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REVIEW ARTICLE

Effects on the sex hormone profile in obese patients undergoing bariatric surgery

Efectos en el perfil hormonal sexual en pacientes obesos sometidos a cirugía bariátrica

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Abstract

We aimed to carry out a systematic review and meta-analysis of the effects of bariatric surgery on fertility in men with obesity. To assess the methodological quality of the included studies, the Cochrane-ROBINS-I tool for non-randomized studies was used. Three hundred and eighty-four articles were found. A statistically significant improvement in total testosterone levels was evidenced in all the patients; some studies did not find a correlation between this increase and the improvement in seminal parameters. Only one article showed a slight increase in estradiol levels (not statistically significant, 33.3-32 pg/mL, p: 0.68). Normal or low levels of LH and FSH were present both before and after the procedure. The total sperm count decreased at 6 months and was significantly lower at 12 months. There was not evidence of changes in seminal volume, sperm motility, and vitality. Although our systematic review shows changes on sexual hormonal parameters in men, with an increase in total testosterone levels, a negative one was also found on semen quality. More prospective and randomized studies are required, hopefully of the Latin American population, which can help confirm this association.

Keywords: *Obesity. Bariatric surgery. Urology. Fertility. Hormones.*

Resumen

Nuestro objetivo fue realizar una revisión sistemática y un metaanálisis de los efectos de la cirugía bariátrica sobre la fertilidad en hombres con obesidad. Para evaluar la calidad metodológica de los estudios incluidos, se utilizó la herramienta Cochrane-ROBINS-I para estudios no aleatorios. Se encontraron 384 artículos. Se evidenció una mejoría estadísticamente significativa en los niveles de testosterona total en todos los pacientes; algunos estudios no encontraron una correlación entre este aumento y cambios en los parámetros seminales. Solo un artículo mostró un ligero aumento en los niveles de estradiol (no estadísticamente significativo, 33,3 a 32 pg/ml, p: 0,68). Los niveles normales o bajos de LH y FSH estaban presentes tanto antes como después del procedimiento. El recuento total de espermatozoides disminuyó a los 6 meses y fue significativamente menor a los 12 meses. No hubo evidencia de cambios en el volumen seminal, la motilidad y la vitalidad de los espermatozoides. Aunque nuestra revisión sistemática muestra cambios sobre los parámetros hormonales sexuales en hombres, con un aumento de los niveles de testosterona total, también se encontró uno negativo sobre la calidad seminal. Se requieren más estudios prospectivos aleatorizados, ojalá en población latinoamericana, que ayuden a confirmar esta asociación.

Palabras clave: *Obesidad. Cirugía bariátrica. Urología. Fertilidad. Hormonas.*

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Introduction

Obesity, defined as excess body fat, with a body mass index (BMI) above 30 kg/m^2, has become a public health problem, affecting more than 650 million adults worldwide in 2016[1,2].

In the urological field, obesity has been associated with an increased risk of urolithiasis, infertility, obstructive urinary symptoms, urinary incontinence, genital prolapse, erectile dysfunction, and chronic kidney disease[3,4]. In recent years, interest in the impact that obesity has on sexual function and fertility has increased[5], although it has been seen that abnormalities in sexual reproduction and function are often ignored or not studied in comparison with cardiovascular comorbidities[6]. Surgical treatment of obesity has been associated with improvement in reproductive hormones, seminal parameters, and symptoms associated with hypogonadism.

The objective of our work is to carry out a systematic review of the effects of bariatric surgery on fertility in patients with obesity.

Materials and methods

Study design

The systematic review was carried out using the PICO method to answer the research question: What are the effects on fertility in obese patients undergoing bariatric surgery?

Search strategies

Included articles were identified in the literature by searching the following databases: PubMed, Lilacs, Scopus, and Cochrane. Only articles were chosen between the years 2012 and 2021.

The search strategy was carried out with the following controlled terms such as and free text: "Fertility" OR "Fecundability" OR "Fecundity" OR "Differential Fertility" OR "Fertility Determinants" OR "Subfecundity" OR "Fertility Preferences" OR "Below Replacement Fertility" OR "Marital Fertility" OR "Natural Fertility" OR "World Fertility Survey" OR "Fertility Incentives" AND "Bariatric Surgery" OR "Metabolic Surgery" OR "Bariatric Surgical Procedures" OR "Stomach Stapling" AND "Obesity". The search syntax was carried out with Boolean operators, which were adapted to the databases used.

