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Impact of bariatric surgery induced weight loss on women fertility: A prospective cohort study

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SUMMARY

AUTHORS' CONTRIBUTION: (A) Study Design · **(B)** Data Collection . **(C)** Statistical Analysis · **(D)** Data Interpretation · **(E)** Manuscript Preparation · **(F)** Literature Search · **(G)** No Fund Collection

Background: Obesity is a chronic disease influenced by many factors. It is a significant public health issue worldwide, particularly in Western countries where its prevalence is consistently increasing. Obesity is a major risk factor for various chronic illnesses, including cancer.

Aim of the work: This study aims to assess the effect of weight loss caused by bariatric surgery on female fertility.

Methods: This prospective cohort study was conducted at Ain Shams University Hospitals (ASUH) from June 2022 to December 2022. It involved 75 obese women who underwent bariatric surgery (sleeve gastrectomy) at ASUH.

Results: The BMI of the patients who underwent surgery significantly decreased in the three months after the operation. Additionally, there was a significant loss of excess body weight, with an average of more than a quarter of the excess weight at 29.9 ± 6.6%. The patients' levels of AMH, and LH significantly decreased while levels FSH and FSH/LH ratio significantly increased three months after surgery. Furthermore, there was a significant positive correlation between the BMI at three months and the levels of postoperative AMH and LH. Conversely, there was a significant negative correlation between the BMI at three months and the postoperative FSH/LH levels.

Conclusion: Bariatric surgery can help improve reproductive hormones and menstruation in severely obese women. We found that levels of AMH and LH decrease while FSH increases, leading to improved menstrual cycle regularity.

Keywords: Obesity and women's fertility; Bariatric surgery; Induced weight loss

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INTRODUCTION

Obesity is a multifactorial chronic disease. It is one of the world's most significant public health issues because its prevalence is steadily rising in Occidental countries and because it is a major risk factor for a variety of chronic diseases, including tumors [1].

Clinical obesity prevalence in women aged 16–44 years has increased from 12.4 percent in 1993 to 20.2 percent in 2010. This is according to annual statistics from the health survey [2].

Obesity and reproductive function deficiency have been studied extensively. Polycystic Ovary Syndrome (PCOS), one of the most common causes of infertility, has been linked to obesity [3].

In reality, abdominal obesity has been linked to a worsening of PCOS patients' clinical symptoms, and lifestyle changes based on weight loss are effective in improving reproductive function in these women [4].

Obesity surgery is the most effective treatment for extreme obesity (BMI of 35 or more) with an appropriate surgical risk, regardless of the improvement of all comorbidities, in long-term weight loss evaluations [5].

Regarding weight loss techniques, bariatric procedures are quickly becoming the most common due to their powerful results, low complication rate, and radical impact on the gastrointestinal hormonal profile, contributing to early satiety [6].

As hormonal persistent shifts caused by fatty tissue, obesity is a multifactorial risk factor for the low percentage of unintended pregnancies [7].

Recent research has linked an increased BMI value to higher levels of Anti-Muller Hormone (AMH), Follicular Stimulating Hormone (FSH), Luteinizing Hormone (LH), and FSH/LH ratio, all of which have been linked to ovarian function and follicular development [8].

The impact of bariatric surgery on fertility is still a debatable topic. Although there is evidence of improved ovarian function, scientific proof of increased fertility is yet to be established. Similarly, different researchers have not described the effect of weight loss on AMH, FSH, LH, and FSH/LH ratio [9,10].

AIM OF THE WORK

This prospective cohort study aims to evaluate the impact of bariatric surgery-induced weight loss on women's fertility.

PATIENTS AND METHODS

This prospective cohort study was conducted at Ain Shams University Maternity Hospital and the General Surgery Department at Ain Shams University Hospitals (ASUH) from June 2022 to December 2022. The study was performed on a total of 75 obese women who attended Ain Shams University Hospitals for bariatric surgery (sleeve gastrectomy) after obtaining ethical committee approval from the Faculty of Medicine- Ain Shams University (FMASU 392/2022) and written consent from the patients. The study was prospectively registered at clinical trials. gov (NCT05457413).

