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TESI DI DOTTORATO

## DOES BARIATRIC SURGERY IMPROVE ASSISTED REPRODUCTIVE TECHNOLOGY OUTCOMES IN OBESE INFERTILE PATIENTS?


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## **Background**

*Quod aliis cibus est aliis fuat acre venenum.*

*(Titus Lucretius Carus)*

Weight loss in overweight and obese women has been shown to increase natural conception rates and to improve the course of pregnancy, but there are very few studies investigating the impact of weight reduction in overweight and/or obese women prior to undergoing assisted reproductive technology (ART) treatment. It is rationale to hypothesise that these benefits would also be applicable to women who conceive via ART. Additionally, it is important to highlight that one increasingly common treatment option to obtain weight loss is bariatric surgery. In this setting, the benefits of bariatric surgery in improving fertility status have been well shown in the literature. However, data regarding the safety and efficacy of bariatric surgery on in vitro fertilization outcomes are still controversial.

Prompted by the before-mentioned observations, we aimed to investigate the effect of bariatric surgery on ART outcomes.

To better identify the impact of bariatric surgery on male and female infertile patients, we have separately analysed data about man and women undergoing ART treatment after bariatric surgery.

# Impact of Bariatric Surgery on Infertile Women

## Materials and Methods

### Study Design

This was a retrospective study. Utilizing prospectively maintained databases, all consecutive women who underwent an ART treatment from September 2005 to August 2015 were identified for inclusion in this study. The study population consisted of all obese female patients with a history of ART failure (at least one unsuccessful cycle) that underwent ART treatment cycles both prior to and following bariatric surgery.

ART outcomes before and after bariatric surgery were compared. We considered data from the last cycle (the cycle immediately before bariatric surgery), even for patients who underwent more than one. To exclude any bias related to time interval between the cycles analysed, we included only patients who underwent the cycle after bariatric surgery within 24 months from the cycle before. Only patients with idiopathic infertility without male infertility were included in order to compose an ideal group of patients that does not influence oocyte retrieval and oocyte/embryo quality.

In addition, bias related to advanced maternal age and poor ovarian reserve was excluded, including only women ≤38 years old with an anti-mullerian hormone

(AMH) plasma level >2 ng/ mL and excluding women with a prior poor response to con- trolled ovarian stimulation (COH) (peak E2 < 500 pg/mL at triggering or less than 3 mature oocyte retrieved). On the other hand, to minimize the bias related to the use of different surgical technique and post-surgical managements, only patients who underwent sleeve gastrectomy were evaluated.

Outcomes of ART treatment were evaluated comparing the results before and after bariatric surgery Furthermore, separate analyses have been performed evaluating only the cycles performed after bariatric surgery in order to assess any difference between pregnant and non-pregnant patients.

**Intervention**

Sleeve gastrectomy was performed according to a standardized procedure. The intervention began with the insertion of a supra-umbilical optical trocar and the placement of four secondary trocars. The greater curvature of the stomach was resected using the sealed envelope system, starting 7 cm from the pylorus and extending up to the angle of His. All adhesions to the posterior gastric wall were released. A 34-Fr Faucher tube was inserted prior to the gastric section. The section was performed with a mechanical stapler.

COH protocols employed included only GnRH antagonist protocol. Gonadotropins used included only recombinant FSH, to exclude any bias due to different protocols. In details, we included only cycles when ovarian stimulation was performed using FSHr (Gonal-F: Merck Serono S.p.A. Roma, Italia) 200– 350 UI daily for 11–15 days, starting on the second day of menstruation and continued until at least two follicles ≥18 mm were detected. The starting dose (200–350 UI) depends on the patient's age and ovarian response. Flexible multiple-dose GnRH antagonist protocol was initiated using Cetrorelix 0.25 mg subcutaneous daily (Cetrotide, Merck Serono S.p.A. Roma, Italia) once the leader follicle reached 14 mm in mean diameter and continued until HCG administration. To assess follicular maturation and endometrial thickness, the clinicians performed several trans-vaginal ultrasound scan and measured serial serum E2 levels. Ovulation triggering was made 35–36 h prior to oocyte retrieval, using chorionic gonadotropin 10,000 UI intramuscularly injection (Gonasi Hp, Ibsa Farmaceutici, Lodi, Italy). In our clinic, according to literature, couples with unexplained infertility underwent both ART procedures: in vitro fertilization (IVF) and intra-cytoplasmic sperm injection (ICSI). In details, ICSI was performed in at least half of the oocytes retrieved, to achieve some fertilized embryos and avoid a total fertilization failure.

Concerning oocyte evaluation and handling, on Day 0, cumulus oocyte complexes (COCs) have been denuded 2– 3 h after the retrieval. Mature metaphase II oocytes, showing a 'normal-looking' cytoplasm, the first polar body, proper zona pellucida thickness and perivitelline space have been classified as top-quality oocytes.

Embryo quality was assessed daily by the embryologist or followed by time lapse technology. Embryo/blastocyst grading has been performed according to the Alpha European Society of Human Reproduction and Embryology ESHRE Consensus Meeting (Istanbul, 2010). In particular, an embryo is defined as a top quality if it shows (i) two pronuclei (2PNs) 16–18 h after ICSI, (ii) 4 or 5 blastomeres on days 2 and 7 or more on day 3 (with stage specific cell size for the majority of the cells), (iii) compacted or compacting morula with inclusion of virtually all the embryo volume on day 4, (iv) a fully expanded through to hatched blastocyst (ICM: prominent, easily discernible, many cells/TE: many cells forming a cohesive epithelium) 116 ± 2 h post-ICSI.

