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CLINICAL ASSISTED REPRODUCTION

Does Body Mass Index of Infertile Women Have an Impact on IVF Procedure and Outcome?

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***Purpose**: The objective was to explore whether body mass index (BMI) of women related to the different parameters of the in vitro fertilization (IVF) procedure and outcome.*
***Methods**: This retrospective study on 398 couples analyzed epidemiological features, characteristics of ovarian stimulation, number and quality of retrieved oocytes, as well as pregnancy outcome according to three groups of BMI values: BMI < 20, $20 \leq$ BMI < 25 and BMI ≥ 25 kg/m^2.*
***Results**: The prevalence of underweight and overweight women was 21.8% and 22.3%, respectively. The mean ratio follicle-stimulating hormone–luteinizing hormone increased significantly according to BMI. An increase in the mean number of consummated gonadotropin ampoules together with a decrease in the number of collected oocytes was observed in long stimulation protocol cycles when BMI ≥ 25 kg/m^2. The same observations were made in short stimulation protocol cycles for BMI < 20 and ≥ 25 kg/m^2. No significant difference could be found in clinical pregnancy and miscarriage rates between underweight, normal weight, and overweight patients.*
***Conclusions**: Both underweight and overweight have negative effects on IVF parameters and outcome leading to decreased chances of pregnancy.*

KEY WORDS: Body mass index; intracytoplasmic sperm injection; in vitro fertilization; obesity.

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INTRODUCTION

Higher risks of infertility have been found in both overweight and underweight women (1–3). To appreciate female anthropometry the estimation of Quetelet's body mass index (BMI) defined as weight/height^2 (kg/m^2) is frequently performed. According to this parameter, a BMI range from 20 to 25 kg/m^2 corresponds to normal weight women, whereas a BMI between 25 and 28 kg/m^2 defines overweight women and BMI equal to or greater than 28 kg/m^2 defines obese women. The prevalence of overweight varies worldwide but is estimated to range from 5% (4) to more than 30% (5) in developed countries. Overweight repercussions on fertility are well known. In natural cycles, the fertility of obese women is lower compared to normally weighted women (2) and ovulation disorders are more frequent (5). In case of pregnancy, the miscarriage rate increases (5) with maternal obesity and also is a factor associated with an increased risk of cesarean delivery (6). Concerning infertility treatments, it has been demonstrated that response to gonadotropins for follicular growth is inversely related to body mass (7). In addition the length of the stimulation protocol (8) the number of retrieved oocytes (9) also seem to be disturbed by an increased BMI.

The aim of this study was to find out any eventual correlations between the BMI of patients included in an in vitro fertilization (IVF) program and different steps of the procedure. Following this guideline, data concerning epidemiological features of the population, characteristics of ovarian stimulation, number

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and quality of retrieved oocytes, as well as the pregnancy outcome were studied.

