Effect of Bariatric Surgery Versus Insulin Sensitizers on Ovulation in Poly-Cystic Ovary Patients

Original Article

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ABSTRACT

Aim: To to evaluate the effect of laparoscopic sleeve gastrectomy versus insulin sensitizers on both resumption of ovulation and insulin resistance within a period of six months in patients with poly cystic ovarian syndrome.

Methods: This prospective randomized cohort study was conducted at Alexandria Main University Hospitals (El Shatby Hospital), Egypt from February 2022 until February 2023..

Results: While bariatric surgery has been demonstrated to benefit PCOS, its effect on infertility caused by PCOS is less clear.(25) Currently, pharmacologic treatments such as metformin are widely used to target insulin insensitivity and lower hyperandrogenism in PCOS, which in turn improves the reproductive symptoms of the disease.(26)

Our study revealed that there was improvement of ovulation, fasting insulin level; HOMA-IR and body mass index and percentage of weight loss rated 3 and 6 months post treatment in both study groups but with no significant differences between them.

Conclusion: From our study we can conclude that bariatric surgery and insulin sensitizers promote significant weight loss and resumption of ovulation, which is linked to the improvement of Menstrual irregularities, insulin resistance and ovulatory malfunction. Surgery and insulin sensitizers successfully mediate the resolution of PCOS. There was improvement of ovulation, fasting insulin level; HOMA-IR and body mass index and % of weight loss rated 3 and 6 months posttreatment in both study groups but with no significant differences between them.

Key Words: Complications; Elshatby University Hospital; gynaoncology.

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INTRODUCTION

One of the most common endocrine diseases, polycystic ovarian syndrome affects 7% to 18% of women of reproductive age^[1,2] Additionally, it is a significant contributor to infertility. Stein and Leventhal^[3] first identified PCOS in 1935 as the combination of amenorrhea and polycystic ovaries; five of the original seven individuals also had hirsutism or acne, and four had obesity. Over the past 25 years, a variety of combinations of otherwise unexplained hyperandrogenism, anovulation, and an ultrasound image of a polycystic ovary have been used to develop internationally recognised diagnostic criteria for adults. These combinations are all specified under the Rotterdam consensus criteria. These criteria offer four phenotypes based on the clinical severity of the condition^[4] Although the fundamental aetiology of PCOS is unknown and its basic mechanism is complex, numerous studies have been conducted since then to advance our understanding. Described as a complicated condition that results from the interaction of hereditary and environmental factors, PCOS typically initially appears during puberty when mature gonadotropin levels are reached.

According to the "two-hit" phenomena, the disorder arises as a congenital predisposition ("first hit") that emerges in the presence of a triggering stimuli ("second hit"), the pathophysiology of PCOS can be understood. Congenital influences can be acquired (such maternal drugs or dietary problems that affect the foetus) or inherited (genetic). Insulin-resistant hyperinsulinism, which may have been genetic or acquired postnatally, as a result of conventional medicine, is typically the postnatal triggering cause^[5].

Various PCOS therapies are now available, however the overall influence on fertility is still being studied. The pathophysiology of PCOS makes treatment more difficult. Thus, lifestyle changes and weight loss are the main goals of first-line therapy^[6]. Reduction of body weight makes it easier to respond to hormone therapies and ovulatory induction. Metformin has been used to treat PCOS since it is associated with insulin resistance. While it was hypothesised that metformin use might improve patient reproductive outcomes.

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One type of bariatric surgery is the Roux en Y gastric bypass (RYGB), another is the Sleeve Gastrectomy (SG), and a third is the Adjustable Gastric Band (AGB). Due to malabsorption, these operations are a form of hormonal surgery that alters or lowers gut hormones. An improvement in cardiovascular risk factors (HTN, dyslipidemia) and a large decrease of weight over the long term are all results of surgery, according to studies done over an extended period of time. The majority of surgery patients were able to maintain a healthy state for an average of six years^[7]. At a one-year follow-up, the risk of major complications from bariatric surgery (including anastomotic leakage, intestinal obstruction, and others) occurs in only around 8% of patients on average^[8]. More patients are now suitable candidates for this kind of treatment due to the procedures' increased techniques and safety. Although bariatric surgery has been used to treat PCOS, further study is required to provide guidelines for its use when other frontline therapy have failed. The American Society for Metabolic and Bariatric Surgery noted in 2017 that although certain case control studies have demonstrated that bariatric surgery can increase fertility, Its precise effect on the responsiveness to infertility therapies is yet unknown^[9].

