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Review

Female obesity and infertility: A Narrative Literature Review

Obesidad e Infertilidad Femenina: Una Revisión Narrativa

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Abstract

Obesity is associated with various adverse maternal and fetal effects prenatally, but can also cause infertility. Adipose tissue through the production of many factors, such as leptin, free fatty acids (FFA) and cytokines, can affect the functions of both the ovary and the maturation of oocytes and the receptivity of the endometrial epithelium. Reducing obesity improves women's reproductive health. The objective of this study is to update documentation on female obesity and infertility. Methods: It was a review of the literature. The scientific search was carried out in databases such as Scopuss, Pudmed, Scielo, and in indexed and impact journals, using descriptors in English such as And, Or, In among others, the inclusion and exclusion criteria were taken into account for select from each database. Results: 70 articles were found, of which 40 were left that were eligible. These were mostly original, quantitative research, carried out with surveys, with logistic regression, published within the last 5 years. Conclusions: Obesity may contribute to ovulation problems and irregular menstrual periods. It also contributes to a lower response to infertility treatments and spontaneous abortions.

Keywords: Obesity; Infertility, Female (Source: MeSH, NLM).

Resumen

La obesidad se asocia con diversos efectos adversos maternos y fetales prenatalmente, pero también puede causar infertilidad. El tejido adiposo a través de la producción de muchos factores, como la leptina, los ácidos grasos libres (AGL) y las citocinas, puede afectar las funciones tanto del ovario como de la maduración de los ovocitos y la receptividad del epitelio del endometrio. Al reducir la obesidad mejora la salud reproductiva de las mujeres. El objetivo de este estudio es actualizar documentalmente la obesidad femenina e infertilidad. Métodos: Fue una revisión de la literatura. La búsqueda científica se realizó en base de datos como Scopus, Pudmed, Scielo, y en revistas indexadas y de impacto, utilizando descriptores en idioma inglés como, And, Or, In, entre otros, se tomó en cuenta los criterios de inclusión y exclusión para seleccionar de cada base de datos. Resultados: se encontró 70 artículos, de los cuales se dejó 40 que fueron elegibles. Estos eran en su mayoría investigaciones, originales, cuantitativos, realizados con encuestas, con la regresión logística, publicados entre los últimos 5 años. Conclusiones: la obesidad puede contribuir a los problemas de ovulación y a los períodos menstruales irregulares. También contribuye a una menor respuesta a los tratamientos para la infertilidad y a los abortos espontáneos.

Palabras clave: Obesidad; Infertilidad; Femenino (Fuente: DeCS, BIREME).

Introduction

Infertility is the failure to conceive after twelve months of regular unprotected intercourse, or ineffective assisted insemination according to the Practice Committee of the American Society for Reproductive Medicine [1]. The World Health Organization (WHO) infertility affects approximately 50-80 million women worldwide, with a higher prevalence in developing countries compared to developed countries 44.2% vs 8 % [2]. In terms of sex, the ratio is 1:1, with an estimated 40% depending on individual causes, mainly due to overweight or obesity [3]. A study that compared the risk of infertility in obese women with women with normal weight reported that the risk of infertility was 25% vs. 12%, respectively, concluding that obesity and infertility are pathologies that have a direct relationship [4]. Obesity is a chronic, non-communicable, modifiable disease characterized by the hypertrophy of adipose tissue that currently affects any population group and has increased notably in recent decades [5]. The WHO estimates that by the year 2035, 67% of the population will be overweight or obese [6]. Among the main causes of obesity are genetic factors 10%, cultural factors 5% and individual factors 60% [7]. At the metabolic level, obesity predisposes to multiple pathologies such as type 2 diabetes mellitus, dyslipidemia, coronary heart disease, osteoarthritis, cancer and hormonal alterations [8]. Studies report that obesity is responsible for infertility in both sexes and its relationship with the inadequate functioning of the hypothalamic-pituitary axis with direct effect on gametogenesis and sex hormone synthesis [9][10].

Reproductive Physiology

The hypothalamus, pituitary and the synaptic networks that make up the hypothalamic-pituitary axis are necessary for reproduction [11]. The hypothalamus is a structure located in the diencephalon, with ample irrigation for neurohumoral and neurosynaptic control and regulation. The pituitary is a structure histologically differentiated in two areas adenohypophysis and neurohypophysis, its function is oriented to the secretion of hormones. Both constitute the hypothalamic-pituitary axis, which is a physiological unit that integrates the hypothalamus and pituitary through neuronal networks for the secretion of hormones with metabolic regulatory activity [12].

