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ORIGINAL CONTRIBUTIONS

The Effect of Sleeve Gastrectomy on the Hormonal Profile of Patients with Polycystic Ovary Syndrome

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Abstract

Purpose To prospectively evaluate the hormonal profile and weight loss of women with obesity and PCOS submitted to sleeve gastrectomy (SG).

Methods A Prospective study carried out at the Hospital das Clínicas, Federal University of Pernambuco, Recife, Brazil, in 2018, where 18 patients with PCOS, whose age varied from 18 to 40 years, with an indication for bariatric surgery were evaluated. Plasma estradiol (E2), fasting insulin, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) were measured prior to bariatric surgery and 3 months after surgery. The LH/FSH ratio and BMI of the study participants were also calculated.

Results Postoperative E2 levels were higher (preoperative mean of 63.4 pg/dL versus postoperative mean of 91.0 pg/dL), with no statistical significance then ($p = 0.139$). It was observed, at the postoperative period, statistically significant decreases in mean fasting insulin levels (24.4 mIU/mL vs. 9.0 mIU/mL; $p < 0.001$), LH levels (7.2 vs. 4.5; $p = 0.047$), and an inverted LH/FSH ratio (1.5 vs. 0.9; $p = 0.008$); relevant weight loss occurred (mean BMI, 40.5 kg/m^2 vs. 33.4 kg/m^2; $p < 0.001$).

Conclusion Relevant changes in the hormone profile and significant alterations in the gonadotropic and insulin patterns were seen. In addition to satisfactory weight loss, the observed endocrine alterations revealed an internal environment that was more homeostatic and conducive to reproduction, indicating that SG was able to produce attractive physiological outcomes for women with PCOS.

Keywords Bariatric surgery · Sleeve gastrectomy · Polycystic ovary syndrome · Obesity · Infertility · LH/FSH ratio

Introduction

The World Health Organization (WHO) affirms that obesity is the epidemic of the twenty-first century [1]. According to the WHO, an estimated 700 million adults and 50 million children are obese [2, 3]. In Brazil, more than 50% of the population is overweight, and 17.9% are already considered obese [4]. In addition to type 2 diabetes (T2D) and dyslipidemia, obesity is associated with several endocrine disorders, including polycystic ovary syndrome (PCOS) [5].

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PCOS is an endocrinopathy that affects women of reproductive age, and its manifestations include insulin resistance, hyperandrogenism (either clinically or biochemically), polycystic ovaries, and ovulatory dysfunction, leading to subfertility [6]. In this syndrome, there is an altered pattern of gonadotropin secretion; namely, there is an increased secretion of LH over that of FSH what reflects an increase in the LH/FSH ratio. Insufficient FSH levels lead to impaired follicular development, while increased LH levels contribute to increase the ovarian synthesis of androgens [7].

Two-thirds of women with PCOS also present obesity, and this condition worsens certain symptoms of the syndrome, including menstrual disorders and infertility [8]. Even when modest, weight loss may restore regular menstruation patterns and ovulation cycles [9]. Changes in lifestyle, including diet and physical activity, are low-cost options that may initially be recommended to any patient with obesity [10]. There are also anti-obesity drugs for cases in which significant weight loss is not possible with diet and exercise isolated [11].

It is known that half of obese patients cannot reach or maintain the ideal weight loss only through conservative methods. After unsuccessful conservative therapy, bariatric surgery is the most effective method for treating obesity in terms of sustained weight loss in the long term [10].

A limited number of studies have been performed to assess the effect of bariatric surgery on patients with obesity and PCOS, and even fewer have been performed in Brazil. Moreover, most studies on this topic have been retrospective. Therefore, this study sought to prospectively assess the effects of bariatric surgery, specifically the sleeve gastrectomy (SG), on the hormonal profile of women with obesity and PCOS, besides to determine reproductive prognosis among these patients.

Methods

Study Design

This study was performed during the period between February 2018 and December 2018 at the Hospital das Clínicas, Federal University of Pernambuco, Recife, PE, Brazil, where 18 women with formal indication for bariatric surgery were analyzed. This was a prospective cohort study. The patients were their own controls; each patient's results were compared at two different points: at the preoperative period and 3 months after surgery.

Sample Selection

The study enrolled female patients with PCOS and BMI between 35 and 55 kg/m^2, with an age range between 18 and 40 years. Patients who: presented Cushing's syndrome, hypothyroidism, premature ovarian failure, pregnant women, and patients who were on hormone therapy were excluded from the sample.