High-risk groups:

A variety of conditins seem to be connected to a rise in PCOS prevalence^[10]:

- Oligoovulation-related infertility.
- Obesity and/or insulin resistance, despite the fact that obesity seems to have a minimal impact.
- Diabetes mellitus, either gestational or type 1 or type 2.
 - A pattern of precocious puberty.
 - PCOS in first-degree relatives.
 - Taking antiepileptic medications.

Pathogenesis:

1. Genetics:

The genetic basis of the disorder was established by twin studies and reports showing a higher PCOS frequency in first-degree female relatives of those with the condition^[11].

2. Gonadotropin secretion and action:

The aetiology of PCOS appears to include abnormal LH activity $^{[12]}$.

3. Dysfunction in ovarian folliculogenesis:

Due to insufficient FSH stimulation, local FSH action inhibition, perhaps excessive local AMH, and other intraovarian variables that affect follicular recruitment and growth, the selection of the dominant follicle is abnormal in PCOS^[13].

4. Insulin secretion and action:

The fact that the administration of insulin-sensitizing

agents, especially metformin, has been found to positively impact these features in many patients highlights the insulin resistance of PCOS patients that promotes many of the characteristics of this condition^[14].

5. Weight and energy regulation:

Obesity is associated with the severity of menstrual and ovulatory dysfunction, the degree of hyperinsulinemia, the pregnancy outcome in PCOS, and the aggravation of insulin resistance. Additionally, it is linked to a rise in the prevalence of cardiovascular risk factors, metabolic syndrome, glucose intolerance, and obstructive sleep apnea^[15].

6. Androgen biosynthesis and action:

Although hyperinsulinism alone does not cause PCOS, hyperinsulinism is related with hyperandrogenism in PCOS, suggesting that there must also be an underlying (genetic) susceptibility to hyperandrogenism^[16].

Diagnostic criteria for PCOS:

Recently, anovulation, a polycystic ovary, and unexplained clinical or biochemical hyperandrogenism have been used as diagnostic criteria for PCOS in adulthood. These criteria are represented by four different phenotypes^[17]. Along with the degree of hyperandrogenism, the severity of insulin resistance, degree of obesity, and excess luteinizing hormone (LH) also decreases with decreasing phenotypic specificity. Between phenotypes 1 through 3, the severity of menstrual dysfunction reduces, whereas phenotypic 4 is anovulatory but does not exhibit hyperandrogenism^[18].

- •Hyperandrogenism, oligo-anovulation, and polycystic ovary make up]Phenotype 1 (typical PCOS).
- •Hyperandrogenism with oligo-anovulation is phenotype 2 (hyperandrogenic anovulation).
- •Phenotype 3 (ovulatory PCOS): polycystic ovary and hyperandrogenism without ovulatory dysfunction.
- •Oligo-anovulation and a polycystic ovary are characteristics of PCOS phenotype 4 (non-hyperandrogenic PCOS).

Clinical features:

Realising that PCOS is a syndrome with a range of possible aetiologies and clinical manifestations. Hyperandrogenism and Oligo- or anovulation are its primary traits. Pelvic ultrasonography also reveals polycystic ovaries, oligoovulation-related infertility, insulin resistance and obesity^[19].

Treatement:

Obesity, insulin resistance, ovulatory dysfunction and impaired glucose tolerance are just a few of the disorders that PCOS-affected women suffer. Most women's first line therapy is weight reduction, which can restore ovulation and minimise metabolic hazards. The general strategy is

comparable to that provided by the Clinical Guidelines from the 2013 Endocrine Society. The broad goals of treating PCOS in women include^[20]:

- Reduction of hyperandrogenic symptoms (hirsutism, acne, hair loss on the scalp).
- Managing underlying metabolic imbalances and reducing the risk factors for type 2 diabetes and cardiovascular disease.
- Avoiding prolonged anovulation, which can lead to endometrial hyperplasia and cancer.
- Contraception for women who don't want to get pregnant, as oligomenorrheic women ovulate irregularly and an unintended pregnancy is possible.