Eligibility criteria

As inclusion criteria, articles that discussed the fertility outcomes of patients undergoing bariatric surgery were considered; publications with their own data analyzing the effects of bariatric surgery on fertility; that the language of publication was English or Spanish, and that they were published between the years 2012 and 2021. Articles inaccessible to full text were excluded from the study; as well as those that only had theoretical data; and those that did not have results.

Study selection

The search yielded a total of 384 results. The titles and abstracts of the articles were reviewed by one of the authors. Articles that were duplicated and those that did not meet the eligibility criteria were eliminated. Finally, the remaining articles and their references were thoroughly manually reviewed in search of additional articles that could be included in this review, including five publications.

Data extraction

For each study, data were extracted and recorded in a spreadsheet. The main author of each study was registered with the year of publication, country and affiliation of the authors, design, general objective, number of subjects studied, surgery performed, evaluation methods, evaluation times, BMI at the beginning and at the end, change in BMI/weight, and results/conclusions in terms of fertility.

Quality assessment

To assess the methodological quality of the included studies, the Cochrane-ROBINS-I tool for non-randomized studies[7] was used, which includes the type of biases shown in table 1 and figure 1.

Studies are not excluded based on these results and were classified as high, indeterminate, or low risk. Publication bias was assessed by constructing the funnel plot.

Results

Five articles were analyzed for a total population of 279 patients, whose general objective was to evaluate the impact of bariatric surgery on sperm parameters and/or hormonal parameters. Figure 2 shows the

Table 1. Evaluation of the articles by the ROBINS-I non-randomized study tool

Authors	Confounding bias	Participant selection bias	Bias in intervention classification	Bias due to deviation of interventions	Bias due to missing data	Bias in measurement of results	Bias in selection of results
Carette et al.	✓	✓	✓	✓	✓	✓	✓
El-Bardisi et al.	✓	✗	✓	✓	✗	✓	✓
Wood et al.	✓	✓	✓	✓	✓	✓	✓
Facchiano et al.	✓	✓	✓	✓	✓	✓	✗
Rosenblatt et al.	✓	✓	✓	✓	✓	✓	✗

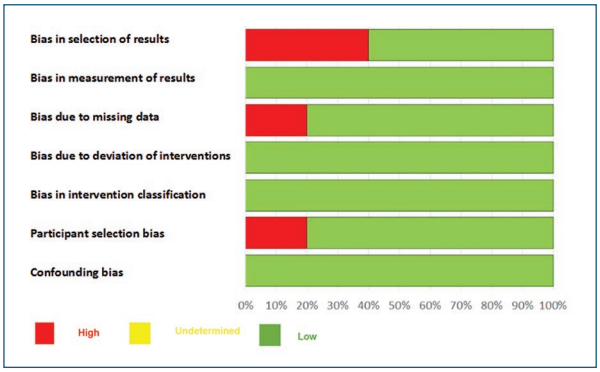

Figure 1. Biases ratio in the included studies.

flowchart that summarizes the search and selection process of the articles.

Characteristics of the studies

Table 2 summarizes the characteristics of the included studies and table 1 summarizes the evaluation of the articles with the ROBINS-I tool. The biases ratio in the studies is found in figure 1.

Hormonal parameters

Total testosterone and free testosterone levels

Regarding total testosterone levels, all the articles measured the values before and after the procedure, finding in all a statistically significant improvement in post-operative levels in patients undergoing bariatric surgery. In the study by Bardisi et al., this increase was equivalent in the three groups, both the initial azoospermia and the oligospermia and patients with previous normal seminal analysis[7], although in some studies, no correlation was found between this increase and the improvement in seminal parameters[8], regarding this increase compared to the age of the patient, no differences were found in the increase of these values between patients younger than 35 years ($p < 0.028$, n: 7) and older than 35 years ($p < 0.972$ n: 13)[9]. In the studies in which these values were compared with control groups, this difference was even more marked in the patients who underwent the surgical procedure, with an average of 537 ng/dL in those operated versus 371.4 ng/dL in those who were not ($p < 0.01$)[10], and 604 ng/dL ($p < 0.0001$) versus 200.5 ng/dL ($p = 0.46$), respectively[11].