In the hypothalamus, about every hour, the arcuate nucleus generates gonadotropin-releasing hormone that causes the release of luteinizing and follicle-stimulating hormones by the pituitary gland [13]. Thus, the increase of these hormones result in stimulating the development of a group of primordial follicles and an increase of estradiol E2, by means of which the cells of the so-called ovarian granulosa, stimulate a dominant follicle that matures in the middle of the menstrual cycle, thus preparing for the ovulation process, so that during this phase, under the trophic predominance of estrogen, the endometrium begins its proliferative cycle, presenting, at the same time, an increase in the thickness of its stroma, its vessels and its glandular structures [14].

Obesity and Infertility

Obesity is associated with menstrual disorders characterized by irregular and anovulatory cycles; it has been observed that pregnant women with BMI 30 present obstetric complications such as spontaneous abortion, preeclampsia, eclampsia and gestational diabetes [15]. In polycystic ovary syndrome, there is hormonal dysregulation due to a decrease in luteinizing hormone and follicle stimulating hormone, responsible for the synthesis of estradiol and follicle capacitation [16]. In obese women, low levels of gonadotropin hormone have been detected, which is responsible for the synthesis of follicle stimulating and luteinizing hormone [17]. As well as decreased synthesis of estradiol, Inhibin B and antimullerian hormone [18]. Therefore, obesity causes dysregulation of the hypothalamic-pituitary axis, producing hypogonadotropic hypogonadism with consequent infertility [19]. It has been demonstrated in several studies that the intake of polyunsaturated fatty acids goes hand in hand with growth in estrogens, in luteal progesterone and less risk of anovulation, in contrast with the consumption of trans fats, endometriosis is observed and a greater probability of anovulatory infertility [42].

Effect of Insulin on Infertility

Obese patients, due to their adipose hypertrophy and hyperplasia, are in a state of permanent oxidative stress, which is characterized by an increase and change in the activity of macrophages from anti-inflammatory Type M2 to pro-inflammatory Type M1 [20]. The increase of proinflammatory cytokines in the obese, such as tumor necrosis factor and protein kinase together with M2 macrophages, inhibit the binding of insulin to the receptor favoring resistance and therefore stimulating increased insulin production [21]. The high levels of insulin stimulate the suprarenal glands with the generation, on the part of the ovary, of androgens, and that, increases the denominated aromatization peripheral of the sexual hormones, also the conversion of excess of androgens to estrogens, in the considered adipose tissue, aspects that tend to the increase of free estrogens, and at the same time, disturb the hypothalamic-pituitary-gonadal axis, with a decrease in luteinizing hormone, triglycerides, insulin, estrone, androstenedione, and low density lipoproteins, a situation that disturbs the secretion of gonadotropin-releasing hormone, which threatens follicular development, and of course, leads to produce anovulatory or irregular cycles [22]. Physiologically, the ovary is influenced by insulin through insulin receptors, such as insulin-like growth components located in the theca, granulosa and stromal cells [23]. This hormonal substance generates steroidogenesis in theca cells, as well as in granulosa cells, and also enhances the stimulatory effect of luteinizing hormone (LH) by increasing the number of receptors allocated for LH [24]. An important action of insulin is established at the level of the

hypophysis, which generates an increase in the sensitivity of the gonadotropins towards the gonadotropin-releasing hormone, known as GnRH, which tends to increase ovarian steroidogenesis [25]. Another relevant action is to harmonize the biological availability of steroids of sexual character, according to the inhibition of the hepatic synthesis of the sex steroid transporting globulin (SHBG) [26][27].

Effect of Adipokine on Infertility

High levels of adipokine, a cytokine with an effect on visceral fat by favoring the synthesis of other adipokines such as leptin and cytokines such as tumor necrosis factor and interleukin 6 [28][29], have been demonstrated in obese individuals. In vitro research has shown that leptin dysregulation influences steroid synthesis pathways in the granulosa [30][31][32][33]. Therefore, in high concentrations leptin produces: alteration in folliculogenesis; alteration in the secretion of gonadotropin-releasing hormone (GnRH), alteration in the regulation of peri-follicular oxygen supply and alteration in the regulation of ovarian steroidogenesis [34].

