

REVIEW ARTICLE

The relationship between overweight and female infertility*A relação do excesso de peso com a infertilidade feminina*Maíra Masello da Costa¹ , Caroline Brandão Andrade¹, Francisca Valdenia Guerreiro Soares¹, Gabriella Pinto Belfort^{1,*} ¹IBMR University Center. Rio de Janeiro, Rio de Janeiro, Brazil.

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KEYWORDSFemale infertility
Mediterranean diet
Obesity
Overweight
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Excessive weight seems to negatively influence fertility, and as it is a modifiable factor, understanding this relationship can contribute to infertility treatment. Adipose tissue is responsible for releasing several hormones and cytokines related to the reproductive system, such as leptin, TNF- α , and Interleukin-6, substances that can negatively impact female fertility. Additionally, a woman's diet and lifestyle can influence body weight and fertility. Food consumption, characterized by a high intake of foods with high energy density, high levels of sugar, saturated fat, and poor nutrients, as well as physical inactivity, can favor excessive weight. Thus, losing body weight obtained through a healthy diet associated with physical activity may restore fertility in overweight women.

PALAVRAS-CHAVEDieta mediterrânea
Infertilidade feminina
Obesidade
Síndrome do ovário policístico
Sobrepeso**RESUMO**

O excesso de peso parece influenciar negativamente na fertilidade e, por ser um fator modificável, a compreensão sobre essa relação pode contribuir para o tratamento da infertilidade. O tecido adiposo é responsável pela liberação de diversos hormônios e citocinas relacionados ao sistema reprodutor, como leptina, FNT- α e Interleucina-6. A obesidade está relacionada com a resistência à insulina e ao hiperandrogenismo ovariano, fatores que podem gerar impacto negativo na fertilidade feminina. Além disso, a dieta e o estilo de vida da mulher podem influenciar o peso corporal e a fertilidade. O consumo alimentar caracterizado pela elevada ingestão de alimentos com alta densidade energética, elevados teores de açúcar, gordura saturada e pobre em nutrientes, assim como a inatividade física, favorece o excesso de peso. A perda de peso corporal obtida por meio de uma alimentação saudável associada à prática de atividade física pode ser capaz de restaurar a fertilidade.

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INTRODUCTION

Infertility represents a complex and growing public health problem with different causes and characteristics that affect the lives of men and women, generating medical, psychological, socio-cultural, and ethical implications¹. A couple is considered infertile if they have sex without contraceptive methods for 12 months and do not become pregnant². In Brazil, it is estimated that 8 million people may be infertile³.

Two types of infertility can be observed. Primary infertility is the biological inability of a person to conceive when there is no record of pregnancy in the couple's history. This is the most common reason. Secondary infertility comes from the inability to conceive after a previous pregnancy, considering that sexual relations are regular and unprotected⁴. Some factors that affect reproductive health and success are advanced maternal age, a diet with inadequate nutrients, tobacco, stress, alcohol/caffeine consumption, exposure to environmental and chemical pollutants, and obesity².

According to the Vigitel survey in 2019, 53.9% of Brazilian adult women were overweight and 21% obese, which can negatively influence the reproductive health of individuals⁵. Obesity may reduce insulin sensitivity, which generates persistent hyperinsulinemia, a characteristic that leads to the pathogenesis of polycystic ovary syndrome and the possibility of infertility. A diet aiming to better control insulin secretion and maintain healthy body mass, with adequate intake of proteins and antioxidants, can reduce toxins, resulting in the protection of egg maturation and preservation of ovarian health and physiology². Additionally, the practice of regular physical activities must be combined with dietary changes⁶.

Understanding how excessive weight can contribute to infertility is essential to optimize the treatment of this condition, as a woman's nutritional status is a factor that can be modified⁷. Thus, this study aimed to identify a relationship between excessive weight and female infertility and establish how this relationship is based.

METHODS

A narrative review of the literature about scientific articles related to "female infertility and overweight or obesity", published in the last 15 years, was conducted.

Scientific articles were analyzed from August to November 2020 on SciELO (Scientific Electronic Library Online) databases, LILACS (Literatura Latino-Americana e do Caribe em Ciências da Saúde), and MEDLINE (*Medical Literature Analysis and Retrieval System Online*). To search for scientific articles, the following descriptors were used, in Portuguese and English: "infertilidade feminina"/"female infertility"; "obesidade"/"obesity"; "Síndrome do Ovário Policístico"/"Polycystic Ovary Syndrome", "Dieta Mediterrânea"/"Mediterranean Diet".

