ASSESSMENT OF THE EFFECT OF LAPAROSCOPIC SLEEVE GASTRECTOMY ON ANTI-MULLARIAN HORMONE (AMH) LEVEL IN MORBID OBESE WOMEN (THE INITIAL EXPERIENCE IN KASR ALAINY HOSPITAL)

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ABSTRACT

Background: Distinguished from other procedures, sleeve gastrectomy seems to be the leading procedure in the near future There is a well– Established connection between obesity and adverse reproductive out-come in woman of reproductive age; the mechanism, however, is complex and Multifactorial Effect of bariatric surgery on fertility is still controversial: amelioration on ovarian function seems clear, but the reality on increasing of fertility is not scientifically confirmed similarly, effect on AMH after weight loss is not well-defined. Our aim is assess anti-mullarian hormone level changes in morbid obese women at reproductive age before & (3, 6 months) after laparoscopic sleeve gastrectomy and it,s reflect on fertility.

Patients and Methods: This case series study was conducted on 46 morbidly obese infertile married female patients for 2 years. They underwent laparoscopic sleeve gastrectomy. AMH level measured before and (3, 6) post the procedure.

Results: Forty-six female patients underwent laparoscopic sleeve gastretomy, AMH level decrease by 2ng/ml after 3 months and 4ng/ml after 6 months postoperative. Preoperative ovarian irregularities decreased from 85.7% to 21.7% at postoperative period .30.5% of the patients get pregnant after 1 year of follow up.

KEYWORDS

AMH , laparoscopic sleeve gastrectomy , BMI,obesity, ELISA

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INTRODUCTION

Overweight and obesity are significant and increasing public health challenges in both economically developed and developing regions of the world, with 33% of the world's adult population overweight or obese [1]. Metabolic and bariatric surgery is the only intervention that has been shown to have consistent, long-term weight loss results and significant improvements for co-morbid conditions in the severely obese population. [2]. sleeve gastrectomy seems to be the leading procedure in the near future. This is attributed to many factors, including relative simplicity of the procedure, lower cost, reasonable outcome in terms of weight loss and improvement of the associated comorbidities, and the available conversion options in case of unsatisfactory outcome [3]. Initiation and maintenance of reproductive function are related to an optimal body weight in females [4]. In 2008. Dag and In 2013 Malhotra published that, there is a well Established connection between obesity and adverse reproductive out- come In woman of reproductive age; the mechanism, however, Is complex and Multifactorial [5-6]. Effect of bariatric surgery on fertility is still controversial: amelioration on ovarian function seems clear but the reality on increasing of fertility is not scientifically confirmed. Similarly, effect on AMH after weight loss is not well defined by different Authors [7].

PATIENTS AND METHODS:

Patients and study design: This case series study was conducted on 46 infertile (2 years) morbidly obese female patient in reproductive age (18 to 40years) with BMI more than 40 or 35 with comorbidities indicated for laparoscopic sleeve gastrectomy in Cairo University hospital in the period between March 2020 and March 2021. • Pregnant Candidates or with a history of 6 months or more using hormonal contraception, Any endocrine disturbances leading to obesity and PCO patients were excluded from the study. It was approved by the Research Ethics Committee of the Faculty of Medicine at Cairo University in July 2020, (IRB: MD-156-2020)

reoperative patient data were collected age, menarche, residence, educational level, fertility, menstrual cycle history. Clinical evaluation aimed at assessment of degree of obesity and detection of associated comorbidities like hypertension and diabetes mellitus. - Assessment of anthropometric data such as height and weight to calculate body mass index. Hormonal and biochemical analysis were collected foe assessment

of AMH by ELISA and routine investigation were done (ECHO, CXR, CBC, INR, abdominal U/S) All the patients were consented to a laparoscopic sleeve gastrectomy. They were informed in detail about the operative strategy of having 5 port incisions and using EGA staplers and may convert to open if facing complication that cannot controlled by laparoscope.