This study involved women between the ages of 20-40 years who were obese with a BMI greater than 35 kg/m^2 and went to Ain Shams University Hospitals for bariatric surgery, specifically sleeve gastrectomy. Exclusion criteria included women with endocrine disorders such as diabetes, thyroid problems, hyperprolactinemia, etc. Women with known causes of infertility other than ovarian factors, such as uterine or tubal factors or male factors, as well as women, who were using hormonal treatment or fertility drugs like oral contraceptive pills and metformin, were also excluded. Women who experienced surgical complications intra-operatively or post-operatively and those who refused to participate in the study were also excluded.

Study procedures: A detailed menstrual history, including information on irregular menstrual cycles, was recorded for all patients. An irregular menstrual cycle was defined as a cycle length of less than 21 or more than 35 days for three successive cycles. Secondary amenorrhea was defined as the absence of periods for more than six cycles or 180 days together [11].

The demographic data (age, height, weight, BMI) were obtained from all included patients. Serum AMH, FSH, LH, and FSH/LH ratios were measured pre-operatively for all patients before bariatric surgery.

The gastric sleeve was performed by a senior consultant in the general surgery department following proper consent.

Outcome measures after 3-month follow-up:

- 1ry outcome: Change in serum AMH 3 month's post-operative.
- 2ry outcomes:
    - ► Changes in serum FSH, LH values, and FSH/LH ratio three months post-operative.
    - ► Change in menstrual pattern.
    - ► Excess body weight loss percentage.

The patients were monitored for three months to assess their weight loss progress. The results were reported as the percentage of Excess Body Weight loss (EBWL %). Excess weight is calculated as the difference between the preoperative weight and the individual's ideal weight, assuming a BMI of 22.5 kg/m^2. The EBWL % was computed using the formula (weight lost in 3 months/ excess weight) × 100.

The Correction of menstrual irregularity was defined as the occurrence of periods (even if irregularly) in patients with amenorrhea and cycle duration between 21 to 35 days in patients with previous irregular periods [11].

Sample size justification: Using PASS 11 for sample size calculation, setting power at 80%, alpha error at 5%, reviewing results from the previous study by Nilsson-Condori, et al. [12] showed that the level of AMH at 6 months postoperatively was significantly lower 19.5 (2.0-83.0) compared to 30.0 (3.1102.5) at the operation time, based on these findings and after 5% adjustment for dropout rate a sample size of at least 75 patients were needed.

Statistical analysis: The study first examined the distribution of serum levels of AMH, FSH, LH, and FSH/LH ratio. These values were then plotted against BMI, age, and expected body weight loss (EBWL %). Nonparametric tests were used to calculate statistical significance since the hormone values were not normally distributed. EBWL % was examined both as a continuous and class variable to determine its association with serum AMH, FSH, LH, and FSH/LH ratio and correction of menstrual pattern. Serum AMH, FSH, LH, and FSH/LH ratio were evaluated as continuous variables to determine changes in the two groups. The contingency table of categorical variables was analyzed using the chi-square test. Mann Whitney U test was applied to see the significant difference in the median of continuous variables in two groups. Spearman correlation test was applied to see the correlation of two continuous variables. All statistical analyses were performed using Medical (Demo Version) software by Inborne Technology Corporation located in Mesa, AZ.

RESULTS

One hundred seven patients were evaluated for eligibility in this study, and 75 were eventually included. Of all eligible patients, 26 were excluded due to not meeting the inclusion criteria, and six declined to participate in the study. Finally, the analysis was based on the data of 75 obese women.

The study found that the average age of the participants was 30.4 ± 5.9 years. Before the surgery, the average Body Mass Index (BMI) was 42.9 ± 5.4 kg/m^2. After three months of surgery, the BMI significantly decreased to 37.8 ± 5.0. Moreover, the amount of excess body weight lost after three months post-surgery was significant at 29.9% ± 6.6% (P<0.001) [Data not Tabulated].