MATERIALS AND METHODS

All couples referred for IVF or intracytoplasmic sperm injection (ICSI) to the Infertility Centre between December 1997 and April 1998 were included in this study. Ovarian stimulation was carried out using human menopausal gonadotropin (hMG) (Humegon® 75 IU/ml, Organon Laboratories, Saint-Denis, France) and/or follicle-stimulating hormone (FSH) injections (MetrodinHP® or Gonal F®, 75 IU/ml, Serono Laboratories, Boulogne, France). Prior to this, pituitary down-regulation and continued desensitization was achieved using daily subcutaneous injections of Buserelin (Suprefact® 1 mg/ml; Hoechst, Paris La Défense, France) administered at a dose of 0.3 to 0.6 mg once daily. The gonadotropin-releasing hormone (GnRH) analogue was used either in a long protocol, with ovarian desensitization starting at the end of the luteal phase of the previous cycle, or in a short protocol begun in early follicular phase to take advantage of the ''flare-up'' effect. In a few cases, stimulation was achieved using clomiphene citrate (Pergotime®, Serono Laboratories, Boulogne, France) combined with FSH or using FSH only without GnRH analogue. The FSH/hMG dose range administered to each patient was determined according to basal hormonal profile and when possible to the results of previous stimulation treatments. Follicular development was monitored by ultrasound scanning and serial assays of serum estradiol concentration. The dose of 5000 IU of human chorionic gonadotrophin (hCG) (Gonadotrophine Chorionique ''endo,''® Organon Laboratories, Saint-Denis, France) was routinely administered as an ovulation trigger. Thirty-four to 37 hr later, oocyte retrieval was performed by transvaginal oocyte aspiration under ultrasound guidance using a 20-ml syringe directly connected to the aspiration needle (Luer lock needle ovum recovery, gauge 17, CCD Laboratories, Paris, France) without flushing the follicles. The aspirates were examined immediately in the IVF laboratory using a stereoscopic microscope (SMZ-2T, Nikon Corporation, Tokyo, Japan) and the oocyte–cumulus complexes were isolated and rinsed in culture medium (IVF Medium, MediCult, Denmark). The cumulus-spreading technique described by Veeck (10) was immediately carried out to observe oocytes. This was performed using an inverted phase-contrast microscope (Nikon, Diaphot 200, Nikon Corporation, Tokyo, Japan) at a magnification of $\times 200$. ICSI procedure was performed as described by Van Steirteghem *et al.* (11). Embryo transfer took place 44–48 hr after insemination or ICSI. Pregnancy was diagnosed by a positive βhCG pregnancy test performed 20 days after embryo transfer. Clinical pregnancy was defined by a serum βhCG concentration >1000 IU/l and early miscarriage was defined by a termination of pregnancy before 12 weeks.

Data collected for analysis included the age of the female partner, the weight (kg) and height (m), the Quetelet's BMI defined as weight/height^2 (kg/m^2), the basal levels of luteinizing hormone (LH) and FSH of the woman (measured the third day of a previous nonstimulated cycle), the type of ovarian stimulation protocol, the total number of consummated ampoules, the day of hCG injection, and the serum estradiol concentration on the day of hCG injection. Other variables included in this study were the total number and maturity of retrieved oocytes, the pregnancy rate per embryo transfer, the miscarriage rate, the delivery rate and the birthweight of the newborns.

Results were expressed as means ($\pm$SD) and percentages. Analysis of variance was used to compare group means, while the χ^2 test was used to compare proportions. The level of significance was set at $p < 0.05$.

RESULTS

General Features

A total of 398 couples were included in this study, 236 relevant to IVF (59.3%) and 162 relevant to ICSI (40.7%). The women's mean age was 33.07 years (SD = 4.4). The medium weight was 62.02 kg (SD = 11.9) and medium height 1.64 m (SD = 0.06). The medium BMI was 23.03 kg/m^2 (SD = 4.3). Four groups of BMI values were considered: BMI $<$ 20 kg/m^2 corresponding to thin women [n = 87 (21.8%)]; 20 $\leq$ BMI $<$ 25 kg/m^2 for normal weight women [n = 222 (55.8%)]; 25 $\leq$ BMI $<$ 28 kg/m^2 for overweight women [n = 41 (10.3%)]; and BMI $\geq$ 28 kg/m^2 which defined obese women [n = 48 (12.1%)]. When the number of available values for some studied parameter was low, only three groups of BMI values were considered: BMI $<$ 20, 20 $\leq$ BMI $<$ 25, and BMI $\geq$ 25 kg/m^2.

Basal Hormonal Levels

Concerning basal FSH and LH levels, data were known for 200 patients who were classified into the

four previously described groups of BMI values. The mean age of the patients in each group of BMI values was not significatively different: 32.9 (SD = 4.1) years for BMI values <20 kg/m^2, 33.3 (SD = 4.3) years for BMI 20–25 kg/m^2, 32.4 (SD = 4.6) years for BMI 25–28 kg/m^2, and 33.3 (SD = 5.3) years for BMI ≥ 28 kg/m^2 ($p > 0.05$).