Lifestyle changes:

For overweight and obese women with PCOS, diet and exercise are the initial steps advised for weight loss. In order to lose weight and reduce insulin resistance and hyperandrogenism, the data to far supports lifestyle therapies (diet, exercise, and behavioural changes). It also seems that there are benefits for reproduction^[21].

Oral contraceptives and risk assessment:

For women with PCOS, oral contraceptives (OCs) constitute the cornerstone of pharmacologic treatment in order to control hyperandrogenism, treat menstrual disruption, and provide contraception. Combined estrogen-progestin contraceptives provide a number of advantages for women with PCOS, including:

- Regular intake of progestin, which inhibits the proliferative effect of estrogen on endometrium
- Contraception for people who aren't trying to get pregnant, as oligomenorrheic women ovulate infrequently and unintended pregnancy is possible.
 - Cutaneous benefits for hyperandrogenic symptoms.

Metformin:

By lowering hepatic glucose synthesis, the medication metformin largely lowers serum insulin concentrations. It has been used either alone or in conjunction with clomiphene to promote ovulation. It is a potential substitute for restoring menstrual cyclicity as it restores ovulatory cycles in approximately 30 to 50 % of women with PCOS. It is regarded as a second-line approach since its ability to provide endometrial protection is less well established. When metformin is used, monitoring is advised to ensure that ovulatory cycles have been established. This can be done with either serum progesterone measurements in luteal phase or transvaginal ultrasonography^[22].

Poly- cystic ovary syndrome and bariatric surgery:

Fundamental first-line care of PCOS entails dietary and lifestyle adjustments that encourage weight loss. Inevitably bariatric surgery should be considered in PCOS options for treatment, given that the advantages of these activities are typically not sustained over the long run^[23].

AIM OF THE WORK

To evaluate the effect of laparoscopic sleeve gastrectomy versus insulin sensitizers on both resumption of ovulation and insulin resistance within a period of six months in patients with poly cystic ovarian syndrome.

PATIENTS AND METHODS

Inclusion criteria:

- Age group (20 40 years old).
- Diagnosed as PCOS according to Rotterdam criteria (oligo or anovulation, hyperandrogenism and 12 follicle measuring 2-9 ml in each ovary by U\S).
- Body mass index more than 35.
- Seeking for fertility.
- Normal computer assisted semen analysis (CASA) of their partners.
- Normal hysterosalpingogram.

Exclusion criteria:

- Diabetic patients.
- Previous history of abdominal or pelvic surgeries.
- History of endometriosis.
- Hypothyroidism.
- Hyperprolactinemia.

This prospective randomized cohort study was conducted at Alexandria. Main University Hospitals (El Shatby Hospital), Egypt from February 2022 until February 2023.

Study population:

Infertile women attended outpatient clinic with the Privous criteria.

Sampling Method "randomization":

Systematic random sampling and women fulfilled the inclusion criteria were randomly assigned to either group. Twenty opaque envelopes were numbered serially and, in each envelope, the corresponding letter, which denoted the allocated group, was put according to randomization table. Then all envelopes were closed and put in one box. Randomization was done using computer generated randomization sheet using MedCalc®version 13.

Sample size:

A total of 20 women were enrolled, after consenting each of them.

Sample size justification:

The required sample size was determined by a statistician, using 80% power and alfa (Type 1 error) set at 0.05. A minimal total sample size of (20) infertile women with PCOS (10 per group) is needed.

Ethical considerations:

Patient information and informed consent: before being enrolled into the study, the patient consented to participate after the nature, scope and possible consequences of the clinical study had been explained in a form understandable to her.

Confidentiality:

Only the patient initials were recorded in the case report from, and when the patient's name appeared on any other document, it was kept in a secure place by the investigators. The investigators maintained a personal patient identification list (Patient initials with the corresponding patient names) to enable record to be identified.

Protocol approval:

Before the beginning of the study and any accordance with the local regulation followed, the protocol and all the corresponding documents were declared for ethical and research approval by the council of OB/GYN department, Alexandria University.

