Increased Body Mass Index Has a Deleterious Effect on In Vitro Fertilization Outcome[1]

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Purpose: *Few studies have addressed the effect of weight on IVF outcome, with some showing a decrease in IVF success and some showing no change in overweight women (BMI > 25 kg/m^2) compared to women with normal weight (BMI < 25 kg/m^2).*
Methods: *One hundred thirty-nine women <40 years old undergoing 180 IVF cycles with fresh embryo transfers were retrospectively evaluated between January 1997 and March 1999, stratified by body mass index (BMI) (cutoff of 25).*
Results: *In the group with BMI > 25 kg/m^2, basal FSH, implantation rates (IR), and pregnancy rates (PR) were significantly lower, while the duration of stimulation, gonadotropin requirements, and spontaneous miscarriages were slightly higher, compared to the BMI ≤ 25 group.*
Conclusions: *Excess weight defined as BMI > 25 kg/m^2 has a negative impact on IVF outcome. Future prospective studies evaluating oocyte and/or embryo quality, and androgen and insulin levels, between overweight women and those with normal weight are needed.*

KEY WORDS: BMI; implantation rate; IVF; obesity; pregnancy rate.

INTRODUCTION

The deleterious effect of obesity on general health includes greater prevalence of chronic medical conditions as well as increased morbidity and mortality secondary to these problems (1,2). Approximately one third of the American population is obese, and recent studies demonstrate escalating incidence (3–5). The association between excess body weight and decreased fecundity is also well known. Support for this association is provided by studies documenting resumption of ovulation and improved fecundity following weight loss (6–8). However, the effect of body weight on the outcome of IVF has not been well established. Some studies have shown lower IVF success in obese women while others could not find a negative effect (9–13). Two recent studies have been published with a large sample size, with one showing no effect of elevated body mass index (BMI) and another showing a linear decrease in pregnancy rates (PR) and an increase in spontaneous miscarriage rates (14,15). We therefore evaluated the IVF outcome in overweight women in our program.

MATERIALS AND METHODS

Population

Data from IVF cycles in our university-based program between January 1997 and March 1999 were analyzed in this study. Exclusion criteria included women ≥40 years of age, women who had blastocyst or frozen embryo transfers, and donor oocyte-derived embryo transfers. BMI was calculated by dividing weight (kilograms) by height (meters^2), and patients were stratified utilizing a cutoff value of 25 to create two groups for outcomes comparison. Epidemiologic

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studies have shown that a BMI of >25 kg/m^2 is considered overweight (3–5).

Stimulation Protocol

Women underwent either a standard long luteal leuprolide acetate (LA) protocol (Lupron, TAP, North Chicago, IL) or a modified microdose LA flare protocol as previously reported (15). In the standard long LA protocol, pituitary desensitization was followed by administration of FSH and/or HMG (Metrodin, Fertinex, Gonal-F, Serono, Randolph, MA; Follistim and Humegon, Organon, West Orange, NJ; Repronex, Ferring, Tarrytown, NY) starting with 2–4 ampules per day. Patients who underwent the modified microdose LA flare protocol received 50 μg of LA two times daily along with six ampules daily of FSH and/or HMG, beginning on Day 3 of a withdrawal bleed following at least 3 weeks of oral contraceptives. When at least three follicles were >18 mm, 10,000 units of hCG (Profasi, Serono, Randolph, MA) were administered. Oocyte retrieval was performed 34–36 h later and embryo transfer was performed 72 h after retrieval under ultrasound guidance, using a Wallace catheter (Edwards-Wallace Catheter, Marlow Technologies, Willoughby, OH). The luteal phase was supported using 50–100 mg of progesterone in oil IM daily. Biochemical pregnancies were considered a failure to conceive. An ultrasound to confirm the number of sacs and fetal viability was performed at 5–6 weeks of gestation. Ongoing PR implies delivered or ongoing pregnancies beyond 20 weeks. Implantation rates (IR) denotes the number of gestational sacs divided by the number of replaced embryos.

Ultrasound and Laboratory Assays

Stimulation response was monitored with serial measurements of serum E_2 and transvaginal ultrasonic evaluation of follicle number and size, as well as endometrial thickness. All ultrasound measurements were performed using a 6.5 MHz vaginal probe (Performa, Acoustic Imaging, Dornier Medical Systems, Phoenix, AZ) by two of the authors (FIS and HDM). Endometrial thickness was recorded at the thickest measurement in the sagittal plane 1 cm from the uterine fundus on the day of hCG administration. Serum FSH was measured on Day 3 of the cycle, prior to initiation of stimulation protocol, utilizing a microparticle enzyme immunoassay (Abbott Axsym system, Abbott Pharmaceutical, Abbott Park, IL). The upper limit of normal in our laboratory is 10 IU/L (conversion factor to SI units, 1.0), which is approximately equivalent to 18 IU/L by RIA Leeco assay (Leeco Diagnostics, Southfield, MI). Serum E_2 was measured utilizing a RIA (Coat-a-count, Diagnostic Products Corporation, Los Angeles, CA).

Statistical Analysis

Data are expressed as mean with standard deviation noted. Chi-square, Mann–Whitney rank sum, or Student's t tests were utilized as appropriate. p values $<.05$ were considered significant.