Concerning basal FSH level, no obvious evolution could be found among the different groups of patients. Basal LH level decreased as BMI increased, but differences were not significant. The mean ratio FSH/LH increased significantly according to the BMI: 1.52 (SD = 1.10) for BMI <20 kg/m^2, 1.71 (SD = 1.10) for BMI 20–25 kg/m^2, 1.78 (SD = 0.93) for BMI 25–28 kg/m^2 and 2.31 (SD = 1.42) for BMI ≥ 28 kg/m^2 ($P < 0.05$).

Type of Stimulation Protocol

According to the different types of stimulation protocol, women's age and BMI were studied. Long protocol was used for ovarian stimulation of 332 patients, medium age of 32.63 years (SD = 4.15) and average BMI of 22.99 kg/m^2 (SD = 4.26). Short protocol was chosen for 50 patients, medium age 36.34 years (SD = 4.63) and mean BMI 23.52 kg/m^2 (SD = 4.97). In 16 cases where no analogues were used, medium age was 31.93 years (SD = 4.51) and average BMI 22.17 kg/m^2 (SD = 2.98). There was a significant difference in the woman's mean age among the three groups ($p < 0.001$) but no significant difference could be found concerning the mean BMI of women stimulated with a long protocol, a short protocol, or another stimulation protocol.

FSH basal level was known for 202 patients who were grouped according to the type of stimulation protocol. For 158 cycles with long stimulation protocol; the mean FSH level was 6.22 IU/liter (SD = 2.23); for 31 cycles with short stimulation protocol the mean FSH level was 7.86 IU/liter (SD = 3.15); and for 13 cycles where the stimulation protocol was carried out without the use of GnRH analogue the mean FSH level was 6.88 IU/liter (SD = 3.50). There was a significant difference ($P < 0.01$) in women's mean basal FSH level regarding to the type of stimulation protocol.

Number of Gonadotrophin Ampoules Used

To study the relationship between BMI and the number of ampoules of gonadotropins used, cycles with long stimulation protocol, cycles with short stimulation protocol, and cycles without analogues were distinguished. For cycles with long protocol, the mean number of ampoules used was 30.45 (SD = 11.16). According to the four groups of BMI values, the mean number of ampoules used increased regularly with BMI but differences were not significant: 28.8 ampoules (SD = 9.74) for BMI less than 20 kg/m^2 (77 cycles), 30.4 ampoules (SD = 11.9) for BMI 20–25 kg/m^2 (182 cyles), 31.6 ampoules (SD = 8.7) for BMI 25–28 kg/m^2 (32 cycles), and 33.0 ampoules (SD = 11.5) for BMI ≥ 28 kg/m^2 (41 cycles). For cycles with short stimulation protocol the mean number of ampoules used was 43.31 (SD = 21.18). Three groups were distinguished according to BMI values: for BMI less than 20 kg/m^2 (eight cycles) the mean number of ampoules used was 55.5 (SD = 24.2), for BMI 20–25 kg/m^2 (31 cycles) the mean number of ampoules used was 36.1 (SD = 14.2), and for BMI values ≥ 25 kg/m^2 (11 cycles) the mean number of ampoules used was 54.7 (SD = 24.6). There was a statistically significant difference between the mean number of gonadotropin ampoules used among these three groups ($P < 0.01$).

Stimulation protocols without GnRH analogues concerned only 16 cases, the mean number of ampoules used was 28.53 (11.9). Considering the three types of stimulation regimen (long protocol, short protocol, and without analogues) there was a statistically significant difference in the mean number of ampoules used of gonadotropins ($P < 0.001$).

