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OBSTETRICAL AND GYNECOLOGICAL SURVEY


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# Nutritional Changes to Improve Female Fertility: Role of Obesity, Hormones, Dietary Patterns and Endocrine Disrupting Chemicals

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**Importance:** Infertility affects around 180 million people in the world and can be influenced by a number of nutritional factors.

**Objective:** The idea of a pretreatment optimization including beneficial weight loss, adequate physical activity, and good lifestyle habits could enhance fertility for many couples who want to conceive a baby.

**Results:** There are different aspects related to nutrition, such as obesity (affecting 23%–30% of reproductive-aged women), dietary patterns (type of diet, good or bad habits, and physical activity), nutrients (vitamins or minerals), hormones (adipokines, among others), and endocrine-disrupting chemicals (phytoestrogens and bisphenol A, among others) that have a clear impact on women's fertility.

**Evidence Acquisition:** Findings have shown that a Mediterranean or balanced diet with an adequate weight loss in case of obesity and an appropriate serum concentration of different nutrients with low endocrine-disrupting exposure could improve female fertility. In addition, the context is quite important, as there are many differences between overweight and low-weight women, and both can encounter difficulties conceiving.

**Conclusions and Relevance:** The aim of this review is to elucidate the impact of obesity and hormones in women's fertility. In addition, how dietary patterns could help people to increase probability of conception and birth using less fertility treatments cycles will be also analyzed. Moreover, the role of endocrine-disrupting chemicals, pollutants, and contaminants will be discussed.

**Target Audience:** Obstetricians and gynecologists, family physicians.

**Learning objectives:** After completing this activity, the learner will be better able to discuss how obesity and hormones impact fertility; explain the role of dietary patterns regarding conception and birth; and describe the effect of endocrine-disrupting chemicals, pollutants, and contaminants.

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The concept of infertility is defined as the failure to become pregnant after 12 months or more of continuous and unprotected sexual intercourse.[1] The number of births during the last 10 years has decreased in developed countries, due in part to the infertility, which affects 180 million people globally.[2] Infertility has become a first-world issue according to the World Health Organization (WHO).[3] There are many causes of infertility in women, some of which have not been

identified, whereas others, such as diabetes, hypertension, hypothyroidism, lifestyle, polycystic ovarian syndrome (PCOS), premenstrual dysphoric disorder, endometriosis, premature ovarian failure, vulvodynia, and chronic pelvic pain, could be related to female infertility, but not as primary causes.[4] Importantly, due to delayed attempts at conception, assisted reproductive treatments (ARTs) have gained importance during the last decades, allowing couples to be parents.[3]

In relation to those possible causes of female infertility, obesity is likely an important factor (Fig. 1). The WHO announced that obesity affects about 600 million adults around the world, including 23%–30% of reproductive-aged women.[5] It is of paramount importance to prevent obesity, and its comorbidities before complications occur. Some of these complications are periconceptional and perinatal morbidity, increased pregnancy loss, hypertensive disorders, and gestational diabetes.[5,6] The main parameter used to measure obesity is the body mass index (BMI) that measures weight related to height.[5,7] This way, bad dietary patterns (daily feeding patron) and lifestyle could induce different pathologies such as hypertension, low high-density lipoprotein cholesterol, and elevated fasting glucose that could increase preconception risk factors, such as inflammation or epigenetic changes.[8] In addition, *trans*-fat intake, low-fat dairy foods, animal protein, soft drinks, toxic chemicals, and high glycemic load diet have also been associated with anovulatory risk.[9] Thus, preconception is an important period when environmental exposures can affect reproductive health.[10] For these reasons, weight loss and physical activity can improve outcomes of fertility treatments.[11]

According to nutrition, a number of vitamin deficiencies have been linked to impaired female fertility. Antioxidants and oxidative stress are closely related to female fertility (Fig. 1). Thus, oocyte maturation, ovarian steroidogenesis, corpus luteum formation, luteolysis, fertilization, embryo development, and pregnancy can be affected by oxidative stress.[12–14] It is known that vitamin D deficiency affects about 50% of reproductive-aged women, diminishing women's chance of pregnancy and live births. Vitamin D serum levels could be important for women who want to get pregnant as it is a regulator of initial embryo implantation.[15]

Following with the role of nutrients in fertility, selenium (Se) affected follicle development and oogenesis.[16] It has been observed to be necessary for reproduction, immunity, antioxidant system, embryonic growth, and other physiological functions.[16,17] Other interesting nutrients are fatty acids (FAs), which includes saturated (SFA), monounsaturated (MUFA), and polyunsaturated (PUFA) (Fig. 1). They play different roles in oocyte maturation and embryo development, depending on the type of fatty acid.[18] Importantly, it was found that high-fat dairy products were related to a lower ovulatory infertility risk than low-fat dairy products.[19]

It is important to highlight the role of hormones directly impacting reproduction, for example, the case of luteal phase deficiency, which affects the corpus luteum.[20] However, not only reproductive hormones are associated with fertility. Hormones associated with

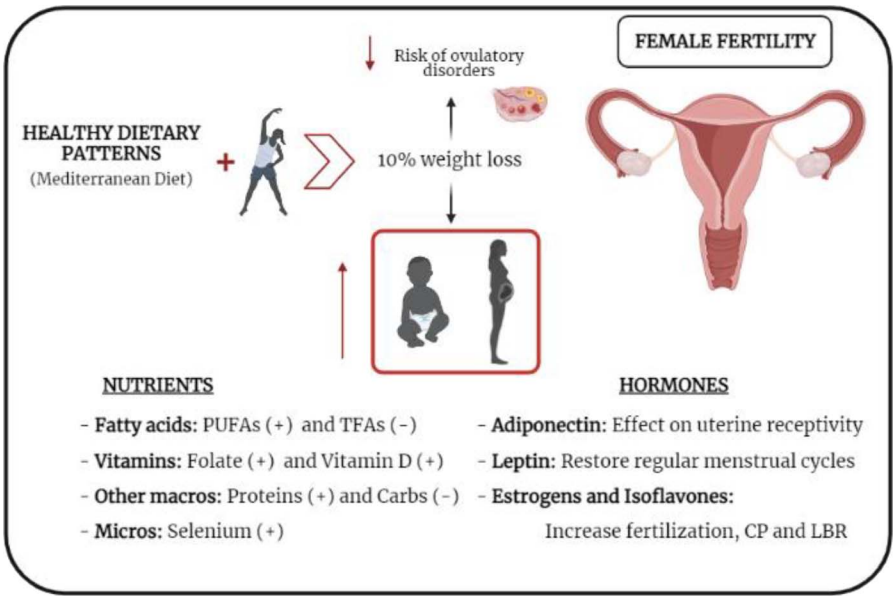


FIG. 1. Effect of healthy dietary patterns, weight loss, nutrients, and hormones in female fertility: (+) beneficial effect, (–) negative effect.

adipose tissue, such as adiponectin and leptin, play important roles related to corporal weight and female fertility[21,22] (Fig. 1).

Finally, the continuous exposure to chemical products in our environment, food, and everyday consumer products can cause an alteration in the synthesis, release, transport, metabolism, and action of endogenous hormones.[23,24] These are called endocrine-disrupting chemicals (EDCs). Some EDCs related to female infertility and alteration of ovarian function include bisphenol A (BPA) and phytoestrogens.[24] Additionally, phthalates and air pollutants have shown endocrine effects demonstrated in *in vitro* and *in vivo* studies.

The aim of this study is to comprehensively review the relation between nutrition and female infertility. For that, the role of obesity, dietary patterns, nutrients, hormones, EDCs, and other contaminants will be thoroughly discussed.