Embryos were transferred on blastocyst stage (after 5 or 6 days of culture) with an AccessET Curved Embryo Transfer Catheter (K-JETS-7019-ET, Cook Medical, Bloomington, IN, USA). The 'freeze-all' approach was used in high-risk patients as a strategy for minimizing risk of ovarian hyper-stimulation syndrome (OHSS). Luteal-phase support was provided with vaginal progesterone (Progeffik, Effik Italia Spa, Cinisello Balsamo, MI, Italy), 200 mg three times daily until the day of β-HCG assay and, in the presence of pregnancy, was continued until 12 weeks of gestation.

β-Human chorionic gonadotrophin (β-hCG) has been evaluated from serum or urine sample 12 days after embryo transfer. A β-hCG serum value >49 m IU/m has been considered as positive. Two weeks after the positive pregnancy test, a transvaginal ultrasound is performed to confirm the presence of an intrauterine gestational sac—defined as positive clinical pregnancy rate.

## Outcomes

Data on patient age, BMI, and variables related to infertility treatment were collected from the files.

Clinical pregnancy was attested identifying a gestational sac at 6–7 weeks of gestation, by ultrasound. Live births were defined by the birth of at least one live infant. The cumulative live-birth rate was defined as the proportion of transfers resulting in at least one live birth, after the first embryo transfer attempt or after subsequent transfers of the frozen–thawed cycles. In details, IVF outcomes were measured by the duration and dose of gonadotrophins used in cycle, the measurement of day 3 FSH; the antimullerian hormone (AMH) dosage; the number of follicles >15 mm; the number of retrieved and fertilized oocytes; the number of metaphase II (MII), metaphase I (MI) and germinal vesicle (VG) oocytes; the number of embryos obtained; the number of top-quality oocytes and embryos; the number of transferred embryo; the pregnancy rate (PR); the live birth rate (LBR) and the miscarriage rate (MR).

**Statistical Analysis**

Statistical analysis was performed with SPSS 16 (SPSS Inc., Chicago, IL, USA). Continuous data are expressed as the mean ± SD, with categorical variables expressed as a percent- age. To compare continuous variables, an independent sample t test was performed. The Wilcoxon test for paired samples was employed as a non-parametric equivalent of the paired sample t test used for continuous variables. The $\chi^2$ test was employed to analyse categorical data. When the minimum expected value was <5, Fisher's exact test was used. All results are presented as two-tailed values with statistical significance if p values were <0.05.

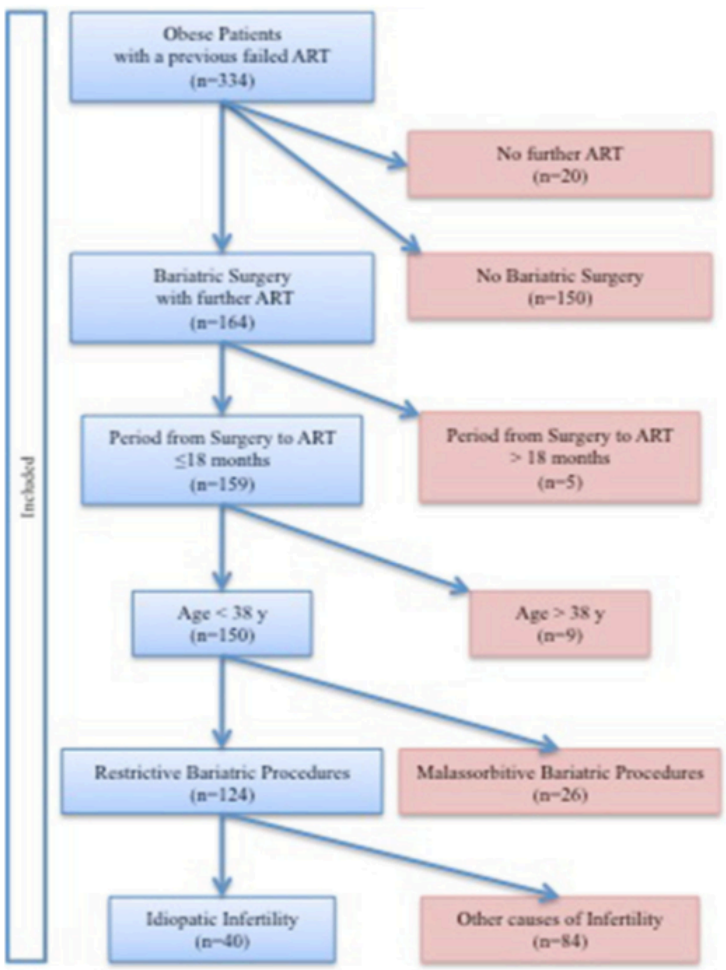
## Results

Obese patients (334) with a previous failed ART cycle were identified. Twenty out of the 334 patients did not undergo further ART. Among the 314 patients who were admitted to ART after the first failure, 150 were excluded because of not undergoing bariatric surgery, 5 women because of ART from surgery >18 months, 9 because of age >38 years old, 26 be- cause of malabsorptive bariatric procedures performed and 84 couples because of no idiopathic infertility. Thus, 40 women with idiopathic infertility were included in our study (Fig. 1).

