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ORIGINAL CONTRIBUTIONS

# Bariatric Surgery Improves Hyperandrogenism, Menstrual Irregularities, and Metabolic Dysfunction Among Women with Polycystic Ovary Syndrome (PCOS)

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## Abstract

**Objective** To characterize the impact of bariatric surgery on reproductive and metabolic features common to polycystic ovary syndrome (PCOS) and to assess the relevance of preoperative evaluations in predicting likelihood of benefit from surgery.

**Methods** A retrospective chart review of records from 930 women who had undergone bariatric surgery at the Cleveland Clinic Foundation from 2009 to 2014 was completed. Cases of PCOS were identified from ICD coding and healthy women with pelvic ultrasound evaluations were identified using Healthcare Common Procedure Coding System coding. Pre- and postoperative anthropometric evaluations, menstrual cyclicity, ovarian volume (OV) as well as markers of hyperandrogenism, dyslipidemia, and dysglycemia were evaluated.

**Results** Forty-four women with PCOS and 65 controls were evaluated. Both PCOS and non-PCOS had significant reductions in body mass index (BMI) and markers of dyslipidemia postoperatively ($p < 0.05$). PCOS had significant reductions in androgen levels ($p < 0.05$) and percent meeting criteria for hyperandrogenism and irregular menses ($p < 0.05$). OV did not significantly decline in either group postoperatively. Among PCOS, independent of preoperative BMI and age, preoperative OV associated with change in hemoglobin A1c ($\beta$ 95% (confidence interval) 0.202 (0.011–0.393), $p = 0.04$) and change in triglycerides (6.681 (1.028–12.334), $p = 0.03$), and preoperative free testosterone associated with change in total cholesterol (3.744 (0.906–6.583), $p = 0.02$) and change in non-HDL-C (3.125 (0.453–5.796), $p = 0.03$).

**Conclusions** Bariatric surgery improves key diagnostic features seen in women with PCOS and ovarian volume, and free testosterone may have utility in predicting likelihood of metabolic benefit from surgery.

**Keywords** Polycystic ovary syndrome · Weight loss · Bariatric surgery · Hyperandrogenism · Dyslipidemia · Ultrasound

## Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women accounting for approximately 80% of cases of anovulatory infertility [1, 2]. As defined by the 2003 Rotterdam Criteria, this disorder is characterized by hyperandrogenemia, oligo-anovulation, and polycystic ovarian morphology [3, 4]. Additionally, women with PCOS are at increased risk for impaired glucose tolerance, type 2 diabetes mellitus, and cardiovascular disease [1].

Reproductive and cardiometabolic disease among women with PCOS may be due, in part, to increased rates of obesity

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in this population [5, 6]. Weight loss or prevention of weight gain is currently recommended in all women with PCOS [2]. Bariatric surgery has been suggested as a potential method of weight loss, as this procedure has been found to improve glucose and lipid metabolism as well as hirsutism, hyperandrogenemia, and menstrual irregularities among women with PCOS [7–10]. Furthermore, fertility has been shown to be a key reason women seek bariatric surgery, and weight loss prior to assistive reproductive technologies has been shown to significantly increase live birth rates among women with PCOS [11–13]. Less is known, however, about this procedure's impact on ovarian morphology as well as the relevance of diagnostic criteria for PCOS in predicting benefits from surgery. These questions are highly relevant as currently this procedure is only recommended in patients with a BMI of 40 kg/m$^2$ or greater or 35 kg/m$^2$ or greater with comorbid disease, and whether PCOS should be considered an indication is still controversial [14].

Thus, our primary objective was to characterize the impact of bariatric surgery on women with and without PCOS. Secondly, we aimed to identify if preoperative characteristics common to PCOS predict degree of improvement in metabolic dysfunction after surgery.

## Materials and Methods

A retrospective chart review of all female patients who underwent bariatric surgery at the Cleveland Clinic from 2009 to 2014 was completed. Record review was primarily carried out by a single trained researcher. Further details regarding record review are available in the Supplemental Methods.

