Bariatric Surgery Influences the Number and Quality of Oocytes in Patients Submitted to Assisted Reproduction Techniques

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Objective: To determine differences in follicle stimulation, oocyte retrieval, maturation, and fertilization among patients who underwent bariatric surgery, obese patients, and patients with $18 < \text{BMI} < 30$ kg/m^2 submitted to assisted reproduction techniques and check that these patients may have some impairment in ovarian response.

Methods: The study comprised three groups: GI: 29 patients who had undergone restrictive and/or malabsorptive bariatric surgery; GII: 57 obese patients (BMI $>$ 30 kg/m^2); and GIII: 94 patients ($18 < \text{BMI} <$ 30 kg/m^2) with infertility due to a male factor. BMI, weight loss until oocyte retrieval, vitamin supplementation, and anemia were evaluated. Data were compared with the number of follicles observed, the number of oocytes retrieved, and the maturation status of these oocytes. Results were analyzed statistically.

Results: A statistically significant difference in the number of follicles observed by ultrasound ($P < 0.01$), the number of oocytes retrieved ($P = 0.013$), and the number of metaphase II oocytes ($P < 0.01$) between the patients with prior bariatric surgery and both GII and GIII group was found.

Conclusions: The weight loss resulting from bariatric surgery can be very beneficial to the overall health of the woman, but the reproductive process can be impaired. Bariatric surgery appears to have an important impact on the formation of follicles and oocytes.

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Introduction

Obesity is characterized by the excess of fat tissue, due to a chronic imbalance between energy intake and energy expenditure. Several factors have been associated with this energy imbalance, such as lifestyle (diet and physical activity) and neuroendocrine disorders, associated to the individual genetic background (1).

This condition has become a major health problem across the world. In the UK, obesity affects one-fifth of the female population, and 18.3% of the female population in the reproductive age group (16-44 years) are classified as obese (2). In Brazil, 16 million women are overweight, which corresponds to 38% of the female population (3).

The World Health Organization (WHO) classifies obesity based on the body mass index (BMI). By this method, the person's weight (in kilograms) is divided by the square of his or her height (in meters). This index defines the following groups: underweight (BMI $<$ 18.5 kg/m^2), adequate (BMI $<$ 25 kg/m^2), overweight (BMI $=$ 25$-$30 kg/m^2), and obese, subdivided into classes I, II, and III (BMI $\geq$ 30 kg/m^2, $\geq$ 35 kg/m^2, and $\geq$40 kg/m^2, respectively) (4).

Obese women generally present increased risk for infertility, miscarriage, gestational diabetes mellitus, gestational hypertension, preeclampsia, cesarean delivery, and anesthesia-related complications. Maternal obesity also puts the developing fetus at risk for congenital abnormalities, abnormal intrauterine growth, and may lead to lifelong adverse effects, including obesity in the developing child (5).

Unfavorable 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 assisted reproduction techniques (ART) (6). Due to this fact and to the difficulties those women may face during gestation, in some countries there are severe restrictions to performing fertility

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TABLE 1 Distribution of infertility causes in GI (post bariatric surgery), GII (obese) and GIII (control group) patients

Infertility factor	GI (%; *n*)	GII (%; *n*)	GIII (%; *n*)	*P*
Male factor	34.4 (10)	40.3 (23)	100 (94)	0.597
Idiopathic	24.1 (7)	0.0 (0)	0 (0)	<0.001
Endometriosis	13.7(4)	17.5 (10)	0 (0)	0.656
Ovulatory	3.4 (1)	21.0 (12)	0 (0)	0.031
Tubal factor	20.6 (6)	12.2 (7)	0 (0)	0.303
Other	3.4 (1)	8.77 (3)	0 (0)	0.706

treatments in 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 (6).

Bariatric surgery has been shown to be the most effective long-term weight loss strategy in obese women of reproductive age. The objective of the procedure is to reduce food intake, but sometimes it also reduces nutrient absorption. Pregnancy after bariatric surgery appears to be safe and, regarding certain complications, safer for mother and fetus than pregnancy in the obese. In patients with properly maintained and monitored nutrition, the risks for obesity-related obstetric complications, such as gestacional diabetes mellitus (GDM) and hypertensive disorders, are significantly reduced. However, obese women should not be counseled to undergo bariatric surgery solely to improve fertility (6).

The ART procedures after bariatric surgery have so far not been properly explored in the literature. Thus, the objective of this study was to determine whether there are any differences in follicle stimulation, oocyte retrieval, maturation, and fertilization among patients who underwent bariatric surgery, obese patients, and patients with BMI >18 and < 29.9 kg/m^2 submitted to ART.

Methods

We evaluated 2,852 medical records of infertile patients treated at Instituto Ideia Fertil—Faculdade de Medicina do ABC, Santo André/SP—Brazil, between February 2008 and October 2011. Of these patients, 180 met the selection criteria and were therefore included in the study. The mean age of the patients was: 35.0 ± 3.6 years.