Ovarian Stimulation Duration

The mean stimulation duration, defined by the day of hCG administration, was 11.71 days (SD = 1.73) for long protocol cycles, 12.40 days (SD = 2.24) for short protocol cycles, and in cycles without GnRH analogues the average duration of stimulation was 11.4 days (SD = 1.05). For long protocol cycles, no significant difference in the day of hCG administration could be found according to BMI classes: mean 11.5 days (SD = 1.13) for BMI < 20 kg/m^2, mean 11.8 days (SD = 1.35) for BMI 20–25 kg/m^2, mean 11.5 days (SD = 0.94) for BMI 25–28 kg/m^2, and mean 11.77 days (SD = 1.61) for BMI > 28 kg/m^2.

For short protocol cycles, the mean day of hCG administration was 13.6 (SD = 2.7) for cycles with BMI values < 20 kg/m^2, 11.8 (SD = 1.81) for cycles with BMI 20–25 kg/m^2 and 13.11 (SD = 2.7) for BMI values > 25 kg/m^2. No significant difference could be found between these three groups.

Estradiol Level on Day of hCG

The estradiol (E_2) level at the day of hCG was studied. The mean estradiol level in 299 cycles with long stimulation protocol was 2445.6 pg/ml (SD = 954) and in 50 cycles with short protocol the mean E_2 level was 1800.2 pg/ml (SD = 919), the difference between E_2 levels in long and short protocols was highly significant ($P < 0.001$). In protocols without GnRH analogues, mean E_2 level at day of hCG was 1793.7 pg/ml (SD = 941.5).

The relationship between BMI and the estradiol level at day of hCG was studied separately for long protocol and short protocol cycles. In long protocol cycles, mean estradiol levels were comparable whatever the BMI value was: 2472.8 pg/ml (SD = 751.4) for BMI $<$ 20 kg/m^2 (70 cycles), 2405.7 pg/ml (SD = 1009.4) for BMI 20–25 kg/m^2 (163 cycles), 2616.2 pg/ml (SD = 961.4) for BMI 25–28 kg/m^2 (30 cycles), and 2549.2 pg/ml (SD = 1030.3) for BMI $>$ 28 kg/m^2 (36 cycles) ($P > 0.05$). In short protocol cycles also, no statistical significant difference could be found between E_2 levels at the day of hCG according to BMI values: 1194.6 pg/ml (SD = 459.3) for BMI $<$ 20 kg/m^2 (eight cycles), 1993.0 pg/ml (SD = 953.5) for BMI 20–25 kg/m^2, and 1686.8 pg/ml (SD = 978.1) for BMI $>$ 25 kg/m^2 (11 cycles).

Number of Collected Oocytes

In 332 cycles with long protocol, the mean number of oocytes collected per cycle was 11.22 (SD = 6.2) and 6.22 (SD = 3.4) in 50 cycles with short protocol. The difference in the mean number of retrieved oocytes was significantly different between the two types of stimulation protocols ($P < 0.001$). In cycles where stimulation was performed without use of GnRH analogues, the mean number of collected oocytes per cycle was 9.67 (SD = 7.8). For long and short protocol cycles, the mean number of retrieved oocytes was studied according to three classes of BMI values: BMI $<$ 20, 20 $\leq$ BMI $<$ 25, and BMI $\geq$ 25 kg/m^2. Concerning cycles stimulated according to the long protcol, when BMI was 20 kg/m^2 the mean number of retrieved oocytes was 11.82 (SD = 5.5), for BMI 20–25 kg/m^2 the mean number of retrieved oocytes was 11.31 (SD = 6.7), and for BMI $\geq$ 25 kg/m^2 the mean number of retrieved oocytes was 10.39 (SD = 5.5). The number of collected oocytes per cycle significantly decreased when BMI increased ($P < 0.025$).

Concerning short protocol cycles, the mean number of collected oocytes was 4.88 (SD = 1.6) with BMI $<$ 20 kg/m^2, 6.61 (SD = 4.9) with BMI 20–25 kg/m^2, and 6.09 (SD = 3.2) for BMI $>$ 25 kg/m^2. The difference between these three classes was not statistically significant.