Concerning safety and efficacy:

No evidence of harmful effects of study medications.

Study interventions and procedures:

According to inclusion and exclusion criteria; patients were subjected to:

Complete history taking of clinical importance including:

Personal history: Age, residence, occupation, marital status and special habits as smoking, alcohol, etc.

Menstrual history: day of last menstrual period and regularity.

Obstetric history: Gravidity, parity, previous miscarriages or obstetric complications.

Contraceptive history: type, duration of use before pregnancy.

Medical history: Medical comorbidities as hepatic, renal, endocrinal, psychosocial condition, cardiovascular, diabetes, chronic hypertension.

Surgical history: Previous relevant operations or preedures as office hysteroscopy, etc.

Sexual history: Regularity, associated dyspareunia.

Family history of infertility.

Lifestyle: dietary habits, exercise.

Clinical examination with special emphasis on: BMI, acne, hirsutism.

Investigation:

Routine infertility workup investigations as FSL, LH, E2, serum prolactin, TSH, free testosterone, DHEAS, AMH Baseline transvaginal ultrasound examination, which included antral follicular count, uterine and adnexal assessment using Mindray DP-15 Digital Ultrasonic Diagnostic Imaging System and GE Logiq E9

ultrasound machine, 2–5MHz wide band convex, curved array transducer. Eligible participants were women with anovulatory infertility due to PCO diagnosed by Rotterdam's criteria which entailed finding any two of the following: Oligo and or anovulation Androgen excess identified either by raised modified ferryman gallwey score or raised serum testosterone Polycystic ovarian morphology on ultrasound. Threshold for defining polycystic ovarian morphology was ≥ 12 follicles of <2-9mm and/or individual ovarian volume >10ml.

Defined population was determined and senior consultant who performed transvaginal ultrasound (TVS) for outcome assessment and statistician help will be requested.

Intervention:

This study was a pilot study to assess the feasibility, duration, cost and adverse effects of bariatric surgeries.

The cases were subjected to the following:

Phase 1: Collection of sample according to inclusion and exclusion criteria:

- Group A: 10 patients who already decided to undergo sleeve gastrectomy (from bariatric surgery clinic) that fulfilled inclusion and exclusion criteria (cases).
- Group B: 10 patients from infertility clinic will receive metformin (500mg) three times per day for a period of six months (controls).

Phase 2: After three and six months all patients underwent:

- Detailed history: detailed physical examination.
 - Three dimentional ultrasound.
 - Laboratory investigations: fasting insulin level and HOMA-IR test.

Statistical Analysis:

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) Qualitative data were described using number and percent. The Shapiro-Wilk test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation, median and interquartile range (IQR). Significance of the obtained results was judged at the 5% level.

The used tests were:

- 1- Chi-square test: For categorical variables, to compare between different groups.
- **2- Fisher's Exact Correction:** Correction for chisquare when more than 20% of the cells have expected count less than 5.
- *3- Cochran's test:* For qualitative variables, to compare between more than two periods with Post Hoc Test (Dunn's) for pairwise comparisons.

- **4- Student t-test:** For normally distributed quantitative variables, to compare between two studied groups.
- **5-** ANOVA with repeated measures: For normally distributed quantitative variables, to compare between more than two periods, and Post Hoc test (Bonferroni adjusted) for pairwise comparisons.

.RESULTS

Table (2) showed that there was improvement of ovulation rated 3 and 6 months posttreatment in both study groups but with no significant differences between them.

Table (3) showed that there was improvement of fasting insulin 3 and 6 months posttreatment in both study groups

but with no significant differences between them.

Table (4) showed that there was improvement of HOMA-IR 3 and 6 months posttreatment in both study groups but with no significant differences between them.

Table (5) showed that there was significant decrease of body mass index 3 and 6 months posttreatment in both study groups.

Table (6) indicates that there was a significant increase in percentage of weight loss after 3 an 6 months in bariatric group than the other group.