The study comprised three groups of patients: GI: 29 patients who had undergone restrictive and/or malabsorptive bariatric surgery; GII: 57 obese patients (BMI> 30 kg/m^2); and GIII: 94 patients (BMI< 29.9 kg/m^2) with infertility due to a male factor. The BMI was calculated according to the Quetelet formula: weight/height^2 (kg/m^2). GIII group was chosen due to the consideration that these patients have no problems on ovarian response.

The inclusion criterion was to have undergone at least one cycle of controlled ovarian hyperstimulation (COH). We considered data from the first cycle, even for patients who underwent more than one. The exclusion criterion for GII and GIII patients was any previous surgery for weight reduction. Importantly, all patients were matched by age, with at least three fertile controls and two obese patients for each patient who had had bariatric surgery, in order to compare oocyte retrieval results.

We evaluated BMI, weight loss until oocyte retrieval, vitamin supplementation, and anemia. These data were compared with the number of follicles observed, the number of oocytes retrieved, and the maturation status of these oocytes.

All patients were submitted to antral follicle count, follicle-stimulanting hormone (FSH), and estradiol dosages before the use of controlled ovarian stimulation medication.

Controlled ovarian stimulation protocol

Ovarian stimulation was performed by the administration of a dose of 200 IU of FSHr for 10 days, starting on the second day of menstruation. From day 6 to day 10, the antagonist was also administered. Between days 10 and 11, when the follicles reached a diameter of approximately 18 mm, as determined by transvaginal ultrasound, the patient was given a dose of human chorionic gonadotropin (hCG), and on day 13 the oocytes were retrieved. Patients without an expected response within the first eight days, i.e., with follicles which did not show satisfactory growth (at least 14 mm) for further treatment, had their cycles discontinued. A new cycle with the same or a higher dosage could be started, according to medical indication.

Statistical evaluation

Given the non-normality of the data (Shapiro-Wilk test, $P < 0.05$), it was decided to present them based on median values, the 25th and 75th percentile. The Kruskal–Wallis test was used to compare the distribution of quantitative variables according to groups (0 = not overweight, 1 = post-bariatric surgery, 2 = obese women without bariatric surgery). All statistical analyses were done using the software package Stata version 11.0 (Stata Corp., College Station, TX).

The estimated pregnancy rate of GIII and GII was compared to GI according to regression model Poisson with robust variance estimate of relative risk (7).

Results

The BMI distribution observed in the three groups studied was the following: GI: BMI = 26.6 (22.8-35.8); GII: BMI = 32.8 (30.1-46.2); GIII: BMI = 23.5 (17.5-29.6). The patients in the three groups were classified by their different causes of infertility. In group I, 24.1% were classified as idiopathic infertility, a factor not observed in the other groups. On the other hand, 21.0% of patients in group II presented ovulatory causes (14.0% with—polycystic ovary syndrome—PCOS), in contrast with only one in group I. The percentage of male cause was similar between groups I (34.4%) and II (40.3%) (in GIII it was used as inclusion factor), as was the tubal factor (20.6% in group I and 12.2% in GII). The distribution of the causes of infertility is shown in Table 1.

Regarding the oocytes of these three groups, we observed a decreased number of follicles on ultrasound ($P = 0.0063$), oocytes

TABLE 2 Data concerning oocyte parameters in GI, GII, and GIII groups of patients

Parameters	GI	GII	GIII	*P*
Follicles on ultrasound	5 (3-7)	6 (4-8)	7 (5-10)	0.0063[a]
Retrieved oocytes	5 (3-7)	6 (3-8)	6.5 (4-11)	0.0130[a]
Metaphase II oocytes	3 (2-4)	4 (2-6)	5 (3-7)	0.0006[a]
Metaphase I oocytes	0 (0-0)	0 (0-1)	0 (0-1)	0.5851
Prophase I oocytes	0 (0-1)	0 (0-1)	0 (0-1)	0.0596
Degenerated/abnormal oocytes	0 (0-0)	0 (0-0)	0 (0-1)	0.0876
Inseminated oocytes	4 (3-5)	4 (2-7)	5 (3-7)	0.1119

[a]Statistical significance

TABLE 3 Pregnancy rates of GIII and GI groups compared to GII rates

Group	Relative risk (CI 95%)[a]	*P*
GII	1	-
GIII	1.45 (0.73-2.88)	0.293
GI	1.82 (0.82-4.07)	0.143

[a]Retrieved Poisson regression with robust variance
CI, Confidence interval 95%.

retrieved ($P = 0.0130$), and metaphase II follicles ($P = 0.0006$) in patients of group I compared to controls and to the obese patients of group II. No differences were observed for metaphase I, prophase I, degenerated/abnormal, or inseminated oocytes. These results are shown in Table 2. Table 3 shows the pregnancy rates observed and compared among the groups.

Considering the patients submitted to bariatric surgery, 19 (70.3%) reported the use of vitamin and mineral supplementation after surgery with gestational vitamin supplements or a general vitamin supplement; 10 (37.0%) of them were anemic.