Oocyte Quality

According to Veeck's (10) classification oocytes were classified into five groups: germinal stage oocytes (GV), metaphase I, metaphase II, postmature, and fractured zona oocytes (FZO). To simplify the analysis of the results, metaphase I and II oocytes were classified together as ''good quality'' oocytes, whereas GV, postmature oocytes, and FZO were classified together as bad quality oocytes. In 332 cycles with long protocol, 65.2% of the collected oocytes were of good quality; (2430 out of 3726). In 50 cycles with short protocol, there were 60.4% of good quality oocytes (188 out of 311), whereas in 16 cycles stimulated without gonadotropins 66.9% of the collected oocytes were of good quality. No statistically significant difference was observed in the rate of good quality oocytes according to the stimulation regimen; as a consequence oocyte quality was analyzed according to BMI without taking into account the stimulation protocol. When BMI value was $<$20 kg/m^2, 64.2% of the retrieved oocytes were of good quality; for BMI 20–25 kg/m^2, 66.7% of the retrieved oocytes were of good quality; and for BMI $\geq$ 25 kg/m^2, 60.9% of the retrieved oocytes were of good quality. There was a significant difference in the rate of good quality oocytes between the three classes of BMI value ($P < 0.01$). These results are presented in Table I. Overweight and underweight women had significatively worse quality oocytes than normal weight women. The rate of good quality oocytes was not statistically different considering overweight women (BMI 25–28 kg/m^2): 57.6% and obese women (BMI $\geq$ 28 kg/m^2): 63.7%.

Pregnancy Rate and Issue

Eighty-five pregnancies were initiated given a pregnancy rate of 21.36% per attempt; 46 pregnancies were obtained after IVF and 39 after ICSI. There

Table I. Oocyte Quality According to BMI Values

BMI values	$<$20	20–25	$\geq$25	p
Good Quality oocytes (%)	64.2	66.7	60.9	$<$0.01

was no difference in the pregnancy rate between IVF and ICSI cycles (19.5 and 24.1%, $P > 0.05$). Fifty-six deliveries occurred, whereas 23 women miscarriaged and 6 ectopic pregnancies were observed. The occurrence and issue of the initiated pregnancies were studied according to the women's age: group 1 (patient younger than 38) concerned 325 cycles, 80 pregnancies were initiated with 53 deliveries, 21 miscarriages, and 6 ectopic pregnancies. Group 2 (women of 38 years old or more) concerned 73 cycles; 5 pregnancies were initiated with 3 deliveries and 2 miscarriages. The pregnancy rate per attempt was significantly different between groups 1 and 2 (24.6 and 6.8%, respectively, $P < 0.001$).

Inside group 1, occurrence and issue of pregnancy were studied according to BMI values as presented in Table II. A decrease in the delivery rate per attempt was observed when BMI values increased (20.8%, 15.2%, and 14.3%, respectively, for BMI $<$ 20 kg/m^2, 20–25 kg/m^2 and 25 kg/m^2) but without reaching significant difference ($P > 0.5$). The miscarriage rate per initiated pregnancy increased with BMI values but no significant differences could be detected (respectively, 15.0, 27.5, and 35%, $P > 0.3$). In consideration of the low number of pregnancies in group 2, the breakdown by BMI values was not studied.

Occurrence of Multiple Pregnancy

When considering the 56 deliveries occurring in this study, 45 were singletons, 10 twins, and 1 triplet. Patients who had multiple pregnancy seemed to be younger (30.7 years old, SD = 3.9) and to have a lower BMI (22.06 kg/m^2, SD = 5.87) than patients with single pregnancy (31.9 years old, SD = 3.6, and 22.8 kg/m^2, SD = 4.56, respectively) but no significant difference could be observed.