➢ **Surgical technique:**

- After prophylactic antibiotics, Ampicillin-Sulbactam (Unasyn) 3gm intravenously, and general anesthesia were administered, the patient was placed in the French position with Elastic compression stockings were placed on the legs.
- The operation was done with three surgeons; the surgeon was standing between the patient's legs. The camera man was standing on the right side of the patient. The assistant was standing on the left side.
- Laparoscopic technique began with CO2 insufflations by veress needle until the working pressure reached 14 mm Hg. The insufflation site was Palmers point, 2 cm below the left costal margin along the midclavicular line.
- The operation was carried out using 5 ports. The first trocar for the optical port was placed slightly above and to the left of the umbilicus using a 10 mm port by the closed technique. We used 30 degree optic.
- After entering abdominal cavity, the position of Veress needle was inspected as well as the possible organ injury. The procedure continued by exploration of the abdominal cavity, with particular attention to potential adhesions, mobility of the omentum and small intestine mesentery.
- A two 12 mm ports or one 15mm and one 12 mm were placed in both right and left hypochondria of the patient in the mid clavicular line respectively as the surgeon's working hands and another 5 mm or 10 mm according to the liver size in the epigastrium as a liver retractor.A fifth 5 mm port was placed in left anterior axillary line for the assistant **(figure 1).**

Figure 1: (port sites of laparoscopic sleeve gastrectomy)

- In steep reverse Trendelenburg position, dissection began with opening of the greater omentum using Ligasure (Autosuture Bariatrics Covidien) along the greater curvature of the stomach approximately 6 cm proximal to the pylorus.
- The dissection continued cephalad to the gastroesophageal junction and the right crus. The short gastric vessels were ligated carefully, and care was taken to avoid injury to the spleen **(figure 2)**
- The right crus was completely free of any attachments to avoid leaving a posterior pouch when constructing the sleeve in this region. The dissection was completed by freeing any posterior attachments of the stomach to the pancreas.

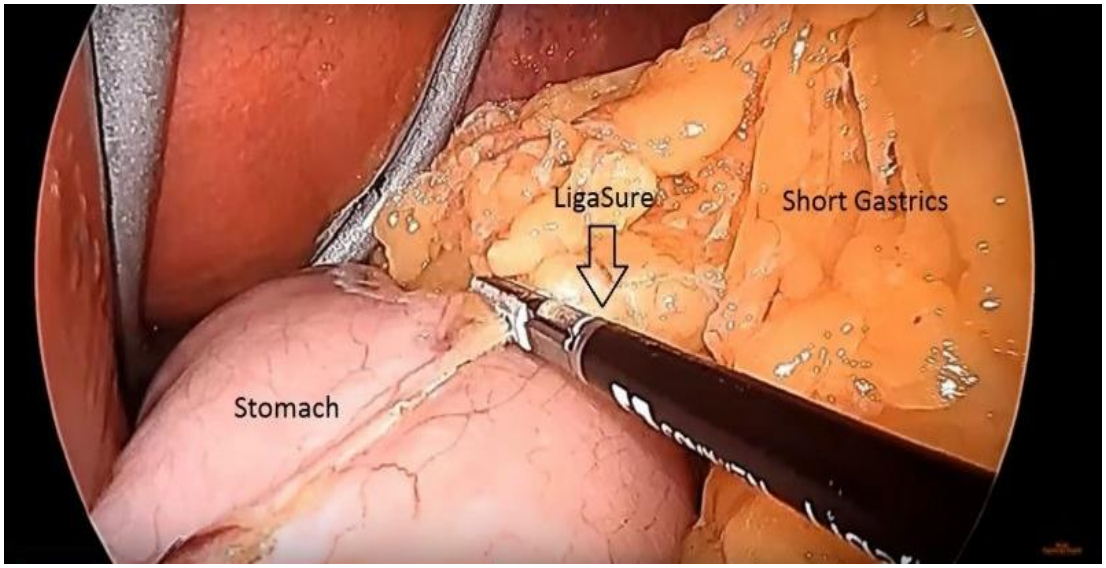

Figure 2: (laparoscopic view of gastrocolic ligament dissection during sleeve gastrectomy)

- Once the dissection part was over, a 36 Fr bougie was introduced orally by the anaesthisiologist through the oesophagus and inside the stomach.
- The surgeon then guided it along the lesser curvature and into the pyloric channel and duodenal bulb. The greater curvature of stomach was transected by a linear stapler (Echelon or Covidien 60 Endopath Stapler and Cutter) from antrum (6 cm from pylorus) to angle of His **(figure 3).**