Our study investigated hormonal changes in patients undergoing surgery. The baseline preoperative AMH was found to be 3.5 ± 1.9 ng/mL. After three months post-surgery, significant decreases in AMH and LH were observed among the studied cases. Additionally, there was a significant increase in FSH and FSH/LH among the studied cases during the same period (p value <0.001).

Out of 75 patients, 44% reported irregular menstrual cycles (28 patients had oligohypomenorrhea, and five had amenorrhea). After three months, 18.7% of patients still had irregular cycles (P<0.001) [Data not tabulated].

After three months postoperatively, there was a significant decrease in AMH and LH but a significant increase in FSH and FSH/LH (As shown **Tab.1.**).

Tab. 2. Displays significant positive correlations between preoperative BMI and AMH/LH and a significant negative correlation between preoperative BMI and FSH/LH.

Tab. 3. Indicates significant positive correlations between 3rd month BMI and postoperative AMH and LH and a significant negative correlation between 3rd month BMI and postoperative FSH/LH.

Tab. 4. demonstrates that patients who experienced irregular menstruation three months post-surgery had significantly higher BMI and AMH levels during the same period.

DISCUSSION

Obesity can negatively affect female fertility by reducing spontaneous and assisted conception rates, increasing miscarriage rates, and raising the risks of premature labor, stillbirth, gestational diabetes, hypertension, menstrual irregularity, and endometrial pathology [13].

Bariatric Surgery (BS) is the most efficient therapy for severe obesity, which has beneficial effects on metabolic parameters and obstetrical as well as perinatal complications. It benefits fertility; however, research on ovarian reserve is scant [14].

Studies on the effects of bariatric surgery on reproductive function show inconsistent results. Some studies report significant improvements, while others found decreased follicular and oocyte formation postoperatively.

Tab. 1. AMH, FSH, LH and FSH/LH Preoperative and 3-months post-operative among the studied cases.

Variables		Mean ± SD	Range	p-value
AMH (ng/mL)	Preoperative	3.5 ± 1.9	0.5 – 8.1	<0.001*
	Month-3	2.6 ± 1.5	0.5 – 7.0	
	#Change	-0.9 ± 0.8	-3.5 – 0.0	
FSH (IU/L)	Preoperative	6.9 ± 2.6	3.0 – 15.3	<0.001*
	Month-3	7.2 ± 2.1	3.5 – 16.0	
	#Change	0.4 ± 1.2	-2.0 – 3.6	
LH (IU/L)	Preoperative	7.6 ± 4.1	2.5 – 17.5	<0.001*
	Month-3	5.1 ± 2.2	2.0 – 12.0	
	#Change	-2.6 ± 2.6	-10.2 – 3.1	
FSH/LH	Preoperative	1.1 ± 0.7	0.3 – 2.9	<0.001*
	Month-3	1.6 ± 0.7	0.7 – 3.5	
	#Change	0.5 ± 0.5	-1.0 – 2.4	

Total=75. #Change = Month-3 – preoperative, negative values indicate reduction. Paired t-test. *Significant

Tab. 2. Correlations of preoperative BMI with laboratory findings.

Preoperative Lab	Preoperative BMI	
	r	p-value
AMH	0.279	0.015*
FSH	-0.002	0.988
LH	0.295	0.010*
FSH/LH	-0.230	0.048*

Tab. 3. Correlations of post-operative BMI with laboratory findings.

3rd Month Lab	3rd Month BMI	
	r	p-value
AMH	0.420	<0.001*
FSH	-0.025	0.830
LH	0.229	0.049*
FSH/LH	-0.277	0.016*

Tab. 4. Comparison according to preoperative menstrual pattern in relation to 3-months post-operative laboratory findings.