Free testosterone was calculated in two of the five articles: Facchiano et al. showed an increase from 0.204 nM to 0.251 nM, without achieving a statistically significant difference ($p = 0.1$)[9], while in the control groups, these values were lower (303.9) compared with the operated patients (365) $p < 0.03$[10].

Estradiol levels

Regarding estradiol levels, these presented a slight decrease in their values in the post-operative period, from 135 pg/mL to 130 pg/mL (7), 35-33 pg/mL (8), 149.5-112 pmol/L ($p = 0.002$)[9], where only one article showed a slight increase, being 33.3-32 pg/mL not statistically significant ($p = 0.68$)[11]. In relation to the studies of operated patients versus control groups, levels of 39 pg/mL were found in control groups versus 35 pg/mL in those treated ($p < 0.01$)[10].

LH and FSH levels

Consistent with the secondary hypogonadism that obese patients present, normal or low levels of LH and

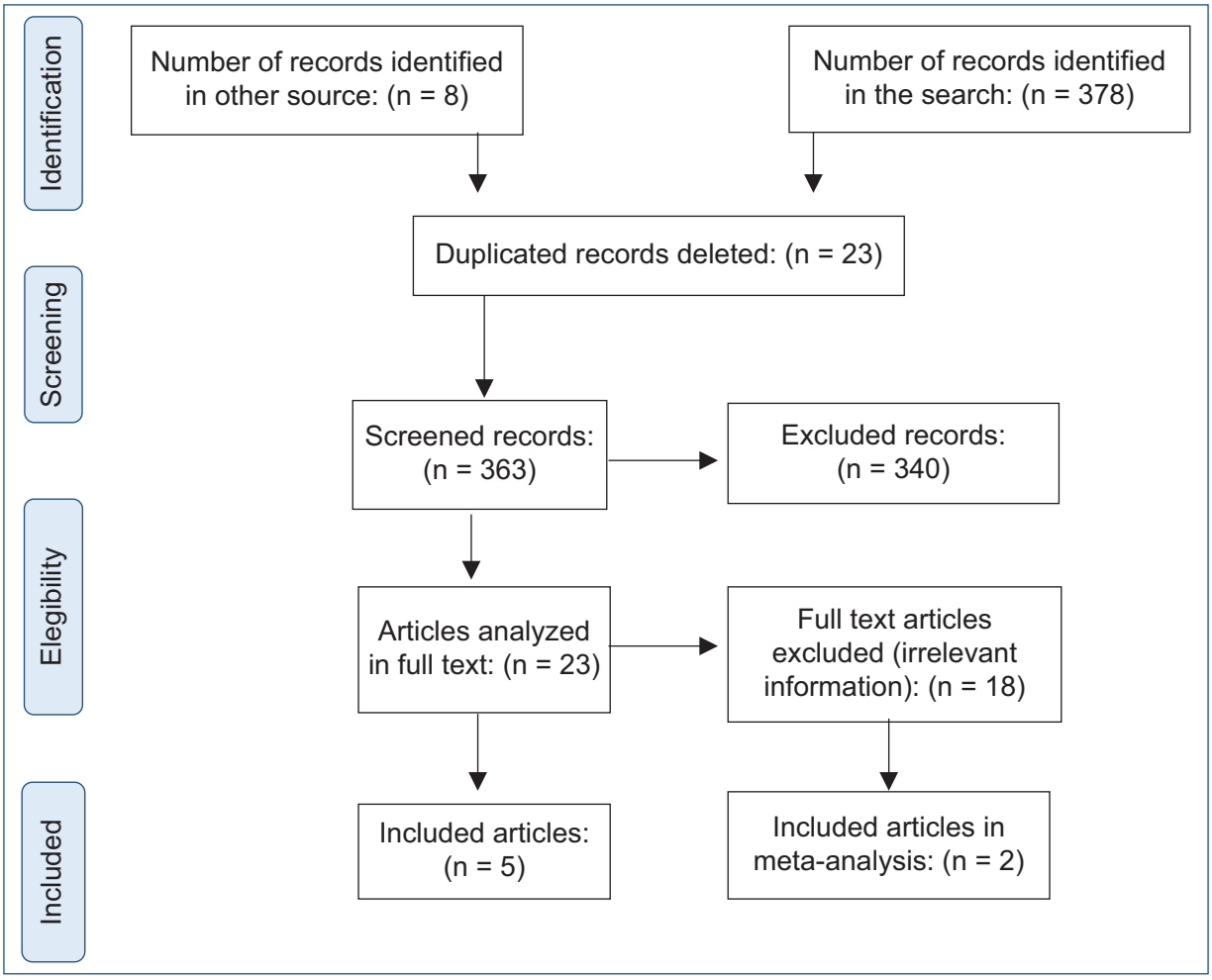

Figure 2. PRISMA flowchart for systematic review.