DEVELOPMENT

According to the World Health Organization (WHO), obesity is considered a major public health problem, and its incidence almost tripled between 1975 and 2016 worldwide. It was estimated that in 2016, 1.9 billion adults in the world aged 18 or older, were overweight and of these, more than 650 million were obese⁸.

Overweight and obesity are responsible for 25% to 50% of the causes of female infertility⁹. The imbalance between excessive food consumption and low practice of physical activity is the fundamental cause of excessive weight, which induces the production of several hormones that can affect fertility and cause negative obstetric and perinatal outcomes. Among these outcomes, some risks are increased: miscarriage, gestational diabetes, pre-eclampsia, preterm delivery, longer duration of labor work, fetal macrosomia, anomalous presentations, and increased instrumented or cesarean delivery. Furthermore, maternal overweight during pregnancy, based on intrauterine metabolic programming and in the postnatal period, increases the risk of obesity in children and the emergence of other diseases such as diabetes and cardiovascular diseases in the future⁶.

The evaluation of overweight is measured using the body mass index (BMI), which is also used as a parameter to assess possible health problems arising from excess weight and associated with a high waist circumference. However, a limitation of this index is that it does not consider the individual's body composition and shape. Women of reproductive age with a high BMI (above 25 kg/m²) have a higher risk of ovulatory problems^{10,11}.

According to the increase in BMI in the population, there is an increase in the proportion of women with oligomenorrhea (associated with excessive abdominal fat), amenorrhea, and anovulation (more common in obese women)⁹. Possible factors for changes in ovulation are changes in sex steroids, changes in ovarian metabolites, altered gene expression, poorer quality of oocytes and embryos, and changes in the uterine environment¹¹.

The time to conceive appears to be longer in women with a BMI greater than 25 kg/m² or less than 19 kg/m², and both overweight and obesity are significantly related to reduced pregnancy rate².

The impact of obesity in regulating hormones involved with the reproductive system

The impact of obesity on the reproductive system is related to endocrine mechanisms, interfering with neuroendocrine and ovarian functions, reducing ovulation. Body weight determines the presence of factors that can impair fertility, such as insulin resistance and ovarian hyperandrogenism, regardless of polycystic ovary syndrome, which can lead to anovulation⁹.

Due to the excessive accumulation of lipids, including in non-adipose tissues, the production of oocytes can be compromised, which can cause menstrual dysfunction and insulin resistance¹¹.

Obese women may present with glucose tolerance alterations even without diabetes mellitus, as there is an intermediate stage between glucose homeostasis and diabetes⁷. Insulin resistance may be involved in infertility due to the impact on the frequency and amplitude of the secretion of the luteinizing hormone (LH), which can interrupt follicular growth, generate early luteinization of granulosa cells, and cause damage to oocyte quality. Unlike muscle, liver, and adipose tissue, which become insulin resistant, the ovaries remain sensitive, being exposed to the effect of hyperinsulinemia. In central obesity, insulin resistance and hyperinsulinemia contribute to menstrual, ovulatory, and fertility disorders¹².

The higher level of circulating insulin in obese women stimulates increased production of androgens by the ovary and, consequently, affects the gonadotropin production, causing menstrual irregularities and ovulatory dysfunctions¹¹. A mechanism by which hyperinsulinemia causes hyperandrogenism is via hepatic suppression in the synthesis of sex hormone-binding globulin (SHBG). SHBG is a glycoprotein that binds to sex hormones to transport them biologically inactive^{11,13}.

Overweight is also related to an increase in sex steroids, estrogens (17 β -estradiol-E2 and estrone-E1), and androgens (testosterone-T, dihydrotestosterone-DHT, androstenedione, and dehydroepiandrosterone), and reduced serum concentrations of SHBG globulin. In obese women, SHBG suppression provides free circulation of estradiol in the bloodstream, making this hormone bioavailable. Thus, in obesity, there is an increase in the availability of androgens, estrogens, and a condition of relative functional hyperandrogenism that can affect ovarian function^{11,13}.