Table 1: Comparison between the three studied periods according to Ovulation in each group:

	Ovulation							
	At begi	inning	Three months later		Six months later			
_	No.	%	No.	%	No.	%	— <i>Q</i>	p
Bariatric surgery (n= 10)								
Negative	10	100	6	60	4	40	9.333	0.009
Positive	0	0	4	40	6	60		
Sig. bet. Periods.		i	$p_1 = 0.046, p_2 = 0$.003, <i>p</i> 3= 0.317				
Metformin (n=10)								
Negative	9	90	6	60	5	50	6.5	0.039
Positive	1	10	4	40	5	50		
Sig. bet. Periods.			P1= 0.066, p2= 0	0.014, p = 0.540				

Q: Cochran's test, Sig. bet. periods was done using Post Hoc Test (Dunn's); p: To compare the three examined periods, use the p value; p1: p value to compare at the start and three months afterwards; p2: p value to compare at the start and at six months afterwards; p3 p value for contrasting three and six months after the event; *: Statistically significant at $p \le 0.05$

Table 2: Comparison between the three studied periods according to Fasting insulin in each group:

	Fasting insulin							
	At beginning Three months later				Six months later	F		
	No.	%	No.	%	No.	%	— г	p
Bariatric surgery (n= 10)								
$\begin{aligned} & \text{Min.} - \text{Max} \\ & \text{Mean} \pm \text{SD.} \\ & \text{Median (IQR)} \end{aligned}$	16.6-2 19.23± 18.85(18.	1.79	11.2-16.9 14.09±1.79 13.8(13.1-15.8)	12.3	0.10 5±2.22 0.7-13.8)	37.662	0.001<	
Sig. bet. Periods.			P1=0.001, p	2>0.001, p	3 = 0.003			
Metformin (<i>n</i> = 10)								
Min. –Max. Mean±SD. Median (IQR)	9.4-20 15.77± 16.25(14	3.96	8.3-19.8 15.09±4.1 15.3(12.5-1	8		6.9-18.5 14.15±4.14 14.9(11.8- 17.6)	23.971	0.001<
Sig. bet. Periods.			P1 = 0.033, p2	2 = 0.001, p	3= 0.003			

IQR: Inter quartile range; SD: Standard deviation; F: F test (ANOVA) with repeated measures, Sig. bet. periods was done using Post Hoc Test (Bonferroni); P: To compare the three examined periods, use the p value; p1: p value to compare at the start and three months afterwards; p2: p value to compare at the start and at six months afterwards; p3p value for contrasting three and six months after the event; *: Statistically significant at p5q6.05.

Table 3: Comparison between the three studied periods according to HOMA-IR in each group:

		HOMA-IR			
	At beginning	Three months later	Six months later	F	P
Bariatric surgery (n= 10)					
MinMax Mean±SD. Median (IQR)	2-3.9 3.16±0.6 3.25(2.9- 3.7)	1.6–3.1 2.46±0.52 2.35(2.10-3)	1.4-3.1 2±0.52 1.85(1.6-2.3)	36.355	0.001<
Sig. bet. Periods.		P1>0.001, p2>0.001, p3= 0.021			
Metformin (<i>n</i> = 10)					
MinMax. Mean±SD. Median (IQR)	2.1-3.80 2.87±0.57 2.8(2.4-3.1)	1.7-3.8 2.63±0.64 2.6(2.1-3.1)	1.5-3.4 2.36±0.65 2.25(1.8-2.9)	36.031	0.001<
Sig. bet. Periods.		P1= 0.039, p2>0.001, p3= 0.002			

IQR: Inter quartile range; SD: Standard deviation; F: F test (ANOVA) with repeated measures, Sig. bet. periods was done using Post Hoc Test (Bonferroni); F: To compare the three examined periods, use the p value; p1: p value to compare at the start and three months afterwards; p2: p value to compare at the start and at six months afterwards; p3p value for contrasting three and six months after the event; *: Statistically significant at $p \le 0.05$.

