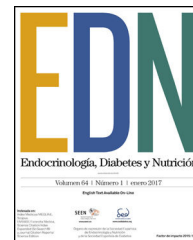




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CONSENSUS DOCUMENT

Obesity and fertility. Position statement

Obesidad y fertilidad. Documento de posicionamiento



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The position statement has been produced by the Sociedad Española de Endocrinología y Nutrición (SEEN) [Spanish Society of Endocrinology and Nutrition], through its Grupo de trabajo de Obesidad (GOSEEN) [Working Group on Obesity], to highlight the relationship between obesity and infertility and propose an approach and specific treatment based on scientific evidence, but without attempting an in-depth review of obesity and infertility. Other societies involved in the care of these patients have subscribed to this position: Sociedad Española para el Estudio de la Obesidad (SEEDO) [Spanish Society for the Study of Obesity]; Sociedad Española de Fertilidad (SEF) [Spanish Fertility Society]; Asociación Española de Urología (AEU) [Spanish Association of Urology]; Sociedad Española de Ginecología y Obstetricia (SEGO) [Spanish Society of Obstetrics and Gynaecology]; and the Sociedad Española de Dietética y Nutrición (SEDYN) [Spanish Society of Dietetics and Nutrition]. Our aim is to show that people with obesity and infertility require specialised and multidisciplinary treatment and, in the event of being candidates for bariatric surgery, should be considered as a priority group when the likelihood of pregnancy is diminishing in the short term due to age.

Infertility as a disorder associated with obesity

Obesity is a chronic disease of epidemic proportions in the western world and has become one of the most difficult challenges facing public health. In Spain, the estimated prevalence of overweight in the adult population (aged 25–64) is 39.3% and that of obesity, 21.6% (22.8% in males and 20.5% in females), increasing with the age of the population.¹ If the current rate of growth continues, by 2030, 29.4% of Spanish adults will suffer from obesity.²

Obesity is associated with, or is the direct cause of, many other well-known disorders and diseases, such as hypertension, type 2 diabetes mellitus, dyslipidaemia, sleep apnoea-hypopnoea syndrome, fatty liver disease, bone and joint diseases and the risk of developing different cancers.³ This means that people with obesity have increased cardiovascular risk and morbidity and mortality rates.⁴ Obesity is also the cause of lesser-known diseases, such as both female and male infertility, which can significantly compromise the health and quality of life of those affected.⁵ In Spain, depending on the definition, infertility attributable to the female can be as high as 17.5% in the 30–49 age group.⁶ About 23% of women who undergo in-vitro fertilisation techniques are overweight or obese.⁷ The significance of obesity in the aetiology of infertility is difficult to determine due to the multifactorial contributions.

Female obesity and infertility

Obese women are less likely to conceive spontaneously. Excess weight is associated with anovulatory menstrual cycles, with the likelihood of anovulatory infertility in women with a body mass index (BMI) ≥ 32 kg/m² estimated to be more than double that of women with normal weight (RR 2.7 [2–3.7]).^{8,9} There is a common association between obesity and polycystic ovarian syndrome (PCOS), this being the most frequent cause of infertility due to anovulation.¹⁰ Obesity exacerbates different reproductive and metabolic

aspects of PCOS, contributing to an increased likelihood of irregular menstruation and oligo-anovulation and having a negative impact on fertility in these patients. In this context, obesity can lead to changes, including insulin resistance, an increase in androgens, a reduction in sex hormone binding globulin (SHBG) and increased peripheral conversion of androgens to oestrogens, which in turn are the causes of altered secretion of gonadotropins by the hypothalamus and hinder the formation of follicles.^{11,12}

However, anovulation is not the only cause of subfertility associated with obesity. It is estimated that for every point increase in BMI above 29 kg/m², the chances of spontaneous pregnancy are reduced by 5% in women with ovulatory cycles.¹³ Possible causes of this phenomenon may be the impact of obesity on sexual desire and on the quality of the ova and their capacity to be fertilised, and alterations in the endometrium which hinder implantation and contribute to a higher rate of abortions.

