterone levels, Sex hormone binding globulin (SHBG) by ELISA and calculation of free androgen index (FAI), before operation and compared to 6 months and 1 year after operation.

Results: Before bariatric surgery, all women had abnormally high levels of free and total testosterone, low sex hormone binding globulin, and high free androgen index. After surgery, levels of free and total testosterone dropped significantly, with a rise in SHBG and a significant drop in FAI ($P < 0.001$) 6-month and 1-year after bariatric procedure.

Conclusion: excess weight loss by bariatric surgery leads to normalization of androgenic milieu, and improves SHBG and FAI in PCOS patients.

Keywords: Bariatric surgery, polycystic ovary syndrome, SHBG, FAI

Introduction:

Polycystic ovary syndrome (PCOS) is the most common aetiology of female factor subfertility. Many definitions exist for polycystic ovary syndrome, and in all definitions, hyperandrogenism is a common characteristic feature of PCOS. Hyperandrogenism is either chemical (elevated free and total testosterone levels, low Sex hormone binding globulin and high Free androgen index), or clinical (as hirsutism, acne and even alopecia in some cases).[1] Other features of PCOS include menstrual dysfunction, and the abnormal morphology of the ovary on ultrasound.

Other causes of menstrual irregularities should be ruled out (e.g. thyroid dysfunction or elevated prolactin hormone levels). Also other causes of hyperandrogenism as suprarenal gland tumors, congenital adrenal hyperplasia and virilizing ovarian tumors should be excluded before siagnosing polycystic ovary syndrome. Once other endocrine conditions have been excluded.[2] *polycystic ovary syndrome is not clearly understood on an etiological level. But* Insulin resistance is actually a key mechanism and hyperinsulinemia plays a fundamental role in the pathogenesis of the endocrine and metabolic process. Unfortunately over half of PCOS patients are obese, and with little weight loss, normal ovulation often resume. Polycystic ovary syndrome patients are in danger of developing metabolic syndrome on the long run.[3] Thus it has been advised that fertility treatment should be postponed till women's BMI falls below 35 kg/m^2. Among means of weight loss, bariatric surgery is a rapid and effect means of excess weight loss. Bariatric surgery has undergone marked revolution and laparoscopic techniques have rendered bariatric surgery more patient friendly.[4] Bariatric procedures are either restrictive, malabsorptive or combined. Malabsorptive procedures include bilio-pancreatic diversion, restrictive procedures include gastric banding and sleeve gastrectomy, while Roux en Y gastric bypass is considered a combined approach.[5] Epidemiological studies have suggested that the rapid and sustained weight loss in the first one or two years after bariatric procedures can enhance the opportunity of these patients to get rid of symptoms and signs of PCOS and also get pregnant. But, the oputcome of pregnancy after weight loss by bariatric surgery needs lkong term studies to be sufficiently assessed. [6]

Methodology:

This one year Cohort study was carried out in Zagazig University Hospital outpatient clinic. The study was approved by Zagazig University Institutional Board review (ZU-IRB) and consent was obtained from all cases before getting enrolled in the study.The sample size is 36 cases which met the following criteria for selection: mean age 18-35y, primary or secondary infertility due to polycystic ovary syndrome and obesity (inability to get pregnant naturally after at least one year of regular marital life, after exclusion of other factors of infertility), and no associating medical comorbidities or use of contraceptive pills. Patients underwent bariatric surgery for weight loss with BMI $\leq$ $35kg/m^2$ after surgery. The exclusion criteria are: Cases with HTN, DM or other medical diseases, patients > 35 years old, post-bariatric surgery BMI > 35 kg/m^2, history of other factors of infertility or those using hormonal contraceptive methods. Full history taking and thorough clinical examination is done for all cases. Ultrasound evaluation of the pelvis and ovaries. Laboratory samples are withdrawn from all patients for measuring free and total testosterone levels and SHBG by ELISA , and calculation of FAI as the ratio of the total testosterone level divided by the sex hormone binding globulin (SHBG) level, and then multiplying by a constant(100). All patients underwent standard bariatric procedures (laparoscopic sleeve gastrectomy or laparoscopic gastric bypass), with no complications during or after surgery.

Follow up of the patients for one year after surgery. The primary outcome was to assess the effect of bariatric surgery on the improvement of SHBF and FAI levels. The secondary outcome was to assess conception rate and time interval between bariatric surgery and occurrence of pregnancy and pregnancy outcome (if occurred).

