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Book I

OBESITY EPIDEMIC AND SERBIA

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OBESITY AND HUMAN REPRODUCTION

RENATO PASQUALI[1]

A b s t r a c t. – The price of obesity is represented by a long list of co-morbidities and social, psychological and demographic problems. There is evidence that infertility is growing in parallel with the obesity epidemic, in both males and females. This phenomenon may be due to a spectrum of factors, including social and cultural ones, environmental pollution, globalization of food industries and eating behavior, and others. In adult women the risk of ovulatory infertility increases in women with increasing BMI values. The abdominal pattern of fat distribution has a specific impact on ovulation and fertility, which obviously implies the role of metabolic disturbances, chiefly insulin resistance and associated hyperinsulinemia. Chronic oligo-anovulation is likely more pronounced in obese women with PCOS. There is evidence for decreased live birth rates in obese patients with spontaneous pregnancies or following ART. In men, obesity can affect fertility by altering the hormonal milieu, favoring erectile dysfunction, and by altering sperm count and physiology.

Key words: obesity, female infertility, PCOS, male infertility, erectile dysfunction

[1] University Alma Mater Studiorum, Bologna, Italy. Full address: Professor Renato Pasquali, Via Santo Stefano 38, 40125, Bologna, Italy
E-mail: renato.pasquali@unibo.it. Phone number: +39 3386415222

THE WORLDWIDE EPIDEMIC OF OBESITY

We are facing a worldwide public health emergency due to the increasing epidemic of obesity and related disorders [1]. Recent estimates show that the growing prevalence of obesity is recognized worldwide, with few exceptions. The International Obesity Task Force estimates that at least 1.1 billion adults are currently overweight, including 312 million who are obese, and that with the new Asian body mass index (BMI) criteria, the number will be even higher [2]. Similar expectations are also evident for children and adolescents of both sexes [2].

The price of obesity is represented by a long list of co-morbidities and social, psychological and demographic problems. Obese women are characterized by similar co-morbidities to men, particularly type 2 diabetes (T2D) and cardiovascular diseases [3]. In parallel, there is evidence that infertility is growing in parallel with the obesity epidemic, in both males and females (1). This may be due to a spectrum of factors, including social and cultural ones, environmental pollution, globalization of food industries and eating behavior, and others, as depicted in Table 1.

Table 1. The future of infertility across the world: it is expected that fertility will further decrease in the next decades

Potential factors and conditions:
• The increasing rate of obesity worldwide
• Social differences, political and economic factors
• Globalization (food, eating behaviors, etc.)
• Climate and environmental pollution
• Women's reproductive status (*early vs late fertile age*)
• Maternal mortality (*Africa, Asia, etc.*)
• Expanding infections worldwide (*HIV/AIDS, Zika, etc*)
• Changes in societies
• The use/misuse of OC pills (*delayed time for fertility*)
• The potential role of epigenetic factors

The evolutionary perspective may be of importance in understanding the link between body composition, specifically body fat amount and topography and fertility processes. About 2 million years ago, our ancestors stood up for the first time and, at that time, the uniform layer of subcutaneous fat in primates of both sexes probably became differentiated, eventually producing the specific human and sexual characteristics seen today. Fat in women developed in the lower part of the body in relation to the upright posture, the mechanical condition of pregnancy and the need to have reserves for the newborn. By contrast, in men,

fat was less useful and was reduced by half, deposited predominantly in the upper body, where it was less likely to hinder mobility and the aptitude for wrestling. It can be expected that natural selection probably increased this differentiation. For a correct understanding of the mechanisms responsible for infertility, it is therefore important to consider that the biology of body fat and, consequently, its pathobiology, differ between men and women. Gluteo-femoral and mammary fat have high energy resolution potency in women, whereas centrally distributed fat has a high energy resolution for muscle work [3]. The different mechanisms of fat biology may refer to different biological targets that become altered in the presence of obesity. Excess fat, in fact, disrupts biological processes by altering regulatory hormones, including their secretion, transport and action that, in turn, affect metabolic pathways, fuel partitioning and, finally, fertility processes.