FSH are present both before and after the surgical procedure, findings evidenced in all the studies analyzed in this review.

Sex hormone binding globulin (SHBG) levels

SHBG levels were measured in three of the five studies analyzed, evidencing as expected considering the pathophysiology of hypogonadism secondary to obesity given by the decrease in the levels of this globulin, the patients showed a marked and statistically significant increase of its values, from 19 to 39 nM ($p < 0.0001$)[9], and lower levels in the placebo group (27.7 nM) versus those undergoing bariatric surgery (48.8 nM)[10].

Seminal parameters

Regarding the spermogram parameters, mixed findings were found. Although one study found a statistically significant improvement in sperm concentrations in patients with azoospermia ($p = 0.02$) and oligospermia ($p = 0.001$), with sperm finding in the ejaculate of 6 of 13 (43%) patients who initially had azoospermia[7], other studies showed a reduction in total sperm count at 12 months after bariatric surgery in patients without a history of infertility (177.7 × 106 vs. 108.2 × 106 at 12 months $p = 0.087$), despite of improvements in the levels of total testosterone and sex hormone transporter globulin; this deterioration was seen even in patients without a history of infertility, taking into account that < 20% of the patients in this cohort had baseline oligozoospermia[8]. Wood et al. also evidenced that patients undergoing bariatric surgery presented a reduction in sperm concentration (110 vs. 67.3 × 106/mL $p = 0.002$), and in total sperm count 133.5 × 106 versus 80.7 × 106 ($p = 0.002$) at 6 months; even two patients with a sperm count of 0.1 and 82 million/mL presented azoospermia 6 months after being operated on[11].

Table 2. Summary of the characteristics of the included studies

Study (lead author, year, country)	Design	General objective	n	Surgery performed	Monitoring	Initial BMI (kg/m^2)	Final BMI (kg/m^2)	Results
El Bardisi et al. 2016 Qatar	Prospective - Observational	Changes in spermogram and serum hormones	46	Sleeve gastrectomy	12 months	71.4	46.9	Gastrectomy significantly increases serum testosterone levels ($p < 0.001$). Seminal parameters were not affected. Sperm concentration increased significantly in azoospermics ($p = 0.02$) and oligospermics obese people ($p = 0.001$).
Facchiano et al. 2013 Italy	Prospective - Observational	Serum hormone levels	20	Gastric band: 8 Roux-en-Y gastric bypass: 10 Biliopancreatic diversion: 2	6 months	43.6	34.8	Improvement of the post-operative sexual hormonal profile: E2 ($p = 0.002$), TT ($p < 0.001$), SHBG ($p < 0.0001$), FSH ($p < 0.001$), and y LH ($p = 0.048$)
Wood et al. 2020 Brazil	Prospective - Cohort	Effects of obesity and impact of bariatric surgery on spermogram parameters and DNA fragmentation.	Phase 1: obese (42) versus fertile control groups (32) Phase 2: bariatric surgery (18) versus observation (13)	Roux-en-Y gastric bypass: 15 Sleeve gastrectomy: 3	6 months	Sx: 45.1 Control: 27.1	Sx: 32.3 Control: 45	Phase 1: Obese patients had higher levels of estradiol, LH, and FSH, with low levels of total testosterone, associated with worse sperm parameters (reduction in ejaculate volume, sperm concentration, motility, morphology), and higher levels of DNA fragmentation. Phase 2: The group that underwent surgery presented an elevation of almost twice the total testosterone values ($p < 0.0001$), with improvement in DNA fragmentation, but worsening of sperm concentration and ejaculated sperm volume were found. None of these changes were found in the control group.
Carette et al. 2019 France	Prospective - Observational	Sperm modifications	46	Gastric bypass: 20 Sleeve gastrectomy: 26	6 years 12 months	44.1	6 months: 33.2 12 months: 31.4	Sperm count is lower after Sx: decrease of 69.5×10^6 at 12 months (CI 95% - $p < 0.0001$). No changes in sperm volume, motility, or vitality. Total DNA fragmentation average decreased 2.2% at 12 months (CI 95% - $p = 0.0005$)