Table 4: Comparison between the three studied periods according to Body mass index in each group:

	В	ody mass index (Kg/ m²)			
	At beginning	Three months later	Six months later	F	P
Bariatric surgery (<i>n</i> = 10)				•	
Min. –Max Mean±SD. Median(IQR)	36.8-46.20 42.01±3.63 42.45(38.1-45.2)	27.7–33.5 30.29±1.96 30.15(28.3–31.9)	24.3-30.90 27.31±1.91 27.15(26.2-28.3)	183.849	0.001<
Sig. bet. Periods.	P1>	>0.001, <i>p</i> 2>0.001, <i>p</i> 3>0.001			
Metformin (n= 10)					
Min. –Max. Mean ±SD. Median (IQR)	36.7–42.50 39.23±2.12 39.15(37.2–41.2)	30.40-35.20 32.35±1.69 32.1(30.7-33.3)	27.1- 34.6 30.97± 2.21 31.10 (29.2 – 32.5)	120.883	0.001<
Sig. bet. Periods.	P1>	0.001, p2>0.001, p3= 0.059			

IQR: Inter quartile range; SD: Standard deviation; F: F test (ANOVA) with repeated measures, Sig. bet. periods was done using Post Hoc Test (Bonferroni); P: To compare the three examined periods, use the p value; p1: p value to compare at the start and three months afterwards; p2: p value to compare at the start and at six months afterwards; p3p value for contrasting three and six months after the event; *: Statistically significant at p5 0.05

Table 5: Comparison between the two studied groups according to % of weight loss:

	Bariatric surgery (n=10)	Metformin (n=10)	t	P
% of weight loss after 3 months				
Min. – Max Mean±SD. Median (IQR)	20.86–36.03 27.64±4.84 26.02(24.7–1.8)	7.34-15.84 12.38±2.92 13.21(10.8-14.3)	8.543	0.001<
% of weight loss after 3 months				
Min. –Max. Mean±SD. Median (IQR)	29.4–43.07 34.73±5.02 32.75(31.3–38.9)	4.35–21.86 15.87±5.87 17.61 (12.2–20.7)	7.734	0.001<

IQR: Inter quartile range; SD: Standard deviation; t: Student t-test; p: p value for comparing between the two studied groups; *: Statistically significant at $p \le 0.05$.

DISCUSSION

While bariatric surgery has been demonstrated to benefit PCOS, its effect on infertility caused by PCOS is less clear^[25] Currently, pharmacologic treatments such as metformin are widely used to target insulin insensitivity and lower hyperandrogenism in PCOS, which in turn improves the reproductive symptoms of the disease^[26]. Consequently, this study was conducted and aimed to evaluate the effect of laparoscopic sleeve gastrectomy versus insulin sensitizers on both resumption of ovulation and insulin resistance in patients with PCOS. This prospective randomized cohort study was carried out at Alexandria Main University Hospitals (El Shatby Hospital), Egypt from February 2022 until February 2023. During this study, 20 infertile women were enrolled, after consenting each of them and two groups are formed; group A included 10 patients who already decided to undergo sleeve gastrectomy (from bariatric surgery clinic) that fulfilled inclusion and exclusion criteria (cases) and group B included 10 patients from infertility clinic received metformin (500mg) three times per day (controls). To the best of our knowledge, there are no studies to date, however, that compared the effects of bariatric surgery to those of metformin on ovulation and most of other studies that disagreed with our results were due to several causes as different study methodology, outcomes, sample size and different medical conditions of studied cases at time of enrollment.

Our study revealed that there was improvement of ovulation, fasting insulin level; HOMA-IR and body mass index and percentage of weight loss rated 3 and 6 months post treatment in both study groups but with no significant differences between them. In our study, percentage of weight loss in bariatric group was 26.02% and 32.75% after three and six months respectively. A comparable study conducted by Carlin AM *et al* (2013) that also indicates 69% excess weight loss (EWL) with RYGB at one-year follow-up provides additional support for these findings^[24]. In our study, the bariatric surgery group recorded significant changes in BMI from 42.45 at the beginning to 30.15 and 27.15 at three and six months after surgery respectively.

CONCLUSION

The present study demonstrated that PE was accompanied by a significant increase in neutrophils, monocytes, and basophils values compared to healthy subjects. We concluded that monitoring of hematological parameters can be used as clinical indicators in the assessment of severity of PE and may be taken as a useful parameter to prevent complications of PE. However, further multicenter prospective cohort studies with large sample size are required to verify the role these parameters in the diagnosis of PE and assessment of disease severity.

CONFLICT OF INTERESTS

There are no conflict of interest.

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