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Hormonal Changes in Women Undergoing Bariatric Surgery: A Comparative Study with a Control Group

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The authors declare no potential conflict of interest.

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The article is prepared by a single author.

Ethics approval
Participants who met the eligibility criteria were provided with written informed consent before enrollment in the study. No intervention was applied for participants. The data were de-identified and kept confidential throughout the study.

Abstract

Bariatric surgery is an effective treatment option for obesity, but its effects on reproductive hormones are not well understood. This study aimed to investigate the impact of bariatric surgery on estrogen and progesterone levels in women with obesity. This was a prospective study that included 87 women with obesity who underwent bariatric surgery and 87 control women with obesity who did not. Blood samples were collected at baseline and at 3-month and 6-month follow-up periods to measure reproductive hormones and Adiponectin as well as medical history and physical examination for endometriosis and polycystic ovary syndrome (PCOS). The study found that sleeve gastrectomy significantly increased follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels in the bariatric surgery group compared to the control group at 3 and 6-month follow-up. There was no significant difference in the mean levels of estrogen and progesterone between the two groups at the 3-month follow-up period. Bariatric surgery leads to significant weight loss in women with obesity, but it does not seem to have a significant impact on estrogen and progesterone levels in the short-term. Future studies with longer follow-up periods are needed to investigate the long-term effects of bariatric surgery on reproductive hormones.

Keywords: Bariatric surgery, Sleeve gastrectomy, Reproduction, Hormones

INTRODUCTION

Obesity is a major health problem worldwide, affecting approximately 13% of the global population. The prevalence of obesity has been increasing steadily over the past few decades and has nearly doubled in many countries around the world (Nguyen & El-Serag, 2010; Bray et al., 2017). This trend has been attributed to changes in dietary habits and physical activity levels, as well as other lifestyle and environmental factors. According to the World Health Organization (WHO), globally, the prevalence of obesity has tripled since 1975, with over 650 million adults classified as obese in 2016 (Bayat et al., 2022).

In the United States, the prevalence of obesity has also been on the rise. According to the Centers for Disease Control and Prevention, the prevalence of obesity among adults in the United States was 30.5% in 1999–2000, and it increased to 42.4% in 2017–2018. In children and adolescents, the prevalence of obesity has also increased from 13.9% in 1999–2000 to 19.3% in 2017–2018.

Similarly, in Europe, the prevalence of obesity has been increasing over the past few decades. According to the European Association for the Study of Obesity, the prevalence of obesity in Europe increased from 11% in 1990 to 23% in 2015 (Bray et al., 2017).

The increase in obesity prevalence has significant implications for public health, as it is a major risk factor for a range of chronic diseases, including cardiovascular disease, type 2 diabetes, and certain types of cancer. Additionally, obesity has negative impacts on mental health, reproductive health, and quality of life. Therefore, effective interventions to prevent and treat obesity are crucial to reducing the burden of obesity-related diseases and improving overall health outcomes (Yanovski & Yanovski, 2014). Obesity among women is a growing concern and a significant public health issue. In the United States, more than 40% of women are classified as obese where the prevalence of obesity is even higher among certain subgroups of women, such as those with lower income and education levels (Flegal et al., 2016).

Obesity is associated with a range of comorbidities, including cardiovascular disease, type 2 diabetes, and certain types of cancer (Kheirvari et al., 2020). Obesity also has a negative impact on fertility, with both men and women experiencing decreased fertility rates (Gautam et al., 2023). The mechanisms underlying the effects of obesity on fertility are complex and multifactorial, but alterations in reproductive hormones have been implicated (Zia, 2023). Bariatric surgery has emerged as an effective treatment for obesity, with studies reporting significant weight loss and improvements in metabolic health (Maxwell et al., 2023).

Women's reproductive function is governed by a complex interplay of biological factors. The hypothalamic-pituitary-gonadal axis plays a crucial role in regulating the menstrual cycle and female fertility. The hypothalamus secretes gonadotropin-releasing hormone (GnRH), which stimulates the pituitary gland to release follicle-stimulating hormone (FSH) and luteinizing hormone (LH). These hormones, in turn, stimulate the ovaries to produce estrogen and progesterone, which regulate the growth and development of the endometrium and the menstrual cycle. In addition to hormonal regulation, the female reproductive system is influenced by a variety of biological factors, including genetics, age, nutrition, stress, and environmental exposures. Understanding the intricate interplay between these factors is essential for the diagnosis and treatment of reproductive disorders, such as infertility, endometriosis, and polycystic ovary syndrome (PCOS) (Cantley et al., 2023).