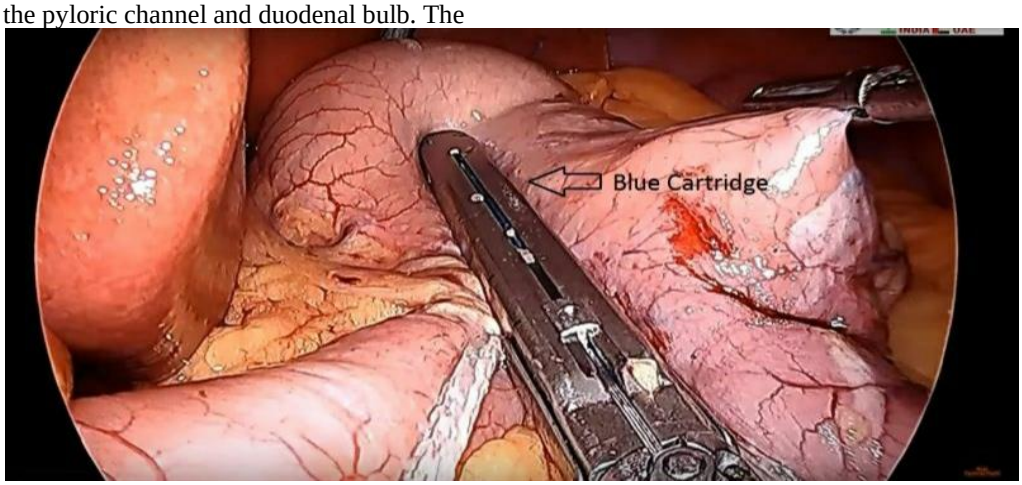

Figure 3: (laparoscopic view of gastric dissection& stapling during sleeve gastrectomy)

- A methylene blue test was applied after stapling to check the integrity of the staple line then drain was placed.

Postoperative care

- Patients were encouraged to move out of bed few hours after surgery. All patients were given Ampicillin-Sulbactam (Unasyn) 3gm, opioids, proton pump inhibitors and antiemetics.
- All patients started oral fluids (if tolerated) after confirming that there is no leakage in intraoperative methylene blue test. Special attention was taken to staple line hemorrhage, leaks, and wound infection. The drain was removed before discharging the patients.
- The patients were on a liquid diet only for two weeks that is then advanced to semi-solid diet and mashed food for another two weeks. They are then advanced to a regular healthy diet.
- Proton pump inhibitors were given for 2months.Antihypertensive and oral hypoglycemic agents were continued and adjusted by primary care physician. Patients were given twice daily multivitamins, vitamin D and calcium supplements.
- Anticoagulant (clexane)were given subcutaneously once daily for two weeks(40mg) as prophylaxis of thromboembolism.
- All patients were followed up for early post-operative complications (<30 days) like bleeding, leaks and infections.
- After 3and 6 months blood sample were taken for measuring AMH and detection of any ovarian cycle irregularities and pregnancy by asking the patients.

RESULTS

Forty_six infertile morbid obese female patient underwent laparoscopic sleeve gastrectomy in the period between March 2020 and march 2021. **Table 1** shows the patients' demographic characteristics. Their ages ranged between 20 and 40 years old with mean age 32 years old BMI range between 35 and 50 kg/m2 with mean 39 kg/m2. Their preoperative AMH level between .7and 19.1 ng/ml with mean 10.4ng/ml. The average postoperative (3 months) AMH level ranged between 1 cm to 18.1ng/ml and after 6 months between 1.5 to 15.9 ng/ml.

Table 1: demographic Characteristics of the studied patients

	mean	median	minimum	maximum	Standard deviation	Percentile 25	Percentile 75
Age	32	30	20	40	7	27	38
BMI	39	39	35	50	4	37	41
AMH preoperative (ng/ml)	10.4	10	7	19.1	5.3	5.2	15
AMH 3months (ng/ml)	8.4	9.1	1	18.1	4.4	3.9	11.2
AMH 6months (ng/ml)	6.4	6.7	1.5	15.9	3.3	3.2	8.5

Correlation between preoperative and postoperative ovarian irregularities **Table 2**. Most of the patients complained from ovarian irregularities (Dysmenorrhea, Menorrhagia, and Amenorrhea) **85.7%** were successfully decline to **21.7%** at postoperative follow up with ***P VALUE (0.001***

Table 2: Correlation between preoperative and postoperative ovarian irregularities

			Pre-operative ovarian irregularities		Total	P value
			Yes	No		
Post-operative ovarian irregularities	Yes	Count	4	6	10	0.001
		% within Pre-operative ovarian irregularities	14.3%	33.3%	21.7%	
	No	Count	24	12	36	
		% within Pre-operative ovarian irregularities	85.7%	66.7%	78.3%	
Total		Count	28	18	46	
		% within Pre-operative ovarian irregularities	100.0%	100.0%	100.0%	

Correlation between AMH and pregnancy **table 3.** Fourteen female patients in our study get pregnant at 1 year of follow up.