The median time between surgery and infertility treatment was 4.81 years (0.4-10), and the median weight loss by the beginning of the infertility treatment was 46.04 kg (23-90).

Discussion

Researchers around the world have observed that obese women generally present a delay in spontaneous conception, high prevalence of infertility, miscarriages, and poorer ovarian response to COH (8,9).

Ovarian stimulation in obese women usually results in fewer growing follicles, lower concentrations of intrafollicular hCGs, lower peak estradiol levels, lower number of mature oocytes, fewer oocyte retrieval, higher cancellation rate, impaired oocyte quality, lower fertilization rate, poorer embryo quality, lower incidence of embryo transfer, and lower mean number of transferred embryos (9). The cause of this phenomenon is unclear, but recent research 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 (8).

After bariatric surgery, women generally show increased fertility when compared to obese controls, mainly those diagnosed with PCOS, once losing weight can reduce symptoms of hyperandrogenism and insulin resistance (10).

Another hypothesis for patients undergoing in vitro fertilization (IVF) is that being overweight can negatively affect circulating levels of hCG (11) as well as excess skin generated by the weight loss in patients who underwent bariatric can also contribute negatively to the levels of hCG (12).

Previous studies have demonstrated varied degrees of relative fertility compared to non-obese controls. Some reports showed slightly worse outcomes, while others did not find any significant differences in fertility between normal and postoperative women. In addition, food intake restriction or impaired nutrient absorption associated to the loss of weight can induce malnutrition and pregnancy complications (13).

In the present study, we found a statistically significant difference in the number of follicles observed by ultrasound, the number of oocytes retrieved, and the number of metaphase II oocytes between the patients with prior bariatric surgery and both GII and GIII patients. The values found for post-surgery patients were lower even compared to obese women. This information is especially relevant for a clinical decision involving the reproductive conduct in obese patients.

Corroborating our data, there is a report of two male patients with a marked reduction in sperm parameters observed during a period of twelve to eighteen months after bariatric surgery, considering the pre-operatory parameters of the same men (14). However, a study conducted with 10 obese patients submitted to bariatric surgery showed that surgery-induced massive weight loss does not interfere with sperm quality, but can increase the quality of sexual function, testosterone, free testosterone and FSH levels, and reduce prolactin levels. Data about impact of bariatric surgery is still sparse.

We hypothesized how bariatric surgery could have a negative impact on fertility. A complication frequently associated with bariatric surgery is the decrease in specific nutrient ingestion. The most common nutrient deficiencies concern iron. Vitamin B12 and fat-soluble vitamins such as thiamin, folate, and vitamins A, E, D, E, K (15). It was postulated that the periconceptional period is critical in determining fetal development and health. The origin of several fetal malformations and pregnancy-related disorders such as congenital abnormalities, fetal loss, miscarriage, insufficient fetal growth, premature birth, and preeclampsia may indeed lie in this period (16).

In an early study in mice, maternal protein undernutrition for 2 or 4 weeks prior to mating and during the preimplantation period adversely affected the fertilization and blastocyst development rates (17). Another study showed a decrease in the number of embryonic cells both in the inner cell mass and in the trophoectoderm of undernourished mice (18).

The process of oocyte fertilization seems to be simple, but it involves many signaling 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 (19).

To our best knowledge, this is the study with the largest number of cases evaluated with regard to reproductive parameters in the literature. Furthermore, we used a control group three times larger than the case group, which gives greater statistical power to the correlations made. However, there was a bias to our study, since we had no information about the reproductive status of the patients before the bariatric surgery, as they came to our Human Reproduction Center only after the surgery.

In group GI, most of the causes of infertility were due to male factors (33.3%) or classified as unexplained infertility (29.6%), in contrast to GII, where 23.4% of the patients presented ovulation problems. However, even presenting ovulatory infertility factors, the results for GII were still better than those of GI, thus excluding the hormonal factors as cause of infertility in the GI patients and suggesting that the poor fertilization results might be caused by a nutritional disorder.

The weight loss resulting from bariatric surgery can be very beneficial to the overall health of the woman, but the reproductive process can be impaired. While the excess of weight is related to increased morbidity during pregnancy, bariatric surgery appears to have an important impact on the formation of follicles and oocytes.

Both male and female factors can interfere with the fertilization and gestational processes. In our study, we found no difference between the groups regarding pregnancy outcomes. However, we need to be conscious that our control group was composed by fertile female patients, submitted to IVF procedures due to male factor infertility. Therefore, semen quality may be an aggravating factor for the gestational results. An ideal control group composed by non-obese patients, with no male factor of infertility or with a female factor that do not influences oocyte retrieval is really difficult to compose. By this reason we emphasized our findings regarding the number of oocytes, as it reflects only female factors.

In patients who remain infertile after bariatric surgery, close monitoring of food intake and supplementation of specific absent macro- and micronutrients should be performed, according to the nutritional deficiencies found. A balanced judgment and a personalized case-by-case management with patient involvement in decisions are fundamental in this setting, and the indication of cryopreservation of oocytes should be considered in specific circumstances. O

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