OBESITY AND INFERTILITY IN WOMEN

The association between excess body fat and infertility was described many centuries ago by Hippocrates (4th century B.C.) in his "Essay to the Scynthians". He wrote that "… the girls get amazingly flabby and podgy fatness and flabbiness is to blame. The womb is unable to receive the semen and they menstruate infrequently and little". At present, we know that obesity may affect infertility and reproduction in women in different ways: (i) by affecting menses cycles and ovulatory function, (ii) by interfering with assisted reproductive technology (ART) efficiency and outcomes, (iii) by altering endometrial receptivity and by increasing rates of miscarriages, (iv) by worsening the physiological processes of pregnancy and therefore the maternal-fetal environment and, finally, (v) by altering the delivery processes.

The relationship between excess body fat and reproductive disorders appears to be stronger for early-onset obesity particularly during the adolescent age [4]. There are several epidemiological studies which suggest that changes in body weight or body composition are critical factors regulating pubertal development in young women, and the discovery of leptin provided critical evidence for an endocrine regulation of puberty and the fertile reproductive system, particularly in females [5]. In adult women, according to the Nurses' Health Study [6] the risk of ovulatory infertility increases in women with increasing BMI values. Several other cross-sectional and prospective studies have produced similar findings [7]. The abdominal pattern of fat distribution has a specific impact on ovulation and fertility, which obviously implies the role of metabolic disturbances, chiefly insulin resistance and associated hyperinsulinemia. This is exemplified by the findings of Zaadstra and coworkers [8], who found that abdominal fatness was associated with a decreasing chance of conception more negatively than total body fat.

The paradigm of PCOS: effects of obesity on fertility and reproduction

The polycystic ovary syndrome (PCOS) is characterized not only by a hyperandrogenic state and ovarian dysfunction (oligo-amenorrhea and chronic anovulation) but also by the presence of insulin resistance and hyperinsulinemia, as well as obesity and the metabolic syndrome. The prevalence of obesity in PCOS women appears to be much greater than what is expected in the general population, with an estimated prevalence rate in more than 30 % of cases and, in some series, a percentage as high as 75 % [9]. Mechanisms by which obesity influences the pathophysiology and clinical expression of PCOS are complex [10] and, among others, its role is of importance in the development of hyperandrogenemia, only partly dependent on the direct role of insulin excess in stimulating ovarian steroidogenesis and in determining an increase of free testosterone availability due to the decrease in the hepatic synthesis of its blood carrier, the sex hormone-binding globulin (SHBG) [11]. In addition, chronic oligo-anovulation is likely more pronounced in obese women with PCOS [9]. Other than ovulatory dysfunctions, obese PCOS women are characterized by blunted responsiveness to pharmacological treatments to induce ovulation, recurrent miscarriages, more frequent early pregnancy loss and a reduced incidence of pregnancy.

Obesity and ART outcomes

Obesity can impair the outcome of ART and by raising BMI by one unit, the odds for pregnancy decreased by 0.84 in *in vitro* fertilization (IVF); by contrast, the reduction of BMI by one unit after life style intervention has been shown to increase the chance of pregnancy by 1.19 [12]. Moreover, there is evidence that higher gonadotropin requirements in obese women undergoing controlled ovarian hyperstimulation for ART are necessary, which suggests some degree of resistance to exogenous gonadotropins [13].

Longer periods of ovarian stimulation and higher cancellation rates and higher incidence of follicular asynchrony have been found in obese patients undergoing controlled ovarian hyper-stimulation (COH) and IVF [12, 14]. Various studies have shown that decreased peri-ovulatory human chorionic gonadotrophin (hCG) concentrations and an inverse correlation between HCG levels and BMI are associated with diminished fertilization rates [12], and that lower peak estradiol concentrations (hCG/day) noted in obese women undergoing COH for in-vitro fertilization (IVF) were associated with an impaired cycle outcome [15]. Reduced oocyte retrieval in overweight and obese women

has also been reported [16], mainly due to their poorer ovarian response, and even when PCOS is associated [12]. Oocyte quality *per se* can also be impaired as a result of obesity, which may imply lower fertilization rates [16]. Finally, a lower incidence of embryo transfer and lower mean number of transferred embryos have been observed in linear association with increasing BMI in some, but not in all studies [12].