Cases of PCOS were identified via International Classification of Diseases (ICD) coding using the ICD-9 code 256.4 and ICD-10 code E28.2. Furthermore, non-PCOS women were identified as those women without an ICD code for PCOS and who had undergone one or more pelvic ultrasound scans identified using Healthcare Common Procedure Coding System (HCPCS) number G8806.

Patient records were reviewed for pre- and postoperative data on anthropometric characteristics including weight and height. Menstrual cycle status was obtained from a review of outpatient visit notes. A woman was coded as having irregular menses if her medical record reported oligo-amenorrhea or cycles lasting 35 days or longer or if it described the woman's cycle as irregular. Women with cycles lasting 21–35 days or described as regular were coded as having regular menses. Women who were post-menopausal, taking hormonal contraceptives, or had an intrauterine device were excluded from menstrual cycle assessment. Menstrual cycle assessments were excluded because of contraceptive use for two women in the preoperative period and one woman in the postoperative period.

Ultrasound scans were reviewed for assessment of OV. Measurements previously obtained and reported in the patient records were used to calculate OV using the formula 0.52 × length × width × height. In one case, the ultrasound report only contained two measurements and thus, one measurement was duplicated in order to calculate OV. An average of the right and left ovary was used for analyses. If an ovary contained a large cyst, the OV of that ovary was omitted and the volume of the contralateral ovary was duplicated, as per the method previously reported by Johnstone et al. [15]. Elevated ovarian volume was defined as an OV ≥ 10 mL [3, 4]. All ultrasound scans were completed transvaginally except for two transabdominal scans completed for non-PCOS women and one transabdominal scan completed for a woman with PCOS.

Records were reviewed for pre- and postoperative biochemical measurements. Data obtained on markers of metabolic disease included HbA1c, fasting glucose, triglycerides, total cholesterol, low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C), and high-density lipoprotein-C (HDL-C). Additionally, non-HDL-C was calculated by subtracting HDL-C levels from total cholesterol levels. As per standard hospital protocol, women are asked to fast for at least 12 h prior to the measurement of fasting glucose, triglyceride, and cholesterol levels. Laboratory measurements for fasting glucose, HbA1c, triglycerides, total cholesterol, LDL-C, VLDL-C, and HDL-C that were obtained when patients were not taking either glucose-lowering or lipid-lowering agents respectively. If all measurements in a patient's record were taken while the patient was on these medications, this data was omitted from analysis. Patients were categorized as having elevated cholesterol in the pre- and postoperative periods if the following criteria were met: elevated cholesterol = total cholesterol ≥ 5.2 mmol/L, HDL-C < 1.4 mmol/L, LDL-C ≥ 3.4 mmol/L, non-HDL-C ≥ 4.1, VLDL-C ≥ 1.0 mmol/L, or triglycerides ≥ 2.3 mmol/L. Threshold levels for lipid panels were derived from the upper limits of normal provided by laboratory medicine at the Cleveland Clinic Foundation. If a patient did not have any measured lipid levels greater than the described threshold, she was considered as having normal cholesterol levels. For those women without complete lipid panel data, patients were considered as having normal cholesterol if all available markers of dyslipidemia were normal.

Data obtained on markers of hyperandrogenemia included total testosterone, free testosterone, and dehydroepiandrosterone sulfate (DHEAS). Hyperandrogenism was defined as either an elevated free testosterone or total testosterone (> 31.2 pmol/L or > 2.1 nmol/L respectively).

Assays used to measure all serum values are detailed in Supplemental Methods.

PCOS and non-PCOS women were compared using the Mann-Whitney *U* test for continuous variables and the chi-squared test for categorical variables. Changes between the pre- and postoperative periods were compared within PCOS and non-PCOS using paired *t* tests for continuous variables and McNemar's paired test for categorical variables. For some variables, women had only either preoperative or postoperative values. When there was little overlap between which women had preoperative and postoperative values, it was determined that preoperative and postoperative measurements could be considered independent groups, and the Mann-Whitney *U* test and chi-squared test were used to compare continuous and categorical variables respectively.

