Obesity and Male Infertility

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10.1 Definition

Infertility means not being able to get pregnant after a year of constant and unprotected intercourses [1]. Infertility and sterility are two very different concepts. Sterility is the permanent inability to reproduce. Infertility, on the other hand, can be either a permanent or temporary inability for fertilization to occur, because of one or more interfering factors [1]. In recent decades, the quality of the male semen compared to the 1999 classification by the World Health Organization (WHO) has become increasingly worse so that in 2010 (Table 10.1) normospermia was defined as having a sperm concentration ≥15 mil/ml, a progressive motility ≥32 %, and a morphology with a percentage of normal forms ≥4 % where for each parameter the percentile was identified, and where the minimum parameter corresponded to the 5th percentile, which meant that out of 100 people, 95 % had the best fertility parameters. In other words, just referring to the morphology, only 5 % of people had 4 % of fertile sperm in their normal form [2].

Obesity, defined as abnormal or excessive fat accumulation that presents a risk to health, has important effects on fertility [3].

Obesity is a multifactorial disease caused by energy imbalance between calories consumed and calories expended, resulting in the accumulation of body fat. The condition of obesity is defined using the body mass index (BMI) which is a biometric datum, expressed as the ratio between the individual's weight and the square of the height, and it is used as an indicator of ideal weight (Table 10.2) [4].

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Table 10.1 Spermiogram parameters by the WHO [2]

Spermiogram parameters by the World Health Organization	1999 ed.	2010 ed.
Volume	≥2 ml	≥1.5 ml
Concentration	20 mil/ml	15 mil/ml
Ntot sperm cells	40 mil	39 mil
Total motility	≥50 %	≥40 %
Progressive motility	≥25 %	≥32 %
Morphology % normal	≥30 %	≥4 %
Vitality	≥50 %	≥58 %

Table 10.2 The worldwide classification of the body mass index (BMI) [4]

	BMI (kg/m^2)	
Classification	Main cutoff points	Additional cutoff points
Underweight	<18.50	<18.50
Critical thinness	<16.00	<16.00
Moderate thinness	16.00–16.99	16.00–16.99
Mild thinness	17.00–18.49	17.00–18.49
Normal weight	18.50–24.99	18.50–22.99
		23.00–24.99
Overweight	≥25.00	≥25.00
Pre-obese	25.00–29.99	25.00–27.49
		27.50–29.99
Obese	≥30.00	≥30.00
Obese class I	30.00–34.99	30.00–32.49
		32.50–34.99
Obese class II	35.00–39.99	35.00–37.49
		37.50–39.99
Obese class III	≥40.00	≥40.00

10.2 Epidemiology

Infertility is caused by male factors in 25.5 % of infertile couples [5]. Body mass index or BMI is a simple and widely used method for estimating body fat mass. The healthy BMI range varies with age and sex; obesity in children and adolescents is defined as a BMI greater than the 95th percentile. In children, obesity is more severe and shows an even distribution of the body fat mass, which involves the whole body, including the upper and lower limbs, normally excluded by the adult obesity which has a typical central arrangement. Obesity is one of the most common diseases among the industrialized countries where the incidence rates are increasing so much that according to the data of the WHO, 54 % of the adult population is overweight

Table 10.3 Causal factors of couple's infertility [5]

Causal factors of couple's infertility	(%)
Male factor	25.5
Ovulatory endocrine infertility	16.9
Endometriosis	6.0
Male or female factor	17.3
Unexplained infertility	29.1
Others	5.3

and 25 % is obese [4]. Infertility, especially in the highly industrialized countries, contributes to the dramatic fall in the birth rate. Epidemiological studies in the USA sorted out that the male fertility has been gradually reduced in the industrialized countries since 1936 by recording a severe incidence of obesity. Over the past 70 years, the semen quality got worse, with an incidence in the male population between 15 and 18 % [3] (Table 10.3).

Numerous data in the medical literature confirm that the reduction in male fertility depends on nutritional factors [6–8]. There is an inverse correlation between BMI and the main hormones that mediate male fertility, where the obese have increased levels of estrogen and low levels of FSH, LH, inhibin B, and total and free testosterone [9–11]. Several studies confirm that the increase in BMI would refer to a reduction in sperm concentration (oligospermia), motility, and sperm morphology (asthenoteratospermia) and to an increase in nemaspermic DNA fragmentation (Table 10.4) [23–25].

10.3 Etiopathology

There is a close relationship between fertility and lifestyles [26]. As a matter of fact, the reduction of fertility in men is also connected to nutritional factors [6]. Energy intake in obese subjects is chronically larger than the energy expenditure, but the phenomena that give rise to this chronic alteration are not known. However, in humans, we can clarify the physiopathological mechanisms that regulate energetic homeostasis through constant regulation of body weight and balance between body fat and lean mass [27].