Another hormonal change that can contribute to infertility in overweight women is reduced plasma levels of growth hormone (GH). This hormone is essential for successful reproduction by stimulating the growth of follicles, acting in the final stages of folliculogenesis and luteinization, and facilitating the development of the dominant follicle. Furthermore, this hormone increases the production of estrogen and progesterone in the ovaries¹¹.

Advanced glycation end products (AGEs) are also receiving much attention. They are produced when there is excessive sugar consumption and, because they are slowly metabolized, are associated with an increase in blood glucose. High serum levels of circulating AGEs slow down the formation of follicles, the rate of fertilization and hinder the embryo's development. Moreover, the endothelial cells are also damaged, affecting infertility¹⁴.

Also, obese women have higher production of pro-inflammatory adipokines such as leptin, tumor necrosis factor alpha, and interleukin-6 (IL-6) and lower serum levels of circulating adiponectin, which have an anti-inflammatory function. Reproductive tract tissues are not immune to the effects of inflammation, and exposure to IL-6 stimulates the accumulation of fatty acids in these tissues, generating lipotoxicity. Furthermore, although the inflammatory pathways are essential in reproduction, helping break

the follicle in ovulation and invasion of the endometrium by trophoblasts, in obese women, chronic inflammation can be present, exerting a negative influence on the process¹¹.

Serum leptin concentration is directly related to body fat, responsible for regulating the remodeling of the endometrial epithelium and stimulating the proliferation of apoptotic cell pathways. In obesity, increased leptin production by adipose tissue also contributes to peripheral insulin resistance, indirectly interfering with follicle production and egg maturation¹².

Leptin can also cause changes in the circadian cycle and in circulating estradiol concentrations. This adipokine acts on the hypothalamus, thus modifying the release of gonadotropin-releasing hormone (GnRH), which in turn, will act on the pituitary gland, inducing the release of the GnRH receptor (GnRHR), with consequent LH secretion. Moreover, the LH is fundamental for the ovary, Theca cells, and follicle-stimulating hormone (FSH) secretion, which acts on cumulus cells^{14,15}.

Polycystic ovary syndrome

The polycystic ovary syndrome (PCOS) is a heterogeneous endocrine disorder presented by 5% to 10% of women of reproductive age, where at least two of the following factors confirm the presence of the syndrome: chronic anovulation; clinical or biochemical signs of hyperandrogenism; the presence of polycystic ovarian ultrasound pattern¹⁶.

PCOS is responsible for approximately 80% of cases of anovulatory infertility. Obese women have a lower response to ovarian stimulation medications, so treatment should begin with lifestyle changes. The loss of 5% to 7% of body weight can improve the hormonal profile, restore menstrual regularity and restore fertility. The practice of physical activity is also responsible for improving metabolic changes related to reproduction¹⁷.

Some of the risk factors for developing the syndrome are insulin resistance, dyslipidemia, diabetes mellitus, hypertension, and, particularly, central obesity, which aggravates these factors. Among the anthropometric variables for the diagnostic assessment of central obesity, measurement of waist circumference, waist-to-hip ratio, and, more recently, taper index and waist-to-height ratio should be considered¹⁷.

Obesity in PCOS is characterized by an increase in fat cell size (hypertrophic obesity) rather than an increase in adipocytes numbers (hyperplastic obesity). This hypertrophy results in alterations both in the deposit and in the lipolytic capacity of adipocytes. The impairment of the lipolytic function of the adipose tissue may be secondary to hyperandrogenism in women with PCOS, which would lead to greater insulin resistance¹⁸.

Vitamin D deficiency is prevalent in women with PCOS and may be associated with the clinical features of the syndrome. Despite having few studies in humans, supplementation of this vitamin seems to contribute to menstrual regulation and follicular development¹⁷.

The influence of lifestyle and diet on female infertility

The individual's diet directly influences reproduction. Poor nutrition can affect oocyte maturation, embryo quality, and implantation efficiency in women. Unbalanced diets with high amounts of sugar and saturated fat and contributing to excess weight have a negative impact on ovulation^{2,19}.

The main lifestyle-related factors that negatively affect women's reproductive health are alcohol, smoking, excessive coffee intake, nutritional imbalance, and a sedentary lifestyle. Excessive alcohol consumption indirectly affects fertility when associated with nutritional or secondary health disorders; however, no conclusive studies define what would be the safe intake dose².