## MATERIALS AND METHODS

Published data from this review were identified in PubMed, Elsevier, and ScienceDirect. Reference lists from relevant articles, reviews, and books on the subject were obtained. A 3-step approach was used, including articles from the last 6 years of publication. First, a search with the keywords "female fertility," "obesity," "dietary patterns," "nutrients," and "hormones" was performed. Second, the relationship among different nutrients and hormones with female infertility was evaluated, adding them to a second selection: "female fertility," "Mediterranean diet," "physical activity," "carbohydrates," "proteins," "fatty acids," "selenium," "adiponectin," and "leptin." The last quest was carried out to analyze different diseases that could directly impact on female fertility, with the keywords "female fertility," "PCOS," "amenorrhea," and "endometriosis." Bibliographies of all selected articles and review articles about nutrition and female infertility were also reviewed for other relevant articles.

## PHYSIOPATHOLOGY OF FERTILITY

Women are born with a million germ cells that migrate to the gonadal ridge where they become primary oocytes forming the "ovarian reserve." These are used for the ovulation process (after the release of the luteinizing hormone [LH]), and they are needed for the formation and maintenance of the ovary.[25]

The hypothalamic-pituitary-ovarian (HPO) axis could be impacted by reproductive pathologies. The HPO axis produces gonadotropic and steroid hormones that facilitate the ovarian cycle. The menstrual cycle is a process where the endometrium prepares for implantation, whereas there is a selection of a dominant follicle for ovulation. The ovary releases the hormones that allow follicular development and oocyte maturation.[26] Follicle is regulated by paracrine and autocrine signals.

Before ovulation, change to follicle-stimulating hormone (FSH) promotes production of estrogens by growing follicles. Rising estrogen triggers the LH surge, which luteinizes the follicle, leading to secretion of progesterone, which prepares the endometrium for implantation. Ovulation is initiated by the dominant follicle's expansion and ends with its rupture if there is no fertilization, forming the corpus luteum, which is composed of different types of cells producing progesterone, estradiol, and androgens.[26]

LH is responsible for oocyte cumulus expansion and meiotic maturation, but more mediators are needed because LH levels are not high enough. Meiotic maturation and LH effects are mediated by prostaglandin $E_2$ ($PGE_2$). The release of LH increases $PGE_2$ levels, which increases the production of cyclic adenosine monophosphate, a maturation meiotic mediator that favors the maturation and cumulus expansion of oocytes.[27] LH and $PGE_2$ also stimulate angiotensin II, blocking the inhibitory effect of theca cells and promoting meiotic maturation[27] (Fig. 2).

According to the WHO, infertility issues can be divided on hypothalamic-pituitary failure, HPO axis dysfunction, and ovarian failure.[26]

Hypothalamic-pituitary failure negatively affects pubertal development, amenorrhea, and fertility. This group is characterized by hypogonadotropic hypogonadism that appears due to the absence of gonadotropic-releasing hormone (GnRH), which leads to low LH and FSH levels, ending on the dysfunction of full folliculogenesis and ovulatory ovarian function[28,29] (Fig. 3).

HPO axis dysfunction includes the PCOS, weight abnormalities, and endocrinopathies. PCOS appears in 6%–10% of reproductive-aged women and is used to lead oligo- or anovulation. This dysfunction is caused by several ovarian cells defects, resulting in an excessive androgen synthesis.[30]

Ovarian failure is the third group of ovulatory disorders. Physiologically, the number of oocytes decreases during the life of women, resulting in a decrease in quantity and quality of available oocytes after approximately 35 years old, very low levels in the 40s, and leading to menopause by the 50s. But elevated FSH or low estradiol levels before the 40s are defined as premature ovarian insufficiency. There are multiple causes that could lead to this pathology.[25]

## NUTRITION AND FERTILITY

There are several nutritional factors with potential interest based on their significant relationship with

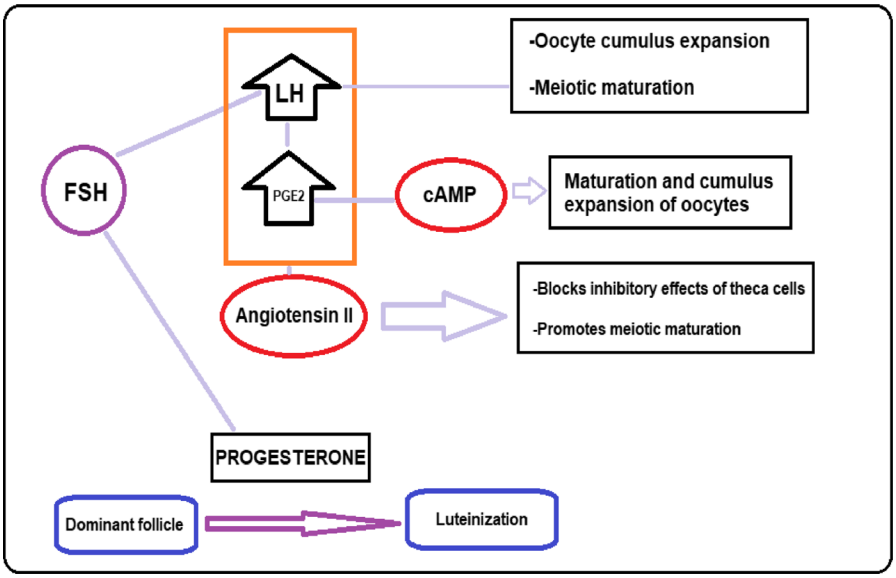


FIG. 2. **FSH induces LH release and the presence of progesterone receptors on granulosa cells.** The increase in progesterone stimulates the start of luteinization. LH is responsible for oocyte cumulus expansion and meiotic maturation. $PGE_2$ increases the production of cAMP, also favoring the maturation and cumulus expansion of oocytes. LH and $PGE_2$ stimulate angiotensin II, blocking the inhibitory effect of theca cells and promoting meiotic maturation. cAMP, cyclic adenosine monophosphate.

fertility in women. Obesity, dietary patterns, nutrients (fatty acids, vitamin D, folic acid, carbohydrates, and proteins, among others), and hormones (adiponectin, leptin, and vegetal sterols) have been highlighted as modifying parameters associated with female fertility according to a great number of studies and clinical trials.

## Obesity and Female Fertility

The follicular environment in obese women is altered with elevated levels of insulin, triglycerides, and inflammation markers.[5] The mechanism that inhibits regular ovulation is not clearly understood, but it is hypothesized that increased insulin levels could decrease FSH and decrease LH, thus augmenting androgen levels. Higher insulin levels could also decrease sex hormone–binding globulin and subsequently increase androgens, thus producing free testosterone levels and increasing selective ovarian tissue insulin resistance.[22] In the final stage, this milieu could block follicular growth, favoring anovulation (Fig. 4).

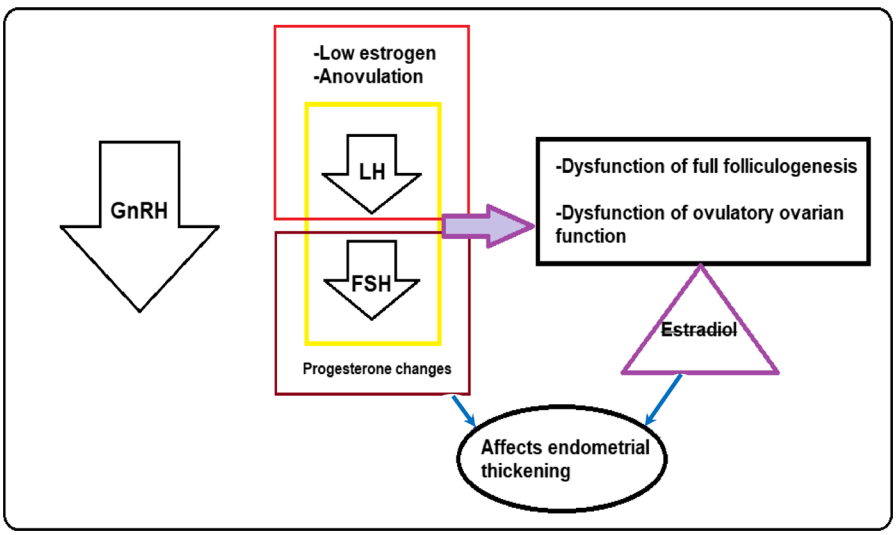


FIG. 3. **Hypothalamic pituitary failure is characterized by a suppression of GnRH pulsatility that finally ends with a decrease in LH (related to a low estrogen state and anovulation) and FSH (progesterone changes, which finally inhibit estradiol discharge).** These hormones cause the dysfunction of folliculogenesis and ovulatory ovarian function.

