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Body mass index and fertility: is there a correlation with human reproduction outcomes?

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Abstract

Considering the existing conflicts about how an elevated body mass index (BMI) affects fertility, this study had the objective of evaluating the impact of overweight and obesity on the results of IVF/ICSI (*in-vitro* fertilisation/intracytoplasmatic sperm injection) performed at the Human Reproduction Centre of Faculdade de Medicina do ABC. Retrospective data from 208 IVF cycles of 191 women, performed at our laboratory from February through June, 2008, were used to calculate their BMI. On the basis of the results, the patients were divided into two groups: Group 1: BMI <25 kg/m^2 and Group 2: BMI ≥ 25 kg/m^2. Of the 208 cycles, 137 were from patients with BMI <25 kg/m^2 and 71 cycles from patients with BMI ≥ 25 kg/m^2. Patients' ages and the number of cycles with gonadotrophin-releasing hormone agonist and antagonist were similar in both groups. The doses of follicle-stimulating hormone used for ovarian induction per cycle, the number of retrieved oocytes, fertilisation rate, embryo quality and number of transferred and frozen embryos, the hyperstimulation, pregnancy rates, miscarriage rate and live birth rates showed no statistically significant differences. BMI does not appear to be a good parameter for the definition of IVF success. The association with other methodologies may produce more consistent data about body composition and its impact on fertility.

Keywords: *BMI, fertility, IVF, ICSI*

Introduction

Overweight and obesity have become major health problems worldwide. More than one billion people in the world are overweight. Around 75% of women over the age of 30 years are overweight in countries such as Mexico, South Africa, Egypt and the United States of America. Estimates are similar for men, with 75% overweight in Argentina, Germany, Greece, the United Kingdom, Kuwait and New Zealand [1]. In Brazil, around 40% of the population is overweight or obese [2].

Recently, obesity and overweight have been associated to subfertility because they cause a relative state of hypogonadotrophic hypogonadism. Obesity can modify the insulin levels produced by the pancreas and cause androgen hyperproduction, besides an increase in oestrogen production, reflected by irregular menstrual cycles, reduction of ovulatory cycles and low fecundity rates [3].

Clark et al. [4] observed a positive association between excess body weight and decreased fecundity, based on studies reporting resumption of ovulation and improved fecundity following weight loss. Obesity has also been associated with poor pregnancy outcomes, such as unexplained intrauterine death [5].

The recommended classification of overweight and obesity according to the World Health Organisation (WHO) is defined by the body mass index (BMI), calculated by dividing the weight in kilograms by the squared height in metres (kg/m^2). This classification allows assigning the patients to the following groups: underweight (BMI <18.5 kg/m^2), normal (BMI <25 kg/m^2), overweight (BMI $=25$–30 kg/m^2) and obesity classes I, II and III (BMI ≥ 30 kg/m^2, ≥ 35 kg/m^2 and ≥ 40 kg/m^2, respectively) [1].

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The association of overweight and obesity with *in-vitro* fertilisation (IVF) results is still controversial. Lashen et al. [6] published a case–control study with 333 women undertaking IVF and concluded that extremes of body mass (BMI $\geq$30 and $\leq$18 kg/m^2, respectively) do not adversely affect the outcome of hyperovulation and IVF. A similar conclusion had been previously published by Lewis et al. [7].

Maheshwari et al. [8] conducted a systematic review of observational studies on overweight and obesity in assisted reproductive technology and concluded that women with BMI $\geq$25kg/m^2 showed decreased pregnancy rates, required higher doses of gonadotrophins for ovulation induction in IVF [1] and had high miscarriage rates, but they stated that more prospective studies with clear entry criteria and uniform reporting of outcomes were needed.

Thus, body composition seems to be an important condition for fertility, although there is no consensus in the literature. Considering the existing conflicts, the objective of this study was to evaluate the impact of overweight and obesity on the IVF/ICSI (*in-vitro* fertilisation/intracytoplasmatic sperm injection) results obtained at the Human Reproduction Centre of Faculdade de Medicina do ABC.

Materials and methods

Subjects

Retrospective data from 208 IVF cycles of 191 women, performed at our laboratory from February through June, 2008, were analysed. Frozen embryo transfers and donor oocyte-derived embryo transfers were excluded from the study. BMI was calculated according to the Quetelet formula, by dividing the weight in kilogram by the squared height in metres (kg/m^2). On the basis of this calculation, the patients were divided into two groups: Group 1: BMI $<$25 kg/m^2, and Group 2: BMI $\geq$25 kg/m^2. There were no patients with BMI $<$18 kg/m^2.