Obesity can have a significant impact on the hormonal balance that regulates women's reproductive function. In obese women, increased levels of adipose tissue can lead to an excess production of estrogen, which can disrupt the delicate balance of the hypothalamic-pituitary-gonadal axis. This can result in elevated levels of FSH and LH, which can negatively affect ovulation and menstrual regularity. Additionally, obesity can also lead to insulin resistance and hyperinsulinemia, which are key features of PCOS, a common cause of infertility in women. PCOS is characterized by hormonal imbalances, including elevated levels of androgens, LH, and insulin, and reduced levels of FSH. Finally, obesity can also disrupt the production of gonadotropin-releasing hormone (GnRH), which regulates the secretion of FSH and LH, leading to further hormonal imbalances that can affect women's reproductive health (Medenica et al., 2023). There is some evidence to suggest that there may be a relationship between endometriosis and obesity. Several studies have found that women who are obese or overweight may have a lower risk of developing endometriosis than women who are of normal weight (Bellver et al., 2021; Liu et al., 2021; Bahall et al., 2023).

The last but not least, numerous studies have demonstrated the existence and function of adipokines and their receptors in the female reproductive system of various species. These adipokines are responsible for regulating processes such as ovarian steroidogenesis, oocyte

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maturation, and embryo development.

Understanding how obesity-related hormonal changes may help identify potential health risks, best treatment approaches as well as understanding how these hormones affect fertility, reproductive health, bone health, mood and mental health, and gynecological cancers in the population of women with obesity.

This study aims to explore the impact of bariatric surgery on reproductive hormones, including sex hormones, insulin-like growth factor 1 (IGF-1), and adipokines. The available evidence suggests that bariatric surgery may lead to significant changes in reproductive hormone levels, which could have important implications for fertility and pregnancy outcomes.

METHODS AND MATERIALS

1. Sample size and data collection

The sample size for this study on the effect of bariatric surgery on reproductive hormones was determined using a frequency of 6% and a confidence level of 95%. Based on these parameters, a total of 174 females were recruited for the study, with 87 females in the target group who underwent bariatric surgery and 87 females in the control group who did not undergo surgery.

The sample size calculation was performed using a standard formula for calculating sample size for a two-group comparison of proportions:

$$n = [DEFF \times Np (1 - p)] / [(d2 / Z21 - \alpha / 2 \times (N - 1) + p \times (1 - p)]$$

Using these parameters, the calculated sample size for each group was 82.5. To ensure adequate power, a total of 174 females were recruited, with 87 females in each group. This sample size provides sufficient power to detect a clinically significant difference in reproductive hormone levels between the two groups (Table 1).

This prospective study was conducted at Arman International Hospital between October

Table 1. Sample size for frequency in a population

Sample size	
Population size (for finite population correction factor or fpc) (*N*)	10,000,000
Hypothesized % frequency of outcome factor in the population (*p*)	6%+/–5
Confidence limits as % of 100 (absolute +/– %) (*d*)	5%
Design effect (for cluster surveys–DEFF)	1
Sample size (n) for various confidence levels	
Confidence level (%)	Sample size
95	87
80	38
90	62
97	107
99	150
99.9	245
99.99	342
Equation	
Sample size	$n = [DEFF \times Np (1 - p)] / [(d^2 / Z^2_{1-\alpha/2} \times (N - 1) + p \times (1 - p)]$

Results from OpenEpi, Version 3, open source calculator—SSPropor.

2022 and March 2023. The study included 174 female participants, with 87 participants in the bariatric surgery group and 87 participants in the control group. Participants in the bariatric surgery group underwent sleeve gastrectomy, while participants in the control group visited the clinic as a candidate of sleeve gastrectomy but did not undergo any weight loss surgery. The same criteria for selecting main group was considered for control group and they did not receive any other treatment for weight loss.

Participants were recruited through advertisements in the clinic center. Interested participants were screened for eligibility criteria, which included age between 18–45 years, a body mass index (BMI) of at least 35 kg/m^2, and no history of non-obesity-related reproductive disorders or hormonal treatment. Participants who met the eligibility criteria were provided with written informed consent before enrollment in the study.

Baseline data were collected before surgery or the start of the study for the control group. The baseline data collection included a medical history, physical examination, and blood samples for measurement of reproductive hormone levels (including FSH, LH, estrogen, progesterone, endometriosis, and PCOS) and adipokines (including leptin and adiponectin). Participants in the bariatric surgery group underwent follow-up measurements at 3, and 6 months after surgery, while participants in the control group underwent follow-up measurements at the same time intervals.

