

R E V I E W

Female obesity and infertility: outcomes and regulatory guidance

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Abstract. Obesity has been associated with reduced fertility, although the dynamics and mechanisms which link excess weight to reduced fertility are not yet fully clarified. Obese women, especially those with central obesity, are less likely to conceive per cycle. Obese women suffer from perturbations of the hypothalamus-pituitary-ovary axis, disturbances of the menstrual cycle and are up to three times more likely to suffer from oligo/anovulation. A delicate hormonal balance regulates follicular development and the maturation of oocytes and it has been observed that obesity can alter the hormonal environment: adipocytes, in fact, are responsible for the production of a hormone called leptin (present in high quantities in obese women) which has been associated with reduced fecundity. In addition to compromising ovulation, obesity negatively affects the development and implantation of the endometrium. The expression of polycystic ovary syndrome (PCOS) is regulated, in part, by weight, so obese women with PCOS often have a more severe phenotype and higher subfertility rates. Furthermore, obesity impairs women's response to medically assisted procreation (MAP) treatments. The authors have set out to delineate a broad-ranging overview of obesity's impact on female fertility, by drawing upon sources spanning the 1994-2022 period. Assisted reproductive technology (ART) procedures are also discussed as they relate to obese patients. In addition the dynamics by which maternal obesity reportedly affects fetal, neonatal and child development have also been briefly enunciated. (www.actabiomedica.it)

Key words: obesity, fertility, polycystic ovary syndrome (PCOS), Assisted reproductive technology (ART)

Background

Obesity is an increasingly widespread health burden in modern society and especially throughout the westernized world. Overweight or obese women are estimated to account for more than 75% of the more than \$ 400 billion in excess direct health care costs. Despite efforts to tackle it, the global incidence of obesity is constantly growing (1, 2). The World Health Organization (WHO) estimates that around one billion people around the world are overweight and that over 300 million of them are obese. Obesity derives mainly from the imbalance between reduced exercise, excess intake of foods high in calories, lifestyle changes

and diet composition. In 2013, the American Medical Association recognized obesity as a disease. Obesity, in addition to being a disease itself, has been shown to be a condition closely linked to systemic diseases such as diabetes mellitus, cardiovascular disease, hyperlipidemia, sleep apnea, cancer and osteoarthritis. In addition, female obesity also has a significant impact on reproductive function and hormonal structure. Most obese women are not sterile, however, obesity and its negative impact on fecundity and fertility are well documented. Research findings have shown obesity to damage fertility through its negative effects on ovulation control, oocyte, embryonic and endometrial development, in addition to compromising the progression

and overall quality of the implant. Obese women are three times more likely to suffer from infertility than women with a normal BMI (3). The mechanism through which its effect is exerted is still controversial today. The definitions of obesity may vary, but the most widely recognized definition adheres to the WHO BMI criteria (kg/m^2). Obesity is in these patients directly correlated with an increase in insulin resistance and frequently found in patients with polycystic ovary syndrome (PCOS). It is now demonstrated that inositol is a first choice therapy, sometimes an alternative to metformin in maintaining glycemic levels both in patients with overt PCOS (4,5) and in the treatment of gestational diabetes (6) up to symptoms in the perimenopausal period (7). A person is defined as obese if their BMI is $\geq 30 \text{ kg}/\text{m}^2$. There are different levels of obesity: obesity class 1 ($30.0\text{--}34.9 \text{ kg}/\text{m}^2$), class 2 ($35.0\text{--}39.9 \text{ kg}/\text{m}^2$) and class 3 ($\geq 40 \text{ kg}/\text{m}^2$). The secondary parameters used for the assessment of obesity include waist circumference and the waist-hip ratio. A waist circumference under 80 cm in women is an accepted indicator of visceral fat accumulation (8).

Search Methods

The authors have set out to outline a broad-ranging overview as to the impact of obesity on female fertility, by conducting a thorough search on PubMed/Medline, Embase, Web of Science, drawing upon sources spanning the 1994-2022 period. A total of 124 sources were identified (i.e. those providing data and detailing correlations between obesity and sequelae thereof, in addition to fertility issues). Guidelines and recommendations from the International Federation of Gynecology and Obstetrics, American Society of Reproductive Medicine, British Fertility Society, the Canadian Task Force on Preventive Health Care, the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology were taken into account as well, in order to provide as comprehensive a picture as possible of the fertility repercussions of obesity including patients undergoing assisted reproductive techniques. For the legal limits on assisted reproductive techniques, policy papers and ministerial decrees for European countries have been sifted through whenever available. Lastly, the

dynamics by which maternal obesity reportedly affects fetal, neonatal and child development have also been briefly enunciated, in addition to obesity treatments (pharmacological and surgical options).