Postoperative Lab	Regular (Total=61)	Irregular (Total=14)	p-value
BMI (kg/m²)	36.9 ± 4.1	41.9 ± 6.4	0.013*
AMH (ng/mL)	2.4 ± 1.3	3.5 ± 1.9	0.049*
FSH (IU/L)	7.2 ± 2.1	7.6 ± 2.0	0.437
LH (IU/L)	5.0 ± 2.3	5.4 ± 1.4	0.498
FSH/LH	1.7 ± 0.7	1.5 ± 0.4	0.168

Our results and their interpretation

Our results revealed that bariatric surgery significantly decreased AMH and LH, while FSH and FSH/LH ratios were significantly increased. Additionally, there was a significant loss of excess body weight, with an average of more than a quarter of the excess weight at 29.9 ± 6.6%.

There are two possible explanations for the drop in AMH levels observed after surgery. The first suggests that it may be related to the surgery itself, such as malabsorption of key precursors that could affect AMH gene expression. Alternatively, the drop may be a temporary result of the surgery-induced stress on the ovaries.

Our study results showed a significant improvement in menstrual regularity three months after surgery (p-value <0.001).

Obese women tend to have higher estrogen levels. When they lose weight, estrogen declines and the testosterone to estrogen ratio increases. This is due to a reduction in sex hormone-binding globulin and luteinizing hormone secretion. This can cause anovulation and abnormal menstrual cycles in severely overweight premenopausal women.

In correlation with the hormonal profile, our study results revealed that there were significant positive correlations between each of preoperative and postoperative BMI with each of preoperative and postoperative AMH and LH respectively. There was significant negative correlation between each of preoperative BMI and 3rd month BMI with preoperative and postoperative FSH/LH respectively.

Comparison of our results to similar studies

In concordance with our findings, Lv, et al. conducted a systematic review and meta-analysis that enrolled 725 patients to evaluate the effects of bariatric surgery on the menstruation and reproductive-related hormones of obese women of childbearing age without PCOS and revealed that bariatric surgery led to a significant decrease in anti-Mullerian hormone (AMH) (MD = -0.40 ng/mL, 95% CI: -0.67–-0.13, P = 0.003) [14].

A meta-analysis by Tian, et al. enrolled 552 PCOS patients to evaluate the impact of bariatric surgery on PCOS. It showed that levels of AMH and LH decreased, while FSH and LH/FSH did not show significant changes during the 3-month follow-up. However, the lack of statistical significance may be due to the small sample size, high heterogeneity, and inadequate follow-up time [15].

According to a study by Al-Taee, et al. 60 obese women were enrolled in a cohort study to evaluate the levels of AMH in obese women before and after bariatric surgery during their reproductive age. The study showed a significant decrease in BMI and waist circumference at baseline value and post-operative value, as well as a significant decrease in AMH between baseline values and post-operative values (3.6 ± 2.92 *vs.* 3.27 ± 2.61) ng/ml [13].

However, some studies have reported decreased AMH concentrations after bariatric surgery [16-20]. Bhandari, et al. reported a 36% decrease in AMH concentration in women without PCOS at 6 months post-BS [21]. In a prospective study including 18 patients without PCOS and that underwent BS, Chiofalo, et al. reported significant variation in AMH at 1-year post-surgery [22].

In contrast to our findings, Al-Taee, et al. [13] revealed that there is a significant negative correlation between BMI and AMH level, whether before or after weight loss from Bariatric surgery. But this correlation is contradictory to our study and some other studies at base line value [19], this disparity may be attributed to sample size or duration of follow up. The effect of obesity in particular on AMH levels remains largely unclear. Obesity may indirectly affect AMH levels through its potential disruption of the ovarian follicular environment.

Moreover, Jamil, et al. [19] showed that AMH levels are not correlated with BMI, while Pilone, et al. in their Cohort study on of 53 women underwent laparoscopic SG. The AMH levels increased significantly at 6-month post SG, there was also an improvement in the regularity of menses [23].

Lv et al. [14] showed no significant difference in LH and FSH at pre- and postoperatively (MD=2.34 U/L, 95% CI: -0.93–5.62, P=0.16; MD=0.78 U/L, 95% CI: -0.26–1.82, P=0.14) respectively.

