

BODY WEIGHT

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The increasing prevalence of obesity in developed countries is the result of a combination of reduced exercise, changes in dietary composition and increased caloric intake. In USA and most European countries, 60% of women are overweight (≥ 25 kg/m²), including 30% who are obese (≥ 30 kg/m²) and 6% who are morbidly obese (≥ 35 kg/m²). Obesity affects the general and older population, but also young women who become or try to become pregnant. Therefore, obesity is increasing among women of childbearing age that may be potential candidates for assisted reproduction technology.

Obese women are almost three times as likely to be at risk of infertility and to fail to become pregnant in both natural and assisted conception cycles. Some common endocrine and metabolic disturbances have been classically associated with obesity, such as functional hyperandrogenism, hyperinsulinism and alteration of secretion and action of several hormones related to energy balance and homeostasis (leptin, ghrelin, adiponectin, resistin). Obese women frequently present oligo-anovulation and association with polycystic ovary syndrome. However, a poorer reproductive outcome has been also described in obese women with regular ovulatory cycles.

Most reports show lower live birth rates in obese patients. The lower probability of a healthy liveborn seems to be the result of a combination of lower implantation and pregnancy rates, higher preclinical and clinical miscarriage rates and increased complications during pregnancy for both mother and fetus. Most complications in the second and third trimester of pregnancy are due to maternal manifestations of the metabolic syndrome of obesity. However, what occurs between conception and the end of the first trimester seems to be the result of an abnormal dialogue between the oocyte (and, thus, the resulting embryo) and the endometrium.

Regarding the oocyte-embryo complex, several reports have shown a lower ovarian response to controlled ovarian stimulation in obese women undergoing IVF and a significant impairment in the oocyte and embryo quality including reduced oocyte retrieval, lower number of mature oocytes, poorer oocyte quality with subsequent lower fertilization rates, poorer embryo quality, lower incidence of embryo transfer and lower mean number of transferred embryos. However, other authors have found no differences in those parameters according to the BMI. Hence, there is a current lack of consensus with regard to the supposed oocyte and embryo impairment in obese women undergoing IVF, and to what degree they are altered. Recently, an implication of male obesity on sperm quality and on natural and assisted conception outcome has been also described.

The endometrium may be also affected by obesity. The best human model for dissecting both components (embryo and endometrium) is the ovum donation model, in which oocytes from healthy, young, non-obese donors are given to recipients with different BMIs and the subsequent outcome is studied. Recently, a huge sample of first-cycle recipients of ovum donation without risk factors of miscarriage (n = 2656) was assessed by our group. The ongoing pregnancy rate per cycle initiated was significantly lower in obese women than in lean and normal controls, pointing out that the endometrium, or its environment, plays a role in the poor reproductive outcome of obese women. Moreover, another recent study performed in our centre, including 6500 IVF cycles and 81581 oocytes found a similar oocyte and embryo number and quality among women with different BMIs, but a poorer implantation, pregnancy and live birth rate as BMI increased. Therefore, despite the fact that the real implication of gametes, embryos and endometrium is not yet known, uterine environment seems to play an important role. Current studies are focused in the assessment of the endometrial receptivity in obese women.

Several approaches have been evaluated to improve fertility in obese women through lifestyle changes. Those strategies have shown to improve ovulation and pregnancy rates in natural conception but have not been tested in assisted reproduction. The main approach consists of weight reduction by diet and exercise. Calorie restriction is better than whole food intake restriction or changes in diet composition. A low-calorie, low-fat diet is recommended, but there is not currently a clear benefit of low-carbohydrate, high protein diet versus low-protein, high carbohydrate diet. Moderately intense exercise should be adapted to the physical condition of the patient and performed at least 150-200 minutes per week. However, exercise seems to be more useful for weight maintenance than for weight reduction. Only with just 5% or more loss of body weight ovulation and pregnancy rates can be improved or even restored, because energy restriction *per se* is better than the change in body shape or total weight, and due to the fact that reduction of visceral fat, which is most related to the endocrine and metabolic disturbances seen in obese women, is firstly achieved with small reductions of weight.

For the long-term compliance of a weight loss programme a psychological support is essential. Sensible eating habits need to be learned and behavioural therapy together with a close monitoring of the patients is strongly advisable. A multidisciplinary team, including psychologists, endocrinologists, gynaecologists, nutritionists and social workers, should be involved in this lifestyle therapy. Reduction of stress levels as well as unhealthy habits, such as alcohol and tobacco consumption, should be also associated. Metformin does not seem to be useful for weight reduction. In addition, it is not better than clomiphene citrate for ovulation induction. The use of appetite suppressants or anti-absorptive drugs, such as Orlistat, Sibutramine or Rimonabant, for reproductive purposes is not usually recommended due to their side-effects, the small weight reduction achieved and the rapid weight regain after discontinuation. Similarly, bariatric surgery, which is the best option for rapid weight reduction and long-term maintenance of weight loss in morbidly obese women, and also for the improvement of co-morbidities, has not been tested for reproductive purposes and presents many surgical complications. Hence, to date, it should not be considered as an option in infertile obese women.

Regarding underweight, menstrual periods often cease after a 10-15% decrease in normal body weight. Especially in women with bulimia or anorexia nervosa (prevalence of 5% in women of reproductive age) and female athletes, anovulation is a consequence of a decrease in GnRH pulses from the hypothalamus, which in turn decreases the pulsatile secretion of FSH and LH and shuts down stimulation of the ovary. However, underweight does not seem to affect reproductive outcome in ART, but increases obstetric complications (hyperemesis gravidarum, anaemia, IUGR, preterm delivery, caesarean deliveries, post-partum complications and depression, low birth weight).

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