Results: 36 women who met the inclusion criteria were recruited for this study, the mean age of the women was 26.2 ± 4.2 years, as shown in table 1 that presents the basic characteristics of the study group. The mean BMI was 43.6 ± 1.76 kg/m2 before bariatric surgery. All women had irregular cycles at the start of the study. Sixty percent of them suffered from 1ry infertility, and the remainder had 2ry infertility due to PCOS (other infertility causes have been excluded by history and proper investigations when needed).The mean free serum testosterone level 55.5 ± 17.5 pg/ml and the mean total testosterone level 5.67 ± 0.5 ng/dl. The mean SHBG level 14.3 ± 2.2 nmol/L. Among the studied group, 60% underwent laparoscopic sleeve gastrectomy, while 40% underwent laparoscopic gastric bypass. There were no intraoperative or postoperative complications. The follow-up period was 6 and 12 month post procedure. No cases got pregnant during the 1 year follow up. As shown in table 2, all cases showed significant reduction in BMI from 43.6 ± 1.76 before bariatric surgery to 29.1 ± 1.17 kg/m2 one year after operation. Also significant drop in SHBG from 14.3 ± 2.2 before operation to 27.3 ± 4.21 after one year from surgery. There was also highly significant improvement of free androgen index from 0.2 ± 0.05 before bariatric surgery to 0.05 ± 0.02 one year after surgery.

Discussion:

The results from this study prove that excess weight loss by bariatric surgery leads to improvement of sex hormone binding globulin and free androgen index in polycystic ovary syndrome obese women with infertility. The results from this study are consistent with the most recent study of ***Singh et al., 2020*** who performed a prospective observational study of 50 women where 36% were diagnosed with PCOS with obesity and similar inclusion criteria to this study. The mean age of the women with PCOS was 29.7 ± 5.9 years. Sixty-six percent underwent laparoscopic sleeve gastrectomy, while 27% had laparoscopic gastric bypass and 5% underwent mini gastric bypass/one anastomosis gastric bypass, and were followed up for 12 months. The mean BMI was 44.9 ± 7.5 kg/m^2. The authors observed a progressive and sustained drop in free androgen index and significant elevation in sex hormone binding globulin after excess weight loss by bariatric surgery. Unlike this study, ***Singh et al., 2020*** also included 8 cases (16%) who had irregular cycles but not PCOS, and also proved improvement of cycle regularity after excess weight loss with bariatric surgery.

Also the results from ***Robert Lee et al., 2020*** who reviewed the impact of bariatric surgery on polycystic ovary syndrome, come in agreement with our results as the authors observed that the effective short term weight loss achieved by bariatric surgery results in amelioration of hyperandrogenism and its related manifestations and restores fertility in polycystic ovary women with significant changes in androgen hormone levels ($p<0.005$). On the other hand, ***Różańska et al., 2020,*** performed a cross-sectional study of 515 pre-menopausal women who had undergone bariatric surgery between 1999 and 2017 in a bariatric center. In contrast to our study, authors actually did not observe any improvement in hirsutism or any other clinical symptoms of hyperandrogenism in the studied group of patients after bariatric surgery. The results of the systemic review and meta-analysis by ***Ying et al., 2019,*** also agree with our results. 234 obese PCOS patients were followed up after bariatric surgery, and there was a significant reduction in body mass index, improved hyper-androgenism and its clinical manifestations and a highly significant decrease in the serum total testosterone level and serum free testosterone level, SHBG and free androgen index as well. *Similarly,* ***Abiad et al. 2018,*** analyzed the effects of weight loss by sleeve gastrectomy among 22 obese women at three, six, and twelve months.

BMI among the six obese PCOS patients substantially dropped one year later (36.28%) compared to obese non-PCOS patients (33.04%) (P=0.002) . Both SHBG (58.62±30.44, P=0.005) and total testosterone (10.29±6.30, P=0.011) significantly improved within the first three months, but both also held constant in further months.Also, ***Christ et al., 2018,*** performed a retrospective chart review of records from 930 women who had undergone bariatric surgery at the Cleveland Clinic Foundation from 2009 to 2014, Forty-four women with PCOS and 65 controls were evaluated. Both PCOS and non-PCOS had significant reductions in body mass index (BMI) postoperatively ($p < 0.05$). PCOS had significant reductions in androgen levels ($p < 0.05$) and SHBG. In addition, ***Mette et al., 2017 evaluated*** the effect of RYGB on polycystic ovary women and observed that SHBG increased progressively and was doubled after 12 months. On the contrary, both total and free androgens and decreased by about 50% after bariatric surgery and 85% of women restored normal menstrual pattern one year post bariatric surgery.Also, ***Hector F. et al, 2017*** performed a systematic review and meta-analysis, where 29 studies were included in the quantitative synthesis. They observed that after bariatric surgery, resolution of PCOS was found in 96% of affected women. Sex hormone-binding globulin concentrations increased after bariatric surgery in women. Also total testosterone concentration decreased .In addition, a more focused study by ***Turkmen et al. 2016,*** evaluated the effect of bariatric surgery, particularly RYGB in13 obese women with PCOS for six months. At the end of follow up period, mean BMI significantly decreased from 47.15±7.57 kg/m^2 to 35.46±7.04 kg/m^2. By the end of the study, Testosterone and SHBG normalized in all patients. ($p<0.005$). ***Wang et al. 2015,*** also studied two groups of 24 obese patients with PCOS and compared treatment with laparoscopic Sleeve Gastrectomy to that of lifestyle modifications. Body mass and BMI were found to be significantly reduced in the bariatric patient group three months after surgery, with maximum loss observed at six months after surgery. Comparatively, patients in the bariatric group showed greater weight loss ($P<0.0001$). Androgen levels dropped significantly following surgery ($P=0.012$) and SHBG levels significantly raised ($p<0.005$). Also ***Eid et al., 2014***, reviewed the outcomes of 24 women diagnosed with PCOS who had undergone weight loss surgery at the University of Pittsburgh between July 1997 and November 2001. Amelioration of clinical symptoms was associated with significant improvements in testosterone levels and SHBG at 6 and 12 months after RYGB when compared to baseline. Similarly, ***Legro et al. 2012,*** published a study of 29 obese women treated with RYGB. Significant weight loss was noted at 12 and 24 months follow up. Androgen hormone levels showed significant changes. SHBG notably increased within the first month, which correlated to a peak drop in testosterone and estradiol levels at the three- to six-month.