General issues of reproductive function and obesity

The alleged causes of delayed conception in obese women can be conceptually categorized as pathophysiological, psychosocial and sociobiological. This article aims to elaborate on the physiopathological aspects, although it is known that obese women can have reduced fertility due to psychosocial and sociobiological factors linked above all to a lower frequency of sexual intercourse, despite the presence of cohabiting partners, or to the regular overconsumption of fats and sugars responsible for blunting libido. There are several studies that have shown a state of subfertility in overweight or obese women, compared to the rest of the female population (3,9). A similar effect emerged in an observational study conducted on 2112 pregnant women for whom a $\text{BMI} > 25 \text{ kg}/\text{m}^2$ correlated with a prolongation of time to pregnancy (10).

The distribution of body fat also has important repercussions on the reproductive abilities of couples and it has been observed that central obesity, defined by an increase in waist circumference or a high WHR (hip-to-waist ratio), has a negative impact on fertility. A Dutch study has in fact shown that an increase of 0.1 units of WHR correlates with a 30% decrease in the probability of conception per cycle (11). Obesity can produce effects on the hypothalamus-pituitary-ovary (HPO) axis and as such affect menstrual cyclicity and ovulation. Indeed, severely obese women have a 3.1 times higher rate of menstrual disturbances than normal-weight women (12, 13).

Furthermore, a fact that should not be underestimated concerns the greater probability for obese women to lose the product of conception: in fact, high rates of spontaneous abortion are observed both after natural conception and after MAP programs, i.e. a significantly high probability of experiencing miscarriage regardless of the mode of conception (14). A retrospective analysis of women with PCOS undergoing induction of ovulation demonstrated a higher rate of miscarriage among obese women ($\text{BMI} > 28 \text{ kg}/\text{m}^2$).

m²) than in the population female with normal body weight control (60 vs 27%) (15). A retrospective analysis of 5019 IVF/ICSI cycles in 2660 women in a Norwegian clinic observed a linear association between higher BMI and early miscarriage (<6 weeks) and miscarriage (6-12 weeks). The OR for early pregnancy loss was 1.69 (95% CI 1.13-2.51, P = 0.003) in obese women (BMI > 30 kg/m²) compared to normal weight women (16). A recent meta-analysis demonstrated an increased risk of spontaneous abortion among obese women (BMI > 30 kg/m²) undergoing assisted conception (IVF/ICSI; OR = 1.53, 95% CI 1.27-1.84) (17).

Obesity, endometrial receptivity and implantation

A complex hormonal environment functions to keep in perfect balance and to control the menstrual cycle, ovulation and the development of the endometrium. It has been shown that obesity disrupts this balance through various direct and indirect mechanisms. Excess adipose tissue, in fact, if on the one hand it hinders the secretion and bioavailability of sex hormones, on the other hand it contributes to the excess secretion of leptin, insulin and adipokines which act negatively at a central and peripheral level, affecting follicular development and maturation. Several studies have observed that overweight or obesity can have a negative effect on the quality and/or maturity of oocytes. In a study conducted to evaluate the impact of isolated obesity on the outcome of ICSI (Intra-Cytoplasmic Sperm Injection), it was observed that obese women required higher total doses of gonadotropins for ovarian stimulation, suggesting that obesity may independently be a risk factor for reduced oocyte maturation (18-22). A marker of egg quality in the context of in vitro fertilization is the fertilization rate.

In a prospective evaluation of the effect of obesity on in vitro fertilization/ICSI in 162 patients, he highlighted how obese women had a 45% lower fertilization rate than women with controlled weight (23).

The increase in body weight correlated with the increase in age is one of the reasons, along with other socio-cultural and economic contributing factors, for which young women are advised to resort to Social Freezing through oocyte vitrification (24), which often employs the antagonist GnRH in ovarian stimulation

protocols (25). The same procedure is also used in the preservation of fertility in cancer patients who, following a diagnosis of carcinoma of the female genital sphere (26-28), need to freeze their gametes before a fertility-sparing surgical treatment (28,29).