Obesity seems to have a negative impact on assisted reproductive technology (ART). Patients with obesity treated by controlled ovarian stimulation require higher hormone doses, more days of stimulation, and a higher rate of cancellation due to inadequate response.¹⁴ According to data from the Society for Assisted Reproductive Technology (SART),¹⁵ a high BMI leads to a decrease in the number of oocytes retrieved and the quality of the embryos, as well as a reduction in the rates of fertilisation and implantation and in the live birth rate, which falls from 31.4% in women with BMI in the normal range to 21.2% in cases of BMI above 50 kg/m². The causes of less success in assisted reproduction in obese women are multiple but may include alterations in folliculogenesis, implantation defects and alterations in embryonic development.¹⁴ However, a recent systematic review concludes that the negative impact of obesity on clinical pregnancy, live birth and spontaneous abortion rates after ART is weak in absolute terms and more consistent studies are needed on this subject.¹⁶

Although not the focus of this statement, pre-pregnancy obesity increases the risk of obstetric complications such as gestational diabetes, pregnancy-induced hypertension, caesarean section and macrosomia, complicating the final part of the pregnancy, in addition to increasing the risk of obesity in the offspring.¹⁷

Male obesity and infertility

The male factor accounts for 20–50% of infertility cases in couples¹⁸ and obesity may play a significant role. Two systematic reviews substantiate that if the male partner is obese, there is a greater risk of him being sterile (OR: 1.66 [95% CI, 1.53–1.79]) and poorer outcomes in ART.^{19,20} The causes are multiple and are detailed below.

Firstly, as in women, obesity in men, causes a cascade of hormonal changes, which can lead to functional hypogonadotropic hypogonadism. This is caused by the decrease in SHBG, the aromatisation of androgens to oestrogens in adipose tissue, which, combined with other mechanisms, including insulin resistance, hyperleptinaemia and low-grade inflammatory state, cause a decrease in the secretion of gonadotropins.^{21,22}

In addition, obesity in men is associated with a higher rate of erectile dysfunction, which can occur in up to 75% of men with grade 2 and 3 obesity.²³ This association may be due to the hormonal changes described, the presence of metabolic syndrome or treatments for that, or secondary vascular damage.

In terms of semen quality, the data are less conclusive, although some studies report a higher prevalence of oligozoospermia and asthenozoospermia,^{19,24,25} alterations in the DNA, a reduction in mitochondrial activity and an increase in oxidative stress in the sperm in people with obesity.^{26–28} It has been suggested that these changes could be secondary to functional hypogonadotropic hypogonadism itself, to an increase in scrotal temperature secondary to increased adiposity, or to the detrimental effect of the proinflammatory state and oxidative stress on spermatogenesis.²⁹

Impact of weight loss on fertility

In women, weight loss through lifestyle changes or bariatric surgery has been shown to restore ovulation, regularise menstrual cycles and improve fertility.^{30,31} Although the impact of weight loss on the success of fertility treatments is less clear, current evidence suggests that it could help achieve a greater number of spontaneous pregnancies, in addition to reducing the necessary dose of gonadotropin treatment.^{5,32,33}

Although pharmacological treatment of obesity offers proven health benefits,³⁴ the information available on the improvement of fertility is limited and has only been studied in women.^{35–37} Studies are therefore needed to evaluate whether or not weight loss through anti-obesity drugs improves fertility results, in addition to defining for each specific drug the precise moment it should be discontinued, according to the pharmacokinetics and pharmacodynamics, before planning the pregnancy.

In men, weight loss, either through lifestyle changes or bariatric surgery, leads to a clear improvement in the hormonal changes characteristic of functional hypogonadism secondary to obesity^{38–42} and in erectile function.⁴³ At present, the data on sperm parameters are less clear. Improvement in spermatogenesis after lifestyle intervention has been found in isolated studies,⁴⁴ but the effects of bariatric surgery do not seem to provide any benefit.⁴⁵

The amount of weight loss necessary to see any benefits in parameters related to fertility is variable. However, with weight loss of 5–10% achieved through diet and exercise, there is an improvement in functional hypogonadism associated with obesity, irregular menstruation and anovulation associated with PCOS, and even in the pregnancy rate.^{5,40,46}

Recommendations on the treatment of excess weight and obesity in people with infertility