**Appendix**

**Fig, 1**

Patients included in the study



The BMI significantly decreased from 40.7 ± 2 to 35 ± 2.6 after surgery ($p < .001$). Similarly, the weight significantly de- creased after surgery (from 113.5 ± 9.6 to 97.3 ± 8.9 kg; $p < .001$). The mean age increased from 31.4 ± 4.7 to 32.4 ± 4.4 years in the interval between the ART cycles before and after bariatric surgery without any statistical difference

($p = 0.3$). No significant difference was found in the distribution of FSH or AMH dosage before and after surgery (Table 1).

**Table 1** Patients' characteristics before and after surgery

| | Before surgery (±SD) | After surgery (±SD) | *p* |
|---|---|---|---|
| Age | 31.4 (±4.7) | 32.4 (±4.4) | 0.3 (n.s.) |
| BMI | 40.7 (±2) | 35 (±2.6) | <0.001 |
| FSH | 5.9(±1) | 6.1 (±0.9) | 0.2 (n.s.) |
| AMH | 3.5 (±1.0) | 3.4 (±1.1) | 0.7 (n.s) |

We registered a significant decrease in the total number of gonadotropin units required and in the length of stimulation in IVF cycle following bariatric surgery ($p = .001$), with an increase of the number of follicles ≥15 mm ($p = .005$), of the number of retrieved oocytes ( $p = .004$), of the number of top-quality oocytes ($p = .001$) and of the number of MII oocytes ($p = .008$). More oocytes were fertilized (4.2 ± 1.7 before surgery vs 5.3 ± 2.4 after surgery; $p = .02$). After surgery, we have registered also a better number of top-quality embryos (0.5 ± 0.6 pre-surgery vs 1.1 ± 0.9 post-surgery; p = .003). Pregnancy rate following the bariatric surgery increased to 15/40 (37.5%) (p < .001), and LBR increased to 14/40 (35%) in the post-surgery group (p < 0.001) (Tables 2 and 3).

**Table 2** Results of ovarian stimulation before and after surgery

| | Before surgery | After surgery | *p* |
|---|---|---|---|
| Total dose gonadotropin (U) | 4136.87 (±943.05) | 3489.37 (±734.58) | 0.001 |
| Duration of stimulation (days) | 13.17 (±1.4) | 12.12 (±1.3) | 0.001 |
| Number of follicles >15 mm (n) | 6.4 (±1.6) | 7.8 (±2.7) | 0.005 |
| Retrieved oocytes (*n*) | 6.6 (±1.7) | 8.1 (±2.5) | 0.004 |
| MII oocytes (*n*) | 5.5 (±1.6) | 6.9 (±2.8) | 0.008 |
| TOP quality oocytes | 1.8 (±1.2) | 3.3 (±2.4) | 0.001 |
| MI oocytes (*n*) | 0.9 (±0.7) | 0.7 (±0.6) | 0.28 (ns) |
| VG oocytes (*n*) | 0.2 (±0.4) | 0.3 (±0.6) | 0.5 (ns) |

**Table 3** IVF outcomes before and after surgery

| | Before surgery (±SD) | After surgery (±SD) | *p* |
|---|---|---|---|
| Fertilized oocytes (*n*) | 4.2 (±1.7) | 5.3 (±2.4) | 0.02 |
| Fertilization rate (%) | 0.7 (±0.1) | 0.7 (±0.1) | 0.8 (ns) |
| Total number of embryos obtained (*n*) | 2.4 (±0.7) | 3.1 (±1.4) | 0.009 |
| TOP quality embryo (*n*) | 0.5 (±0.6) | 1.1 (±0.9) | 0.003 |
| Transferred embryo (*n*) | 1.8 (±0.9) | 2 (±0.7) | 0.2 (ns) |
| Pregnancy rate (%) | 0 | 15/40 | <0.001 |
| Live birth rate (%) | 0 | 14/40 | <0.001 |
| Miscarriage rate (%) | 0 | 1/40 | 1 (ns) |

One out of the 40 women (2.5%) had a miscarriage in post-surgery group and a suction curettage was performed. No ectopic pregnancy occurred.

In order to obtain a critical analysis of data and to understand if there was a factor involved more than the other in the pregnancy outcomes, we compared all the previous mentioned parameters in a separate analysis comparing pregnant and non-pregnant women after surgery.

The BMI was significantly lower in the group of patients who obtained a pregnancy after surgery (32.8 ± 2.3 vs 36.3 ± 1.8; $p < .001$). Of interest, Youden's index showed that the best cut-off for the prediction of pregnancy was a BMI value of <34.5 units.

Age, FSH level and AMH dosage were not statistically different in the two groups (Table 4).

**Table 4** Patients' characteristics in pregnant and non-pregnant women

| | Pregnant (±SD) | Non-pregnant (±SD) | *p* |
|---|---|---|---|
| Age | 31.4 (±5.3) | 33 (±3.8) | 0.2 (ns) |
| BMI | 32.8 (±2.3) | 36.3 (±1.8) | <0.001 |
| FSH | 6 (±1) | 6.2 (±0.9) | 0.6 (ns) |
| AMH | 3.5 (±1.2) | 3.3 (±1.1) | 0.7 (ns) |

No significant difference was found in the pregnant and non-pregnant group in the distribution of total dose gonadotrophins; duration of stimulation; number of follicles >15 mm, retrieved oocytes; MII, MI and VG oocytes; fertilized oocytes and the number of transferred embryos. Although it is not statistically significant, a trend toward better top-quality oocytes(2.9±1.7vs2±1.2;p=0.08)and embryos(1.1±0.8vs o.6 ± 0.6; p = 0.058) has been identified (Tables 5 and 6).