The relationship between preoperative characteristics and changes in markers of cardiometabolic disease was first evaluated by univariate Pearson's correlation analyses. These analyses were primarily used to determine which preoperative features of PCOS best informed changes in cardiometabolic profiles. Those variables which significantly ($p < 0.05$) associated with markers of cardiometabolic disease were then entered into multivariate regression analyses controlling for age at surgery and BMI.

## Results

Between 2009 and 2014, 930 female patients underwent bariatric surgery at Cleveland Clinic, 44 of which were identified as having a diagnosis of PCOS. Another 69 women without an ICD-coded diagnosis of PCOS had adequate preoperative ultrasound scans with data on ovarian volume for inclusion. Upon chart review of 4 of the women without ICD coding for PCOS, it was found that these women had discussed a possible PCOS diagnosis with their healthcare provider but official confirmation of diagnosis was not obtained. These 4 women were thus excluded from analysis due to inadequate information for proper assignment to PCOS or non-PCOS groups. Thus, there were 65 women without PCOS and 44 women with PCOS included in our analyses (Table 1).

Women with and without PCOS were on average (median ± standard error) 36.1 ± 2.3 vs 41.7 ± 1.2 years of age at the time of preoperative ultrasound and 38.3 ± 2.0 vs 50.1 ± 1.7 years of age at the time of postoperative lipid panel analyses respectively ($p < 0.001$ for differences in age between PCOS and non-PCOS in the pre- and postoperative periods and for paired difference within PCOS and non-PCOS groups) (Table 1). The median time between surgery and metabolic assessments was 1.9 ± 0.3 years for women with PCOS and 2.6 ± 0.3 years for women without PCOS (differences between groups were not significant).

Women had a median preoperative BMI of 44.2 ± 2.1 and 40.4 ± 1.9 kg/m$^2$ for the PCOS and non-PCOS groups, respectively ($p < 0.001$ for between-group differences). Postoperatively, both the PCOS and non-PCOS groups had significant reductions in BMI, and postoperative BMIs no longer differed between PCOS and controls (35.4 ± 1.5 and 35.6 ± 1.2 kg/m$^2$, respectively). Preoperatively, compared to non-PCOS women, women with PCOS had significantly higher triglyceride levels (1.4 ± 0.1 vs 1.2 ± 0.1 mmol/L) and lower HDL-C (1.2 ± 0.1 vs 1.3 ± 0.1 mmol/L) and HbA1c (5.6 ± 0.3 vs 5.9 ± 0.2%) levels. Both the PCOS and non-PCOS women had significantly higher HDL-C levels postoperatively (1.2 ± 0.1 vs 1.4 ± 0.1 mmol/L, $p = 0.002$; 1.3 ± 0.1 vs 1.6 ± 0.1 mmol/L, $p = 0.003$, respectively). The PCOS women also had significant improvements in triglyceride (1.4 ± 0.1 vs 1.1 ± 0.1 mmol/L, $p = 0.001$) and VLDL-C (0.6 ± 0.1 vs 0.5 ± 0.1 mmol/L, $p = 0.002$) levels postoperatively (Table 1).

Among women with PCOS, 92.5 and 81.5% of women met criteria for elevated cholesterol pre- and postoperatively ($p = 0.103$). Among controls, 80.3 and 43.2% of women met criteria for elevated cholesterol pre- and postoperatively ($p = 0.008$). All *p* values are for paired differences between the pre- and postoperative periods (Fig. 1).

Compared to women without PCOS, women with PCOS had significantly greater preoperative total testosterone (2.2 ± 0.2 vs 1.4 ± 0.3 nmol/L), free testosterone (29.8 ± 4.5 vs 14.2 ± 6.9 pmol/L), DHEAS (5428.0 ± 1177.9 vs 2119.6 ± 502.1 nmol/L), and OV (8.4 ± 1.2 vs 4.9 ± 0.4 mL) (Table 1). Among women with PCOS, total testosterone and free testosterone levels declined in the postoperative period (1.2 ± 0.2 and 29.8 ± 4.5 nmol/L, respectively) ($p = 0.055$ and $p = 0.056$, respectively for paired *t* test, $p < 0.05$ for both comparisons when treating groups as independent). Among both non-PCOS and PCOS women, there were no significant reductions in OV in the postoperative period compared to the preoperative period.