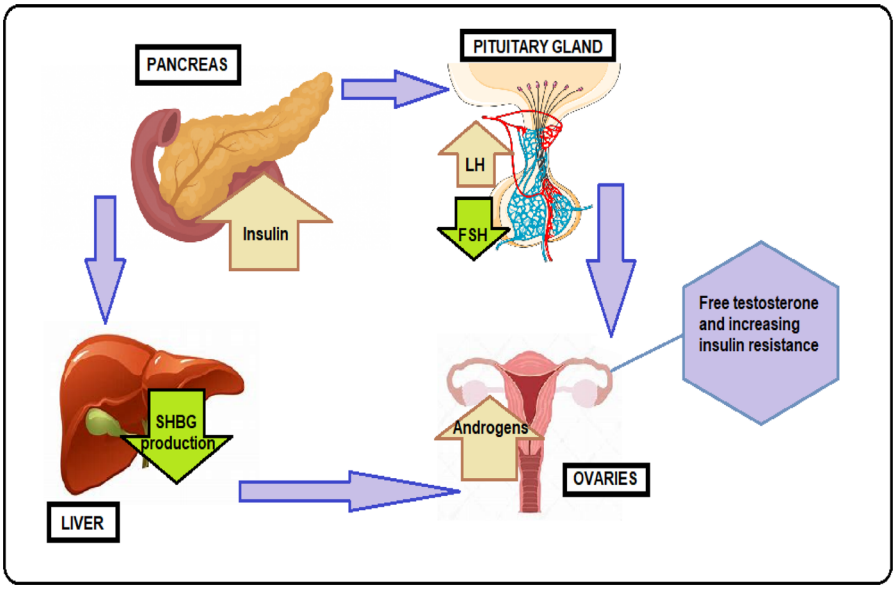


FIG. 4. **The increase in insulin levels decreases FSH and increases LH and decreases SHBG, which increases androgens.** Thus, augmenting free testosterone levels and increasing selective ovarian tissue insulin resistance. SHBG, sex hormone–binding globulin.

Regarding fertility and obesity, different studies have shown that appropriate weight loss could help to improve female fertility in overweight or obese women. The first related to this weight loss is by Kort et al,[31] who showed that a 10% weight loss in 63 overweight women led to an 88% higher conception rate than women who did not achieve 10% weight loss ($P = 0.049$).[31] In addition, a 10% weight loss in 71% overweight women had higher live birth rates than women who did not achieve 10% weight loss ($P = 0.024$) (Table 1). Subsequently, it was observed that a meaningful weight loss could improve fertility by better pregnancy and live birth rates, which also showed beneficial effects of weight loss on fertility treatment plans for overweight patients.[31] After them, Sim et al[32] made a similar study where weight loss had an important impact. It this study, 2 different groups were compared. One of them was the "weight loss intervention group" (27 women) treated with diet, exercise, and psychological advice for 12 weeks with a mean weight loss of 4.6 to 6.6 kg. The other group, the "standard care" (22 women), was advised to see their practitioner for weight loss advice. The intervention group had a significant weight loss, decreased BMI, and waist circumference (WC) compared with the standard group ($P = 0.001$).[32] Furthermore, the intervention group achieved a pregnancy rate of 48% when compared with the standard group, with 14% ($P = 0.007$). In addition, the intervention group took a mean of 2 treatment cycles to get pregnant, whereas the standard group required a mean of 4 treatment cycles ($P = 0.002$). Furthermore, a marked increase in live births was also observed when the intervention group was compared with the standard group (44% vs 14%, respectively; $P = 0.02$).[32]

As weight loss cannot be separated from caloric restriction, some studies have taken into account a restrictive nutrition plan, which helps in proportional and adequate weight loss. Proving the beneficial effects of these 2 points, Legro et al[11] enrolled 149 overweight/obese women (BMI 27–42 kg/m$^2$) separated in 3 groups during 16 weeks before fertility treatment: women with previous oral contraceptive treatment, lifestyle program women, and combined women (with both characteristics).[11] The lifestyle program included a weight loss goal of 7%, caloric restriction, behavioral modifications, and increased physical activity. Higher live birth rates appeared in the combined group compared with the previous oral contraceptive group ($P = 0.04$), and higher ovulation rates appear in the lifestyle group compared with the combined group ($P = 0.002$). The contraceptive treatment group did not achieve significant weight loss, and in addition, an increase in the prevalence of metabolic syndrome, including worst triglycerides ($P = 0.006$), glucose area under the curve ($P < 0.05$), and insulin sensitivity ($P < 0.01$) levels was observed. Thus, a significant relation between decreased body weight and better fertility rates was observed.[11] In a similar study, lifestyle modifications in 48 women during 16 weeks (caloric restriction, antiobesity medication, and increased physical activity) showed better ovulation ($P = 0.003$), clinical pregnancy ($P = 0.04$), and live birth rates ($P = 0.004$), compared with 47 women who took oral contraceptive

TABLE 1
Studies Associating the Impact of Obesity With Female Infertility

| Purpose | Patients and Samples | Main Findings | References |
|---|---|---|---|
| Evaluate the impact of meaningful weight loss on fertility outcomes | 63 overweight women | A 10% weight loss increased conception and live birth rates. | 31 |
| Evaluate a 12-wk program in obese women undergoing fertility treatments | 49 obese women | A 4.6- to 6.6-kg weight loss increased live birth rates and clinical pregnancy. | 32 |
| Evaluate a 16-wk program in overweight/obese women | 149 overweight/obese women | Combined group had higher live birth rates. Lifestyle group had higher ovulation rates. | 11 |
| Evaluate a 16-wk program in overweight/obese women | 95 women | Lifestyle modifications had better ovulation, clinical pregnancy, and live birth rates. | 6 |
| Evaluate the impact of obesity in embryo development | 218 oocyte from 29 women | Obesity affected quality embryos. Oocytes from obese women were smaller and less likely to complete development postfertilization. They also suffered metabolic modifications. | 33 |
| Evaluate obesity as a disruptor of female fertility | 2660 infertile overweight, obese and normal-weight women subjected to ART | Embryo quality decreased in obese women as an effect of lipotoxicity. Overweight and obese women needed higher doses of gonadotropins and had longer treatment courses, increased miscarriage rates, and reduced pregnancy, and live birth rates. | 34 |
| Evaluate the relation between BMI and female fertility | 116,678 women | Women with a BMI >32 kg/m$^2$ had 3 times greater relative risk of infertility as compared normal-weight women. | 35 |
| Link abdominal obesity to female infertility | 3239 women between 18 and 45 y | WC was a positive predictor of female infertility, independent of BMI. | 36 |

SHBG, sex hormone–binding globulin.



continuously during 16 weeks before fertility treatment without lifestyle modifications.[6] Thus, a pretreatment lifestyle modification could improve ovulation and live birth rates.