According to the clinical practice guidelines conducted by the US Public Health Service, one of the female reproductive consequences of smoking can be mentioned ovarian follicular depletion. These smokers require higher mean gonadotropin doses for ovarian stimulation during in vitro fertilization (IVF). Female smokers appear to have fewer retrieved oocytes, more canceled cycles, lower implantation rates, and more cycles with failed fertilization. Nonsmoker women, but with excessive exposure to tobacco smoke, can have reproductive consequences as significant as those observed in smokers^{20,21}.

Moderate caffeine consumption (less than 200 mg per day) does not appear to be the main contributing factor to miscarriage or premature birth, and the relationship of caffeine to fetal growth restriction remains undetermined. High caffeine intake is associated with a longer period to the conception and an increased risk of pregnancy loss^{2,20}.

The stress caused by everyday life, especially in women who work long hours, can contribute to infertility, as symptoms related to anxiety and depression are described as more frequent in infertile women².

The increase in the percentage of overweight women reveals that due to the evolution in the quality of life of Brazilians in the last 20 years, Brazil passed to present obesity prevalence closer to developed countries. Excess weight, just like diet and lifestyle, is a modifiable factor that can improve reproductive health²².

Maintaining adequate body weight should occur through appropriate eating and moderate physical activity. In food, priority should be given to the consumption of complex carbohydrates, vegetables, fibers, mono- and polyunsaturated fats (omega 3), proteins of vegetable origin, and to limit the consumption of saturated, trans, and animal proteins. Particular attention should be paid to the intake of micronutrients such as folic acid, vitamin B12, vitamins A, D, C and E, calcium, iron, zinc, selenium, and iodine, which are associated with good reproductive system health²³.

A randomized clinical trial, conducted with 149 infertile women with PCOS and overweight, evaluated the effect of changes in lifestyle versus the use of continuous contraceptives or the association of these two interventions in the reproductive abnormalities of

these women. The intervention lasted 16 weeks and, after this period, with ovulation induction, the authors identified that the ovulation rate increased after weight loss, being higher in the group that received the lifestyle modification intervention than in the group that received only oral contraceptives²⁴. In another study of 195 Pennsylvania women, the impact of bariatric surgery on morbidly obese infertile women was assessed, and it was identified that 71% of study participants regained ovulation after surgery. Additionally, women who recovered ovulation had a more significant weight loss than those who remained with anovulation²⁵.

More recently, interest has emerged to understand how diet in a more general way can affect reproductive outcomes, reflecting the way food is consumed and considering the interactions between the nutrients in the diet. Human studies on how dietary patterns may affect fertility are generally associated with IVF treatment²⁶.

In Iran, the Isfahan Fertility and Infertility Center conducted a prospective cohort study with 140 women with primary infertility to verify the association between dietary patterns and infertility. The following was considered results of assisted reproduction techniques: the mean number of total oocytes and metaphase II oocytes, the fertilization rate, the proportion of good and poor quality embryos, and biochemical and clinical pregnancy. A 168-item food frequency questionnaire was used to estimate food intake over the past year, and three main dietary patterns were identified: healthy diet, rich in vegetables, seeds, pulses, fruits, and nuts; Western diet characterized by high consumption of sweet drinks, sweets, caffeinated drinks, potatoes, oil, fast food, refined grains, whole grains and salt; and unhealthy diet characterized by frequent consumption of foods such as mayonnaise sauce, butter, junk food, and solid oils. As a result, it was observed that there was a significant increase in the mean number of total oocytes and metaphase II oocytes only in the group with the "healthy diet" dietary pattern. Furthermore, women with high adherence to the "unhealthy" diet pattern had a lower chance of becoming pregnant²⁷.

In a clinical trial investigating the effect of the DASH (Dietary Approaches to Stop Hypertension) diet on androgens, body weight, and antioxidant status, 60 women with PCOS and overweight were randomized and allocated in the two study groups. The intervention group received the DASH diet (rich in fruits, vegetables, whole grains, and low-fat dairy products, as well as low in saturated fat, cholesterol, refined grains, and sweets), and the control group received a standard diet for 12 weeks. After the intervention, the group that received the DASH diet showed an increase in antioxidant status and significantly reduced weight, fat mass, and androstenedione²⁸. Figure 1 demonstrates the dietary characteristics of the DASH diet²⁹.