(Continues)

Table 2. Summary of the characteristics of the included studies *(continued)*

Study (lead author, year, country)	Design	General objective	n	Surgery performed	Monitoring	Initial BMI (kg/m^2)	Final BMI (kg/m^2)	Results
Rosenblatt et al. 2017 Brazil	Ambispective - Cohort	Influence of bariatric Sx on sperm parameters and fertility	79 in four groups: Sx > 5 years: 23 Sx 1-2 years: 23 Obese control groups: 18 Thin control groups: 15	Roux-en-Y gastric bypass	> 5 years: 1 1-2 years: 2	1: 59.8 2: 49.7	1: 35.1 2: 32.2	Evident seminal alterations in pop, without statistical significance. No changes in pop fertility. Long-term persistently elevated androgen levels, and stable estrogen levels (TT [$p < 0.01$], FT [$p = 0.03$], SHBG [$p < 0.01$], E2 [$p = 0.006$]) in Sx. BMI positively correlated with oligoasthenoteratospermia ($p = 0.008$).

BMI: body mass index

Discussion

Our systematic review shows the results of five studies from different countries, all prospective, with a low number of patients, and with high heterogeneity.

Obesity in men has been associated with a decrease in testosterone and SHBG; in addition to an increase in estradiol, leading secondarily to hypogonadotrophic hypogonadism[12,13]. Male obesity-related secondary hypogonadism (MOSH) brings with it endocrine dysfunction, being reported in up to 45% in patients with moderate-severe obesity[14]. Regarding the compromise of the seminal parameters, these patients have a higher risk of presenting azoospermia or oligospermia, but the mechanism in which obesity affects fertility is complex and heterogeneous, both hyperinsulinemia and hyperleptinemia have a direct effect on spermatogenesis secondary to the oxidative stress and associated inflammatory state, leading to loss of DNA integrity[15,16].

Campbell et al. found clear data in a meta-analysis that paternal obesity negatively affects fertility and reproductive potential[17]. These results have also been demonstrated in experimental studies in animals[18,19]. In addition, evidence has been found in both animals and humans that changes in lifestyle habits, such as physical exercise and a balanced diet, with consequent weight loss, can improve fertility[20].

Sermondade et al., in a retrospective series of three cases, reported that the rapid weight loss associated with bariatric surgery was associated with significant changes in the spermogram parameters (severe oligoasthenozoospermia), which in one of the patients spontaneously improved at 2 years of the procedure and did not require assisted reproductive therapy. Our data show that bariatric surgery is associated with negative changes in the spermogram, and positive changes in sexual hormonal parameters[21]. It has been suggested that negative changes in the spermogram may be secondary to a catabolic state and consequently an accumulation of reactive oxygen substances at the testicular level, causing damage to both sperm and DNA[22]. However, more prospective studies with a greater number of patients are still needed to clarify the origin of this sperm damage, most of these studies being reports or case series[6,23]. Moxthe et al., carried out a systematic review of the effects of bariatric surgery on both male and female fertility, included seven studies in men, finding a significant improvement in hormonal parameters and sperm count; although the review has important weaknesses in terms of the methodology between the studies, which do not specify possible

confounding variables[24]. Samavat et al. found an improvement in seminal count, motility, and ejaculate.

Samavat et al. found an improvement in seminal count, motility, and ejaculate after bariatric surgery, and showed a decrease in sperm DNA fragmentation[25]. On the contrary, Legro et al. found no improvement in the seminal parameters of patients taken to gastric bypass[26]. Some reports have shown a negative effect on semen quality secondary to the nutritional deficit associated with surgical procedures related to a catabolic state (extrapolated data from very weak evidence, which require randomized studies to be corroborated)[21,23,27].

Our study has certain limitations, starting with the low number of studies found to carry out the systematic review, the high degree of heterogeneity that existed in the studies for most of the measures, which reduced the comparison of the different hormonal and sperm parameters.

Conclusions

Our systematic review shows the positive results of bariatric surgery on sexual hormonal parameters in men, with an increase in total testosterone levels. No positivity was found in post-surgical sperm changes. More prospective and randomized studies are required, hopefully of Latin American population, which can help confirm this association to draw more conclusions in the future.

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Conflicts of interest

The authors deny conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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