Table 3: AMH and pregnancy correlation

	Post-operative 1 year get pregnant	**N**	**Mean**	**St. Deviation**
AMH 3months	**Yes**	**14**	**8.671**	**4.2052**
	No	**32**	**8.228**	**4.4864**
AMH 6months	**Yes**	**14**	**6.300**	**2.4280**
	No	**32**	**6.394**	**3.6828**

DISCUSSION:

Bariatric surgery is a field in rapid evolution with continuous attempts by surgeons to offer patients procedures that achieve their needs and objectives. Laparoscopic Sleeve Gastrectomy has established itself as a definitive weight loss procedure across the globe. Recently, it has taken over the number one position from the current 'gold standard'—Roux-en- Y Gastric bypass. This is attributed to relative technical ease of this procedure, excellent efficacy with combination of restrictive and hormonal effects and minimal anatomic changes [8].

Obesity-related gynecological alterations are very common in women population, although many diseases are multifactorial and resolution is partial after weight loss. It has frequently been linked, in Occidental countries, to low percentage of spontaneous pregnancies and it has been linked to worse outcomes in women that were undergoing fertilization in vitro with Embryo Transfer (FIVET). It is known that the obesity impairs the ovarian function [9].

In the last year, a great number of studies have been made to Established if the weight loss, post-bariatric surgery, can improve the fertility increasing the probability to have a pregnancy. the researchers of Institute '**Southern California'** examined more than 1000 hospitals to establish the number of women in reproductive age undergoing bariatric surgery1998–2005 and to evaluate the impact of surgery on pregnancy, on the risk factors before pregnancy, and the consequences of pregnancy, included neonatal outcomes. It has been demonstrated that there is an important increase of fertility in women undergoing bariatric surgery; it demonstrated an increase number of pregnancies after weight loss, post Gastric banding and gastric bypass [10].

Another retrospective study carried out by **Musella et al** evaluated the improvement in fertility on 110 infertile women treated with an intragastric balloon, lap band surgery, sleeve gastrectomy, and gastric bypass in obesity women that could not have pregnancy [11]. An interesting study about anovulation question demonstrated that the 71.4% of obese women undergoing bariatric surgery have gained regular menstrual cycle; interestingly, 28 patients that remain anovulatory had weight loss less than the patients that regained ovulation [12].

Our analysis of obesity-related ovarian alterations strictly depended from the evaluation of AMH that can be considered a sensitive index to evaluate ovarian function. Strict level of AMH depends on cell populations of growing follicles and the same AMH supervises the recruitment and the growth of primary follicles [13]. In adults, the AMH level is representative of the quality and of the

number of ovarian pool [14]. It is expressed very well during the reproductive time and then it is undetectable after the menopause [15]. The measure of AMH level, in association with the count of antral follicles, is proposed as the best indirect method for estimating the ovarian reserve [16]. The advantages of the measure of AMH are minimally invasive procedure and low variability intra- and inter-menstrual cycles that permits dosage of this hormone every time of the menstrual cycle [17].

In this case theory evaluation, we observed a progressive decrease of AMH level in obese women after LSG that became significant at 6 months after LSG. This can explain another possible effect of bariatric surgery strictly related to EWL%. Like other gynaecological alterations for which we observed important amelioration this decrease may explain a significant effect on women fertility with an objective effect on ovarian function. This results agreed with **Nilsson-Condori E, Hedenbro JL et al**.In their study of Impact of diet and bariatric surgery on anti- Mullarian hormone levels. Demonstrated that AMH levels increased after very low calorie diet (VLCD) before surgery and decreased at 6 and12 months after Roux-en-Y gastric bypass (RYGB), beyond expected normal age-related decline [18].

Similar results were recently reported by an Italian group in a pilot study on 39 patients after LSG and gastric bypass [19]. **Bhandari** [20] and **Chiofalo** [21] evaluated results on AMH after bariatric surgery in patients with PCOS. Since data by **Chiofalo** evidenced a trend towards reducing AMH in non-PCOS patients, at 6-months follow up, we attended to this early follow up, in order to confirm this reduction We did not consider PCOS as a specific inclusion criteria, although this disease is strictly related to high-serum AMH levels because this subgroup presented a peculiar higher value of AMH, also in non-obese women, and this was evaluated as a possible bias.