Even though weight is significant, there are serum parameters related to overweight and obesity with a significant influence in female health and fertility. It is widely accepted that hypercholesterolemia, increased nonesterified fatty acid concentrations, hyperglycemia, and insulin resistance are elements of metabolic dysfunction in overweight and obese women. In addition, an inflammatory state has been described.[37] In a retrospective, observational analysis of 218-oocyte size and the subsequent developmental kinetics from 29 women being treated with intracytoplasmic sperm injection (ICSI), it was observed that human oocytes from women presenting for fertility treatment with a BMI exceeding 25 kg/m$^2$ were smaller ($P = 0.001$) and therefore less likely to complete development postfertilization ($P < 0.001$).[33] Moreover, the resulting blastocysts from overweight women contained fewer cells in the trophectoderm ($P = 0.01$), and the resulting blastocysts also had reduced glucose consumption, modified amino acid metabolism, and increased levels of endogenous triglyceride ($P < 0.001$, for all). Furthermore, these differences were independent of male BMI. Similar results were obtained in a retrospective study with 2660 infertile women who underwent a total of 5019 treatments of in vitro fertilization (IVF) or ICSI segregated in 3 groups.[34] Results from obese, overweight, and normal-weight women were compared, finding that embryo quality decreased in the first group ($P < 0.005$) compared with the other 2 groups as an effect of lipotoxicity on the embryonic cells. Oocyte maturation was affected by the altered balance of driver hormones, insulin, glucose, lactate, triglycerides, and C-reactive protein.[34] The causative mechanisms of miscarriage in obese women were unclear, but it could be associated with an impaired stromal decidualization producing placental abnormalities, stillbirth, and preeclampsia. Furthermore, overweight and obese women submitted to ART needed higher doses of gonadotropins and longer treatment courses, had increased miscarriage rates and reduced pregnancy and live birth rates, and poorly responded to ovulation induction ($P < 0.001$, for all of them).[34]

Following serum parameters, inflammation has been also associated with obesity. Adipocyte hypertrophy promoted necrosis, infiltration of adipose tissue in circulating macrophages and T cells, and the production of proinflammatory cytokines, such as tumor necrosis factor $\alpha$, interleukin 6, and interleukin 8. When inflammation became chronic, an increase in reactive oxygen species (ROS) was observed, thus favoring ovarian function abnormalities and increasing the incidence of ovarian fibrosis.[38] The oxidative stress was observed in a study comparing the expression of inflammatory

and oxidative stress markers in oocytes from 11 obese women and 13 normal-weight women undergoing fertility treatments.[39] Oocytes from these obese women had increased expression of proinflammatory and oxidative stress–related genes compared with normal-weight women.

Oxidative stress is considered one of the major factors involved in the initiation of reproductive pathologies of females, such as preeclampsia, recurrent pregnancy loss, embryonic resorption, intrauterine growth restriction, and fetal death.[40] Normal levels of ROS are essential for various signal transduction pathways of oocyte maturation, folliculogenesis, luteolysis, and fetoplacental development; however, overabundance of ROS exerts damaging effects, and for that reason, the body has different enzymatic and nonenzymatic antioxidant defense mechanisms to work against the oxidative stress.[41] Natural antioxidant compounds found in fruits, vegetables, various medicinal plants, and other dietary sources can be broadly divided into 3 groups: vitamins, carotenoids, and phenolic compounds. Numerous studies in animals and humans have shown a decrease in the levels of oxidative stress markers after consumption of vegetables and fruits or antioxidant supplements.[42] Low consumption of antioxidant sources such as fruits and vegetables by females seems to increase their risk of endometriosis, one of the causative factors for female infertility.[43] Conversely, consumption of food and beverages enriched with polyphenols elevated the antioxidant capacity of plasma in humans and reduced the in vitro and in vivo oxidative stress in the human placenta and placental trophoblasts, respectively.[44] Another study demonstrated the significance of natural antioxidants vitamin C and vitamin E in reducing the oxidative stress in intrauterine growth–restricted pregnant women.[45] Regarding carotenoids, women with spontaneous preterm birth defects have been found to have a lower concentration of carotenoids in the serum, and premature birth risk is reduced with elevated serum concentrations of α- and β-carotene, α- and β-cryptoxanthin, and lycopene.[46] In a recent study performed in nonlactating dairy cows, the daily administration of β-carotene considerably improved the β-carotene availability in the microenvironment of the oocyte, regardless of the energy balance, thus favoring oocyte quality and development of follicles during maternal metabolic stress.[47]

Interestingly, parameters such as weight or BMI affect the health of an organism due to the problematic environment of higher and lower adipose tissue state. As an example, the cohort study of 116,678 female nurses registered in the United States reported that obese women with a BMI >32 kg/m$^2$ had 3 times greater relative risk of infertility as compared with normal-weight women, whereas overweight women with BMIs between 24 and 26 kg/m$^2$ had increased relative risk (1.3) of infertility. This was attributed to obesity that induced ovulatory and menstrual cycle dysfunction.[35] Conversely, another study showed that low BMI may indicate inadequate energy intake and status, thereby impacting gonadotropin concentration, follicle growth, and oocyte quality.[48] One study analyzing IVF outcomes found a significantly increased incidence of miscarriage in underweight women (BMI <18.5 kg/m$^2$) compared with normal-weight (BMI 18.5–25 kg/m$^2$) women ($P$ = 0.049). This study also reported reduced live birth, particularly for low-BMI women older than 35 years (24.6% vs 38.1%, $P$ = 0.003). This fact could be explained because excessively low body weight affects hormonal balances as well as reproductive physiology at the organ level, thus disrupting fertility.[48]

Very recently, a cross-sectional study including 3239 female participants aged 18–45 years analyzed the relationship between WC and infertility among women of childbearing age in the United States.[36] Interestingly, it was observed that WC was positively associated with female infertility independent of BMI after adjusting for BMI and other potential confounders. Moreover, when WC was divided into 5 equal groups, women in the highest quintile had 2.64 times' risk of infertility as those in the lowest quintile (odds ratio, 2.64; 95% confidence interval, 1.31–5.30), thus showing that WC was a positive predictor of female infertility, independent of BMI, and that moderate exercise can lower the risk of female infertility associated with abdominal obesity. To sum up, these studies demonstrated the importance of the context to make a decision in female fertility treatment.

All these observations highlight the importance of obesity in female infertility from different pathways, including increased inflammation and oxidative stress, oocytes with lower size and/or with meiotic deficiencies, poor embryos' quality, and deficient embryos' implantation, among others.

## Dietary Patterns and Female Fertility

Dietary patterns have been also associated with female infertility (Table 2). Fat intake has an important role in fertility, as observed in animal and human studies. In one of them, total fat intake in 240 infertile women was associated with the number of retrieved oocytes ($P$ < 0.05) and lower embryo quality rates ($P$ < 0.01).[49] These results were also confirmed in another study carried out in women with PCOS from the United States (n = 343) and Italy (n = 301). The first ones,

TABLE 2
Studies Analyzing the Impact of Dietary Patterns in Female Infertility

| Purpose | Patients and Samples | Main Findings | References |
|---|---|---|---|
| Evaluate the effect of a HFD in women's fertility | 240 infertile women | Total fat was associated with the number of retrieved oocytes and lower embryo quality rates. Alterations in menstrual cycle length and changes in reproductive hormone levels were also observed. | 49 |
| Evaluate the impact of caloric distribution in fertility | 644 women with PCOS from the USA and Italy | US women had higher saturated fat intake ending with higher BMI, more cardiovascular risks, and, subsequently, more difficulties to get pregnant. | 50 |
| Evaluate the relation between Mediterranean diet and pregnancy | 161 couples undergoing IVF/ICSI | Mediterranean diet correlated with an increased chance of pregnancy with an odds ratio of 1.4. | 51 |
| Evaluate the relation between Mediterranean diet and fertility | 17,544 women | Women's fertility was significantly associated with Mediterranean diet. Mediterranean diet and regular physical activity, among others, reduced 69% the risk of ovulatory disorders. | 52 |
| Evaluate preconception dietary patterns and time to pregnancy | 5598 nulliparous women | Preconception decreased fruit and vegetable consumption increased time to pregnancy, and the lack of fast-food intake was associated with lower time to pregnancy. | 53 |
| Evaluate adherence to Dutch diet and pregnancy outcomes | 199 women underwent a first IVF/ICSI treatment | A diet full of whole grains, fruits, vegetables, MUFAs and PUFAs, meat, and fish was related to pregnancy outcomes. | 54 |
| Investigate the association between nutrients and female infertility | 1713 women between 18 and 45 y | Higher intake of carbohydrate, vitamin A, vitamin C, magnesium, iron, lycopene, and total folate was associated with a lower risk of female infertility. | 55 |

HFD, high-fat diet.



with similar caloric intake, had higher saturated fat intake ending with higher BMI and more cardiovascular risks (impaired glucose tolerance, elevated low-density lipoprotein cholesterol, among others) and, subsequently, more difficulties becoming pregnant.[50] Furthermore, as observed in animal model studies, fat intake was associated with altered menstrual cycle length and changes in reproductive hormone levels, finally affecting reproductive outcomes.