**Table 5** Results of ovarian stimulation in pregnant and non-pregnant women

| | Pregnant | Non-pregnant | *p* |
|---|---|---|---|
| Total dose gonadotropins (U) | 3420 (±716.5) | 3532 (±756.6) | 0.6 (ns) |
| Duration of simulation (days) | 12.4 (±1.2) | 11.9 (±1.3) | 0.3 (ns) |
| Number of follicles >15 mm (*n*) | 6.8 (±1.5) | 6.8 (±1.7) | 0.9 (ns) |
| Retrieved oocytes (*n*) | 7.2 (±2.3) | 7 (±1.6) | 0.8 (ns) |
| MII oocytes | 6.4 (±2.3) | 6 (±1.5) | 0.5 (ns) |
| Top-quality oocytes (*n*) | 2.9 (±1.7) | 2 (±1.2) | 0.08 (ns) |
| MI oocytes (*n*) | 0.6 (±0.8) | 0.8 (±0.6) | 0.4 (ns) |
| VG oocytes (*n*) | 0.1 (±0.3) | 0.2 (±0.4) | 0.4 (ns) |

**Table 6** IVF outcomes in pregnant and non-pregnant women

| | Pregnant (±SD) | Non-pregnant (±SD) | *p* |
|---|---|---|---|
| Fertilized oocytes (*n*) | 4.5 (±2.2) | 4.4 (±1.3) | 0.9 (ns) |
| Fertilization rate (%) | 0.6 (±0.1) | 0.7 (±0.1) | 0.1 (ns) |
| Total n. of embryos obtained (*n*) | 2.7 (±1.2) | 2.4 (±0.8) | 0.4 (ns) |
| TOP quality embryos (*n*) | 1.1 (±0.8) | 0.6 (±0.6) | 0.058 |
| Transferred embryos (*n*) | 1.7 (±0.5) | 2 (±0.8) | 0.2 (ns) |

# **Impact of Bariatric Surgery on Infertile Men**

## Materials and Methods

### Study Population

For this retrospective study, a prospectively maintained database was used and all consecutive men who was involved in an ART treatment from September 2016 to August 2020 were identified for inclusion in this study. The study population consisted of all obese male patients with a history of ART failure (at least one unsuccessful cycle) that underwent ART treatment cycles both prior to and following bariatric surgery.

We considered data from the last cycle (the cycle immediately before bariatric surgery), even for patients who underwent more than one. To exclude any bias related to time interval between the cycles analysed, we included only patients who underwent the cycle after bariatric surgery within 24 months from the cycle before. In addition, bias related to erectile disfunction or follicle-stimulating hormone (FSH), prolactin (PRL), estradiol (E2) and Glucose (GLU) levels were excluded, including only man with all these normal parameters. On the other hand, to minimize the bias related to the use of different surgical technique and post-surgical managements, only patients who underwent laparoscopic sleeve gastrectomy (LSG) were evaluated.

Outcomes of ART treatment were evaluated comparing the results before and after bariatric surgery.

**Bariatric procedure**

LSG was performed according to a standardized procedure. The intervention began with the insertion of a supra-umbilical optical trocar and the placement of four secondary trocars. The greater curvature of the stomach was resected using the sealed envelope system, starting 6 cm from the pylorus and extending up to the angle of His. A 36-Fr orogastric tube was inserted prior to the gastric section. The section was performed with a mechanical stapler.

**ART procedure**

We included only cycles when ovarian stimulation was performed using FSHr (Gonal-F: Merck Serono S.p.A. Roma, Italia) 200–350 UI daily for 11–15 days, starting on the second day of menstruation and continued until at least two follicles ≥18 mm were detected. Flexible multiple-dose GnRH antagonist protocol was initiated using Cetrorelix 0.25 mg subcutaneous daily (Cetrotide, Merck Serono S.p.A. Roma, Italia) once the leader follicle reached 14 mm in mean diameter and continued until HCG administration. Ovulation triggering was made 35–36 h prior to oocyte retrieval, using chorionic gonadotropin 10,000 UI intramuscularly injection (Gonasi Hp, Ibsa Farmaceutici, Lodi, Italy). Couples with unexplained infertility underwent both ART procedures: in vitro fertilization (IVF) and intra-cytoplasmic sperm injection (ICSI). In details, ICSI was performed in at least half of the oocytes retrieved, to achieve some fertilized embryos and avoid a total fertilization failure. Embryo quality was assessed daily by the embryologist or followed by time lapse technology. Embryo/blastocyst grading has been performed according to the Alpha European Society of Human Reproduction and Embryology ESHRE Consensus Meeting (Istanbul, 2010). Embryos were transferred on blastocyst stage (after 5 or 6 days of culture) with an AccessET Curved Embryo Transfer Catheter (K-JETS-7019-ET, Cook Medical, Bloomington, IN, USA). The 'freeze-all' approach was used in high-risk patients as a strategy for minimizing risk of ovarian hyper-stimulation syndrome (OHSS).

**Outcomes**

Pre- and post-surgery data on patient age, BMI, and variables related to male fertility (semen volume, concentration, motile sperm count and sperm morphology) were collected from the files. Moreover, IVF outcomes previous and after bariatric surgery were measured by: the number of metaphase II (MII) oocytes; the number of top-quality oocytes and embryos; the number of fertilized oocytes; the number of transferred embryo; the implantation rate (IR); the pregnancy rate (PR); the live birth rate (LBR) and the miscarriage rate (MR). Clinical pregnancy was attested identifying a gestational sac at 6–7 weeks of gestation, by ultrasound. Live births were defined by the birth of at least one live infant.