The Effect of Obesity on Sexual Cycle

The sexual cycle of the woman is the product of endocrine systematization, in such a way that the possibility of human gestation results from the interaction between the hypophysis, the ovaries, the hypothalamus and the uterus [35]. The menstrual process in women comprises the endometrial cycle and the ovarian cycle; the ovarian cycle consists of two phases, the luteal and the follicular; the endometrial cycle, on the other hand, contains three phases: secretory, proliferative and desquamation [36]. Physiologically, during the maximum level of luteinizing hormone, at the level of the theca of the ovary the concentration of neutrophils and M2 type macrophages increases, which secrete cytokines that favor the migration of activated lymphocytes that indirectly increase the development of the pre-antral follicle and decrease granulosa cell proliferation with the consequent synthesis of estradiol and progesterone [37]. In vitro studies have shown that the concentration of macrophages and the production of interleukin 8 IL-8 mark the beginning of luteinization, while Interleukin 1 IL-1 favors ovulation [38].

Obesity, having an effect on inflammation by stimulating the production of proinflammatory cytokines mediated by M1 type macrophages, acts directly on follicle development [39]. It has been shown that obesity increases antral apoptosis in addition to the increase of antral follicles, atresic follicles and decrease of primordial follicles triggering loss of follicular reserve and infertility [40].

Effect of Obesity on the Endometrium

Endometriosis is a pathology that affects women due to the growth of the stroma and endometrial glands occurring outside the uterine cavity [43]. The consequent inflammation and ectopic endometrial tissue can cause infertility, interfere in the transit of the fallopian tubes (15%), dysmenorrhea, chronic pain and dyspepsia [45]. The endometrium in turn is also susceptible to increased levels of adipokines, such as leptin, which affects steroidogenesis, producing stromal decidualization in obese women and causing sub fertility [46]. It also favors the development of gynecological cancers such as endometrial and breast cancer [47].

Effect of obesity on fertilization

It has been determined that obese women tend to have a propensity to acquire ovulatory dysfunction, due to a dysregulation of the hypothalamus-pituitary-ovary axis, producing the so-called hypogonadotropic hypogonadism, which manifests itself due to a decrease in the concentrated grouping of the hormones luteinizing, follicle stimulating and estradiol. This condition is manifested when there are weight disorders or with excessive exercise [48].

In women, obesity causes a decrease in egg quality and menstrual alterations. According to the latest National Activity Report of the Spanish Fertility Society (SEF), 180906 assisted reproduction treatments were performed in 2019. Dr. Luis Martínez Navarro, president of the SEF, mentions: “In addition to age, obesity and its complications are the factors that in our environment have the greatest influence on the decrease in fertility. Obesity decreases the rate of live newborns and clearly increases the rate of miscarriage” [49].

According to the coordinator of the SEEN Obesity group, Dr. Ana de Holanda, estimates that for every point increase in BMI (Body Mass Index), the probability of spontaneous pregnancy decreases by 10%. Ana de Holanda, estimates that for the growth or increase of each point in the BMI (Body Mass Index) the probability of spontaneous pregnancy decreases by 10%, in addition, it is calculated that after assisted reproduction techniques, for each point increase in BMI, the number of live births is reduced by 9%, that is, obesity is related to alterations in ovulation, even without the presence of polycystic ovary obesity alters the ovulation process [50].

In short, women with obesity are less likely to become pregnant after assisted reproduction techniques or spontaneously, and the probability of pregnancy in women with severe obesity is projected to be half that of women of normal weight [51].
Women who suffer from obesity take longer to become

pregnant spontaneously, as it turns out that these pregnancy rates are lower than the normal ones, since the risk of infertility is 3 times higher in obese women, and an inverse relationship between weight and fertility can be established, especially in women under 35 years of age [52]. Thus, overweight is related to anovulation, to alterations of the embryo and its development, to low oocyte quality, to decreased uterine receptivity, as well as to reduced embryo implantation in the uterus [53]. In addition, in the case of successful pregnancy, obesity has been associated with gestational diabetes, premature delivery, low birth weight and increased risk of miscarriage, congenital defects and fetal death [54].

Infertility Treatment

Diet in obesity and fertility

In the study by Berry *et al* (2020), it was observed that calorie restricted diets had a positive impact on the fertility rate, which increased to 7%. Similar data were obtained from the Svetkey study, in which the fertility rate increased to 5% in patients on restrictive diets monitored by applications. Another study showed that fertility success after weight control increased by 5%. Among the diets proposed, a restrictive scheme at 800 Kcal/day has been shown to have an effect on fertility [56].

Controlled clinical studies have been developed to compare the impact of calorie-restricted vs. fat-restricted diets on fertility, finding that diets limited to 40g/day have greater effects on fertility [57].

In another study it was shown that weight loss of 2.5 kg has a greater effect on fecundity, a weight loss limit was not established to have a greater probability of fecundity, however it has been corroborated that from the moment a woman begins to lose 1.4 kg, there is a progressive increase in pregnancies [58].