In view of the currently available evidence, assessing for excess weight or obesity should be mandatory at Andrology or Gynaecology consultations for infertility. To achieve this, it will simply be necessary to measure weight, height and waist circumference (Fig. 1). In the presence of obesity and infertility, treatment should focus primarily on achieving a healthy weight loss which is sustained over time through

lifestyle changes, including diet modification, physical exercise and behavioural changes. This first approach is the basis of any intervention aimed at weight loss and should be considered in all overweight and obese patients who come to the Gynaecology or Andrology clinic because of infertility. As a negative synergistic effect on fertility has been observed when both partners are obese,^{47,48} weight loss is recommended for both partners, although the effect on male fertility is less conclusive. It should also be noted that a preventive approach probably offers a wider window of action. As a gynaecology appointment for routine check-up is often the only contact a woman of childbearing potential has with the healthcare system, this consultation is a key point in the prevention of excess weight and obesity. We therefore recommend the systematic assessment of patients in whom excess weight or obesity are identified, and referral to the general practitioner or Endocrinology and Nutrition specialist in order to establish an agreed treatment plan.

In people with BMI ≥ 27 kg/m² with associated complications, or ≥ 30 kg/m², along with lifestyle modifications, the addition of drugs to reduce body weight should be considered, bearing in mind that the evidence regarding improvement in fertility is limited and any drug treatment should be stopped before attempts to become pregnant or starting fertility treatment, in accordance with each drug's pharmacokinetics and summary of product characteristics. In cases of grade 2 obesity (BMI ≥ 35 kg/m²) with obesity-associated disorders or grade 3 obesity (BMI ≥ 40 kg/m²), the possibility of bariatric surgery should be considered, bearing in mind that the resulting effects on fertility are clearer in women, with less evidence in men.

Fig. 1 summarises the approach to the prevention and treatment of obesity associated with infertility. We have to take into account, however, that despite the negative impact of obesity on fertility, in women aged 38 or over the negative impact of age is much greater and, in these cases, achieving pregnancy should take priority over weight loss.⁴⁹

Areas for improvement in the treatment of obesity associated with infertility

The approach to excess weight and obesity therefore has to be multidisciplinary, including both the general practitioner, endocrinologists, dietitians/nutritionists, psychologists, physical exercise specialists, nurses, gynaecologists and urologists. Effective communication between the different healthcare professionals is key to agreeing on the best approach in each case. Unfortunately, such multidisciplinary programmes are few and far between and obesity units are limited to the treatment of severe obesity. It is essential to promote the creation of these programmes in Primary Care in coordination with endocrinologists specialising in the treatment of obesity, in order to respond to the growing demand, and where patients with a lesser degree of obesity can receive care.

In the case of drug treatment for excess weight and obesity, as we are awaiting the approval of new agents which are more potent in terms of achieving weight loss, studies will be needed to assess their impact on fertility, and others on the pharmacoeconomics, in order to obtain financing from the National Health System.

