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MEETING REPORT

Body Weight and Fertility

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Abstract: Obesity presents an increasing prevalence in developed countries and impairs human reproduction in both natural and assisted conception cycles. A healthy liveborn is less probable among obese women due to a combination of lower implantation and pregnancy rates, higher preclinical and clinical miscarriage rates and more frequent complications during pregnancy for both mother and fetus. Gametes, embryos and uterus seem to be negatively affected by the abnormal hormonal and metabolic environment present in obese men and women. Lifestyle therapy for weight reduction based on hypocaloric diet and exercise is the best approach for improving the reproductive performance of these patients. Pharmacotherapy does not seem to be useful and bariatric surgery indicated only for fertility purposes is currently considered a risky and understudied procedure.

Keywords: obesity, infertility, reproduction, endometrium, oocyte, lifestyle

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The interaction between a genetic predisposition, a prenatal overnutrition ("programming of appetite") and postnatal lifestyle and environmental factors lead to obesity, but contributes differently in each subject. 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/m^2), including 30% who are obese (≥30 kg/m^2) and 6% who are morbidly obese (≥35 kg/m^2). Obesity affects the general and older population, but also young women who become or try to become pregnant. In a recent study performed in the United Kingdom with 36821 women, the trend in maternal obesity between January 1990 and December 2004 was calculated in young women with a mean age of 24–28 years old. The prevalence of obesity was 9.9% in 1990 and 16% en 2004, and was estimated to be 22% in 2010. Therefore, obesity is increasing among women of childbearing age that may be potential candidates for assisted reproduction technology.

Obesity increases morbidity and mortality as a result of a variety of associated pathologies, such as cardiovascular and cerebrovascular diseases, type 2 diabetes, sleep apnoea, gastrointestinal diseases, osteoarthritis and cancer. In the field of reproduction, 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 (PCOS). However, a poorer reproductive outcome has been also described in obese women with regular ovulatory cycles. Due to the increased risk of infertility, assisted reproduction is more frequently performed in this population.

The ovarian response to gonadotrophins or clomiphene citrate has been shown to be lower in obese women undergoing ovulation induction for timed intercourse or intrauterine inseminations, while the effect on pregnancy rates remains controversial. That said, some papers have suggested a lower possibility of conception than in the normoweight population, especially when PCOS or central adiposity is associated. IVF and ICSI procedures in obese women undergoing controlled ovarian hyperstimulation (COH) require higher doses of gonadotrophins due to the "gonadotrophin resistance" that characterises these patients, also observed when PCOS is associated. Doses of gonadotrophins need to be raised as body mass index (BMI) increases in both long and short stimulation protocols. Indeed, obese patients undergoing COH have been shown to require longer periods of ovarian stimulation and exhibit higher cancellation rates in both ovulation induction and IVF/ICSI, which may be the result of an insufficient response. Fertilization rates have been shown to be negatively affected by low concentrations of periovulatory human chorionic gonadotrophin. Estradiol concentrations have been seen to peak at lower levels in obese women undergoing COH for IVF.

Higher doses of gonadotrophins, a longer period of ovarian stimulation and higher cycle cancellation rates due to insufficient response in obese patients have been attributed to what is known as "gonadotrophin resistance". Similar findings have been observed in obese egg donors. It would represent an attenuated response caused by a reduced absorption of the drug or the way in which it is distributed throughout the body. In this way, the altered pharmacokinetics of gonadotrophins in obese women would seem to result in lower effective concentrations of exogenous FSH. The selection of multiple growing follicles during ovarian stimulation with FSH requires the serum FSH concentration to exceed a certain threshold. The threshold effect of exogenous FSH is lower among obese women, leading to a lower number of selected follicles, fewer collected oocytes and the need for higher doses of FSH for stimulation. Leptin serum concentration is also thought to induce gonadotrophin resistance. Leptin levels are related to the amount of adipose tissue in the body. The stimulatory effect of FSH on steroid synthesis by granulosa cells *in vitro* is inhibited by leptin, and high concentrations of intrafollicular leptin have been related with relative gonadotrophin resistance during ovarian stimulation for IVF in PCOS women. In these women, the higher incidence of android obesity has also been associated with a poorer IVF outcome.