Conclusions:

Bariatric surgery results in effective and sustained weight loss in obese PCOS patients, and improves biochemical abnormalities such as serum androgen levels as free and total testosterone , increase SHBG level and improve free androgen index.Weight loss through bariatric surgery improves reproductive milieu in polycystic ovary syndrome.This study recommends bariatric surgery for rapid Weight loss to improve PCOS androgen milieu and PCOS related infertility in obese women.

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Table 1: Basic characters of the patients

	Studied group N=36
	Mean SD
Age	26.2 ± 4.2
Range	**18 - 35**
Cause of infertility	**N (%)**
1ry infertility	**60%**
2ry infertility	**40%**
Laparoscopic sleeve gastrectomy	**60%**
Laparoscopic gastric bypass	**40%**

Table 2: the change in BMI, free and total testosterone, SHGBG and FAI after bariatric surgery

	Before operation N=36	**After 6 month N=36**	**After 1 year N=36**	***P*-value**	***Paired t-test in between groups***
BMI					**P1<0.001 HS**
	43.6 ± 1.76	**33.5 ± 1.36**	**29.1 ± 1.17**	**<0.001 HS**	**P2<0.001 HS**
					P3<0.001 HS
FT					**P1<0.001 HS**
Mean ± SD	**55.5 ± 17.5**	**32.3 ± 11.1**	**26.6 ± 9.2**	**<0.001 HS**	**P2<0.001 HS**
					P3<0.001 HS
TT					**P1<0.001 HS**
Mean ± SD	**5.67 ± 0.5**	**2.75 ± 0.57**	**2± 0.47**	**<0.001 HS**	**P2<0.001 HS**
					P3<0.001 HS
SHGB					**P1<0.001 HS**
Mean ± SD	**14.3 ± 2.2**	**23.4 ± 3.51**	**27.3 ± 4.21**	**<0.001 HS**	**P2<0.001 HS**
					P3<0.001 HS
FAI					**P1<0.001 HS**
	0.2 ± 0.05	**0.1 ± 0.03**	**0.05 ± 0.02**	**<0.001**	**P2<0.001 HS**

HS **P3<0.001 HS**

NS:P- value>0.05 is not significant S: P-value<0.05 is significant HS: P-value<0.001 is high significant * test of significance repeated measures ANOVA
P1: Baseline reading vs 6 months P2: Baseline reading vs 1 year P3: after 6 months reading vs 1 year
Table 1: Changes of BMI, OV, Androgen profile, SHBG & FAI among studied group pre-op, 6 months and 1 year post-op

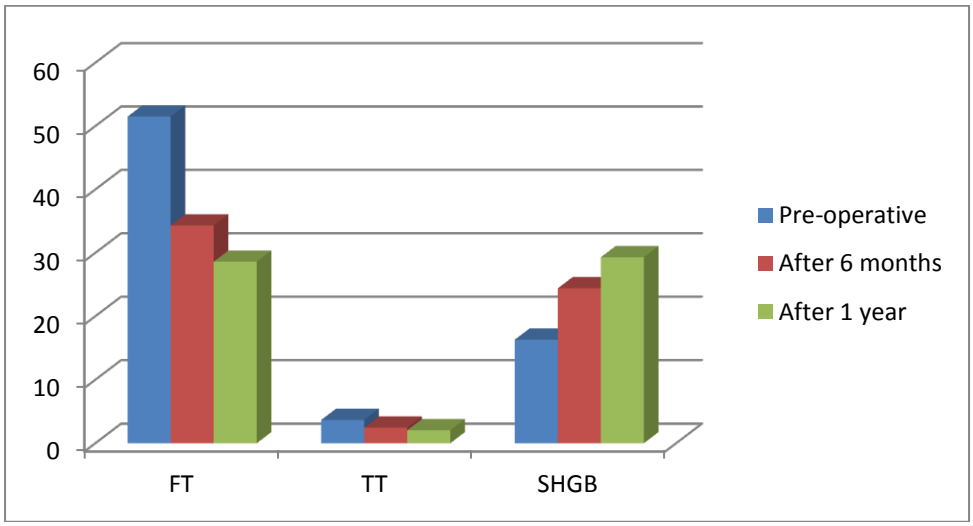

Figure (1): Changes in the serum free testosterone, total testosterone and SHBG among studied group before operation, 6 and 12 months after bariatric surgery.