In this regard, an incorrect diet from childhood has a negative impact on the intestine and on the composition of the microbiome leading to obesity and possibly colorectal cancer (CRC) in adults (30). Other authors, on the other hand, have pointed out an increase in spontaneous abortion rates, attributing this condition to a reduction in the quality of oocytes or altered embryonic development (31-33). A reduced capacity of oocyte development, in fact, can compromise the potential development of the embryo, which can lead to a reduced implantation rate and the subsequent implantation anomaly/trophoblastic invasion (33) despite all the techniques being adopted to date known to support growth and maintenance of the endometrium (29).

Since early embryonic development is largely driven by the oocyte, one might expect that if obesity affects oocyte development, then it also affects embryonic development. Inconsistent results have been reported regarding the effect of obesity on the quality of the embryo (14, 16, 19, 34, 35).

Most of the studies herein cited show higher BMI to result in a higher need for drugs for ovulation induction. Large doses of Clomiphene Citrate (CC) up to 200mg per day are necessary to ensure ovulation in overweight or obese women (36), always considering its impact on the breast and on women's health. Similar trends were also observed in the doses of gonadotropins necessary for ovulation (37, 38). Obesity therefore appears to entail a resistance to the agents used to stimulate ovulation. BMI ≥ 30 kg/m² can in fact lead to a refusal from doctors to start an MAP cycle in order to avoid endangering the patient's health.

Poor reproductive prospects in obese women, in both natural and assisted conception cycles, may be the result of a combination of lower implantation rates, higher preclinical and clinical miscarriage rates, and higher pregnancy complications for both mother and the fetus. These have been related to various endocrine and metabolic disorders, such as effects on steroid metabolism and alterations in the secretion and action of insulin and other hormones, such as leptin,

resistin, ghrelin and adiponectins (39), which can affect follicle growth, the function of the corpus luteum, the early development of the embryo, the function of the trophoblast and endometrial receptivity. Obesity is in fact known to bring about hormonal changes which have major effects on endometrial function, embryo implantation and abnormal proliferation, which can even lead to endometrial hyperplasia (40).

Obesity and polycystic ovary syndrome (PCOS) are rather widespread metabolic disorders which have been linked to subfertility. Obesity and PCOS have effects on endometrial receptivity at the time of implantation which have been extensively researched, stemming from metabolic alterations affecting glucose metabolism, hyperinsulinemia, and hyperandrogenism and capable of regulating decidualization. The alteration of endometrial receptivity arising from metabolic disorders can negatively impact proper embryonic implantation, leading to higher miscarriage rates and subfertility. Such complications have been linked to the effects of glucose metabolism imbalances, compensatory hyperinsulinemia in insulin-resistant patients (a condition quite common in obese and PCOS patients), and hyperandrogenism (the primary consequence of androgen overproduction in the ovaries and adrenals caused by increased luteinizing hormone LH

and hyperinsulinemia due to insulin resistance) on the endometrium during the window of implantation (41). Obesity has been hypothesized to cause considerable changes in uterine receptivity and markers of decidualization and implantation, which seems to point to molecular mechanisms of endometrial dysfunction (42).

Since it is clear that obesity affects reproductive function at various levels, such as the ovary and the endometrium, good reproductive counseling should be provided to all couples with fertility issues arising from overweight or obesity. It is in fact essential to advise young obese women to lose weight, especially in the case of assisted pregnancy. The negative impact of obesity on reproductive capacity is summarized in Table 1.

It is worth noting how these patients need a specific gender oriented approach (43, 44) in their relationship path, as well as psychological support, often as a result of reproductive failures (45).