In a recent metanalysis performed by Maheshwari and coll. [17], aimed at assessing the effects of obesity on the outcome of ART, it was found that, compared with women with a BMI of 25 or less, women with a BMI > 25 have a lower chance of pregnancy following IVF (OR 0.71), require higher doses of gonadotropins (weighted mean differences: 210.08) and have an increased miscarriage rate (OR 1.31). By contrast, they found no evidence on the effect of BMI on live birth, cycle cancellation, oocyte recovery and ovarian hyperstimulation syndrome. The oocyte donation model has still not definitively established this hypothesis, but recent studies are showing findings in this direction, although further research is required in this exciting issue.

Obesity and pregnancy outcome

Most reports show decreased live birth rates in obese patients with spontaneous pregnancies or following ART. It has been suggested that obesity and associated hormonal alterations may affect the function of the corpus luteum, that of the trophoblast, the early embryo development and, finally, the endometrial receptivity [12]. Implantation seems also to be negatively affected by obesity, although this is still controversial [15]. Furthermore, whether obese women have lower pregnancy rates following ovulation induction or ART is still controversial [12], although some studies showed that the probability of achieving at least one pregnancy during the ART treatment was reduced by almost 30 % in women with a BMI of 30–35, and by 50 % in those with a BMI greater than 35. These findings and others supported the National Guidelines in the United Kingdom in inviting infertile women to reduce their BMI before ARTs, and in avoiding these procedures in those with BMI values higher than 35 [18].

Miscarriages can occur more frequently in pregnant obese women and particularly in those undergoing ARTs. Although no consensus exists, it is commonly accepted that only those women with a BMI greater than 30 should be considered at high risk [18]. Notably, in most studies the potential role of abdominal or visceral fat enlargement was not considered.

Obesity is also associated with a higher risk of obstetric causes of maternal death and of anesthesia-related deaths. Obese women present higher rates of complications in pregnancy, mainly in the third trimester, such as hypertension,

preeclampsia, gestational diabetes, thromboembolism, urinary tract infection, fetal macrosomia, preterm labor and delivery, sudden and unexplained intrauterine death, operative vaginal deliveries, shoulder dystocia, cesarean section delivery, anesthetic and surgical complications, postpartum hemorrhage, postoperative wound infection and dehiscence and endomyometritis in the puerperium [19]. The negative impact of obesity can also be extended to fetal malformations, such as defects of the central nervous system (neural tube defects), great vessels, ventral wall and intestine [7]. Apart from congenital anomalies, children of obese mothers run a higher risk of intrauterine fetal death, head trauma, shoulder dystocia, brachial plexus lesions, fractures of the clavicle, meconium aspiration, fetal distress and increased risk of death within the first year [7].

OBESITY AND INFERTILITY IN MEN

In men, obesity can affect fertility by (i) altering the hormonal milieu, (ii) favoring erectile dysfunction (ED), and, finally, by altering sperm count and physiology. These topics will be addressed in the following paragraphs.

Male obesity as a hypotestosterinemic state

Research trends and perspectives of male infertility have increased considerably in the last years, according to bibliometric analyses of 20 years of scientific literature [21]. Moreover, in the last fifteen years an important scientific achievement has been obtained in relation to the recognition that low testosterone levels are very common in adult men, and are strongly associated with erectile dysfunction and poor semen quality (including oligo-astenospermia), etc.