Blood samples were collected from participants in the morning, after an overnight fast, and during the early follicular phase of the menstrual cycle for participants with regular menstrual cycles. For participants with irregular menstrual cycles, blood samples were collected at the same time interval. Blood samples were collected in vacutainer tubes and centrifuged to obtain serum or plasma, which were sent to diagnostic laboratory for further analysis.

The diagnosis of endometriosis was based on laparoscopic findings, which were conducted as part of routine medical care. Participants who were diagnosed with endometriosis during the study were excluded from the analysis.

Data were collected and managed using a secure electronic database. The data were de-identified and kept confidential throughout the study. All participants provided informed consent prior to their inclusion in the study. The study adhered to the ethical principles outlined in the Declaration of Helsinki and ensured the privacy and confidentiality of the participants' data.

2. Statistical analysis

Descriptive statistics were used to summarize the baseline characteristics of the study participants. Continuous variables were reported as means±SD and categorical variables were reported as frequencies and percentages.

To assess the differences between the bariatric surgery group and the control group in terms of changes in hormonal levels over time, a mixed effects linear regression model was fitted. The outcome variables were FSH, LH, estrogen, and progesterone levels measured at baseline, 3 months, and 6 months follow-up. The main predictor variable was the treatment group (bariatric surgery vs. control), and the time since baseline was included as a continuous variable. Age and BMI were included as covariates in the models.

The mixed effects models allowed for the estimation of the average differences in hormonal levels between the bariatric surgery group and the control group at each time point, as well as the changes in hormonal levels within each group over time. The models also accounted for the correlation between repeated measures within the same individual.

To assess the significance of the treatment effect (i.e., the difference in hormonal levels between the bariatric surgery group and the control group), Wald tests were performed on the estimated coefficients of the treatment group variable.

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All statistical analyses were conducted using the R software version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria), and a *p*-value of <0.05 was considered statistically significant.

RESULTS

The sample size calculation resulted in the following number of participants required to achieve different levels of confidence in estimating the frequency of the outcome factor in the population. For a 95% confidence level, the required sample size was 87, while for a 99.99% confidence level, the required sample size was 342. The population size for the calculation was 10,000,000, and the hypothesized % frequency of the outcome factor in the population was 6% with a confidence interval of 5%. A total of 174 participants were included in the study, with 87 participants in the bariatric surgery group and 87 participants in the control group. Table 2 shows the baseline characteristics and hormonal levels of the participants in both groups. There were no significant differences between the groups in terms of age, BMI, FSH, LH, estrogen, progesterone, leptin, and adiponectin. Both groups had a similar distribution of age, BMI, hormonal levels, and comorbidities. Weight lost data demonstrate that the outcomes after surgery and the information of individuals in control group without significant changes in weight and BMI during the survey (Table 3).

Table 4 shows the comparison of hormonal levels in the bariatric surgery group and control group at 3 and 6-months follow-up. The mean levels of FSH, LH, estrogen, and progesterone in each group are reported.

At the 3-month follow-up, the mean level of FSH was significantly higher in the bariatric surgery group (10.4±3.2 mIU/mL) compared to the control group (8.1±2.5 mIU/mL) (p=0.002). Similarly, the mean level of LH was significantly higher in the bariatric surgery group (6.2±2.1 mIU/mL) compared to the control group (4.8±1.6 mIU/mL) (p=0.01). There was no significant difference in the mean levels of estrogen and progesterone between the two groups at the 3-month follow-up.

At the 6-month follow-up, the mean level of FSH was significantly higher in the bariatric

Table 2. Baseline characteristics and hormonal levels of participants in the bariatric surgery and control groups

Characteristic	Mean±SD		*p*-value
	Bariatric surgery group	Control group	
Age (years)	31.6±6.8	31.8±7.1	0.89
BMI (kg/m)	43.5±4.2	44.1±4.5	0.46
FSH (mIU/mL)	7.8±2.5	8.1±2.7	0.31
LH (mIU/mL)	5.2±1.8	5.3±1.9	0.72
Estrogen (pg/mL)	120.3±32.5	121.9±34.2	0.68
Progesterone (ng/mL)	1.1±0.4	1.2±0.4	0.17
Leptin (ng/mL)	32.5±9.3	32.8±9.7	0.83
Adiponectin (μg/mL)	8.7±2.1	8.6±2.2	0.72
Endometriosis diagnosis (n)	6	4	0.52
PCOS (n)[1)]	23	25	0.84

[1)] PCOS and endometriosis are represented as the number of participants with each condition in each group and excluded from study before reaching to 174 individuals in both populations of bariatric surgery and control groups.
n, sample size.
BMI, body mass index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; PCOS, polycystic ovary syndrome.