Obesity and infertility treatment

A survey of studies and research findings reporting the effect of obesity on the outcome of ART techniques has produced rather heterogeneous results, although the study design and definition of obesity

Table 1: Impact of obesity on reproduction

Condition	Associated risks
Menstruation and menorrhagia	↑ Menstrual dysfunction: amenorrhea, oligomenorrhea (46).
Functional changes in the Hypothalamo-Pituitary-Ovarian (HPO) axis	↓ Lower natural pregnancy rates. Exogenous gonadotropins indicated to counter the risk (46, 47).
Lower adiponectin serum levels and reduced adiponectin synthesis	↓ Possible negative effect on ovulation control, despite still inconclusive data (48); obesity-related ovarian dysfunction.
Impaired stromal decidualization in obese women which is responsible of	↑ Placental abnormalities, stillbirth and preeclampsia (49).
Infertility treatment	↓ Poor response to induction of ovulation, needing higher doses of gonadotropins and longer treatment and ovulatory cycles for follicular development. Lower oocyte yield and a higher rates of cycle failure. Ovarian stimulation producing fewer follicles, hence fewer harvested oocytes. Low embryo quality and poor fertilization rates (50).
Miscarriage	↑ The risk of miscarriage has been found to be as high as 40% in obese women as opposed to less than 15% in normal weight patients, although data as to the causative underlying dynamics are still inconclusive (51).

are variable. However, most studies suggest that obesity can adversely affect MAP outcomes. Obesity has been proven to negatively impact ovarian stimulation in women undergoing treatment. Reported effects include prolonged ovarian stimulation, increased gonadotropin dose required, increased incidence of follicular asynchrony and increased cancellation rates (23, 52-55). In a cohort study of women with PCOS who underwent ovulation induction with clomiphene or gonadotropins, a high BMI was shown to negatively affect ovulation rates. In this study, obese patients had significantly lower ovulation rates at 6 months of treatment: 79% in women with a BMI of 18-24 kg/m² compared with 15.3% with a BMI of 30-34 kg/m² 12% if BMI > 35 kg/m² (56). Some authors, however, have not been able to demonstrate any difference in ovarian response to stimulation in obese women (31, 57, 58).

Follicular recruitment during ovarian stimulation requires that the serum concentration of FSH exceed a therapeutic threshold; this threshold varies among patients but has been observed to be higher in women with elevated BMI. Higher doses of gonadotropin required in obese women may be related to impaired pharmacodynamics, impaired metabolism and reduced sex hormone-binding globulin (SHBG) concentrations (8). It has been observed that the absorption, metabolism and clearance of injected gonadotropins differ in obese women with PCOS (59).

Obese women undergoing IVF/ICSI have lower live birth rates. This is thought to be the cumulative effect of lower implantation and pregnancy rates, higher miscarriage rates and increased obstetric complications (60).

Body fat distribution is also important, since visceral obesity has a worse impact on fertility. A study involving 20 women undergoing in vitro fertilization found that a WHR > 0.8 was associated with a significant reduction in the pregnancy rate (OR 0.42, 95% CI 0.2-0.9), but did not find BMI to be related to the outcome of in vitro fertilization (61). Weight changes were observed to affect the success of treatment, an increase in the BMI unit in fact greatly reduces the likelihood of achieving pregnancy after IVF of 0.84 and, conversely, weight loss improves the odds of achieving

pregnancy by a factor of 1.19 for each unit reduction in BMI (62).

Countering the spread of obesity as a disease of extraordinary relevance globally can positively influence birth rates in any given country. The British Fertility Society has issued recommendations stating that obese female patients ought to aim to lower their BMI to normal levels before embarking upon any form of ART procedure (63). Any fertility treatment should be postponed until the patient's BMI is less than 35 kg/m², albeit in patients under the age of 37 (hence with more fertile years at their disposal) and normal serum FSH concentration, it would be advisable to aim for an even lower BMI (under 30 kg/m²). In fact, although MAP methods are becoming mainstream and constantly improving, scientific progress is often hindered by the internal policies of each country, which emphasize varying maximum ages as a requirement to access ART (64). Still, given the difficult and time-consuming process of losing large amounts of excess weight, it would be advisable to take such factors into account when addressing the needs of obese women trying to access ART (65). In Europe, 34 out of 43 countries have legal age limits for the treatment of couple infertility and 21 (including the Czech Republic, Denmark, Greece, Portugal, Spain, Sweden, United Kingdom) males and females must be over 18 years of age. Maximum female age is also a legal limit in 18 countries, ranging from 45 years in Denmark and Belgium (in the latter this limit applies to egg retrieval while embryo replacement and insemination are allowed up to 47 years) at 51 in Bulgaria. There are no legal age limits in Finland, Germany, Norway, while current legislation in Spain sets an upper limit for women at the age of "menopause" and in the Netherlands at the age of 49. Some countries, including Austria, Hungary and Poland, have not set an age limit for granting access to the MAP (66-68). In 2017, the biomedical authority in France set an age limit of 43 for women. While such a limit is still in place, in June 2021 French lawmakers amended legislation to lift the ban on single women and lesbian couples from accessing MAP procedures (69). Italian law n. 40/2004 points to "fertile age" among the subjective requirements for access to MAP care (art. 5), without setting the maximum age of access, but rather establishing that the average age