Table II. Pregnancy Occurrence and Issue According to BMI Values for Women Younger than 38

BMI kg/m^2	$<$20	$\geq$20 and $<$25	$\geq$25	p
Number of cycles	77	178	70	
Initiated pregnancies	20	40	20	
Pregnancy rate per cycle	26.0	22.5	28.6	$>$0.5
Deliveries	16	27	210	
Delivery rate per cycle	20.8	15.2	14.3	$>$0.5
Miscarriages	3	11	7	
Miscarriage rate per pregnancies	15.0	27.5	35.0	$>$0.3
Ectopic pregnancies	1	2	3	

DISCUSSION

General Features

In this study, the weight and height of women included in an IVF or ICSI protocol were systematically noted on the day of oocyte retrieval for 5 months.

This study focused on the role of female BMI on the response to ovarian stimulation protocol, occurrence of pregnancy, and its evolution. Indications for infertility treatment, male parameters as well as fertilization rate and embryo quality were deliberately not analyzed. In the studied population, the prevalence of underweight and overweight women was, respectively, 21.8% and 22.3%. More precisely, obese (BMI $>$ 27.9) and extremely underweight (BMI $<$ 19) patients formed about 25% of our IVF practice. These high rates compared to another study (12) warranted investigating the impact of women's weight on the results of their IVF attempt. Patients with obvious polycystic ovarian syndrome (PCOS), characterized by hirsutism, anovulation, multiple cysts in the ovaries, insulin resistance, and often obesity, were excluded for the studied population. The coexistence of obesity and PCOS, readily suggests the possibility that these phenomena may be causally related. However, because the two conditions may be multifactorial in origin, the presence of obesity in PCOS actually may be coincidental (13).

Basal Hormonal Levels

Concerning basal FSH and LH levels, Galtier-Dereure *et al.* (14) assessed that in overweight and underweight women, the concentration of FSH remains generally unaffected, whereas obesity is associated with excessive LH concentrations and that undernourished women exhibit low LH concentrations. Grodstein *et al.* (3) reported that BMIs $>$ 27 or $<$ 17 kg/m^2 were associated with an increased risk of primary ovulatory infertility. No significant differences could be noted in our study concerning FSH and LH levels, but the FSH/LH ratio significantly increases with the BMI. It may be interesting to correlate this finding with a previous study (15) that demonstrated that an elevated FSH/LH ratio predicts a poor response to controlled ovarian hyperstimulation.

Response to Ovarian Stimulation Protocol

Different parameters actually lead to indicate that

an optimal response to ovarian stimulation is more difficult to obtain in overweight patients. In this analysis, the mean number of gonadotropin ampoules used increased with BMI. This phenomenon has already been described (16,17) using clomiphene citrate treatment: with increasing body weight the dose of clomiphene citrate had to be increased progressively, and there was a positive correlation between clomiphene citrate dose and body weight. BMI also was found to be significantly correlated with both the number of FSH ampoules administered and the length of stimulation (8). In this study, the number of collected oocytes significantly decreased with an increase of BMI. Wass *et al.* (18) were unable to confirm these results, whereas Crosignani *et al.* (7) observed the same fact but suggested that it could be related to the accessibility of the oocytes or technical difficulties in retrieval associated with overweight. Concerning oocytes quality, an increased number of atretic follicles and increased ovarian hyalinization has been observed in obese women (19), but it is interesting to notice here that both overweight and underweight patients had significantly less oocytes of good quality than normally weighted women.

Pregnancy Rate and Issue

No statistically significant correlation could be found between BMI and pregnancy rate in this study, as described elsewhere (17). However, the miscarriage rate appears to be increased in obese women. This observation could be correlated with a previous study of Clark *et al.* (5) concerning a population of 67 overweight (BMI $\geq$ 30 kg/m^2) infertile women who obtained an important weight loss (10.2 kg). The miscarriage rate after weight reduction was 18%, compared to 75% prior to diet and exercise.

CONCLUSIONS

The effects of extremes of patients' body mass on the IVF procedure and outcome still remain a controversial subject (12). In the described study, different parameters are impaired in overweight as well as in underweight patients, leading to decreased chances of normal pregnancy.

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