It has been reported that overweight and obese men have an up to 50 % higher rate of subfertility when compared to normal-weight men [21]. This effect persists even when confounding factors such as diseases, age, smoking, alcohol use, and obese female partner have been controlled [3]. Obesity is strongly linked to reduced spermatogenesis, poor quality of sperm, and a reduced percentage of normal sperm morphology [23]. Men's diets, in particular the amount and type of different fats they eat, could be associated with their semen quality. According to the results of a study [14], it has been found that men who ate omega-3 polyunsaturated fats (the type of fat often found in fish and plant oils) had better-formed sperm than men who ate less. A diet full of saturated fatty acids would cause a reduction in sperm count, while a diet rich in omega-3 fatty acids would

Table 10.4 Scientific evidence between obesity and male infertility

Reports	Number of patients	People	Results/conclusion	Ratio BMI/ infertility
Eisenberg et al. [12]	501	Couples from a longitudinal investigation on infertility and environment	No modified semen parameters No DNA fragmentation in the sperm cell	No
Jensen et al. [13]	701	Cross-sectional study of young men attending the military service	A high intake of saturated fats reduces the sperm concentration and total sperm count	Yes
Attaman et al. [14]	99	Men attending fertility clinic	A higher intake of omega-3 fats is positively related to sperm morphology	Yes
Fariello et al. [15]	305	Male patients of a cross-sectional study	Decreased progressive motility Increased sperm DNA fragmentation	Yes
Rybar et al. [16]	153	Men of infertile couples	No modified semen parameters	No
Martini et al. [17]	794	Male patients of a blind prospective study	Deleterious effects of obesity on seminal quality	Yes
Safarinejad [18]	160	Fertile and infertile men	A higher intake of omega-3 fats is positively related to semen parameters	Yes
Chavarro et al. [19]	483	Men of infertile couples	Hypospermia Reduction of sperm cell if BMI >35 DNA fragmentation in the sperm cell	Yes
Hofny et al. [20]	122	Only fertile and infertile obese men	Reduction in the sperm count and motility Increase of atypical sperm cells, sexual hormones alteration	Yes
Pauli et al. [21]	87	BMI 16.1–7.0 kg/m^2	Any meaningless correlations with sperm parameters, reduced fertility	Yes/no
Agbaje et al. [22]	56	Men with diabetes type 2	DNA fragmentation and reduction of the semen volume	Yes

contribute to a better sperm morphology. Men with a high intake of saturated fat have a 35 % lower total sperm count than men with a low intake and a 38 % lower sperm concentration [13]. A number of previous studies had investigated the link between BMI and semen quality, with mixed results (Table 10.4). The mechanisms by which obesity is associated with hypogonadism are mostly unknown, but it is likely that insulin or other hormonal factors released from the adipose tissue may have a role in regulating the production of pituitary LH [22]. In men, one of the main causes of infertility determined by obesity is closely related to the hyperactivity of aromatase, an enzyme which is present in high percentage in the so-called white adipose tissue, which converts testosterone into estradiol. The increase of estradiol concentration is proportional to the quantity of adipose tissue, and estrogens exert a negative feedback action on the pituitary secretion of both FSH and LH, the essential hormones for the normal growth and differentiation of sperm [28]. The white adipose tissue is also the main site of synthesis of leptin, a hormone which regulates the energetic stability and body weight by modulating the energy intake and expenditure at the level of the central nervous system. So an increase in fat mass, resulting from a caloric excess, corresponds to an increased secretion of the hormone on behalf of the adipose tissue. Leptin circulates in plasma at concentrations that parallel the amount of fat reserves. In obese males, androgen levels decline in proportion to the degree of obesity. When leptin is produced in exaggerate amounts, it can reduce the level of androgens, and as its receptors are found in the testicular tissue, this can have a direct effect on the functionality of the sperm [20].

Another characteristic of the adipose tissue that may interfere on male fertility is the increased production of resistin, a protein associated with insulin resistance. Plasma levels of this cytokine are increased in obese individuals [29]. Hyperinsulinemia is related to inhibition of spermatogenesis, and it also produces a deterioration of spermatic DNA, which causes not only a reduction in fertility but also a higher incidence of spontaneous abortions in female partners [22].

Obesity and diabetes mellitus are insulin-resistant states with different abnormalities in oxidative stress, protein glycation, and cellular processes that lead to impaired endothelial function, vascular inflammation, and hemostasis: processes which give rise to impaired function of the microcirculation [22]. A large body of scientific evidences indicates that overweight or obese men frequently suffer from erectile dysfunction (ED) which is a cause of infertility. Sedentary life, prolonged sitting, and fat deposition in the lower abdomen can reduce male fertility, likely through increased testicular temperature to the level of body core temperature [30].