In conclusion, it has been shown that weight control plus regular physical activity improve the fertility rate, in addition to decreasing the 6% weight, ovulation increases as well as the estrogen level, it has been estimated that diet and physical activity decreases infertility 2 to 3 times, as well as insulin resistance and fetal malformations [59].

In the controlled clinical trial study by Yahya et al (2019) of 45 women with obesity and infertility, it was found that the addition of dietary supplements such as vitamin D and Coenzyme Q10 improved ovulation rates by 47% in obese women and in women with polycystic ovary syndrome who were resistant to clomiphene citrate [60].

The study by Zhang *et al* (2020) evaluated the prescription of a high-protein diet in 2217 infertile women with menstrual disorders over 18 years of age and found that diets rich in meat promote ovulation in obese infertile women and women with polycystic ovary syndrome (54.60 % vs. 41.30 %, RR 1.69 (95 % CI 1.28-2.23), $p < 0.01$) [61].

Obesity and fertility surgery

The study by Joice et al (2020), in which a prospective analysis of 71 women with superobesity and a history of impobility of pregnancy was carried out, they underwent bariatric surgery of the malabsorptive type and a follow-up of 3 years. In this study the group was divided into 2 groups, the first group with a history of polycystic ovary and the second group with primary infertility, a reduction in BMI was observed, in addition 42.9% of the women with primary infertility could be fertilized 3 months after normalizing their BMI, 57.1% achieved natural fertilization, the majority of deliveries were vaginal in 63% [62].

In the study by Wang *et al* (2022) a retrospective analysis was made of 31 women with fertility difficulties and alterations in menstruation, the analysis showed normalization of menstrual disturbances in 77% as well as other comorbidities such as type 2 diabetes mellitus and hypertension. In addition, it was seen that 53% achieved natural fertilization, only 3% had complications during pregnancy, in this study showed that women with obesity and infertility undergoing restrictive bariatric surgery, the average time to achieve a natural fertilization is 2 years [63].

In the study by Gema et al (2022), an analysis of the impact of obesity surgery on infertility and polycystic ovary syndrome was carried out in a retrospective descriptive analysis of 872 women who underwent bariatric procedures, 40% achieved natural reproduction 12 months after the procedure. In relation to the surgical procedure performed and its correlation with fertility, it was found that laparoscopic vertical gastrectomy presented 17.8% of reports of natural fertilization, followed by gastric Bypas with 7%, in patients with polycystic ovary there was evidence of 52.9% of normal menstrual dysregulation [64].

The study by Hannes et al (2023), which evaluated the time to fertilization after surgical procedures for the management of obesity in infertile women, it was found that of 1060 women who gave birth, those who achieved fertilization after 12 months of surgery, only 5% had complications during pregnancy, In the group of women who achieved fertilization at 24 months, only 1% presented complications, therefore it was concluded that a time between 24 to 34 months is recommended to reduce complications during pregnancy, it is important to note that despite the complications, no malformations or alterations in the development of the newborn were reported [65].

Pharmacologic treatment for obesity and fertility

In relation to the use of pharmacological mediation for weight control and its effect on fertility in the study by

Chen et al (2022), a retrospective cohort study was carried out that included 380 infertile obese people who were subjected to a 2-month treatment of orlistat for weight reduction. In a subsequent follow-up of 12 months, it was observed that 100% of the women achieved conception and gave birth to a child; no complications were reported during pregnancy. Among the results obtained, the normalization of the HOMA index was significantly related to the onset of ovulation [66].

In the study by Reem et al (2022) who conducted a meta-analysis to analyze whether the use of metformin and its effect on weight reduction has an effect on mortality, the study analyzed 2640 patients with a history of obesity and polycystic ovary syndrome, the results showed that the use of merformin compared to placebo increases the chance of pregnancy by 2.7%, in addition it was found that in comparison with clomiphene citrate it was associated with a lower risk of multiple pregnancies combined risk index = 0.36 [0.07, 1.92], 95 % CI, p = 0.23, 3 studies, in relation to miscarriage, it was found that it is better to associate metformin to clomiphene citrate as it reduces the risk of miscarriage compared to metformin alone pooled risk ratio = 2.67 [1.32, 5.39], 95 % CI, p = 0.006 [67].

Conclusions

Obesity and infertility are intrinsically related in women of childbearing age between 20 and 30 years of age. Infertility is a problem with great repercussions in the health system and at a social level, and therefore importance should be given to it. The promotion of physical activity and an adequate nutritional plan is essential to promote ovulation and fertilization. Infertility should be treated comprehensively from all possible perspectives.

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