However, macronutrients' distribution is only one of the parts included in a nutritional treatment; the important point is the global diet followed by each patient. As an example, it was observed that the adherence to a Mediterranean diet was correlated with an increased chance of pregnancy in 161 couples undergoing IVF/ICSI with an odds ratio of 1.4.[51] Previously, a study performed in a cohort of 17,544 women also showed that fertility was significantly associated with the Mediterranean diet (a diet full of monounsaturated fat, vegetable protein rather than animal sources, dairy products, low glycemic carbohydrates, and multivitamins). In addition, Mediterranean diet, weight control, and regular physical activity reduced by 69% the risk of ovulatory disorders.[52] Thus, this nutritional pattern might prove adequate treatment for infertility.

Nevertheless, a balanced diet (a diet that contains different kinds of foods in certain quantities and proportions so that the requirement for calories, proteins, minerals, vitamins, and alternative nutrients is adequate) could be a good treatment, as not every country or culture knows about or follows the Mediterranean diet. These balanced diets were studied in nulliparous women where the preconception intake of fruit and vegetables and fast-food intake was recorded.[53] It was observed that when fruit and vegetable consumption was lower than 1–3 times per month before conception, time to pregnancy increased ($P = 0.007$), whereas the lack of fast-food intake before conception was associated with a decrease in time to pregnancy ($P = 0.001$).[53] The adherence to the Dutch diet and its relationship with pregnancy outcomes were analyzed in 199 women who underwent a first IVF/ICSI treatment within 6 months after preconception counseling. This is a diet consisting of whole grains, fruits, vegetables, monounsaturated or polyunsaturated oils, meat, and fish. A significant positive association between the Dutch diet and pregnancy outcomes was obtained ($P = 0.02$).[54] Finally, a balanced diet showed similar evidence to Mediterranean diet, proving that it could be an adequate treatment against infertility.

More recently, a study investigated the association between nutrients and female infertility with a cohort of 1713 women between 18 and 45 years.[55] The result demonstrated that higher intake of carbohydrate ($P = 0.018$), vitamin A ($P = 0.009$), vitamin C ($P = 0.020$), magnesium ($P = 0.009$), iron ($P = 0.012$), lycopene ($P = 0.022$), and total folate ($P = 0.003$) were associated with a lower risk of female infertility. Importantly, in women with BMI >24.9 kg/m$^2$, higher intakes of magnesium, iron, and total folate were associated with a decreased risk of female infertility,[55] thus showing that changes in

potentially modifiable lifestyle factors, such as diet, could be associated with a lower risk of female infertility. This way, a balanced diet, such as the Mediterranean diet and the Dutch diet, both rich in fruit, vegetables, monounsaturated, and polyunsaturated oils, could be of paramount important to avoid female infertility.

## Nutrients and Female Fertility

Regarding nutrients, the impact of several macronutrients and micronutrients in fertility has been thoroughly reviewed and discussed (Table 3). The relationship between fat intake and ovulatory infertility was analyzed in 18,555 married women, without a history of infertility, from 24 to 42 years.[54] During follow-up, 438 incidents of ovulatory infertility were reported. It was observed that total fat, cholesterol, and most types of fatty acids intake were not related to ovulatory infertility. Conversely, ovulatory infertility risk was increased by approximately 70% when 2% of energy intake derived from carbohydrates or ω-6 polyunsaturated fats was substituted by *trans*-unsaturated fat consumption. In addition, more than doubled risk of ovulatory infertility was observed than this 2% of energy intake that came from monounsaturated fats.[56] Confirming these results, in another study, an elevated intake of *trans*-fatty acids in 823 generally healthy women was associated with higher risk of diabetes mellitus type 2 ($P = 0.02$) and higher blood levels of inflammatory markers, such as C-reactive protein ($P = 0.05$) and tumor necrosis factor α receptors 1 and 2 (STNF-R1 and STNF-R2; $P < 0.001$), which could negatively affect ovarian functions,[57] showing that *trans*-unsaturated fats increased the risk of ovulatory infertility when consumed instead of carbohydrates or other unsaturated fats.

Later, the relationship between fat intake and endometriosis was analyzed in 70,709 women using laparoscopic confirmation.[58] It was observed that a high

TABLE 3
Studies Analyzing the Impact of Nutrients in Female Infertility

| Type | Patients and Samples | Main Findings | References |
|---|---|---|---|
| Fatty acids | 18,555 women | Ovulatory infertility risk was increased when energy intake from carbohydrates, MUFAs, or ω-6 fatty acids was substituted by TFA consumption. | 54 |
| | 823 healthy women | High intake of TFAs was associated with higher risk of DM2 and higher blood levels of STNF-R1 and STNF-R2 and inflammatory markers. | 55 |
| | 70,709 women | TFAs consumption increased the risk of endometriosis, whereas ω-3 FA intake decreased it. | 56 |
| | 38 obese women | Higher PUFA intake increased the incidence of pregnancy. Higher ω-6 levels improve pregnancy. | 57 |
| | 105 women | Oleic acid was positively related to the mean numbers of oocytes. EPA was associated with pregnancy and palmitic acid with no pregnancy. | 18 |
| | 259 women | PUFAs were associated with higher progesterone levels. | 58 |
| Other macro | 35 PCOS women | Increasing protein intake reduced circulating androgen levels and improved insulin sensitivity, leading to better menstrual cyclicity. | 59 |
| | 18,555 women | Vegetable protein intake instead of carbohydrates and/or animal proteins decreased ovulatory infertility risk. | 54 |
| | PCOS women | Lower carbohydrates and high protein intake improved insulin sensitivity and decreased testosterone levels. | 60 |
| Micro | 43 IVF women | Serum and follicular Se low levels were associated with lower fertility rates. | 61 |
| | 69 PCOS women | Low Se levels have been associated with PCOS and with hyperandrogenism. | 62 |
| | 141 women | Low Se levels and elevated mercury were associated independently with infertility. | 63 |
| Vitamins | 232 women | Total folate intake increased implantation, clinical pregnancy, and live birth rates. Supplemental folate increased implantation clinical and fertilization rate and shows fewer maturate oocytes. | 64 |
| | 279 subfertile women | The increase in follicular folate was related to high pregnancy rates. | 65 |
| | 11,129 women | Folate intake higher than recommendations reduced the risk of spontaneous abortion and also related to lower frequency of sporadic anovulation and higher live birth rates. | 66 |
| | 223 women | Folate supplementation was related to better embryo quality, pregnancy outcomes, and lower ovulatory infertility. | 67 |
| | 540 women | <20 ng/mL 25-OH vitamin D circulating levels reduced ovulation; >45 ng/mL 25-OH vitamin D circulating levels increase live birth rates. | 14 |
| | 2700 women | Higher vitamin D levels increased clinical pregnancy. | 15 |

DM2, diabetes mellitus type 2; Macro, macronutrients; Micro, micronutrients; SFAs, saturated fatty acids; TFAs, *trans*-fatty acids; STNFR, tumor necrosis factor α receptors; ω-3, omega-3; ω-6, omega-6.