The Rotterdam criteria were used to diagnose PCOS, which requires two of the following: oligo/anovulation, hyperandrogenism, and ultrasonographic evidence of polycystic ovaries.

Technical Procedures

Plasma LH, FSH, estradiol, and fasting insulin levels were requested in addition to the routine preoperative laboratory tests for bariatric surgery.

All patients were submitted to sleeve gastrectomy (SG). After surgery, at the 3-month follow-up, new laboratory tests were performed. Blood samples were collected during the follicular phase (between days 3 and 5 of the menstrual cycle). BMI and LH/FSH ratio values were also assessed before and after the procedure.

Statistical Analyses

As part of the data analysis, a database was created in Microsoft Excel and was then exported to SPSS, version 18, where the analysis was performed. The markers were evaluated using means and standard deviations. The Spiro-Wilk test was applied to assess the normality of the distribution. The mean values of the makers before and after surgery were also compared. Student's *t* test was applied to compare paired samples when the distribution of the variable was normal. The Wilcoxon signed-rank test was applied when the normality of distribution was refuted. The sample size was calculated, and the minimum number of observations to perform this research was 14. All conclusions were made considering a significance level of 95%.

Results

Overall, 18 women with PCOS and formal indication for bariatric surgery participated in this study between February 2018 and December 2018. The mean age of the sample was 33.1 ± 4.8 years.

There was a significant ($p = 0.001$) reduction of mean BMI after the surgical procedure (preoperative mean = 40.5 kg/m^2; postoperative mean = 33.4 kg/m^2). All results are expressed in Table 1.

An increase in mean estradiol levels was observed in the postoperative period (preoperative mean = 63.4 pg/dL; postoperative mean = 91.0 pg/dL), with no statistical significance then ($p = 0.139$).

There was a relevant decrease in insulin levels after surgery (preoperative value = 24.4 mIU/mL; postoperative

Table 1 Means and standard deviations of the variables in the preoperative and postoperative periods

Variable	Time of assessment		*p* value*
	Preoperative	Postoperative	
BMI	40.5 ± 4.4	33.4 ± 3.6	< 0.001
Estradiol	63.4 ± 49.2	91.0 ± 61.1	0.139
Insulin	24.4 ± 9.1	9.0 ± 3.6	0.001
FSH	4.7 ± 2.2	5.9 ± 4.2	0.306
LH	7.2 ± 4.8	4.5 ± 2.2	0.047
LH/FSH	1.5 ± 0.9	0.9 ± 0.5	0.008

*p value of Student's t test for paired samples

mean = 9.0 mIU/mL), and it was statistically significant ($p < 0.001$).

There was an increase in FSH levels after surgery (preoperative mean = 4.7 U/L; postoperative mean = 5.9 U/L), with no statistical significance ($p = 0.306$). Meanwhile, LH levels were found to have significantly ($p = 0.047$) decreased after surgery (preoperative mean = 7.2 U/L; postoperative mean = 4.5 U/L).

There was a decrease in the mean LH/FSH ratio after surgery (preoperative = 1.5; postoperative = 0.9). The preoperative mean value of the ratio was greater than 1, indicating that LH levels were higher than FSH levels. On the other hand, after the surgical treatment, the mean ratio was found to be lower than 1, indicating that mean FSH levels were higher than LH levels after bariatric surgery. This decrease in the LH/FSH ratio was statistically significant, presenting a p value of 0.008.

Discussion

Anovulation in women with PCOS is characterized by an anomalous secretion of gonadotropins. In relation to women with no menstrual disorders, patients with PCOS typically present increased serum concentrations of LH, normal or low FSH, and an increased LH/FSH ratio through an increase in both frequency and amplitude of LH pulses [12]. In the present study, there was an important alteration in gonadotropin secretion after bariatric surgery, with an increase in FSH synthesis and a decrease in LH synthesis. These alterations, produced by the SG, were able to invert the LH/FSH ratio.

This scenario, after bariatric surgery, marked by a different pattern of gonadotropins secretion (inverted LH/FSH ratio), aside with a decrease in plasma insulin, contributes to reduce the hyperandrogenism, favors the complete development of the antral follicles, and enables the ovulation. The ovulation process leads to the formation of the corpus luteum, a structure that keeps releasing progesterone, a hormone that opposes the estrogen secretion, thus reducing the risk of endometrial hyperplasia and cancer [6].