Gonadotropin levels often tend to be reduced in obese men, as are their responses following luteinizing-hormone releasing hormone (LHRH) stimulation [22]. This specifically occurs in obese men with high BMI values, probably due to impaired secretion of the hypothalamic gonadotropin releasing hormone (GnRH) at hypothalamic level [22]. The association between obesity and impaired glucose tolerance states further justifies the decrease in testosterone blood levels. In most of these men, a true condition of hypogonadotropic hypongonadism may therefore occur [22]. The absence of classic clinical signs of hypogonadism is rather common and can be explained by the fact that the testosterone free-fraction is only 2 % of total testosterone, and that obesity predominantly affects circulating bound testosterone, due to the concurrent decrease of SHBG production, as a result of hepatic synthesis inhibition by

circulating insulin in excess. However, as demonstrated in women [9], insulin may stimulate testosterone production *in vivo* also in men [23]. Additional factors may be inappropriate estrogen feedback [9], increased activity of the hypothalamic-pituitary-adrenal axis [24] and increased leptin levels and action [25]. In fact, studies in obese men have shown a significantly negative relationship between leptin levels and basal and hCG stimulated testosterone levels [22].

The hypotestosteronemic condition of men with obesity and the metabolic syndrome [26] cannot be confused with the effects of aging. In fact, the decrease of testosterone blood levels with aging is associated with increased gonadotropin blood concentrations and an increase in SHBG levels [27], whereas, as mentioned above, low gonadotropin levels and low SHBG characterize the hypotestosteronemic dysmetabolic condition in men [22]. It is expected that the altered hormonal balance in obese may therefore be responsible for reduced fertility rates, although other aspects should be discussed, as indicated below.

Erectile dysfunction

Erectile dysfunction (ED), a still underestimated problem, is very common in obese men and tends to increase with increasing BMI values. In the Massachusetts Male Aging Study [28], which was performed in a large cohort of men aged 40–70 years, the overall prevalence of ED was 17 %, but it increased to 45 % in subjects with BMI values greater than 30. In the Health Professionals Follow-up Study, it was found that men with BMI higher than 28.7 had a 30% higher risk for ED than those with a normal BMI (<25) [29]. However, there are no studies on the prevalence of ED in obesity, although clinical studies indicate a very high prevalence and that it can be reversed by weight loss [30]. Since ED represents an indirect but very common cause of infertility in men, this should be taken into consideration in the clinical background. This is further emphasized by the strong association between ED and type 2 diabetes and recent findings demonstrating that ED represents a risk factor for cardiovascular diseases.

Erectile dysfunction (ED) must be considered another potential factor associated with male infertility, particularly in dysmetabolic obese men. The causative factors responsible for ED in obese men may be related not only to the presence of low testosterone but also to the negative effects of proinflammatory cytokines (particularly IL-6, TNFα), which are able to raise endothelium ROS and reduce nitric oxide and their vasodilatory effects [31]. Several recent review articles published in the last few years may help the reader in understanding the pathophysiological aspects and psychological correlates of ED in obese men [32, 33].

Altered sperm count and function

An important factor in explaining fertility problems in obese males is represented by altered sperm count and function. Data from three epidemiologic studies [the Agricultural Health Study [34], the Danish National Birth Cohort [35], the Norwegian Mother and Child Cohort Study [36] indicate that with increasing BMI rates of infertility in males also tend to increase. The negative effect of obesity on a couple's infertility has also been found in male patients undergoing ART. In fact, some studies found a decrease in sperm concentration of the male partner. In particular, it has been shown that with increasing paternal BMI a decreased rate of pregnancy in the female partner may occur [37], although contradictory findings have also been reported [38]. An important aspect is that in obese dysmetabolic men, low testosterone blood levels can be associated with altered sperm count.