should be taken into account at which women and men can reproduce “naturally” with their own gametes, i.e. around 51 for women. Even the Italian Constitutional Court, in its judgments which modified law no. 40 of 2004 (72-75), clearly stated that the legislator cannot impose decisions on technical-scientific issues, but must allow experts or doctors to reasonably adapt the rules to different situations. Therefore, it is the doctor who is tasked with establishing what risks an obese woman would incur following the application of a technique (e.g. ovarian stimulation), the achievement of pregnancy (probability of miscarriage, for example) or at childbirth, following a thorough clinical evaluation on a case-by-case basis and considering the patient’s overall conditions. For this reason, lawmakers have chosen not to set strict age limits, trusting the physician’s autonomy and responsibility with clinical risk assessment of each individual case. Another aspect worth considering concerns the limitations that the Italian law still places against some methods of MAP, such as surrogacy. This regulatory gap, even if integrated by legal interpretation, encourages the so-called “fertility tourism”, with consequent economic, ethical and legal implications (73), not unlike other ethically controversial practices for which health professional can even object on conscience grounds (74, 75). Furthermore, assisted reproduction techniques give rise to a wide range of issues, such as embryonic legal status, the donors’ right to secrecy, partial anonymity or full disclosure of information about their identity (76-81). In the so-called phase two of the COVID-19 health emergency, scientific societies and advocacy groups (82) asked the Ministry of Health to raise the age limit for women in order to prevent those who had reached such a limit during the suspension of the activity, or about to reach it, from being unfairly denied access through the NHS (83).

Impact of maternal obesity on maternal and fetal health

High BMI in pregnant women has been reported to be linked to higher rates of cesarean section (CS), higher maternal or neonatal morbidity as well as to neonatal/prenatal intensive care, longer hospital

stay, as in the case of uterus rupture (84, 85). In fact, maternal obesity, in addition to higher rates of maternal hypertension, cardiovascular disease, diabetes, non-alcohol-related fatty liver disease, cancer and arthritis, also entails specific risks for both the fetus and the mother, both during pregnancy and at the time of labor and delivery (86). In fact, the risks for hypertension in pregnancy, venous thromboembolism and amniotic fluid embolism (especially following abdominal trauma) (87-90), spontaneous abortion, induction of labor, infections and dehiscence of the surgical wound are reportedly higher. Fetal macrosomia is frequent, along with higher maternal risk due to newborn weight > 4,500 g. Obese patients may also have difficulty completing the second stage of labor due to soft tissue dystocia with increased risk of arrested labor and caesarean section. In addition, the newborn of an obese pregnant woman has an increased risk for head trauma, shoulder dystocia, brachial plexus injuries and clavicle fractures. Maternal obesity also increases the risk of newborn defects, especially those affecting the neuraxial axis, such as spina bifida. Data from the Atlanta Birth Defects Risk Factor Surveillance Study, spanning 5 years, found that babies borne by obese women were more likely to have a baby with spina bifida, omphalocele, heart defects and multiple abnormalities (91). In these cases, highly specialized surgical procedures are required to correct agenesis of the primary and secondary sexual organs (92).

The alleged mechanisms that increase the rates of congenital anomalies include hyperglycemia or insulin resistance and related consequences. Furthermore, the increased risk of congenital malformations in children of obese women can be explained by visualization difficulties during ultrasound and the lack of weight adjustment during the measurement of biochemical markers, as also pointed out by the International Federation of Gynecology and Obstetrics (93, 94).

It is therefore essential to put in place preventive measures against obesity in young women, not only to stave off the effects on the health of the woman herself, but also to avoid compromising fertility capabilities and future pregnancy, with the consequences of providing healthcare for an obese patient, both clinically and financially (95, 96).