Among women with PCOS, 50% met criteria for PCOM, 64% met criteria for hyperandrogenism, and 83% had irregular menses in the preoperative period. Postoperatively, these rates were reduced to 44, 13, and 35% respectively ($p < 0.05$ for difference in percent meeting criteria for hyperandrogenism and irregular menses. Pre- and postoperative hyperandrogenism were treated as independent groups due to limited overlap between groups and pre- and postoperative menstrual cyclicity were treated as paired data due to significant group overlap) (Fig. 2).

In univariate Pearson's correlation analyses, preoperative OV associated with change in HbA1c ($r = 0.733$, $p = 0.016$) and change in triglycerides ($r = 0.597$, $p = 0.024$). Preoperative free testosterone levels correlated with change in VLDL-C ($r = 0.707$, $p = 0.033$), change in total cholesterol ($r = 0.649$, $p = 0.012$), and change in non-HDL-C ($r = 0.622$, $p = 0.018$). No other preoperative features associated with any change in markers of cardiometabolic disease.

Based on simple correlation analyses, preoperative OV and free testosterone were determined to be the best predictors of improvement in markers of cardiometabolic disease. These variables were thus entered into separate multivariate linear

**Table 1** Characteristics of PCOS and non-PCOS in pre- and postoperative periods

| | PCOS ($n = 44$) | | | Non-PCOS ($n = 65$) | | |
|---|---|---|---|---|---|---|
| | Preop | Postop | Pre- vs postop *P* value | Preop | Postop | Pre- vs postop *P* value |
| Age (years) Ŧ | $36.1 \pm 2.3^a$ | $38.3 \pm 2.0^b$ | < 0.001 | $41.7 \pm 1.2^a$ | $50.1 \pm 1.7^b$ | < 0.001 |
| Weight (kg) | $121.8 \pm 5.5^a$ | 93.6 ± 3.5 | < 0.001 | $111.7 \pm 4.2^a$ | 97.1 ± 3.3 | < 0.001 |
| BMI (kg/m$^2$) | $44.2 \pm 2.1^a$ | 35.4 ± 1.5 | < 0.001 | $40.4 \pm 1.9^a$ | 35.6 ± 1.2 | < 0.001 |
| Triglycerides (mmol/L) | $1.4 \pm 0.1^a$ | 1.1 ± 0.1 | 0.001 | $1.2 \pm 0.1^a$ | 1.0 ± 0.1 | 0.085 |
| HDL-C (mmol/L) | $1.2 \pm 0.1^a$ | $1.4 \pm 0.1^b$ | 0.002 | $1.3 \pm 0.1^a$ | $1.6 \pm 0.1^b$ | 0.003 |
| LDL-C (mmol/L) | 2.6 ± 0.1 | 2.8 ± 0.1 | 0.769 | 2.8 ± 0.1 | 2.8 ± 0.2 | 0.556 |
| VLDL-C (mmol/L) | 0.6 ± 0.1 | 0.5 ± 0.1 | 0.007 | 0.5 ± 0.1 | 0.4 ± 0.0 | 0.136 |
| TC (mmol/L) | 4.8 ± 0.1 | 4.7 ± 0.2 | 0.973 | 4.6 ± 0.1 | 4.9 ± 0.1 | 0.391 |
| Non-HDL-C (mmol/L) | 3.5 ± 0.1 | 3.3 ± 0.2 | 0.162 | 3.4 ± 0.1 | 3.2 ± 0.2 | 0.409 |
| HbA1c (%) | $5.6 \pm 0.3^a$ | 5.5 ± 0.1 | 0.189 | $5.9 \pm 0.2^a$ | 5.6 ± 0.1 | 0.002 |
| FG (mmol/L) | 4.7 ± 0.3 | NA* | NA | 4.9 ± 0.2 | 4.2 ± 0.5 | NA |
| Total T (nmol/L) | $2.2 \pm 0.2^a$ | $1.2 \pm 0.2^b$ | 0.055ǂ | $1.4 \pm 0.3^a$ | $0.6 \pm 0.1^b$ | 0.205 |
| Free T (pmol/L) | $29.8 \pm 4.5^a$ | 12.8 ± 3.8 | 0.056ǂ | $14.2 \pm 6.9^a$ | 13.5 ± 4.5 | NA |
| DHEAS (nmol/L) | $5428.0 \pm 1177.9^a$ | 2787.3 ± 844.1 | 0.259 | $2119.6 \pm 502.1^a$ | 1302.7 ± 531.9 | 0.528 |
| Ovarian Volume (mL) | $8.4 \pm 1.2^a$ | 6.0 ± 1.5 | 0.425 | $4.9 \pm 0.4^a$ | 4.8 ± 1.0 | 0.571 |
| Irregular menses (%) | 83 | 17 | 0.001 | 32 | 68 | 0.450 |