Another dietary pattern studied in this population was the Mediterranean diet. This dietary pattern is characterized by the generous contribution of food rich in fiber, nutrients, and bioactive compounds with antioxidant action^{30,31}, which are essential for the functioning of the reproductive system and may contribute to fertility. For women of reproductive age, the Mediterranean diet may also reduce the risk of weight gain, insulin resistance, increase the chances of

getting pregnant and lower risks of maternal and fetal complications during pregnancy, including pre-eclampsia, gestational diabetes, intrauterine growth retardation, and preterm newborns^{30,31}.

The traditional Mediterranean diet has more outstanding characteristics: abundant fresh and natural foods, foods grown according to seasonality, fresh fruits, and sweets consumed only in moderate amounts. It is observed within this dietary pattern the use of olive oil

as the primary source of fat, that dairy products are consumed moderately, red meat is consumed in small quantities, wine is drunk in moderate quantities to accompany meals, and there is also the consumption of fish, more common in regions near to the sea. Fried, buttered and industrialized preparations are uncommon^{30,32}. Figure 2 illustrates the dietary characteristics of the Mediterranean diet³³.

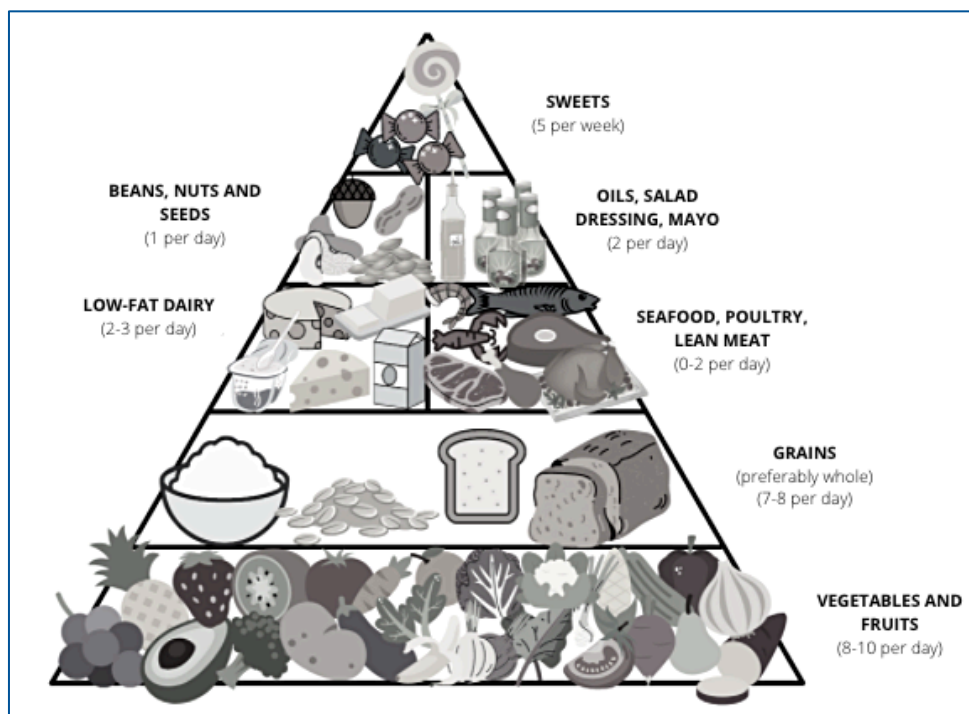


Figure 1 – Food Pyramid of the DASH Diet. Elaborated according to the study by Appel et al.²⁹. Food servings for an energy intake of 2100 kcal/day.