*trans*-unsaturated fat intake, due to a greater animal fat consumption, increased nearly 50% the risk of being diagnosed with endometriosis ($P = 0.001$). Conversely, a long-term higher intake of long-chain fatty acids, *trans*-fatty acids (TFAs), tumor necrosis factor α receptors (STNFR), omega-3 (ω-3), and ω-3 fatty acids decreased nearly 25% the risk of endometriosis ($P = 0.03$).[58] These observations suggest that diet could impact on the prevention of endometriosis, but because the origin and etiopathogenesis of this condition are not well-known yet, more investigation is needed to confirm it. More recently, the impact of diet modifications was analyzed in 38 overweight/obese women aged 18–40 years who underwent IVF with a previous reduced energy diet that included a substitution of a meal by a replacement meal (Optifast; Novartis) and 200 mL reduced fat milk consumption. In addition, they were included in a physical conditioning and walking program.[59] Adjusting BMI and smoking status, women with higher polyunsaturated fat intake and higher total ω-6 fatty acids levels had higher incidence of pregnancy ($P = 0.03$ and $P = 0.045$, respectively).[59] Thus, the alteration of fatty acids could be a relevant point to take into account in pregnancy rates in overweight and obese women going through fertility treatment in addition to lifestyle and physical activity.

Recently, 105 women aged 22–38 years were given a solution made of specific concentrations of oleic, stearic, palmitic, palmitoleic, myristic, arachidonic eicosapentaenoic (EPA), tricosanoic, docosahexaenoic, and liloneic methyl esters to evaluate serum and follicular fluid concentrations on fatty acids in women undergoing ICSI treatment.[18] It was observed that serum levels of oleic acid were positively associated with the mean numbers of mature oocytes ($P = 0.002$). In women who achieved pregnancy, higher concentration of EPA was found ($P = 0.006$), whereas in those who did not achieve pregnancy, higher levels of palmitic acid were found ($P = 0.02$). Moreover, the increase in PUFA levels promoted clinical pregnancy ($P = 0.04$) and live births ($P < 0.05$).[18] Thus, a relationship between certain fatty acids and better outcomes of fertility could be suggested. Confirming these results, PUFA levels were also associated with higher progesterone levels and consequently with a decrease in anovulation risk in 259 women from 18 to 44 years old ($P < 0.05$).[68]

Proteins also play a basic role in female fertility. The increase in protein intake was studied in 35 PCOS overweight women for weight loss. A reduction in circulating androgens levels ($P = 0.03$) and improved insulin sensitivity ($P < 0.05$) were found,[69] leading to a better menstrual cyclicity. In addition, in women older than 32 years, the risk of ovulatory infertility was reduced by vegetable protein intake instead of carbohydrates ($P = 0.01$) or animal protein ($P < 0.001$).[56]

Diets rich in carbohydrates and sugars also impact on women's fertility as they favor dyslipemia and insulin resistance, leading to hormonal and ovulatory disorders by increasing Insulin-like growth factor 1 (IGF-1) and androgen levels (typical on PCOS).[60] In women affected by PCOS, insulin sensitivity ($P < 0.001$) and testosterone levels ($P < 0.05$) were improved after carbohydrate reduction.[61,62] However, if these carbohydrates were substituted by *trans*-fat intake, rates of ovulatory infertility ($P = 0.02$) and endometriosis ($P = 0.001$) both increased.[56]

Micronutrients have also shown an important role in female fertility. In one study, oxidative stress was analyzed in women from 18 to 39 years who underwent IVF and ICSI after micronutrient supplementation.[12] Total antioxidant capacity and ROS were measured in follicular fluid and serum.[12] Higher levels of protein free -SH groups (free cysteine that has antioxidant properties) were observed in women after micronutrient supplementation compared with untreated women ($P < 0.05$), therefore suggesting a decrease in oxidative stress. During supplemented cycles, the number of oocytes not suitable for injection was reduced ($P = 0.01$),[12] thus showing a relationship between the oxidative status and fertility.

The role of micronutrients such as Se was analyzed in depth in one study.[70] Serum and follicular Se low levels were associated with lower fertility rates ($P < 0.05$) in 43 women undergoing IVF.[70] Moreover, low Se levels have also been associated with PCOS in women compared with a control group ($P = 0.002$) and with hyperandrogenism.[63] It has been hypothesized that Se-binding protein I acts as an antigen to ovarian autoimmunity, leading to infertility ($P = 0.02$) and primary ovarian insufficiency ($P = 0.019$).[64] Confirming these results, blood Se and metal levels were tested in 141 women aged 27–45 years. It was found that infertile group showed lower Se levels than control group ($P < 0.05$), and a significant association appeared between elevated mercury and infertility after adjusting Se levels and age ($P < 0.05$).[65]

Regarding vitamins, the relation between folate intake and fertility was analyzed in 232 women aged 18–46 years with at least 1 ART cycle completed.[66] Participants' previous ART diet was assessed by the use of a food frequency questionnaire. In addition, administration of other questionnaires of lifestyle factors, reproductive health, and medical history was performed. Each patient went into 1 of the 3 protocols clinically indicated: a luteal-phase GnRH agonist protocol, follicular-phase GnRH agonist/flare protocol, and GnRH antagonist protocol. Finally, a relation between folate intake and

fertility was obtained. Total folate intake increased implantation ($P = 0.01$), clinical pregnancy ($P = 0.007$), and live birth rates ($P = 0.01$). Supplemental folate increased implantation ($P = 0.03$), clinical pregnancy ($P = 0.03$), and fertilization rate ($P = 0.03$) and showed fewer maturate oocytes ($P = 0.02$).[66] Regarding folate intake, 279 subfertile women who underwent IVF were also supplemented with folic acid in another study.[66] The increase in follicular folate was associated with elevated pregnancy rates ($P = 0.03$) and lower frequency of sporadic anovulation.[67] These observations confirmed previous results of a study in 11,129 women.[71] It was observed that folic acid intake, even at higher levels than recommended, could favor the risk of spontaneous abortion before or during early pregnancy ($P < 0.001$) and favored higher live birth rates ($P = 0.01$).[66] Additionally, better embryo quality, pregnancy outcomes, and lower ovulatory infertility risk were significantly associated with folic acid supplementation in 223 women due to the increased progesterone levels and decreased risk of anovulation.[72]

Vitamin D also plays an important role in female fertility, and the effects of its supplementation have been previously analyzed. In a study, 540 women aged 18–39 years were randomized into 1 of 3 different fertility treatments: clomiphene citrate (for 5 days), metformin XR (twice a day), and a combination of both.[14] Circulating levels of 25-hydroxyvitamin D [25(OH)D] were measured. It was shown that <20 ng/mL circulating levels of 25(OH)D reduces ovulation ($P = 0.003$), whereas >45 ng/mL increases live birth rates ($P = 0.048$),[14] thus supporting the hypothesis that vitamin D affects embryo implantation. Moreover, in a recent meta-analysis, an increase in clinical pregnancies was obtained when comparing 2700 women with normal vitamin D intake versus deficient and insufficient vitamin D groups ($P = 0.02$).[15]

## Adipokines and Female Fertility

Adiponectin is an adipokine (bioactive peptides and proteins produced by the adipose tissue) with important roles in the regulation of energy homeostasis (including glucose and lipid metabolism) and in physiological functions.[72] It is widely known that its production is negatively correlated with obesity. Adiponectin has both local and systemic anti-inflammatory effects, and its impact in fertility has been widely studied[70] (Table 4). In one study, adiponectin concentration was analyzed in 78 women in reproductive age segregated into 2 groups (with and without endometriosis), with no differences in BMI between groups.[73] In women with endometriosis, serum adiponectin concentrations were lower than in women without endometriosis ($P = 0.008$), finding a correlation between serum adiponectin concentrations and endometriosis scores ($P = 0.006$).[74] In the ovary, adiponectin stimulated steroidogenesis by granulosa cells ($P < 0.05$), having a role in preimplantation embryo development and uterine receptivity ($P < 0.01$).[75] Adiponectin also produced an autocrine/paracrine control in pituitary cells, decreasing the GnRH receptor pulse ($P < 0.01$) and mRNA and LH release ($P < 0.05$).[93] Lower adiponectin levels were also found in 31 women with failure during implantation (previous unexplained implantation failures with more than 10 normal embryos) ($P < 0.05$).[94] Similar results were obtained in endometriosis cases ($P = 0.008$).[75] This hormone is detected in ovaries, follicular fluid, oocyte, corpus luteum, and theca cells, all of them important components involved in women's fertility.