An excessive intake of metabolizable food, especially carbohydrates and fats, subdues the individual to an oxidative stress with negative echoes on the reproductive area. In a healthy body there is a balance between the oxidative mechanisms and the antioxidant defenses. In normal conditions, the toxic potential of free radicals (ROS) is neutralized by a complex system of antioxidant factors that represents our physiological mechanism of defense. The relationship between oxidant factors and antioxidant defenses is the so-called oxidative

balance. Oxidative stress is, therefore, the expression of biological damage that occurs when the prooxidant factors (drugs, toxic substances, radiations, inflammations, etc.) exceed the endogenous antioxidant defenses (enzymes such as superoxide dismutase, coenzyme Q10, catalase, peroxidase, etc.) and the exogenous ones (antioxidants found in food). Obesity is a pathological condition which causes oxidative stress with increased ROS in sperm causing its decreased quality. During the last years, andrologists' interest on the diagnostics and treatment of male infertility has focused on the role of ROS in the pathogenesis of male infertility with harmful effects on sperm membrane rich in polyunsaturated fatty acids. The increased production of ROS and the related oxidative stress associated with obesity may be therefore responsible for the increased lipidic peroxidation damage to the sperm cell membrane [31, 32]. Not only the quantity but also the quality of food can have an effect on male fertility, and in recent years a lot of attention has been paid to the so-called endocrine-disrupting compounds, i.e., substances which have a structural similarity to the endogenous hormones, and therefore they are able to mime the hormones themselves, interacting with their transport proteins. A substantial number of environmental pollutants, such as polychlorinated biphenyls, dioxins, polycyclic aromatic hydrocarbons, phthalates, bisphenol A, alkylphenols, pesticides, and heavy metals (arsenic, cadmium, lead, mercury), have shown to interfere with endocrine function as they are released in the environment in different ways such as smoke, sewage, and careless use of pesticides with the direct release on the food. These substances can cause reproductive problems by reducing either the concentration of sperm or its quality [33].

10.4 Diagnosis and Therapy

In this context, prevention has been of great importance in order to protect and preserve the fertility of the individual since childhood. Smoking, obesity or excessive thinness, different environmental substances, physical inactivity, and even unrestrained physical activity are some of the major risk factors capable of influencing the sexual and reproductive health of an individual [34].

In the first 2 years of life, a hyperalimentation can cause not only a hypertrophy of fat cells but can lead to hyperplasia that will develop to a sure adult obesity [35]. The best treatment of male infertility is the correct diagnosis. The andrologist, through a careful diagnostic process, can identify which is the most appropriate medical and/or surgical treatment for the infertile patient and has an important role in referring eventually the infertile couple to medically assisted procreation. Obesity is often associated with metabolic alterations (diabetes, hypertension, dyslipidemia, hyperuricemia) that are important cardiovascular risk factors which may have an impact on male sexual and reproductive health and in determining psychological disorders. Therefore, in the diagnostic algorithm of morbid obesity, it is essential to weigh the patient, to examine some

important parameters about his family history, to know his waist circumference and blood pressure, and to ask for a few diagnostic tests which are essential to a correct understanding of the problems [35]. Laboratory tests are of considerable importance to assess glucose tolerance and lipid and hormone profile as well as an assessment of the seminal fluid. In particular, it is necessary to evaluate the hypothalamic-pituitary-gonadal axis through the determination of FSH, LH, estradiol, and total testosterone and the examination of seminal fluid according to the WHO criteria of 2010 (Table 10.1) [17].

Once the patient's clinical history, state of health, behavior, and food habits have been pointed out, a therapeutic integrated path referring to the different pathologies will be started. Since obesity is an altered balance between energy consumption and caloric intake, dietary therapy and physical activity must become part of a rehabilitation program. Weight reduction (5–10 % of initial body weight) leads to benefits in terms of morbidity and mortality: it is shown that a lasting weight loss allows significant improvements of all the metabolic syndrome parameters, and in particular the reduction of visceral fat is associated with an improvement of the male reproductive function [35]. Moreover, a psychological evaluation is essential. Improving fertility can be a strong motivation for weight loss [36]. Dietary antioxidants may be beneficial in reducing sperm DNA damage, in infertile obese men [37].

In a male who suffers from obesity, diabetes, or metabolic syndrome, with a reduced fertility and hypogonadotropic hypogonadism, it is possible to evaluate a treatment with antiestrogens or aromatase inhibitors that, if properly prescribed, can improve the quantitative and qualitative characteristics of the seminal fluid. Antiestrogens have the ability to bind to estrogen receptors, both at the hypothalamic and the peripheral levels in a competitive manner, thus inducing an increase in plasma levels of gonadotropins and then of intratesticular testosterone [38]. The pharmacological effect on spermatogenesis should be manifested through increased concentrations of FSH, LH, and testosterone, although a direct effect on spermatogenesis cannot be excluded. The first used antiestrogen was clomiphene citrate, replaced by tamoxifen citrate in recent years [39]. Estradiol is derived from the conversion of testosterone, mediated by the aromatase system which occurs in the testicles and peripheral, especially in adipose, tissues. Testolactone, an inhibitor of aromatase, can improve the testicular function through two mechanisms: a decrease of the concentrations of estradiol and a stimulation of the secretion of gonadotropins from the pituitary through a block of the inhibitory feedback exerted by estradiol. Anastrozole, a selective inhibitor of aromatase, at a dose of 1 mg per day, and letrozole (2.5 mg/day) seem to be comparable to the testolactone for its effects on spermatogenesis [28].

The use of these molecules is interesting especially in patients with an altered testosterone/estradiol ratio, as occurs in obese subjects. Further studies will be necessary to evaluate the effectiveness of these drugs in the treatment of male infertility in the obese because of the small number of studied subjects.

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