Maternal and childhood obesity and health hazards: an alarming correlation

A direct relationship has been established between pre-pregnancy obesity and the development of childhood obesity, higher total body fat mass and waist circumference in childhood, increased rates of adolescent obesity, and even cardiovascular diseases in the adult offspring manifesting themselves later in life (97). Animal models have exhibited the linkage between maternal obesity and higher leptin and C-peptide concentrations detected in umbilical cord blood (98). Such a finding points to the intrauterine environment possibly laying the groundwork for the development cardiovascular disease in adult age and even metabolic syndrome. Despite data variability, children from obese gravida have been found to have a tendency toward hypertension, hyperlipidemia, insulin resistance and elevated inflammatory markers as observational studies have concluded (99, 100) Just as significantly, maternal obesity has been shown to affect adipocyte morphology in-utero in the fetus, and result in higher levels of pancreas lipid deposition and higher incidence of ectopic liver (101, 102), which can cause chronic inflammatory, higher levels of oxidative stress, altered lipid profiles and hepatic protein expression, and even a higher tone of sympathetic nervous system. Such developments are all associated with higher risk of cardiometabolic conditions (103). Furthermore, abnormal circadian biological processes have been hypothesized to arise from pathophysiological mechanisms at the root of altered adipocyte deposition and function in fetuses of obese gravidas (104). Maternal pre-pregnancy obesity has also been linked to lower levels of cognitive development in children of 1–2 years of age by two cohort studies, whereas paternal overweight or obesity was not linked to alterations in cognitive development (105). Obesity is considered largely preventable and mainly caused by recent changes in the so-called obesogenic environment, prominently constituted by highly processed and sugar-rich food supply and pervasive use of technologies that reduce or replace physical activity. Genes and gene expression have long been viewed as significant co-factors. In the United States, there has recently been a leveling off of the incidence of obesity in children (106), due in part to changes in school lunch

programs (prioritizing more nutritious foods and less sugary drinks) and more physical exercise. The prevention of obesity in childhood is essential to stave off high obesity rates. In the US, national data on the incidence of pediatric obesity to date have only involved adolescents and young adults; however, since many of the processes leading to obesity start in early childhood, a nationally representative longitudinal study (107) was performed on children starting kindergarten in the fall semester of 1998 (7738 children averaging 5.6 years of age) and who were followed up to the end of the eighth year (aged between 5 and 14 years). The data emerging from this study showed that at an average age of 6.6 years, about 14.9% of children were overweight and 12.4% were obese. The prevalence of obesity was even higher as the children grew, reaching 20.8% in the eighth year of observation (average age of 14.1 years). This study made it possible to highlight the potential ages at which to intervene in order to avoid the risk of obesity in young adulthood. An integral part of the path towards obesity, in fact, is already established around the age of 5. In this study, half of childhood obesity cases involved children who had become overweight during preschool. This shows how body weight and eating patterns at the beginning of life are strongly correlated with a higher risk of obesity (108). The discovery that the tendency to obesity is established at a very young age (5 years) points to possible correlations between genetic predisposition but also intrauterine, preschool and early childhood factors, and of course the role of domestic environment and circumstances.

Practice general recommendations (Lifestyle intervention and behavior modification, pharmacological agents, bariatric surgery)

Treating obesity should be the initial goal in women who are infertile due to metabolic syndrome before undertaking a drug therapy or medically assisted treatment (MAP) to achieve pregnancy (109).

The reduction of body fat, and visceral fat in particular, should lead to an improvement in menstrual function and fertility and a reduction in metabolic risks. A 2-5% reduction in body weight was linked to the restoration of ovulation and a 71% increase in insulin sensitivity (110).