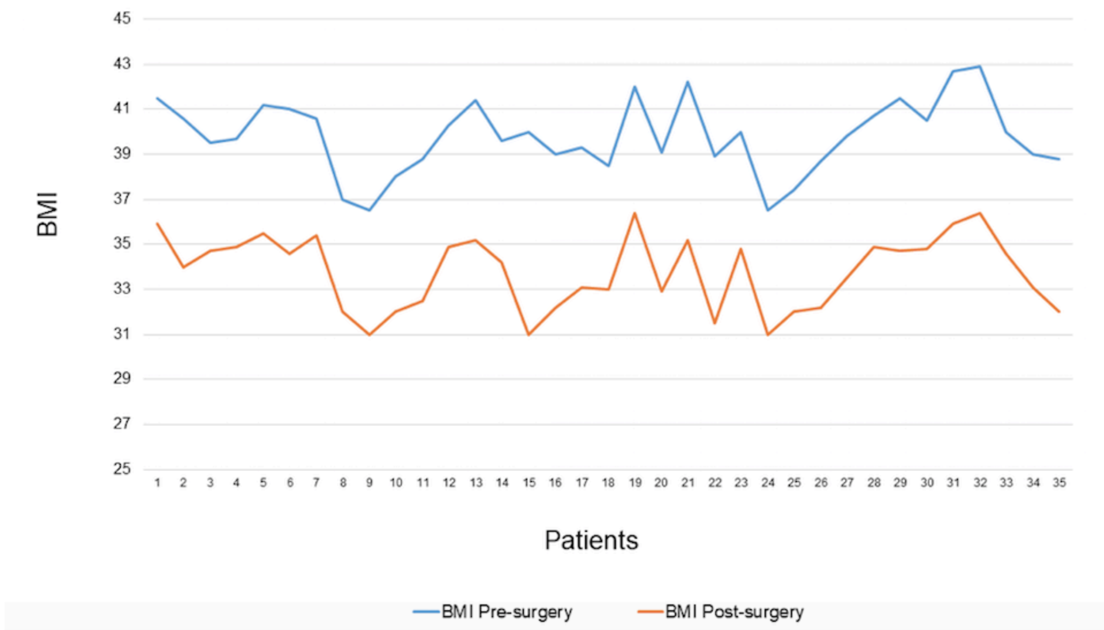
**Statistical analysis**

Statistical analysis was performed using the SPSS 26 system (SPSS Inc., Chicago, IL, USA). Continuous data were expressed as the means ± standard deviation (SD), and categorical variables were expressed as the % changes. The chi-square $\chi 2$ test was used to analyse categorical data, and the Mann-Whitney test was used to analyse continuous variables. All results are presented as two-tailed values with statistical significance defined as p values <0.05.

**Results**

Thirty-five obese men with idiopathic infertility were included in this study. The mean BMI significantly decreased after LSG (32.0±1.22 vs 39.56±1.51 $Kg/m^2$, p=0.001). (Figure 2)

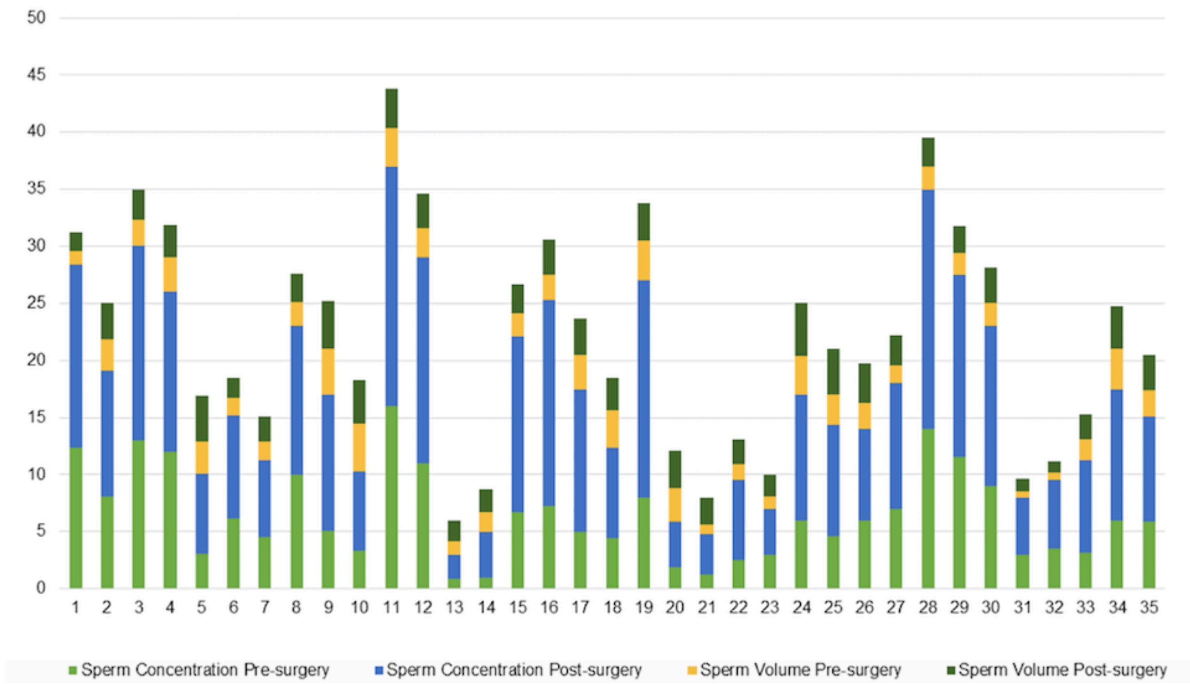
Figure 2: Variation in BMI before and after bariatric surgery




The mean age increased in the interval between the ART cycles before and after bariatric surgery without any statistical difference (38.31±5.13 vs 36.40±5.17 years, p=0.12).