In a more recent study, adiponectin/leptin (A/L) and homeostasis model assessment/adiponectin (H/A) ratios were analyzed in 150 PCOS infertile women and PCOS-recurrent pregnancy loss women in comparison with 50 non-PCOS women.[76] In this study, the A/L and H/A ratios were significantly decreased and increased in women with PCOS, respectively. A significant association was observed between the A/L and H/A ratios with PCOS, as well as PCOS-infertile and PCOS-recurrent pregnancy loss women, even after adjusting for potential confounders.[76] All these findings point the importance of adiponectin in fertility by helping the implantation process.

Leptin, another adipokine, is strongly involved in the control of food ingestion.[73] Leptin and its receptor show a maximum expression during the night in human beings, moment to a time of fewer ingestions and less appetite. Obesity generates resistance to leptin (similar to insulin resistance in type 2 diabetes mellitus), increasing their circulating levels and resulting in an inability to detect satiety despite high energy stores and high levels of leptin.[73] The relationship between leptin and fertility was demonstrated in a study with 52 women with low weight (young female athletes and ballet dancers) with menstrual disorder (within the last 12 months) and 3 years of training period during more than 4 hours per week.[77] After a 9 months' nutritional intervention with an increase in energy and nutrients, body fat mass increased ($P = 0.01$), thus significantly augmenting LH and leptin levels in both athletes and dancers, restoring regular menstrual cycles.[77] Interestingly, low serum leptin levels have been previously associated with a decrease in the GnRH receptor pulse, thus leading to ovulation inhibition, with reduced LH

TABLE 4
Studies Analyzing the Impact of Hormones and Endocrine Disrupting Chemicals in Female Infertility

| Hormone/ Compound | Patients and Samples | Main Findings | References |
|---|---|---|---|
| Adiponectin | 78 women | Serum adiponectin concentrations were lower in women with endometriosis. | 73 |
| | In vitro study | Adiponectin had modulatory effect on uterine receptivity during pregnancy. | 74 |
| | 31 women | Adiponectin levels were lower in women with implantation failures. | 75 |
| | 200 women | A/L and H/A ratios were significantly decreased and increased in women with PCOS, respectively. | 76 |
| Leptin | 52 women | In low-weight women with menstrual disorders, an increase in body fat mass elevated leptin levels, restoring regular menstrual cycles. | 77 |
| | 139 women with IVF treatment | Leptin levels were significantly associated with BMI and lower pregnancy rates with IVF. | 78 |
| | In vitro study | Elevated leptin levels affected embryo development by decreasing trophoblast sensitivity, thus reducing trophoblastic stem cell growth, proliferation, and increasing apoptosis. | 79 |
| | 100 women with primary subfertility and 100 fertile women | Leptin level was higher in women with subfertility compared with the control group. Leptin levels showed high sensitivity, specificity, and accuracy as predictors of subfertility. | 80 |
| Phytoestrogens | 11,688 North American Adventist women | Isoflavone intake was significantly associated with a decrease in the probability of giving birth ($P = 0.05$) and getting pregnant ($P = 0.03$). | 81 |
| | Two different women cohorts | Phytoestrogen intake was not substantially associated with fecundability in either cohort. | 82 |
| BPA | Review studies | BPA intake affected the maturating of the oocyte, decreased reproductive capacity, and delayed or eliminated puberty, was involved in PCOS etiopathogenesis, and decreases estradiol levels (before oocyte retrieval) and/or increased testosterone levels. | 83,84 |
| | 178 women who underwent IVF cycles | Women in the fourth quartile of urinary BPA levels had lower probability of implantation ($P = 0.007$) and clinical pregnancy ($P = 0.03$) than lower quartiles. | 85 |
| Phthalates | 155 maternal and infant pair | Phthalates have been negatively associated with free testosterone and with free testosterone/estradiol ratio measured in the cord serum of female infants. | 86 |
| | 20-d-old female rats | Phthalate ingestion lowered serum levels of progesterone and estradiol. | 87 |
| | 3-generation female mice experiment | Oral administration in female mice decreased estradiol, FSH, and LH levels and caused high pup mortality. | 88 |
| | 55 children at 8 y of age | Phthalate exposure promoted lower sexual development, shorter fundi and uteri lengths, and lowered estradiol levels in girls. | 89 |
| Environmental pollutants | 1463 AMH measurements | AMH was lower in women living in the worst-polluted areas. | 90 |
| | 1916 recruited couples | An increase of 10 μg/m in PM2.5 levels was associated with an adjusted decrease in fecundability of 22%. $NO_2$ levels were also associated with decreased fecundability. | 91 |
| | 17 couples undergoing ART procedures | Higher levels of Pb and Cd influenced oocyte maturation and quality. Cumulus cells showed scarcely active steroidogenic elements. | 92 |

A/L, adiponectin/leptin ratio; H/A, homeostasis model assessment/adiponectin ratio.

secretion associated with delayed menarche and with changes in LH pulse frequency resulting in amenorrhoea.[77]

Conversely, diets rich in fats increased leptin levels (as seen in obese patients), thus interfering with estradiol production and oocyte maturation and ending with reproductive dysfunctions.[63] In another study, leptin levels were compared in 139 women, finding a significant relation between these hormone levels, BMI ($P < 0.0001$), and pregnancy rates with IVF ($P = 0.023$).[78] Multiple logistic regression analyses showed the best correlation between serum leptin and pregnancy success, thus demonstrating that in obese women low levels of leptin were associated with becoming pregnant, whereas higher leptin levels than expected in women with relatively low BMI were associated with difficulties in getting pregnant.[79]

It has also been observed that elevated leptin levels affected embryo development by decreasing trophoblast sensitivity, thus reducing trophoblastic stem cell growth,

proliferation, and increasing apoptosis ($P < 0.01$).[78] In addition, leptin remodeled the endometrium by stimulating proliferation and apoptotic cell pathways and changing endometrial receptivity, which negatively affected implantation.[5] This way, it could be said that moderate levels of leptin are associated with higher pregnancy rates. Thus, in low-BMI women, it is important to increase leptin levels, whereas in obese women, it is mandatory to do the opposite.

In a very recent study, a total of 100 women with primary subfertility and 100 fertile women were included, and the levels of serum leptin were measured.[80] It was observed that the mean leptin level was higher in women with subfertility compared with that of the control group, $26.8 \pm 15.2$ and $6.4 \pm 2.3$ ng/mL, respectively ($P < 0.001$). As observed previously, leptin level significantly increased with a higher BMI ($P < 0.001$). In addition, leptin at a level of 11 ng/mL or higher was a significant predictor of infertility (odds ratio, 2.793). Importantly, leptin levels showed high sensitivity, specificity, and accuracy of 96%, 98%, and 96.9%, respectively, as predictors of subfertility. As a result, it could be said that a high leptin level was a strong and valid predictor of subfertility,[80] thus proving the importance of adipokines in female fertility.

## ENDOCRINE-DISRUPTING CHEMICALS AND FERTILITY

Epidemiologic evidence has shown that exposure to environmental chemicals can have an effect on fecundity, growth, and development in animals and humans. Some of the compounds that are associated with fertility problems are phytoestrogens, BPA, phthalates, environmental contaminants, and air pollutants (Table 4).