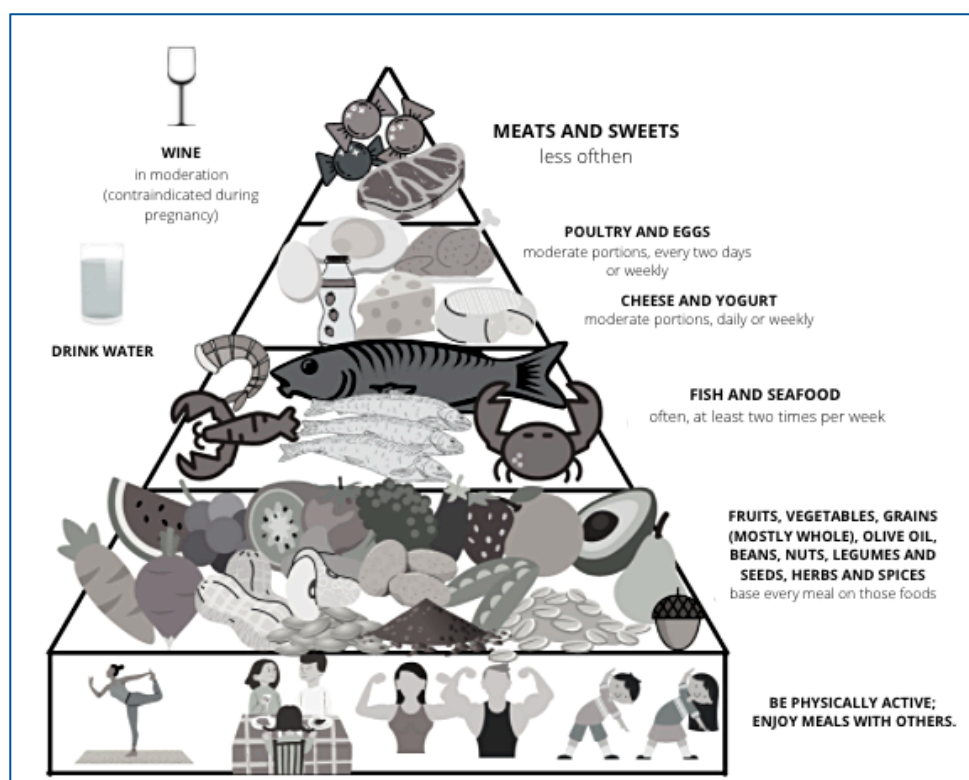


Figure 2 – Food pyramid of the Mediterranean diet. Elaborated according to the study by Willet et al.³³.

The high consumption of linoleic acid from the omega-6 family, a precursor of prostaglandins, may play an essential role at the beginning of the menstrual cycle and, consequently, reduce the risk of ovulatory infertility³¹.

A prospective cohort study in the Netherlands, with 161 subfertile couples undergoing IVF treatment, showed that adhering to the Mediterranean diet provides 40% more chance of becoming pregnant after IVF treatments³⁴. Another case-control survey conducted on 485 women with difficulty getting pregnant and 1,669 controls found that among the participants, those who already had at least one child showed a lower risk of difficulty in becoming pregnant with adherence to the Mediterranean style of diet³⁵.

The possible beneficial effects of the DASH and Mediterranean diets for women with infertility may be associated with both diets having anti-inflammatory potential. A study conducted with women of reproductive age that examined the effect of DASH and the Mediterranean diets on systemic inflammatory markers identified that both were inversely associated with inflammatory markers. This effect can be partly explained by the low glycemic index that these diets have^{36,37}.

The high intake of dairy products, characteristic of the DASH diet, is associated with lower C-reactive protein (CRP) levels. Furthermore, conjugated linoleic acid, riboflavin, and high-quality protein, which are present in dairy products, seem to affect systemic inflammation beneficially³⁸⁻⁴⁰.

In Brazil, the consumption of foods with high nutrient density with antioxidant/anti-inflammatory

action, such as fruits and vegetables, is low among the female population. More recent data from the Vigitel survey (2019) showed that the prevalence of regular and adequate consumption of fruits and vegetables was 20.4% among women aged 18 to 24 years, 25.2% in the age group 25 to 34 years, and 26.7% in the age group from 35 to 44 years⁵.

CONCLUSION

Overweight, and especially obesity, through different aspects, can contribute to changes in the functioning of the female reproductive system, which in turn can impair fertility.

Food can influence the fertility of women in a beneficial or harmful way. A hypercaloric diet with high amounts of sugar, saturated fats, fast food, and ultra-processed foods contribute to the infertility situation, providing an excessive number of certain nutrients that will negatively interfere with the reproductive system and contribute to the development of obesity.

However, a healthy eating pattern such as the DASH and Mediterranean diets contributes to fertility in eutrophic and overweight women. Additionally, the practice of physical activity should be encouraged, as it will contribute to the control of body weight. Therefore, it is essential to change lifestyle habits to improve reproductive performance, including healthy eating, consisting of fresh foods, such as fruits, vegetables, legumes, whole grains, and oilseeds.

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