Regarding reproductive outcome, 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.

Lower pregnancy rates have been described in obese women following ovulation induction or ART. An odds ratio for conception of 0.53 (CI 95% 0.32–0.86) has been observed in overweight women undergoing IVF. Other authors have shown a progressive reduction of the odds ratio for fecundity (defined as the probability of achieving at least one pregnancy throughout the ART treatment: IVF, ICSI or GIFT) in IVF patients from 25 kg/m^2 (OR:0.81, CI 95% 0.68–0.97) to ≥35 kg/m^2 (OR: 0.50, CI 95% 0.32–0.77) of BMI. This represented a reduction of almost 1/3 in obese women (30–34.9 kg/m^2) and 50% in very obese women (≥35 kg/m^2). This effect seems to be more acute in cases of central obesity, in which the waist-to-hip ratio is >0.80. A recent systematic review of the effect of overweight and obesity on assisted reproductive technology has concluded that pregnancy rates in non-overweight women (20–25 kg/m^2) are significantly higher (OR: 1.40, CI 95% 1.22–1.60) than those in overweight women (>25 kg/m^2). Similarly, non-obese women (20–30 kg/m^2) presented significantly higher pregnancy rates (OR: 1.47, CI 95% 1.20–1.80) than obese patients (>30 kg/m^2). Therefore, considering current evidence, it can be concluded that obesity negatively affects IVF pregnancy rates.

In the same recent systematic review, the odds ratio for miscarriage was significantly higher in overweight (>25 kg/m^2; OR: 1.33, CI 95% 1.06–1.68) and obese women (>30 kg/m^2; OR: 1.53, CI 95% 1.27–1.84) than in non-overweight (<25 kg/m^2) and non-obese (<30 kg/m^2) women, respectively. Similarly, a recent meta-analysis regarding the effect of high body mass index on risk of miscarriage after spontaneous or assited conception determined that patients with a BMI ≥ 25 kg/m^2 ran significantly higher odds of having a miscarriage, regardless of the method of conception (OR: 1.67, CI 95% 1.25–2.25). This increased risk was particularly identified in pregnancies obtained by ovulation induction and ovum donation. This evidence would suggest that an increased risk of miscarriage after natural or assisted conception should be considered in overweight and obese women. Some recent theories have postulated that the increased risk of biochemical and first trimester clinical miscarriages in obese women could be related to ovarian or endometrial factors. Regarding ovarian factors, miscarriage in obese women has been associated with an impaired insulin resistance at the time of conception, abnormal corpus luteum function, impaired oocyte quality due to the reduced risk of miscarriage in cases of ICSI in which infertility is attributed to the male factor, and poor oocyte/embryo quality and development. Endometrial receptivity may also be impaired, and exposure of the uterus to high estradiol concentrations produced by the higher doses of gonadotrophins administered in obese patients during ovarian stimulation in order to compensate the state of "gonadotrophin resistance" could also lie behind the tendency towards miscarriage.

Pregnancy complications are higher in obese women, particularly during the third trimester, and include hypertension, gestational diabetes, preeclampsia, thromboembolism, fetal macrosomia, urinary tract infection, preterm labour and delivery, sudden and unexplained intrauterine death, operative vaginal deliveries, caesarean section delivery, shoulder dystocia, anaesthetic and surgical complications, postpartum haemorrhage, postoperative wound infection and dehiscence and endomyometritis in the puerperium. Defects of the central nervous system of the fetus (such as neural tube defects), great vessels, ventral wall and intestine have been described more frequently in obese women. These findings could be explained by insufficient absorption or distribution of essential nutrients such as folic acid, the incipient hyperglycaemia caused by insulin resistance at the time of organogenesis, or the poorer visualization of fetal organs by ultrasound which may lead to subsequent errors in sonographic prenatal diagnosis. Obesity has also been related to an increased risk of chronic disease in the adolescence and adulthood of the offspring, such as obesity, cardiovascular disease and diabetes type II. As obesity can affect all aspects of maternal health, management of pregnancy in obese women is likely to be associated with a substantial increase in costs. For obese women, the cost of antenatal care is approximately five times higher than the average.