Another study that coincide with ours to **Maha Sahab , Hanan A. Al-Taee et al**[22]. In their study of Impact of Bariatric surgery on anti mularian hormone in reproductive age women, the results of study suggest that Anti -mullarian hormone decreases after Bariatric surgery in reproductive age women, and there is improvement in cycle regularity. According to their study there is a significant decrease in WC, HC and WHR at baseline value and post-operative value. Regarding waist circumference, it is a prognosticator for all morbidity causes as it offers a clue about the abdominal fat as reported by many research groups [23]. Their results and ours also corresponding to **Wei et al.** [24], this reduction may be due to the fact that postoperatively have a low calorie intake whatever the type of surgery, so the body uses the storage in the adipose tissue (lipolysis) and later on the muscle and these are accumulated mainly in the abdomen.

Another explanation for the reduction in AMH level after LSG depending on the relative contribution of adipose tissue to whole body steroid metabolism. BMI is positively associated with tissue levels of estrogens. Thus, as fat mass increases in obesity, aromatase expression and, consequently, estrogen levels are also elevated, an effect that is more prominent in postmenopausal women as after menopause adipose tissue is the primary source of estrogen production in the body.94–96 Adipose tissue can contribute up to 100% of circulating estrogen in postmenopausal women and 50% of circulating testosterone in premenopausal women. The ratio of 17βHSD to aromatase is positively correlated with central adiposity, implicating increased local androgen production in visceral adipose tissue.93, 97 Thus; adipose tissue is an important site for both metabolism and secretion of sex steroids [25].

In addition to excess estrogen, a decrease in circulating progesterone levels in obese women, this lack of progesterone due to anovulation, similar to that observed in polycystic ovarian syndrome (PCOS) and can contribute to endometrial cancer risk. Expression and activity of the progesterone receptor are also modulated by a variety of factors, including microRNAs and epigenetic factors that are frequently dysregulated in cancer [26]. Differences in the levels of AMH and progesterone released into the medium by cultured granulosa cells as well as in AMH gene expression were observed between granulosa cells obtained under natural and stimulated IVF protocols. The results suggest that artificial gonadotropin stimulation may have an effect on the intra-follicular metabolism. A significant positive correlation between AMH and progesterone may suggest progesterone as a factor influencing AMH action . so by decreasing adipose mass normal balance between estrogen and progesterone will restored and eventually positively affect AMH[27].

There is a significant decrease in AMH between baseline values and post-operative values (3.6 ± 2.92 vs 3.27 ± 2.61) ng/ml. **Mehri** (2009), **Chiofalo** (2016), and their teams have similar results as their research and ours [28]. The reduction of AMH levels after a surgical weight loss in obese females without PCOS is difficult to explain. Indeed, one would expect an increment in AMH serum level after weight reduction according to improvement of fertility while we found the contrary **Sheiner** and his colleagues in2006, reported a higher use of infertility treatments in patients who previously underwent Bariatric surgery compared with the normal females (not obese) [29]. These investigators implied that the need for fertility treatments reflects a possible contribution of the Bariatric surgical intervention to subfertility. The

reduction of AMH after surgical weight loss related to body weight and its constituent components, which is playing an important role modulating reproductive development and functioning [30].vitamins and minerals that are commonly deficient in this circumstance include vitamin B12, calcium, vitamin D, thiamine, folic acid, iron, zinc, and magnesium [31]. Low AMH may be related to a result of hormonal imbalance in female's body, and she has to consider this problem as overall deterioration of her health due to poor dietary and lifestyles She has been following unknowingly.

There is a possible explanation: AMH drop may be related to an effect of the surgery, like malabsorption of critical precursors that may affect AMH gene expression, or it may be a transient finding due to the stress of the surgery itself on the ovaries [32].

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. Studies have shown that different biochemical markers involved in both inflammatory and oxidative stress responses have been increased in the follicular fluid of obese women compared to their non-obese counterparts [33].

CONCLUSION

Sleeve gastrectomy has demonstrated an overall improvement of the quality of life in morbidly obese women. The results of our study have confirmed a significant decrease of AMH level at 3 and 6 months post-operative.

The weight-loss has determined regularization of menstrual cycle as most of our patients that have menstrual irregularities, their symptoms improved after the operation. Some of our patients get pregnant at 1 year of follow up after the operation and this illustrate that decreasing of body weight have a direct relation to increase fertility

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