The prevalence of insulin resistance among PCOS patients has been found to be as high as 70% [13]. Even though the effects of obesity may vary, it is clear that it interferes in the pathophysiology of PCOS and has a negative effect on insulin resistance and hyperinsulinemia [14]. Hyperinsulinism stimulates the production of androgens, which contributes to maintenance of abnormal gonadotropin secretion by the pituitary gland [12, 14]. In contrast, weight loss results in improved insulin resistance, decreased circulating LH concentrations, and increased reproductive potential [15]. The significant decrease in serum insulin levels, observed in the present study, reflects an improvement in insulin resistance and leads to an attenuation in the androgens production and, consequently, a normalization of the gonadotropin's secretion.

Other authors have used sexual steroids and gonadotropins as preoperative and postoperative markers in cases of bariatric surgery among patients with PCOS; however, no significant changes in LH/FSH ratios were found [16]. The markers most commonly involved in the pathophysiology of PCOS (insulin, gonadotropins, and estradiol) were chosen for this study. Fasting insulin levels alone do not represent the gold standard for the diagnosis of insulin resistance, though it reflects a compensatory hyperinsulinemia. Although gonadotropins' levels exhibit a typical hormonal oscillation over the course of the menstrual cycle, this bias was minimized through the adoption of the LH/FSH ratio as a variable in the analysis, and not only the gonadotropins alone.

Patients with PCOS must undoubtedly be encouraged to make lifestyle changes in order to lose weight and restore ovulation cycles. However, 50% of class III obesity patients, with PCOS, are unable to lose weight or maintain weight loss only through conservative treatment [16, 17]. Therefore, more effective treatment strategies, including bariatric surgery, must be considered, though it is important to emphasize that reproductive management, in cases of PCOS, must be tailored to each patient individually [18, 19].

Eid et al. found, in a prospective study, ameliorations in both clinical symptoms and biomarkers 12 months after Roux-en-Y gastric bypass (RYGB) [16]. They observed that, within the period of study, there were significant improvements in testosterone levels, insulin levels, hirsutism, and menstrual cycles.

Turkmen et al. tried to evaluate menstrual cycle dysfunction through the assessment of the ovarian volume. They did not find a statistically significant decrease in this variable; however, their study was limited to a 6-month follow-up time, and this could not be sufficient to allow the normalization of this organ volume after surgery. Moreover, they found important improvements in insulin resistance markers and also in total testosterone levels after surgery [20].

A systematic review published by Butterworth et al. showed that bariatric surgery results in important ameliorations of menstrual irregularities and hirsutism, and that fertility is likely to improve after bariatric procedures and weight loss [21].

A meta-analysis of 29 studies, assessing the effects of bariatric surgery on gonadal dysfunction, found a prevalence of PCOS resolution of 96% with a CI of 89–100%. They have also found important changes in the androgen secretion, evidenced by an increase of 22.2 pmol/L in the SHBG levels and a decrease of 104 pmol/L in serum estradiol levels [22]. Unfortunately, they did not assess the gonadotropic secretion pattern of obese women with PCOS, what would be of paramount importance to strengthen our analysis in the current study.

The current study has revealed important physical and hormonal alterations in PCOS patients who have undergone SG. Because the phenotype of obesity varies and because infertility involves many other factors, the reproductive prognosis of these patients cannot depend on the new hormonal profile alone. However, it can be inferred that the body becomes more homeostatic and, as a consequence, a more conducive environment to reproduction. Given the role of insulin resistance in the development of metabolic syndrome, PCOS may be considered comorbidity associated with or caused by obesity, and may, therefore, be considered a criterion for indication of bariatric surgery in some selected cases.

Besides the small sample size, the short-term follow-up evaluation can be considered a limitation of our study. A bigger sample and a long-term follow-up evaluation would provide more solid information about the fertility status and hormonal changes, if it is sustained or not. However, our intention in this study was to determine the immediate effect of SG on the hormonal profile of obese women with PCOS, due to the difficulty in recruiting these patients regularly within a long-term follow-up at our center.

Conclusion

Taking the results of the present study into consideration, we conclude that PCOS can be considered comorbidity to set the indication for bariatric surgery. Moreover, we believe that this surgery should be included as part of the treatment of infertility in morbidly obese patients, since this procedure is able to provide physical, hormonal, and reproductive benefits to these patients. However, little is known about the long-term effects of SG on women with PCOS. Thus, further studies are necessary for more robust conclusions to be made regarding the effects of this surgery on this specific condition.

Compliance with Ethical Standards

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This research project was approved by the Ethics Committee for Research involving human beings of the Federal University of Pernambuco's Center of Health Sciences (N. 1.435.611) CAAE: 52297315.7.0000.5208. Informed consent was obtained from all individual participants included in the study.

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

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