Phytoestrogens are plant-derived natural substances that can bind to estrogen receptors causing estrogenic and antiestrogenic effects.[24] The most common sources are isoflavones (including genistein or lignans), which are commonly found in soy products, flaxseed, and oil seeds. Literature suggested that both low and high doses of phytoestrogens could cause a negative effect on ovarian function and folliculogenesis due to their bell-shaped role.[24,80] A cross-sectional study was carried out in 11,688 North American Adventist women aged 30–50 years with a high proportion (54%) of vegetarians and a healthy lifestyle and with a very low prevalence of smoking and alcohol use. It was observed that higher isoflavone intake was significantly associated with a decrease in the probability of giving birth ($P = 0.05$) and getting pregnant ($P = 0.03$).[81] On the other hand, another study performed with 2 different cohorts of women, PRESTO (Pregnancy Study Online) (from the United States) and SF (Snart Foraeldre) (from Denmark) with a record of individual phytoestrogen intake from validated food frequency questionnaires, showed that phytoestrogen intake was not substantially associated with fecundability in either cohort, although in both cohorts some evidence of improved fecundability with increasing isoflavone intake was found. Thus, due to these contradictory results, more studies should be planned to confirm the exact role of phytoestrogens in female fertility.[82]

Another important complex, BPA, is an aromatic organic compound found in plastic used for different scenarios such as food packaging, epoxy resins, and temperature-sensitive papers.[24] In fact, urine samples of a control study showed that everyone is exposed to this substance through skin, inhalation, and/or ingestion.[24] BPA is an endocrine disruptor that mimics estrogen receptors.[24] Its negative effect on female fertility has been proven in several studies: affecting the maturation of the oocyte, decreasing reproductive capacity, delaying or eliminating puberty, being involved in PCOS, decreasing estradiol levels (before oocyte retrieval), and/or increasing testosterone levels.[83,84] In addition, another study observed that women in the fourth quartile of urinary BPA levels had lower probability of implantation ($P = 0.007$) and clinical pregnancy ($P = 0.03$) than lower quartiles.[85] All these results highlight the importance of BPA in fertility and fecundity.

As a large group of compounds, phthalates are used as liquid plasticizers found in products including plastics, coatings, cosmetics, and medical tubing. These products have been negatively associated with free testosterone and with free testosterone/estradiol ratio measured in the cord serum of female infants.[86] In addition, phthalates reduced estradiol serum levels in in vivo and in vitro studies.[87] Similarly, weekly oral administration for 29 weeks of the environmental contaminant 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in female mice decreased estradiol, FSH and LH levels and caused high pup mortality.[88] Furthermore, in a study performed in 55 children at 8 years of age confirmed that high exposure to environmental contaminants such as TCDD and polychlorinated biphenyls promoted in girls a significantly greater proportion in genital stage 1 (lower sexual development), shorter fundi and uteri lengths, and lowered estradiol levels,[89] thus showing that these compounds impaired reproductive development in girls.

Finally, fine particulate matter (PM2.5) presents a substantial global health concern from air pollution. Very recently, the existence of a link between higher air pollution and reduced fertility was assessed by determining serum levels of anti-Müllerian hormone (AMH). This hormone is released by ovarian somatic cells and is used as a marker of a woman's ovarian reserve, which represents the number of viable eggs the

ovaries can produce. After measuring the daily levels of PM2.5–10 and nitrogen dioxide ($NO_2$) in areas around Modena City, serum AMH levels were quantified, finding a significant decrease in AMH in women living in the worst-polluted areas. Although the relationship between AMH levels and the chances of becoming pregnant naturally is still debated, these results support the idea that environmental pollutants can interfere with ovarian physiology.[90] The endocrine effects of environmental pollutants have been demonstrated in in vitro and in vivo studies, thus suggesting that these air pollutants might promote oxidative stress and exert genotoxic effects by the exposition to $NO_2$, ozone, sulfur dioxide, carbon monoxide, and particulate matter (from 2.5 to 10 mm), which were associated with reduced live birth rate and fecundity, whereas they increased miscarriage and stillbirths.[95] In one study, environmental averaged fine particulate matter (PM2.5), carcinogenic polycyclic aromatic hydrocarbons, ozone, $NO_2$, and sulfur dioxide were measured and associated with fecundability.[91] It was observed that each increase of 10 μg/m in PM2.5 levels was associated with an adjusted decrease in fecundability of 22%. $NO_2$ levels were also associated with decreased fecundability, whereas no evidence of adverse effects was found with the other pollutants considered.

In a very recent study, it was observed that exposure to metals such as lead (Pb) and cadmium (Cd) had several adverse effects on human reproductive system.[92] Thus, the potential reproductive effects of Pb and Cd levels on blood and on the follicular fluid and oocytes' and cumulus cells' ultrastructure were investigated in 17 couples undergoing ART procedures, showing that higher levels of Pb and Cd could be associated with morphological alterations of both the oocytes' and cumulus cells' ultrastructure. Importantly, oocytes were affected in maturation and quality, whereas cumulus cells showed scarcely active steroidogenic elements, correlating with delayed oocyte cytoplasmic maturation,[92] thus highlighting the negative impact of heavy metal levels for fertilization, embryo development, and pregnancy.

All these observations confirm that contaminants with endocrine-disrupting effects are quite important in fertility, and EDCs formed from pollutants and plastics can impair the endocrine system and consequently the fertility state.

## CONCLUSIONS AND FUTURE PERSPECTIVES

Obesity is typically related to metabolic dysfunctions (hypercholesterolemia, hyperglycemia, insulin resistance, and inflammatory state) altering the follicular environment. Oocytes decrease in obese women, and the intake of *trans*-fatty acids damages them, also decreasing embryos quality. In addition, obese women have higher inflammatory markers and leptin, worsening endometrial receptivity. In obese and overweight women, higher blood insulin levels were found, producing hyperandrogenism and steroidogenesis, alterations that cause menstrual cycle disorders and oligo- or anovulation, with lower probabilities of pregnancy. Chronic inflammation increases ROS, promoting ovarian function abnormalities and increasing ovarian fibrosis. These dysfunctions end with difficulties in ART, needing higher gonadotropin doses and longer treatment courses for follicular development and ovulatory cycles, spending more money and more time. In overweight and obese women, weight loss before ART increased conception, live birth, and ovulation rates.

Regarding dietary patterns, diets full of fats decrease embryo quality, alter menstrual cycle length, and change reproductive hormonal levels. Otherwise, Mediterranean diet increases the chance of pregnancy and decreases ovulatory disorder infertility and the rates of pregnancy difficulties. Similarly, a balanced diet increases fertility. Furthermore, hypercaloric and hypocaloric diets in women with elevated body weight and low body weight, respectively, affect ovarian function, increasing the risk of women's infertility and time to pregnancy. However, caloric intake is not the only element to take into account, but macronutrients' distribution is also quite important.

In regard to nutrients, higher intake of *trans*-fats increases ovulatory infertility and endometriosis risk. PUFAs reduce the anovulation risk, whereas they increase the incidence of pregnancy and live birth rates. Oleic acid is associated with better embryo quality and pregnancy outcomes and lower ovulatory infertility. Total folate increases implantation, clinical pregnancy, and live birth rates and decreases the risk of spontaneous abortion and frequency of sporadic anovulation. Vitamin D likely increases clinical pregnancy and live birth rates, but more studies are needed to confirm it. The increase in carbohydrate intake elevates IGF-I and androgen levels, thus promoting hormonal and ovulatory disorders. In overweight women, weight loss with a higher intake of proteins has been related to better menstrual cyclicity. Low serum and follicular Se levels have been associated with lower fertility rates and endometriosis.

Regarding hormones, adiponectin levels are low in obese women, decreasing uterine receptivity and producing failure during implantation. Higher leptin levels appear in obese women, causing reproductive dysfunction and affecting embryo development. In very-low-weight

women with menstrual disorders, leptin levels are decreased, and when supplemented, a restoration of the menstrual cycle is achieved, and ovarian and endometrial morphology improves.

EDCs play an important role in human fertility and fecundity. Nowadays, hundreds of environmental chemicals with EDC activity have been discovered and grouped, depending on their effect on human health. Several studies have shown a reduction on fertility, live births, and estradiol and progesterone levels after prolonged exposition to these compounds, especially in early stages of sexual development. This way, it is of paramount importance to establish with further studies safer levels of consumption and exposure as most of the present studies are too small to find strong conclusions.

In the future, more studies analyzing the impact of nutrients, dietary patterns, hormones, and EDCs in women's fertility need to be done. However, new horizons in female fertility might demonstrate that healthy nutritional interventions such as Mediterranean or balanced diet, together with adequate exercise levels, would be a successful pretreatment in fertilization industry.

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