Data expressed as median ± standard error. Preoperative values with an "a" superscript are significantly different between PCOS and non-PCOS. Postoperative values with a "b" superscript are significantly different between PCOS and non-PCOS. NA* is due to insufficient data for summary statistics. NA *P* values are due to insufficient data for statistical comparison. $P < 0.05$ is considered significant

*PCOS* polycystic ovary syndrome, *Op* operative, *BMI* body mass index, *LDL-C* low-density lipoprotein cholesterol, *VLDL-C* very low-density lipoprotein cholesterol, *TC* total cholesterol, *HDL-C* high-density lipoprotein cholesterol, *HbA1c* hemoglobin A1c, *FG* fasting glucose, *T* testosterone, *DHEAS* dehydroepiandrosterone sulfate

Ŧ Age is given at the time of preop ultrasound evaluation as well as postop lipid panel evaluation

ǂ Significant difference between preoperative and postoperative values if values are treated as independent

regression models with preoperative BMI and age at screening as covariates. Preoperative free testosterone significantly predicted change in total cholesterol and change in non-HDL-C ($\beta$ (95% CI); 3.744 (0.906–6.583), $p = 0.015$; 3.125 (0.453–5.796), $p = 0.026$, respectively). Furthermore, preoperative OV significantly associated with change in HbA1c and change in triglycerides ($\beta$ (95% CI); 0.202 (0.011–0.393), $p = 0.041$, 6.681 (1.028–12.334), $p = 0.025$, respectively) (Table 2).

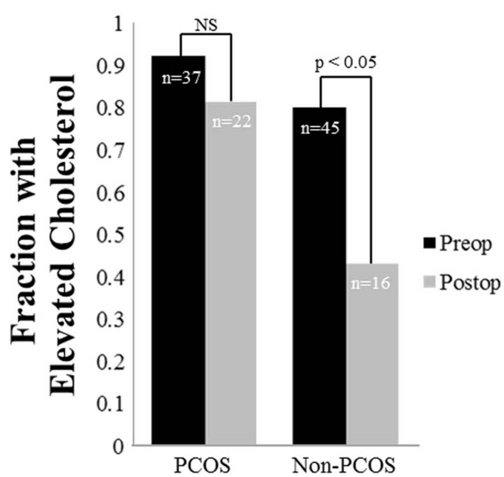


**Fig. 1** Percentage of women with elevated cholesterol in the pre- and postoperative periods. *P* values derived from McNemar's test for paired categorical data. "n" refers to the number of patients meeting each criterion. PCOS—polycystic ovary syndrome, NS—not significant

## Discussion

Using a cohort of patients who underwent bariatric surgery at the Cleveland Clinic Foundation from 2009 to 2014, the present study suggests that bariatric surgery results in improved hyperandrogenism and menstrual irregularities among women with PCOS, but has a limited impact on ovarian volume. Furthermore, surgery results in significant weight loss with resultant improvements in some markers of dyslipidemia for both women with and without PCOS. Finally, among PCOS, ovarian volume and androgens predict the degree of postoperative improvement in dysglycemia and dyslipidemia.