In the last decades various studies have documented a decline in sperm parameters over time [39]. Recent data have shown an inverse relationship between male BMI and waist circumference, with low sperm concentration and count [40]. These findings were also confirmed in a recent meta-analysis [41]. Moreover, obesity has been found to be negatively associated with other sperm parameters, specifically sperm mobility, morphology, and DNA fragmentation [42]. Overall, it has been suggested that these alterations are related to an increased oxidative stress, which often occurs in obese dysmetabolic men. In fact, enlarged visceral fat has been found to be characterized by the presence of macrophages and other inflammatory cells, secreting inflammatory cytokines, which, in turn may locally favor low testosterone levels by paracrine and autocrine mechanisms. In addition, increased oxidative stress and reactive oxygen species (ROS) may occur in the testes, leading to increased DNA damage of spermatozoa and reduction of their ova-penetrating ability [43]. Insulin resistance has also been negatively associated with sperm quantity and quality, and metformin treatment has been shown to improve sperm parameters [44]. Moreover, it has been found that excess ROS production may induce fragmentation of spermatozoa nuclear and mitochondrial DNA, thereby favoring aberrant recombination and/or defective packing [45]. Finally, it should be considered that low inhibin B production rate [42], a marker of Sertoli's cell function, may partly explain the impaired spermatogenesis in the presence of obesity [46]. Finally, the altered spermatogenesis process could also depend on a raised intra-testicular temperature, favored by the enlarged fat (in the suprapubic region and in the medial thighs) around the testicles and the spermatic cord, as supported by findings of autoptic studies demonstrating the presence of scrotal lipomatosis in the majority of men with idiopathic infertility [47]. The potential role of local fat excess has been confirmed by the efficacy of scrotal and suprapubic lipectomy in improving semen quality and pregnancy rate of the couple in a group of 102 infertile men with lipomatosis [48].

SUMMARY AND CONCLUSIONS

Obesity has an important negative effect on fertility in both women and men. Mechanistic factors of infertility in men and woman are different (Table 2). In women, the expanding role of ARTs supports the concept that infertility is growing worldwide. By contrast, awareness of infertility is much lower in men, particularly in those who are obese

Table 2. Impact of obesity on fertility and reproduction in women and men

Women	**Men**
Menses disturbances and oligo-anovulation are more common in the presence of obesity Early onset obesity may predict infertility later in life Obesity affects most women with PCOS and has pathophysiological relevance in determining chronic anovulation and infertility Obesity has adverse reproductive outcomes in PCOS The odds for pregnancy decrease in obese women (included PCOS) Obesity may decrease live birth rates during spontaneous and ART pregnancies Obesity may increase obstetric complications in the mother and rates of fetal malformation	Hormonal alterations: • functional hypogonadotropic hypogonadism • hyperinsulinemia and insulin resistance • Increased leptin • others Erectile dysfunction Poor semen quality may be associated with high BMI Reduced sperm quality has been related to the potential effects of pollutant organochlorines, which have hormone disrupting properties.

PCOS: polycystic ovary syndrome. ART: assisted reproductive technology, BMI: body mass index

In any case, weight loss or an improvement of hormonal and metabolic alterations may improve fertility rates. A lifestyle approach should always be planned in anovulatory infertile obese men and in obese women before planning an ovulation induction or ARTs. Hopefully, this will require closer collaboration between different specialists in order to improve the medical approach and treatment of infertility in both obese women and men.

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Ренато Пасквали

ГОЈАЗНОСТ И ХУМАНА РЕПРОДУКЦИЈА

Р е з и м е

Цена гојазности је представљена дугачком листом коморбидитета и социјалних, психолошких и демографских проблема. Проблем инфертилитета расте паралелно са епидемијом гојазности међу мушкарцима и међу женама. Овај феномен је узрокован читавим спектрумом различитих фактора међу које спадају социјални и културолошки фактори, загађење спољашње средине, глобализација индустрије хране, понашање у исхрани и други. У одраслих жена ризик за овулаторни инфертилитет расте са порастом индекса телесне масе. Абдоминални тип распореда масне телесне масе има специфичан утицај на овулацију и фертилитет, што очигледно намеће улогу метаболичких поремећаја као што је инсулинска резистенција и придружена хиперинсулинемија. Хронична олиго-ановулација је много више изражена међу гојазним женама са *PCOS*-ом. Број живо рођене деце је снижен међу гојазним болесницама са спонтаним трудноћама или након ART-а. Код мушкараца гојазност може да оштети фертилитет тако што доводи до оштећења хормонског миљеа, фаворизовања еректилне дисфункције и оштећења броја сперматозоида и њихове физиологије.

Кључне речи: гојазност, женски инфертилитет, *PCOS*, мушки инфертилитет, еректилна дисфункција