Stimulation protocol

All patients were submitted to IVF based on clinical indications such as tubal factor, endometriosis, male factor or low-complexity technical failure. The criterion for performing either IVF or ICSI was sperm quality.

Ovarian stimulation followed the protocols of the center: ovulation was induced with 100 U of recombinant FSH per day, starting in the initial follicular phase of the menstrual cycle for patients aged $\leq$35 years and without previous induction; and with 200 U of recombinant FSH for patients with low response to previous induction, age $>$35 years, a single ovary or previous surgery with reduction of the ovarian parenchyma. The hypothalamic blockage was chosen according to the history of previous inductions and performed with a gonadotropin-releasing hormone (GnRH) agonist in the secretory phase of the previous cycle or with a GnRH antagonist during the ovulation induction with recombinant FSH. The procedure was controlled by serial ultrasonograms, and human chorionic gonadotropin (hCG) was administered when the follicles attained 17–18 mm on average, after about 9–12 days. The ovarian puncture was guided by ultrasonography and performed 35–36 h after hCG.

Oocyte, embryo selection and transfer

According to nuclear maturation grading, the oocytes were classified into the categories metaphase II or non-metaphase II. ICSI was performed on metaphase II oocytes. After the ICSI or IVF procedure, 2PN (pro-nucleus) formation was assessed with a 40$\times$ objective on an inverted microscope with Hoffman modulation contrast optics, after 16–18 h of incubation, and cultured until the day of embryo transfer, when the morphology of the embryos was evaluated. Zygote scoring was carried out according to Tesarik and Greco [9]. Early cleavage was defined as evidence of cleavage 25 h after insemination or ICSI [10]. Embryos with up to 20% of fragmentation and a number of cells adequate for the day were considered of good quality.

Embryo transfer was performed on the 2nd or 3rd day after fertilisation, using a maximum of three embryos per cycle. Progesterone support was provided vaginally with 600 mg/day starting on the day of the puncture, and pregnancy was confirmed by peripheral blood beta human chorionic gonadotropin (βhCG) dosage, 12–14 days after transfer.

Biochemical pregnancy (early pregnancy loss) was diagnosed when a previously positive pregnancy test became negative before ultrasonographic detection of an embryonic sac in the fifth week of pregnancy or later. Miscarriage was defined as a pregnancy failing to reach the 22nd week of pregnancy after the detection of the gestation sac (s) by ultrasound examination. Live birth was considered when the foetus was born alive beyond the 22nd week of pregnancy.

Statistical analysis

Statistical analysis was carried out using Student's *t*-test and Pearson's correlation, where values of $p \leq 0.05$ were considered significant.

Results

A total of 208 cycles were evaluated, 137 of which were from patients with BMI $<$25 kg/m^2, 59 from patients with BMI between 25 and 30 kg/m^2

(overweight) and only 12 with BMI $\geq$30 kg/m^2 (obesity).

None of the parameters analysed presented any difference between the patients of the overweight and of the obesity group. Since the latter represented only 5.77% of the whole sample, we chose to divide the cycles into two groups: BMI $<$25 kg/m^2 and BMI $\geq$25 kg/m^2.

The frequency distribution of the causes of infertility in these groups is presented in Table I.

The patients' mean age and the number of cycles with GnRH agonist and with GnRH antagonist blockage were similar.

Regarding the dose of recombinant FSH used per cycle to induce ovulation, there was no statistically significant difference either (Box 1).

The laboratory results obtained were also analysed, and no difference between the two groups was found regarding the number of oocytes, fertilisation rate, embryo quality and number of transferred and frozen embryos. There was no difference either between groups regarding the number of cases of hyperstimulation and pregnancy rate (Table II).

The pregnancy rate, miscarriage rate and the live-birth rate were not statistically different between groups (Table III).

The Pearson correlation test was also applied to assess the fertility rates in relation to BMI and we found no statistical significance ($p = 0.2296$).

Discussion

One of the greatest difficulties in assisted reproduction is foreseeing the ovarian response to gonadotrophin stimulation. It is known that some factors, such as the woman's age, the cause of the infertility, and the body mass index, can interfere with this response. Fedorcsák et al. [11] and Dechaud et al. [12] observed that patients with BMI > 25 kg/m^2 needed a higher dose of gonodotrophins compared to those with BMI $<$25 kg/m^2. However, in this study, there was no significant difference between the gonadotrophin doses according to the BMI, but it should be taken into account that in our study group most of the patients were within the overweight rather than the obesity range.