Both groups had significant declines in BMI postoperatively (on average 8.8 kg/m$^2$ for PCOS and 4.8 kg/m$^2$ for non-PCOS). Previous studies however have found considerably greater magnitudes of weight loss than what was presently observed

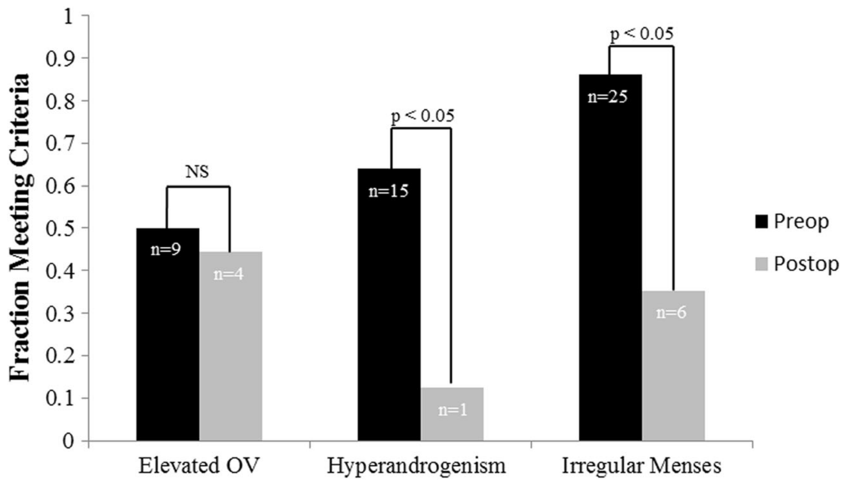


**Fig. 2** Percentage of women with ICD coding for PCOS that met diagnostic criteria for PCOS in the pre- and postoperative periods. Pre- and postoperative evaluations for hyperandrogenism were treated independently as there was little overlap between groups; thus, *p* value was derived from the chi-squared test. Percentage of women with irregular menses and elevated ovarian volume pre- and postoperatively was assessed by McNemar's test for paired categorical data. "n" refers to the number of patients meeting each criterion. PCOS—polycystic ovary syndrome, NS—not significant

[16, 17]. These reports, however, contained women with higher preoperative BMIs than in the present study, and an increased preoperative BMI has been shown to predict greater absolute reduction in weight postoperatively [16, 17]. Surprisingly, non-PCOS women also had a considerably smaller degree of weight loss than PCOS patients. This may again be secondary to this group's lower baseline BMI. Additionally, those with diabetes and impaired glucose tolerance have been found to have reduced weight loss following bariatric surgery [18, 19]. While PCOS is believed to be characterized by a state of insulin resistance, in our cohort, non-PCOS women had higher HbA1c levels preoperatively. More severe dysglycemia among non-PCOS women may have influenced their degree of weight loss after surgery.

Women with PCOS had significant improvements in several of the key diagnostic features of PCOS after bariatric surgery. At baseline, women with PCOS had significantly higher androgen levels than controls. Among PCOS, after surgery, androgen levels declined, fewer women met criteria for hyperandrogenism, and DHEAS and free testosterone levels no longer differed from controls. Additionally, compared to baseline, significantly fewer women with PCOS had a history of irregular menses postoperatively. These results corroborate previous findings which have shown that bariatric surgery reduces androgen levels, hirsutism, and menstrual irregularities (7, 9, 20–22). Contrastingly, ovarian volume did not change in the postoperative period. Previous reports on this topic are conflicting with some studies reporting no change in ovarian morphology [23], while others have found significant reductions in OV and follicle number after weight loss [24, 25]. Groups which have found benefits after surgery only included women with polycystic ovarian morphology (PCOM) at baseline, suggesting only women with PCOM prior to surgery may exhibit changes in this feature [23, 24].