Some studies including big sample sizes have reported a reduction by 25%–35% in the live birth rate in obese women after IVF in comparison to normoweight controls, as a consequence of the abovementioned described complications. 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. At IVI-Valencia we have recently examined the outcome of 6500 IVF cycles according to women´s BMI while controlling for different confounding variables such as age, smoking habit, sperm quality, origin and duration of infertility and protocol for ovarian stimulation. In the obese group ($\geq$30 kg/m^2), there was a significant increase in the dose of gonadotrophins during controlled ovarian stimulation, and significantly lower implantation (26.4% vs. 32.2% when $<$30 kg/m^2; $p = 0.005$), pregnancy (37.9% vs. 44.4% when $<$30 kg/m^2; $p = 0.029$) and live birth rates (23.7% vs. 30.6% when $<$30 kg/m^2; $p = 0.004$) than the other three groups. However, when oocyte and embryo quality were assessed, we found no significant differences among the different BMI groups. These results indicate that the contribution for the poor reproductive outcome of obese women undergoing IVF could be related to the endometrium (or the uterine environment) or to the oocyte/embryo complex, but the conventional embryological criteria employed for selecting the best embryos to transfer in the IVF labs may be insufficient in such cases.

Recently, the role of male partner obesity in the poorer IVF outcome has been evaluated. In fact, some recent studies of young fertile populations have reported a significant alteration in the hormonal male pattern of obese men, leading to a significant reduction in some sperm parameters, including sperm concentration and total sperm count, and a trend towards an impaired morphology. Therefore, the inferior sperm quality of obese men could also impair the quality of embryos after IVF. In fact, a recent study of 26303 planned pregnancies, after controlling for other confounding variables, found an odds ratio for infertility in overweight and obese men that was significantly higher (1.2–1.4) than that in normoweight men. Similarly, other authors with 47835 couples observed a dose-response relationship between increasing BMI and subfecundity (time to pregnancy of more than 12 months) among women and men with a BMI of $\geq$18.5 kg/m^2. Therefore, couples ran a high risk of being subfecund if they were both obese. Couples often share similar lifestyle behaviours, so that some obese women have obese male partners, and the poor reproductive outcome of these couples could be the result of the combination of two low quality gametes in a low quality embryo, that may reach a low quality endometrium.

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. These results are in agreement to those obtained in IVF. 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 (500–1000 kcal/day of energy restriction), 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.

In summary, obesity impairs human reproduction by reducing pregnancy chances and increasing miscarriage rates and obstetric complications for both mother and fetus, leading to reduced live birth rates. This effect seems to occur in all types of conception. Obesity may impair both embryo and endometrial quality, but further studies need to be performed in order to determine the real role of both components. Weight management through diet and exercise is the first measure to be advised in obese women hoping to conceive. This approach can restore ovulation, menstrual pattern and pregnancy chances in cases in which anovulation is the main reproductive problem. Psychological support (cognitive behaviour therapy and supportive group environment) is often necessary for long-term compliance of a weight loss program. The medical, social and ethical issues involved in allocating resources for fertility treatment in overweight women are concerns which raise the question as to whether there should be an upper limit of BMI for enrolling patients in infertility treatment.

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, intrauterine growth restriction, preterm delivery, caesarean deliveries, post-partum complications and depression, low birth weight).

Disclosure

The authors report no conflicts of interest.

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