Frattarelli and Kodama [13] showed that an increased BMI is related to more gonadotrophin ampoules and a decrease in the number of follicles. Ku et al. [14] and Matalliotakis et al. [15,16] confirmed these results and reported further that BMI was also related to a decreased pregnancy rate. In our sample, however, BMI seemed not to interfere

Table I. Infertility causes according to BMI in studies patients.

	BMI $<$25 kg/m^2		BMI $\geq$25 kg/m^2		
Infertility factor	*n*	%	*n*	%	*p*-value
Ovulatory	11	8.03	4	5. 63	0. 731*
Idiopathic Infertility	23	16.79	13	18.31	0. 935*
Tubal	44	32.11	19	26.76	0.524*
Male	59	43.07	35	49.30	0.478*
Total	137	100.00	71	100.00	

*No statistically significant difference: $p > 0.05$ BMI-body mass index

Box 1. Characteristics of patients and cycles.

Parameters	BMI = $<$25 kg/m^2	BMI $\geq$25 kg/m^2	*p*
Cycles	137	71	
BM	21.4 $\pm$ 1.7	27.7 $\pm$ 2.34	0.0001
Age (years)	34.5 $\pm$ 4.8	35.63 $\pm$ 4.9	0.119*
Cycles with GnRH agonist (%)	103(75.2)	45(63.4)	0.105*
Cycles with GnRH antagonist (%)	34(24.0)	26(36.6)	0.105*
Recombinant FSH/cycle (U/cycle)	1545.4 $\pm$ 480.5	1493.6 $\pm$ 489.2	0.465*

*No statistically significant difference: $p > 0.05$ BMI – body mass index U- unities GnRH – gonadotropin-Releasing hormone FSH – follicle-stimulating hormone.

Table II. Laboratory results per in vitro fertilization cycle.

Results per cycle	BMI $<$25 kg/m^2	BMI $>$25 kg/m^2	*p*
No. of retrieved oocytes	7 $\pm$ 4.68	7 $\pm$ 5.13	1.000*
No. of injected or inseminated oocytes	5.5 $\pm$ 3.86	5.08 $\pm$ 3.81	0.456*
Fertilization rate (%)	73.9	76.7	0.785*
No. of embryos of good quality	1.26 $\pm$ 1.52	1.33 $\pm$ 1.50	0.752*
No. of transferred embryos	2.2 $\pm$ 1.21	2.2 $\pm$ 1.19	1.000*
No. of cycles with embryos freezing (%)	14(10.2)	10(14)	0.558*
No. of frozen embryos/patient	5 $\pm$ 2.84	5.4 $\pm$ 3.53	0.283*
No. of cases with hyperstimulation (%)	2(1.45)	2(2.81)	0.885*
Pregnancy rate/transfer (%)	26.01	25	0.996*

*No statistically significant difference: $p > 0.05$ BMI-body mass index.

Table III. Pregnancy outcome of the studied groups.

Results per cycle	BMI $<$25 kg/m^2	BMI $\geq$25 kg/m^2	*p*
Pregnancy rate (%)	26.01	22.22	0.666
Early pregnancy loss rate (%)	7.31	7.93	0.887
Clinical miscarriage rate (%)	4.06	3.17	0.918
Ectopic pregnancy (%)	1.62	1.58	0.567
Live birth rate (%)	13.00	9.50	0.649

*No statistically significant difference: $p > 0.05$ BMI - body mass index.

directly with ovulation induction, since we did not find any statistically significant difference in follicular stimulation or oocyte retrieval between the two groups, and the consequent cases of frozen embryos and ovarian hyperstimulation were also similar in both groups. We had expected that a higher dose of FSH would have to be used in the patients with BMI > 25 kg/m^2 to obtain the same response as in those with BMI < 25 kg/m^2, but this was not observed. There was no statistically significant difference between the doses used for both groups, or between the fertilisation rates, number of embryos obtained and transferred or number of oocytes.

It has been observed that, even after undertaking IVF procedures, obese women have decreased pregnancy rates compared to moderate-weight women, suggesting that there may be intrinsic differences in the oocytes of these patients. Definitive data is lacking however, and thus the effect of obesity on oocyte quality remains one of the biggest controversies in reproductive medicine [3].