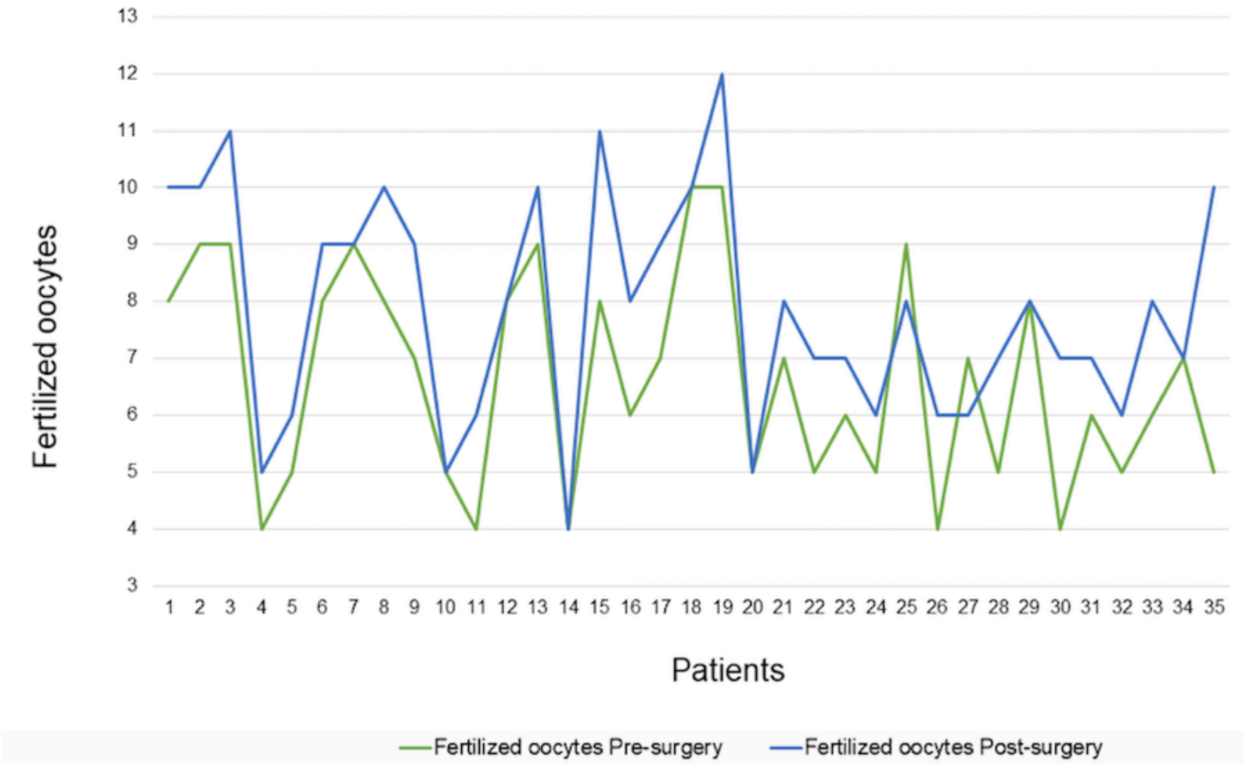
We found a significant increase, after bariatric surgery, in semen volume (2.8±0.85 vs 2.25±0.93 ml, $p=0.001$), sperm concentration (10.85±5.24 vs 6.47±3.96 Mln/ml, $p=0.001$), total sperm concentration (31.71±18.11 vs 15.33±11.33 Mln/ejaculate, $p=0.001$), motile sperm count (23.29±9.09 vs 13.84±8.37 %, $p=0.001$) and sperm morphology (3.0±0.94 vs 2.34±1.11, $p=0.01$). (Figure 3)

Figure 3: Variation in sperm concentration and sperm volume before and after bariatric surgery




About IVF outcomes, mean number of top-quality oocytes (10.11±2.43 vs 8.94±2.09, $p=0.03$), mean number of fertilized oocytes (7.86±1.99 vs 6.63±1.88, $p=0.01$), mean number of embryos obtained (3.94±1.26 vs 2.57±0.98, $p=0.001$) and top-quality embryos (1.69±0.76 vs 0.86±0.69, p=0.001) were significantly increased after bariatric procedure. (Figure 4).

Figure 4: Variation in number of fertilized oocytes before and after bariatric surgery




On the other hand, no statistical differences were found in terms of MII oocyte at retrieval pre- and post-surgery (12.97±3.08 vs 12.26±2.84, p=0.32). Finally, we recorded a significant higher implantation and pregnancy rate (0.23±0.43 vs 0.51±0.61, p=0.03), and live birth rate (0 vs 0.31±0.47, p=0.001) with a reduction of miscarriage rate (0.23±0.43 vs 0.03±0.17, p=0.01) after LSG procedure.

All data are resumed in Table 7.