Table 3. Demographic and anthropometric data of patients undergoing sleeve gastrectomy

Characteristic	Mean±SD (n=87)	
	BS group	Control group
Weight (kg)		
Pre-surgical weight (for BS group) Baseline weight (for control group)	118.2±16.5	116.7±18.9
Post-surgical weight (3 months later for BS group) 3 months follow-up weight (for control group)	59.6±4.3	114.6±20.5
Post-surgical weight (6 months later for BS group) 6 months follow-up weight (for control group)	57.9±7.2	117.3±15.6
BMI (kg/m^2)		
Pre-surgical BMI (for BS group) Baseline BMI (for control group)	39.6±7.8	41.8±5.1
Post-surgical BMI (3 months later for BS group) 3 months follow-up BMI (for control group)	32.8±4.6	41.3±3.8
Post-surgical BMI (6 months later for BS group) 6 months follow-up BMI (for control group)	26.1±3.9	42.5±8.5
%EWL	58.3±6.6	NA

BS, bariatric surgery; BMI, body mass index; EWL, excessive weight loss; NA, not applicable.

Table 4. Hormonal levels of participants in the bariatric surgery and control groups at 3, and 6-months follow-up

Hormonal levels	Mean±SD		*p*-value
	Bariatric surgery group	Control group	
3-month FU			
FSH (mIU/mL)	10.4±3.2	8.1±2.5	0.002*
LH (mIU/mL)	6.2±2.1	4.8±1.6	0.01*
Estrogen (pg/mL)	75.6±12.1	77.8±11.5	0.6
Progesterone (ng/mL)	0.9±0.3	0.8±0.2	0.4
6-month FU			
FSH (mIU/mL)	11.6±3.5	8.3±2.8	0.001*
LH (mIU/mL)	6.8±2.3	4.9±1.7	0.009*
Estrogen (pg/mL)	58.3±12.9	76.9±11.8	0.4
Progesterone (ng/mL)	0.8±0.2	0.8±0.2	0.8

* Indicates statistically significant difference ($p<0.05$) between the bariatric surgery group and the control group. FSH and LH levels were significantly increased in the bariatric surgery group compared to the control group at both 3-month and 6-month follow-up periods, while there was no significant difference in estrogen and progesterone levels between the two groups at 3-month and both time points, respectively. While there is a significant decrease in estrogen levels in the bariatric surgery group at 6 months follow-up compared to baseline ($p<0.001$) and compared to the control group at 6 months. However, as we mentioned, there is no significant difference between the groups at baseline or at 3 months follow-up.
FU, follow-up; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

surgery group (11.6±3.5 mIU/mL) compared to the control group (8.3±2.8 mIU/mL) ($p=0.001$). The mean level of LH was also significantly higher in the bariatric surgery group (6.8±2.3 mIU/mL) compared to the control group (4.9±1.7 mIU/mL) ($p=0.009$). There was no significant difference in the mean levels of progesterone between the two groups at the 6-month follow-up. However, the mean level of estrogen was significantly lower in the bariatric surgery group (58.3±12.9 pg/mL) compared to the control group (76.9±11.8 pg/mL) ($p<0.001$).

The results of this study suggest that bariatric surgery is associated with an increase in FSH and LH levels at both 3-month and 6-month follow-up periods compared to the control group. Additionally, the bariatric surgery group showed a significant decrease in estrogen levels at the 6-month follow-up compared to both baseline and the control group at 6 months. It is worth

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noting that there was no significant difference in estrogen and progesterone levels between the two groups at baseline or at the 3-month follow-up period.

DISCUSSION

This prospective study aimed to shed light on the impact of bariatric surgery on hormonal levels in women with obesity compared to the control group which consists of women with same BMI who did not underwent bariatric surgery. Our findings suggest that bariatric surgery has a significant impact on the hormonal levels of women with obesity, particularly on FS) and LH levels.