In a study developed at the Yale IVF unit between 1996 and 2002, Matalliotakis et al. [15] evaluated a group consisting of 151 women who conceived after *in-vitro* fertilisation with embryo transfer (IVF-ET) and a control group of 146 women who underwent 288 IVF-ET cycles without pregnancy. They showed that there was no association between IVF outcome and race, BMI, age at menarche, length of cycle, duration and amount of flow, menstrual symptoms, other medical problems, medical history of allergies and family history of endometriosis and cancer.

Other studies also failed to find any important negative impact of weight on ovulatory response. Lashen et al. [6] conducted a study with 76 obese patients (BMI > 27.9), 156 controls and 35 underweight patients and found no excess risk of cycle cancellation, reduction of follicles, oocytes or embryos or lower chances of ongoing pregnancy in underweight or overweight woman when compared to normal-weight counterparts. Lewis et al. [7] did in fact observe a higher number of oocytes aspired from normal-weight compared to overweight women, but did not find any difference in the fertilisation rates of these groups.

Sneed et al. [17] found that, when examined as a main effect, BMI did not appear to have a major effect on IVF outcome, but there was a significant BMI $\times$ age interaction. At younger ages, a high BMI had a pronounced negative influence on fertility, but this effect diminished as the patient age increased. According to them, after age 36, BMI has a minimal impact on fertility. Martinuzzi et al. [18], in a study with 417 IVF cycles of women under 35 years old, found that cancellation rates, peak oestradiol levels and mean number of oocytes retrieved were similar in all groups.

However, obesity and overweight do not alter only female fertility, they also contribute to a lower male fertility rate, for they reduce the levels of testosterone and increase those of oestradiol, compromising sperm production. In addition, there are studies indicating that overweight men have a higher sperm deoxyribonucleic acid (DNA) fragmentation rate, which can produce fertilisation failure [19].

Altarejos et al. [20] identified a gene that controls both weight and reproduction. This study indicates that variations in the gene known as *Crtc1* (regulated transcription coactivator 1) can contribute as a genetic component to both obesity and infertility. According to these authors, this gene is as important as leptin, the protein that acts directly on appetite regulation, once leptin turns into Crtc1, which in turn activates a number of genes known for their action in the control of the hunger and fertility processes. In this study, knockout mice for gene *Crtc1* (*Crtc1*–/–) were born healthy and equal to the others, but after 8 weeks they started gaining more weight and became obese as adults, with two to three times more fat than the other animals, besides developing insulin resistance. We also observed that mice of both sexes were infertile, and the uterus and ovaries of the females were anatomically dysfunctional [20].

The impact of overweight on fertility is even stronger when the couple is involved. Ramlau-Hansen et al. [21] published a review on 47,835 Danish couples studied between 1996 and 2002 and found that, if both partners were obese, their chances of having to wait more than 1 year for the woman to get pregnant were 2.74 times higher than those of a couple with ideal weight. For non-obese but overweight couples, the probability of having to wait more than one year for a pregnancy was 1.4 times higher. For this review, the authors used data from a national study on pregnant women that interviewed over 100,000 women. They also evaluated 365 couples in which the woman was overweight or obese prior to the first pregnancy (BMI > 25) and maintained or lost weight during the second pregnancy. In these cases, for each kilogram lost, the waiting time for a pregnancy decreased 5.5 days on average [21].

Thus, BMI may not be a good parameter for the definition of a successful IVF. An association with other methodologies, as for example the waist-to-hip ratio, glycaemia and insulinaemia dosages, evaluation of the couple and not only of the woman and maybe even genetic tests, may reveal more consistent data regarding body composition and its relationship with the assisted reproduction outcomes.

It is worth pointing out that obesity in itself is harmful to the health of men and women and not only regarding the reproduction issue. Overweight can lead to the development of arterial hypertension, alterations in the metabolism of glucose and lipids,

occurring separately or in association (metabolic syndrome), besides cardiovascular diseases, osteoarthritis and coledocolithiasis. Obesity produces even greater damages to the female health, once in obese pregnant women there is a high risk of gestational diabetes, pregnancy-specific hypertension disease, miscarriage, foetal malformations and premature deliveries. Moreover, the percentage of caesarian sections is higher, the obstetric performance is poorer, labour lasts longer and there is also a higher risk of giving birth to newborns that are big for their gestational age, predisposed to hypoglycaemia, diabetes and obesity in adult life.

Thus, further research is necessary to establish the true impact of overweight on fertility, in view of its potential major implications for the population levels, particularly in those parts of the world where obesity and low fertility are increasingly common.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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