Women with and without PCOS also had improvements in some, but not all markers of metabolic disease after bariatric surgery. While both groups had a decline in HbA1c, significant differences were surprisingly only seen among non-

**Table 2** Independent relationships between preoperative PCOS characteristics and changes in markers of cardiometabolic disease in the pre- vs postoperative periods among PCOS

| | Change in TC | | Change in VLDL-C | | Change in non-HDL-C | |
|---|---|---|---|---|---|---|
| | β (95% CI) | *P* value | β (95% CI) | *P* value | β (95% CI) | *P* value |
| Preop free T | *3.744 (0.906–6.583)* | *0.015* | 0.867 (− 0.108–1.842) | 0.071 | *3.125 (0.453–5.796)* | *0.0262* |
| | Change in HbA1c | | Change in TG | | | |
| | β (95% CI) | *P* value | β (95% CI) | *P* value | | |
| Preop OV | *0.202 (0.011–0.393)* | *0.0412* | *6.681 (1.028–12.334)* | *0.025* | | |

β (95% CI) and *P* value derived from multivariate linear regression models controlling for age at surgery and preoperative body mass index

*PCOS* polycystic ovary syndrome, *Op* operative, *TC* total cholesterol, *VLDL-C* very low-density lipoprotein cholesterol, *non-HDL-C* non-high-density lipoprotein cholesterol, *HbA1c* hemoglobin A1c, *TG* triglyceride, *T* testosterone, *OV* ovarian volume

PCOS after surgery. PCOS is characterized by a state of insulin resistance and previous studies have shown that bariatric surgery improves markers of dysglycemia [7, 21, 26]. The present conflicting results may be due to the exclusion of patients on glucose-lowering medications which may have resulted in the omission of those women with the most severe dysglycemia who likely would have benefited most from surgery. Among PCOS, triglycerides, HDL-C, and VLDL-C were improved after surgery and among non-PCOS, HDL-C increased and significantly fewer women met criteria for elevated cholesterol. Furthermore, only HDL-C remained significantly different between groups postoperatively. Benefits did not appear to be universal among PCOS; however, as overall, the percentage of women with elevated cholesterol was not significantly lower postoperatively.

Lack of significant cardiometabolic benefit among all women with PCOS and across all markers of metabolic disease may suggest unique risk factors which modify likelihood of benefit from surgery. We therefore evaluated if any preoperative characteristics common to PCOS related to degree of metabolic improvement in women with this syndrome. Preoperative OV was found to predict degree of improvement in dysglycemia and hypertriglyceridemia, while free testosterone associated with degree of improvement in TC and non-HDL-C. These results support previous reports which have shown that, among women with PCOS, ovarian morphology relates to markers of insulin resistance while hyperandrogenism is associated with worse lipid profiles [27–38]. Thus, ovarian volume and testosterone may share in common pathophysiologic pathways underlying dysglycemia and dyslipidemia. Furthermore, the present results suggest these features may have prognostic value in predicting benefit in these areas after surgery.

This study has several limitations. As a retrospective study, we were limited by the values available in each record and several women had missing values. As such, PCOS diagnosis was based solely on ICD coding and complete phenotyping was not possible. Very likely, the proportion of women with an ICD code for PCOS underestimates the prevalence of PCOS in our cohort, as previous reports have found that 36% of severely obese women undergoing bariatric surgery have PCOS [10]. Additionally, a non-surgical control group was not included in the present study, which limits our ability to distinguish between the effects of surgery and time on our outcome variables.

Overall, the present results suggest that bariatric surgery may resolve some of the key diagnostic and metabolic features of PCOS and that preoperative ultrasound assessments and androgen levels may provide prognostic value when assessing likelihood of benefit from surgery.

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## Compliance with Ethical Standards

This study was approved by the Cleveland Clinic Foundation institutional review board IRB number 15-1326.

**Conflict of Interest** The authors declare that they have no conflict of interest.

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