Table 7:Patient'scharacteristics and IVF outcomes.

| *Characteristics* | *Pre-surgery (n=35)* | *Post-surgery (n=35)* | *p-value* |
|---|---|---|---|
| | | | |
| *Age (mean ± SD)* | 36.40 ± 5.17 | 38.31 ± 5.13 | 0.12 |
| *BMI (mean ± SD)* | 39.56 ± 1.51 | 32.00 ± 1.22 | 0.001 |
| *Sperm volume (mean ± SD)* | 2.25 ± 0.93 | 2.80 ± 0.85 | 0.01 |
| *Sperm concentration (mean ± SD )* | 6.47 ± 3.96 | 10.85 ± 5.24 | 0.001 |
| *Total sperm concentration (mean ± SD )* | 15.33 ± 11.33 | 31.17 ± 18.11 | 0.001 |
| *Motile sperm count (%)* | 13.84 ± 8.37 | 23.29 ± 9.09 | 0.001 |
| *Sperm morphology (mean ± SD)* | 2.34 ± 1.11 | 3.00 ± 0.94 | 0.01 |
| *Top quality oocytes (mean ± SD)* | 8.94 ± 2.09 | 10.11 ± 2.43 | 0.03 |
| *Fertilized oocytes (mean ± SD)* | 6.63 ± 1.88 | 7.86 ± 1.99 | 0.01 |
| *Embryos obtained (mean ± SD)* | 2.57 ± 0.97 | 3.94 ± 1.26 | 0.001 |
| *Top quality embryos (mean ± SD)* | 0.86 ± 0.69 | 1.69 ± 0.76 | 0.001 |
| *Implantation rate (mean ± SD)* | 0.23 ± 0.43 | 0.51 ± 0.61 | 0.03 |
| *Pregnancy rate (mean ± SD)* | 0.23 ± 0.43 | 0.51 ± 0.61 | 0.03 |
| *Miscarriage rate (mean ± SD)* | 0.23 ± 0.43 | 0.03 ± 0.17 | 0.01 |
| *Live birth rate (mean ± SD)* | 0 | 0.31 ± 0.47 | 0.001 |

## Discussion

Obesity is an increasingly prevalent health burden upon modern society. According to data from the National Health and Nutrition Examination Survey (NHANES), 35.7% of American adults are obese, and 17% of children and adolescents aged 2–19 years are obese. In Europe, over 50% of the population is overweight, and 23% is obese.

The negative effect of obesity upon fertility was described firstly by Hippocrates, who wrote in his Essay on the Scythians BPeople of such constitution cannot be prolific fatness and flabbiness are to blame. The womb is unable to receive the semen and they menstruate infrequently and little.

The relationship between obesity and infertility is well established. It is well known that weight loss improves reproductive function in overweight and obese women.

However, considering that weight reduction is not an easy task, it may lead to the decreased probability of conception due to the advancing reproductive age for many obese women.

One of the most effective strategies to obtain weight loss is bariatric surgery. Recent studies have demonstrated that naturally conceived pregnancy after a bariatric procedure is not only safe but may also be associated with fewer risks or complications in comparison to patients who remain obese during their pregnancy.

In addition, recently, a systematic review with meta-analysis of literature has been performed to evaluate the incidence of successful pregnancy after bariatric interventions in infertile women. By pooling together data from 589 infertile obese women, the authors have been able to provide an aggregate estimation of successful pregnancy after weight loss interventions. The results showed an impressive high incidence (58%) of infertile women who become spontaneously pregnant after surgery. Based on these results, bariatric interventions could be included in the treatment of obesity-related infertility.

It is rationale that these benefits would also be applicable to women who conceive via ART. With the increasing prevalence of obesity worldwide, the number of obese women who are seeking ART as a treatment for infertility is on the rise. While an increasing number of obese women are seeking ART, it is by no means an optimum solution for in- fertility in this population. Obesity has been found to impair ART outcomes in most, but not all, studies, as recently reviewed. Obese women have been reported to have a 68% lower odd of having a live birth following their first ART cycle compared with non-obese women. Additionally, obesity is related to the requirement for increased doses of ART medications; more frequent cancellation of cycles (when patients stop treatment prior to oocyte retrieval, most commonly due to poor ovarian response) and lower rates of fertilization, embryo transfer, implantation and pregnancy.

The cause of this phenomenon is unclear, but recent re- search suggests that lipotoxicity causes endoplasmic reticulum stress and dysfunction of mitochondrial and apoptotic pathways. Changes in insulin adipokines, glucose and free fatty acid levels may also play a role in disrupting oocyte development and maturation.

Unfavourable responses to ovarian stimulation such as increased gonadotropin consumption, fewer selected follicles and lower number of retrieved oocytes have been observed in obese women submitted to ART. Due to this fact and to the difficulties those women may face during gestation, in some countries, there are severe restrictions to perform fertility treatments in obese women.

Thus, it is rationale to advocate weight loss prior to performing a fertility treatment, even if weight loss should be obtained by surgery. However, data regarding the effects of bariatric surgery on the reproductive outcome of infertile women undergoing IVF are still scarce and controversial.

Doblado et al. published their description of five patients who underwent IVF treatment following bariatric surgery. All their patients conceived in the first or second IVF cycle following the operation, and none experienced complications during or after IVF treatment cycles. The authors concluded that bariatric surgery is a safe procedure in women undergoing ART. Tsur et al. in a case series observed a significant decrease in the total number of gonadotropin ampoules required during IVF cycle following bariatric surgery, with no adverse effects on the number of follicles ≥15 mm, the number of oocytes retrieved and the number of MII oocytes, emphasizing the safety and cost-effectiveness of bariatric surgery. Conversely, Christofolini et al. comparing ovarian stimulation parameters and treatment outcome among three different groups of patients (a—29 patients after bariatric surgery, b—57 obese patients and c—94 normal-BMI and overweight patients undergoing their first IVF cycle) reported significantly fewer follicles, oocytes retrieved and mature oocytes among patients with a priori bariatric surgery as compared with patients from the two other groups.