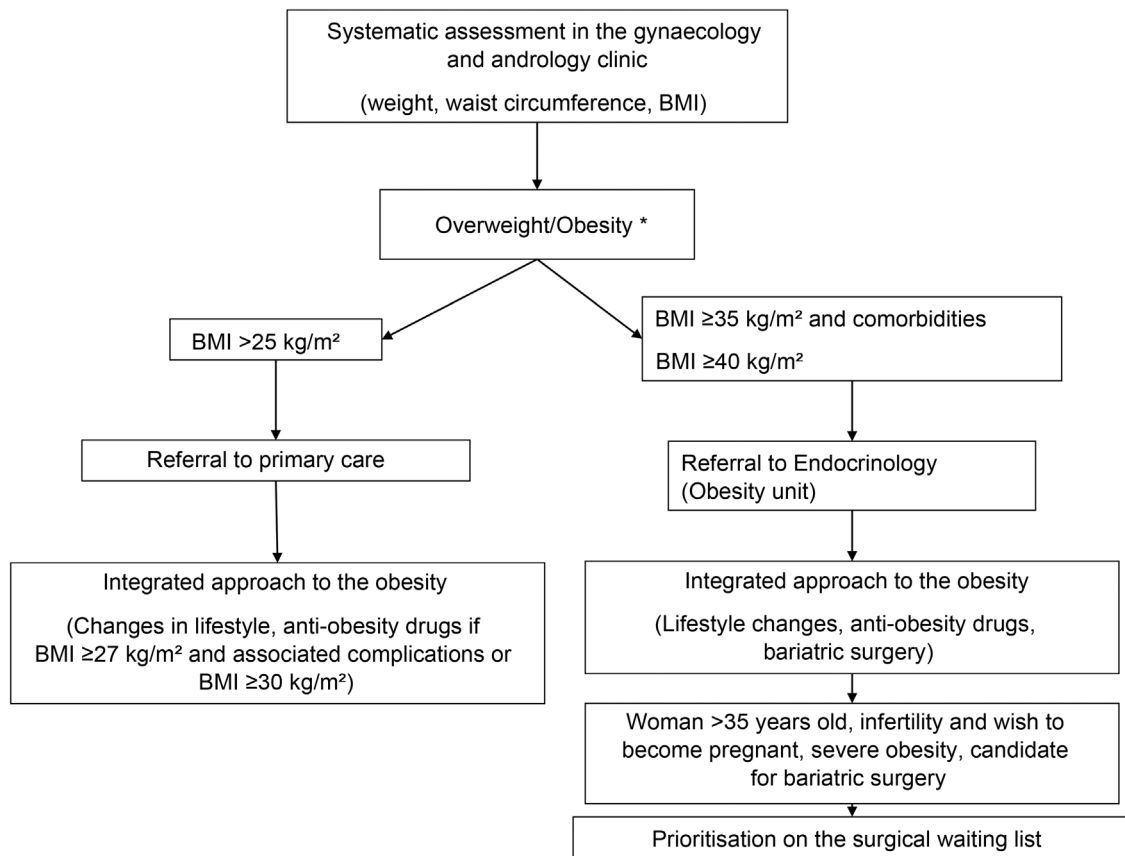


Figure 1 Diagram of the approach to the prevention and treatment of overweight or obesity associated with infertility.

The long and restrictive waiting lists for bariatric surgery represent another limitation in the treatment of obesity in the context of infertility. In view of the already discussed impact of age on fertility, this position paper specifically proposes prioritisation on bariatric surgery waiting lists for women aged over 35 with severe obesity and infertility, bearing in mind that the recommendation is to wait at least 12 months after the bariatric intervention before becoming pregnant.

This document also asserts that, despite the huge repercussions it has on health, obesity continues to be a stigmatised chronic disease with little recognition, from the perspective of both society and healthcare. There are currently very few units for the correct treatment of obesity, there is a lack of funding by the National Health System for drug treatment, and there are long waiting lists for bariatric surgery. This situation contributes to the deterioration in the quality of life and life expectancy of people with obesity. There is little recognition of the association between obesity and infertility and only through the training of healthcare professionals and increasing awareness among people with obesity and society in general, including the health authorities, will it be possible to promote new strategies to ensure proper assessment and the implementation of an effective treatment for improving both female and male fertility. A multidisciplinary approach to this disease is key to improving the care of these patients.

Information for patients

Obesity can be considered an epidemic disease throughout the world, both in western and developing countries. A chronic disease, obesity is associated with, or is the direct cause of, many other well-known health problems and disorders, such as high blood pressure, type 2 diabetes, dyslipidaemia, respiratory disease and joint problems, and even an increased risk of cancer. This means that people with obesity have increased cardiovascular risk and morbidity and mortality rates. Obesity is also the cause of lesser-known diseases, such as both female and male infertility, which can significantly compromise the health and quality of life of those affected. The aim of this joint paper by the societies SEEN, SEEDO, SEGO, SEF, AEU and SEDYN is to draw attention to the impact of obesity on fertility, both male and female, and agree on a common approach. Specifically, it proposes prioritising severely obese women over 35 on the bariatric surgery waiting list. Our aim is to draw attention to the need to allocate National Health System resources for the creation of multidisciplinary units to address obesity, both at a hospital and Primary Care level, and to the need to reduce waiting lists for obesity surgery, assess the financing of anti-obesity drugs and develop strategies with the potential to impact on fertility in patients with obesity.

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