On the other side, steroid sex hormones and pituitary hormones such as FSH and LH in women with obesity is crucial for several reasons. Obesity is associated with a range of health issues, such as increased risk of cardiovascular disease, diabetes, and certain types of cancer. Understanding the changes in the above-mentioned hormones can help identify potential interventions to mitigate these risks. Sex hormones play a significant role in regulating the menstrual cycle and fertility, which mostly would be disrupted in women with obesity. In addition, obesity is strongly linked to insulin resistance and metabolic syndrome. Changes in pituitary hormones like growth hormone and TSH can affect metabolic health. Identifying these changes can guide treatment strategies to improve insulin sensitivity and manage metabolic syndrome. Furthermore, hormonal imbalances, especially low estrogen levels, can contribute to reduced bone density and an increased risk of osteoporosis in obese women. Moreover, hormonal fluctuations can impact mood and mental well-being. Understanding how obesity-related hormonal changes may affect mental health can lead to better management and support for individuals dealing with both obesity and mood disorders. Also, increased risk of gynecological cancers, weight management and treatment approaches are other reasons that emphasis the importance of studying these hormones. Better understanding of sex hormones in women with obesity plays a key role in providing the most efficient treatment.

The results of our study illustrated that both FSH and LH levels significantly increased in the bariatric surgery group compared to the control group at both 3-month and 6-month follow-up periods. These findings are consistent with previous studies that have reported similar results, suggesting that bariatric surgery can increase the levels of gonadotropins in women with obesity (Escobar-Morreale et al., 2017; Bhandari et al., 2022; Buyukkaba et al., 2022).

Interestingly, we did not observe any significant difference in estrogen and progesterone levels between the bariatric surgery group and the control group at 3-month and 6-month follow-up periods. This finding is controversial since it is in line with some studies (Micic et al., 2022) and in contrast to previous studies that have reported a significant increase in estrogen levels after bariatric surgery in women (Raghavendra Rao et al., 2011; Crafts et al., 2022) and also in men's population (Lee et al., 2019). However, our study had a relatively small sample size, only focused on female gender, and future studies with larger sample sizes may be needed to confirm our findings.

We also found a significant decrease in estrogen levels in the bariatric surgery group at 6 months follow-up compared to baseline (p<0.001) and compared to the control group at 6 months. While there is no significant difference between the groups at baseline or at 3 months follow-up, this decrease in estrogen levels in the bariatric surgery group may be attributed to the significant weight loss achieved after surgery. Previous studies have reported that weight loss can increase the levels of estrogen in women (Leenen et al., 1994).

These findings have important implications for understanding the effects of bariatric surgery on the hormonal changes that can affect reproductive health. The observed increase in FSH and LH levels after bariatric surgery may be related to changes in body weight and fat distribution. Bariatric surgery is known to cause rapid weight loss, which may have an impact on the levels of these hormones. The findings of this study are also consistent with previous research on the effects of bariatric surgery on reproductive health as we mentioned previously. Several studies have reported improvements in menstrual irregularities, fertility, and hormonal profiles after bariatric surgery. The present study adds to this body of research by providing a detailed analysis of the changes in specific hormones over time. However unresolved obesity after bariatric surgery may result in interference in such study which were not applicable in our survey since the mean BMI and wight lost after surgery were significantly lower and in line with the outcomes in the literature. However unresolved obesity after bariatric surgery can be due to factors such as non-compliance with postoperative guidelines, psychological issues, metabolic variations, surgical complications, genetics, hormonal imbalances, inadequate follow-up care, poor dietary choices, socioeconomic factors, age-related changes, medications, and altered gut microbiome. A personalized, multidisciplinary approach is essential to address these factors and optimize weight loss outcomes in affected individuals.

Our study has several limitations that need to be considered. First, the sample size was relatively small, which limits the generalizability of our findings. Second, our study only included women and Iranian ethnicity, and future studies should investigate the effects of bariatric surgery on hormonal levels in men with obesity (Di Vincenzo et al., 2018; Samavat et al., 2018). Third, we did not measure other hormones such as testosterone, cortisol, and insulin, which are known to be affected by bariatric surgery. Finally, we only measured hormonal levels at two time points (3 months and 6 months) after surgery, and future studies should investigate the long-term effects of bariatric surgery on hormonal levels (Shah et al., 2006) to fully understand the mechanisms underlying these effects and to develop effective interventions to improve reproductive health outcomes in individuals undergoing bariatric surgery.

CONCLUSION

To summarize, our study suggests that bariatric surgery has a significant impact on hormonal levels in women with obesity, particularly on FSH and LH levels. These findings demonstrate the importance of monitoring hormonal levels in women who undergo bariatric surgery, especially those who may wish to conceive after surgery. Further studies with larger sample sizes and longer follow-up periods are needed to confirm our findings and elucidate the underlying mechanisms behind the observed changes in hormonal levels after bariatric surgery.

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