The rationale to explain the benefit of bariatric surgery on ART outcomes could be easily identified in the weight loss obtained after surgery.

On the other hand, the hypothesis of how bariatric surgery could have a negative effect on fertility is the association with the decrease in specific nutrient ingestion. The process of oocyte fertilization seems to be simple, but it involves many signalling pathways and can be influenced by a variety of factors, including the availability of minerals, specific proteins and other nutrients. Nutrition failure can induce fertilization failure or embryo dysplasia. Historically, women under- going bariatric surgery were advised to delay pregnancy for 12 to 24 months after surgery. This recommendation was intended to both optimize weight loss and minimize adverse effects of nutritional deficiencies. However, recent studies and guidelines emphasize the importance of nutritional balance rather than the time from surgery to conception.

Our study confirms the advantage of weight loss surgery on ART outcomes, even if it is important to highlight that the nutritional balance was guaranteed by the evaluation of restrictive bariatric procedures.

Pregnancy rate significantly increased after bariatric surgery. A significant decrease in the total number of gonadotropin units required was reported, even if it is important to highlight that we cannot exclude the relation with weight loss. Response to ovarian stimulation increased too as confirmed by an increase of the number of follicles ≥15 mm, of the number of top-quality oocytes and of the number of MII oocytes. Furthermore, the results of in vitro fertilization improved as demonstrated by the higher number of fertilized oocytes and the better number of top-quality embryos. These results were corroborated by no significant difference in age in the cycles before and after surgery.

In addition, in a separate analysis comparing pregnant and non-pregnant women after surgery, we demonstrated that pregnancy rate significantly correlated only with the weight loss obtained.

Thus, our results provide the rationale to consider weight loss surgery one of the better ways to improve the results of ART treatment in obese infertile women. Bariatric surgery is confirmed to be one of the most useful interventions to obtain weight loss. Furthermore, bariatric surgery is demonstrated to be safe and effective in increasing the outcomes of ART treatment and on top the pregnancy and the live birth rate.

Chances of conception and childing, even with the help of assisted reproductive technologies, are compromised not only when the woman is obese but also when that condition affects the male partner; by this point of view, an inverse relationship between men′s body weight and semen parameters has already been observed, suggesting a favourable role for weight loss surgery in improving male fertility. Samavat et al. realized a two-armed prospective study performed in 31 morbidly obese men, undergoing bariatric surgery: they found a statistically significant improvement in the sex hormones, a positive trend in the progressive/total sperm motility and number, an increase in semen volume and viability. Finally, Merhi et al. retrospectively evaluated 344 infertile couples undergoing IVF or intracytoplasmic sperm injection (ICSI) cycles: males with BMI >25 kg/m2 exhibited a poorer clinical pregnancy outcome after IVF.

It is rationale that these benefits would also be applicable to couples who conceive via ART. With the increasing prevalence of obesity worldwide, the number of couples with obese men who are seeking ART as a treatment for infertility is on the rise; thus, it is rationale to advocate weight loss prior to performing a fertility treatment, even if weight loss should be obtained by surgery. In fact, a meta-analysis by Sermonande et al. on 21 studies confirmed a decreased probability of live birth following IVF was observed in obese women when compared with normal weight women. Doblado et al. published their series of five patients who underwent IVF treatment following bariatric surgery, demonstrating that all their patients conceived in the first or second IVF cycle following the operation, without experiencing complications. Similarly, Einarsson and colleagues, in a randomized trial on 160 infertile obese women underwent IVF, demonstrated that weight loss can determine a significant higher number of conceptions.

However, there is a lack of data regarding the effects of bariatric surgery on the reproductive outcome of infertile men undergoing IVF and, in our best knowledge, this is the first study which analyse this field.

Our results, confirming the previous cited studies, demonstrated a significant increase, after bariatric surgery, in semen volume, sperm concentration, total sperm concentration, motile sperm count and sperm morphology. Moreover, for the first time, we investigated the effects of men weight loss on IVF outcomes: we found an increased mean number of fertilized oocytes in couples where men underwent LSG with a significant higher implantation, pregnancy and live birth rate, despite a reduction of miscarriage rate. The rationale to explain the benefit of bariatric surgery on ART outcomes could be easily identified in the weight loss obtained after surgery: the seminal vesicles and prostate are under the androgen control and the reduction of IL8 levels, considered one of the responsible for reduced seminal volume, have been found to be associated with high BMI. Moreover, Samavat et al. have already assessed that at post-testicular level, obesity may negatively affect sperm count, motility, volume, and inflammatory components of the semen, as well as DNA integrity of spermatozoa reflected by sperm morphology.

Previous evidence also shows that adipokines expressed by the adipose tissue, hormonal changes secondary to obstructive sleep apnea, and even diabetes-associated inflammation might as well compromise normal reproduction. In a such scenario, our results provide the rationale to consider bariatric surgery, thanks to its effects on obesity-related comorbidities, one of the better ways to improve the results of ART treatment in obese infertile men.

Some limitations of this study have to be addressed. The major limitation lies in its study design; being an evaluation of a prospective maintained database, there is the lack of patients' selection and randomization. However, designing a study in which subjects serve as their own controls permitted to overcome any potentially confounding inter-individual difference. Furthermore, the results cannot be extended to all bariatric procedures, even if sleeve gastrectomy has been selected to homogenize the results.

Thus, although additional research would be useful to draw definitive conclusion, our results appear to be encouraging enough to suggest the use of bariatric surgery in obese infertile subjects seeking an ART treatment.

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