In concordance with our findings, Lv, et al. [14] revealed a significantly lower incidence of abnormal menstruation (relative risk: 0.40, 95% confidence interval [CI]: 0.20–0.79, P=0.008) after bariatric surgery

In support of our findings, Tian, et al. [15] conducted a meta-analysis that enrolled 552 patients with PCOS to assess the impact of bariatric surgery on PCOS patients and further explore the possible mechanism and revealed that the prevalence of preoperative menstrual irregularity and infertility significantly decreased after bariatric surgery.

In correlation with the menstrual pattern, our study results revealed that the cases with preoperative irregular menstruation had significant higher preoperative BMI, AMH and LH, as well as had significant lower preoperative FSH/LH and the cases with 3-months post-operative irregular menstruation had significant higher 3-months post-operative BMI and AMH (p value =0.013, 0.049).

These findings are in agreement with previous studies. Vincentelli, et al. [16] conducted a retrospective study that enrolled 39 women who underwent a sleeve gastrectomy or Roux-en-Y Gastric Bypass (RYGB) to evaluate changes in serum Anti-Mullerian Hormone (AMH) levels in reproductive-age severely obese women at baseline, and 6 and 12 months after bariatric surgery and revealed that the mean age 34.6 ± 1.1 years. The baseline mean AMH was 13.45 ± 1.90 pmol/L for all patients and Mean AMH concentration decreased significantly by 22.1%

at 6 months, and by 38.3% at 12 months compared to concentrations before surgery (p=0.002 and p=0.002), respectively.

Despite the decreased AMH after BS, Vincentelli, et al. [16] reported negative impact of BS on ovarian reserve which reflected the drastic reduction in AMH levels at 1 year after BS in reproductive-age severely obese women, which was not related to weight loss while our study followed up the patients for short period of 3 months.

However, Vincentelli, et al. [16] did not find any correlation between changes in BMI or EWL and changes in AMH, despite an average decrease of 14 points in BMI at 12 months. This discrepancy may be explained by the different criteria of the patients included in the study in which 74% of the patients received hormonal contraception and five patients were diagnosed with type 2 diabetes pre-operatively who excluded from our study.

They hypothesized that postoperative stress of growth follicles in ovaries may be the reason for the reduction in AMH values, indicating the need for prolonged observational studies in order to clarify observed changes [16].

Strengths and limitations of the study

The strength points of this study are that it is a prospective study design and has no patients lost to follow-up during the study period.

It is important to take into account the limitations of this study, such as its smaller sample size compared to previous studies and the fact that it was not conducted at multiple centers, which increases the risk of publication bias. Additionally, the follow-up period for patients after surgery was relatively short-term, which may underestimate the results of bariatric surgery on women's fertility, as most previous literature tracked outcomes for 6 to 12 months postoperatively.

Clinical implication of the study

Bariatric surgery can effectively improve menstruation and reproductive-related hormones for severely obese individuals. It is a viable option for obese patients with reproductive dysfunction who have failed to achieve therapeutic goals through lifestyle interventions and medications.

Recommendation for further studies; Long-term multi-centric studies with a larger number of patients are needed to give a clear role of bariatric surgeries on female fertility and ovarian reserve.

CONCLUSION

As evident from the current study, Antimullarian hormone, LH decreased after Bariatric surgery in reproductive age women with increased FSH, and there is improvement in cycle regularity.

Consequently, bariatric surgery could be effective in improving the menstruation and reproductive related hormones for severe obese individuals. Bariatric surgery may be a reasonable choice for obese patients with reproductive dysfunction who fail to achieve the therapeutic goals through a lifestyle intervention and medications.

As the AMH, LH and FSH levels were assessed 3 months postoperatively, longer follow-up period is essential to understand the impact of bariatric surgery on ovarian reserve. Moreover, further large-scale studies are needed to investigate the effect of bariatric surgery on AMH.

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