As far as pharmacotherapy is concerned, currently available Anti-Obesity Medications (AOMs) are designed to target the underlying neurohormonal imbalances at the root of abnormal BMI. Such derangements in fact also prevent weight loss. Weight loss as a result of diet adjustments can bring about changes in hormonal adjustments as well, e.g. a decrease in leptin (anorexigenic hormone) (111) and the rise of ghrelin (orexigenic hormone) levels (112). Weight loss resulting from diet can also impact energy expenditure through adaptation responses, leading to lower basal metabolic rates which can make it harder to keep the weight off (113, 114). Effective obesity treatment needs to be prioritized since it can benefit both weight and related comorbidities. As stated by the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE), the ultimate objectives of obesity treatment are in fact primary (i.e. preventing disease or injury before it ever occurs), secondary (i.e. reducing the impact of a disease or injury which has already taken place), and tertiary (i.e. mitigating the impact of an ongoing disease or injury with lasting effects) prevention (115); hence, averting the development or exacerbation of obesity and its complications is to be viewed as an absolute priority (116). For example, improvements in cardiometabolic risk factors and reduced diabetes risk have been consistently reported in the Phase 3 trials for AOMs, which despite a considerable degree of patient-response heterogeneity and inter-individual variability, have consistently shown more substantial weight loss linked to AOMs than placebo when combined with lifestyle modifications (116), with average efficacy ranging from 5 to 10% total body weight loss. When dealing with patients with 30 kg/m² BMI or over (condition referred to as morbid obesity), bariatric surgery may be recommended (117). Bariatric surgery is however deemed a last resort option for patients who have already unsuccessfully attempted other forms of treatment such as diet, increased physical activity, psychological/behavioural counseling and support, AOMs. Bariatric surgical procedures can be divided into two general approaches, to be carried out as open surgery or laparoscopically, with some variations for each one of them: malabsorptive (i.e. limit the absorption of food through the bypassing of parts of the gastrointestinal tract, such as Roux-en-Y gastric

bypass), and restrictive (such as vertical banded gastroplasty and adjustable gastric banding, which reduce the size of the stomach by as much as 80%, which makes the patient feel full and unable to overeat) (117, 118). All currently performed procedures have been linked to significant and durable weight loss, albeit data are still somewhat inconclusive for one-anastomosis gastric bypass and sleeve gastrectomy. A growing amount of scientific evidence indicates the benefits of bariatric surgery-induced weight loss on female and male fertility, although fertile women should be advised to avoid pregnancy until their weight has stabilized. That being said, it is worth noting that bariatric surgery may be linked to micronutrient deficiencies, surgical complications such as internal hernias, and small for gestational age (SGA) fetus, and no international consensus as yet exists as to the most indicated time for conception after bariatric surgery (119). A well-rounded comprehensive approach must include psychological support, given how research has recognized that obesity often comes with an array of distinctive character traits such as neuroticism, anxiety, depression, impulsiveness, anger and aggressiveness. The role played by psychological counseling is therefore of utmost importance, in conservative as well as metabolic-bariatric therapeutic approaches (120, 121).

Weight loss results in an increase in SHBG, reduction in testosterone, improvement in menstrual function, the rate of conception and a reduction in the miscarriage rate. Since central adiposity is associated with menstrual disorders and infertility, the loss of abdominal fat is essential to restore ovulation. Several strategies have been suggested to treat obesity, including diet management, physical activity, behavior modification, drug treatment and surgery. However, the fundamental component is long-term adherence to these strategies and the maintenance of weight loss.

The treatment of obesity is therefore not a simple path and above all, it is to be viewed as a long-term endeavor. Therefore, the best strategy to combat infertility from metabolic syndrome induced by excess weight is represented by adequate reproductive counseling and for the youngest by adequate information as to the effects of unhealthy eating habits and bad lifestyle choices can have not only in terms of health, but also on reproductive capacity.

Conclusions

Obesity can severely compromise reproductive outcomes, either natural ones or through MAP techniques. Furthermore, obesity has been universally acknowledged to affect MAP outcome. In light of that highly consequential association, further research is needed to clarify the underlying mechanisms of infertility, especially to try to discern between the negative effect on matrix fertility. Furthermore, the effects that obesity can have on the outcome of pregnancy and therefore on the product of conception should not be overlooked. The British Fertility Society has published guidelines to help doctors in advising obese patients to aim for a normal BMI before starting fertility treatment. Indeed, these guidelines recommend postponing any treatment until a woman's BMI <35 kg/m², and recommend achieving an optimal BMI <30 kg/m² (122). In conclusion, when considering fertility problems in obese women, the obstetric and neonatal consequences of pregnancy should also be carefully weighed. Therefore, adequate pre-conception counseling is essential with the aim of enforcing the achievement of a stable normal weight before natural or assisted conception. It should be emphasized that because of the potential risks associated with surgical options (i.e. bariatric surgery) or weight-loss drugs with anorectic effects, the only weight-loss intervention advocated for by medical societies is incentives (123, 124) and support in embracing healthy lifestyle habits such as healthy eating and exercise, proven to improve fertility prospects and fetal-maternal health in later pregnancies.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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