RESULTS

During the study period, 141 women underwent 182 IVF cycles utilizing fresh embryos for transfer. Two were excluded from the study secondary to missing data points. Seventy women undergoing 87 cycles (47.9%) had a BMI ≤ 25, and 69 women in 93 cycles (51.1%) had a BMI > 25 kg/m^2. Ten (12%) cycles were cancelled secondary to inadequate response in the BMI ≤ 25 group, whereas 16 (17%) cycles were cancelled in the BMI > 25 group ($p =$ NS), leaving 154 cycles for the overall analysis. Fifteen patients in the BMI ≤ 25 and 17 patients in the BMI > 25 group underwent multiple cycles, leaving 122 cycles for analyses limited to initial IVF cycles. Infertility diagnoses included tubal disease (50%), male factor (14%), endometriosis (14%), decreased ovarian reserve (9%), ovulatory disorders (6%), cervical stenosis (1%), and unexplained infertility (6%). There were no differences between the two groups with regard to infertility diagnosis.

Analysis including all stimulation cycles (summarized in Table I) demonstrated no differences in age or parity between the two groups. Mean BMI was statistically different, an average of 22.0 kg/m^2 (SD 1.8) in the BMI ≤ 25 group, and 32.2 kg/m^2 (SD 7.5) in the BMI > 25 group ($p < .0001$). Day 3 FSH was also significantly different, with the BMI > 25 group demonstrating significantly lower baseline FSH than did the BMI < 25 group. Equivalent numbers of patients were enrolled in the two stimulation protocols. Thirty-three of the 77 cycles in the BMI ≤ 25 group (42%) and 38 of 77 cycles (49%) in the BMI > 25 group utilized the microdose protocol ($p =$ NS). Additionally, there were no differences in cancellation rate, peak E_2, P on day of hCG administration, or endometrial thickness. A trend toward increased number of gonadotropin ampules and longer duration of stimulation was noted in the BMI > 25 group; however, these differences

Table I. IVF Outcome Between 70 Women with BMI ≤ 25 and 69 with BMI > 25 kg/m^2

	BMI ≤ 25 (N = 70)	BMI > 25 (N = 69)	p
No. of cycles	87	93	
Age (years)	33.1 ± 3.3	32.1 ± 3.7	NS
Cancellation rate (%)	10 (12%)	16 (17%)	NS
FSH (IU/L)	7.2 ± 1.8	6.4 ± 1.6	<.0001
Peak E_2 (pg/ml)	2583 ± 1084	2368 ± 983	NS
P day of hCG (ng/dl)[a]	1.5 (1.0–2.0)	1.4 (1.0–1.9)	NS
Endometrial thickness (mm)[a]	10.0 (9.1–11.0)	10.0 (8.7–11.0)	NS
No. of ampules[a]	46.0 (35.8–57.0)	51.0 (34.8–63.0)	.22
Duration of stimulation (days)[a]	10.0 (9.0–11.0)	10.0 (9.0–11.3)	.066
No. of oocytes	14.1 ± 6.1	15.1 ± 6.6	NS
No. of ET	3.6 ± 1.0	3.8 ± 1.0	NS
IR (%)	75/280 (26.8)	40/290 (13.8)	.0002
Clinical PR (%)	42/77 (54.5)	24/77 (31.2)	.0056
Spontaneous abortion (%)	3/42 (7.1)	5/24 (20.8)	.13
Ongoing PR (%)	39/77 (50.6)	19/77 (24.7)	.0016

Note. All cycles included. Values are mean ± SD in general; exceptions are indicated by [a] for median and 25–75% quartiles.

were not statistically significant. The average number of oocytes retrieved and embryos transferred was similar for both groups. However, the resultant IR, clinical PR, and ongoing PR were significantly lower in the BMI > 25 group ($\chi^2 = 14.1$, $p = .0002$, $\chi^2 = 7.7$, $p = 0.0056$, and $\chi^2 = 10.0$, $p = .0016$, respectively), as summarized in Fig. 1. There was a trend toward a higher spontaneous abortion rate in the BMI > 25 group compared to the BMI ≤ 25 group ($p = 0.13$).

Analysis limited to initial IVF cycles only demonstrated identical results. As in the overall analysis, there were no differences in age or parity upon enrollment into the program or in cancellation rates between the two groups (data not shown). The BMI ≤ 25 group had a significantly lower mean BMI than did the BMI > 25 group: 22.18 kg/m^2 (SD 1.77) versus 32.3 kg/m^2 (SD 7.45) ($p < .001$). Mean basal FSH was also significantly different, 7.14 in the BMI ≤ 25 group versus 6.43 (SD 1.52) in the BMI > 25 group ($p = .018$). Stimulation parameters including peak E2, *P* on day of hCG, and endometrial thickness were similar between the two groups (data not shown). A similar number of oocytes were retrieved (13.95 (SD 6.2) versus 15.42 (SD 7.0)) and embryos transferred (3.58 (SD 1.0) versus 3.73 (1.0)) in the BMI < 25 and BMI > 25 groups, respectively (p = NS). However, the outcome of the transfers remained significantly different, with the BMI > 25 group having a lower IR, clinical PR, and ongoing PR.

The IVF outcome in the morbidly obese group (BMI > 35) is also summarized here: 18 women underwent 23 cycles. Two cycles were cancelled for poor response, and 21 had an ET. The PR per initiated cycle was 12/23 (52.2%), and PR per ET was 12/21 (57.1%). The IR was 19/73 (26.0%). One pregnancy was an ectopic, three ended in an early pregnancy loss (27.0%), and eight women delivered (one triplet, five twins, and two singletons).

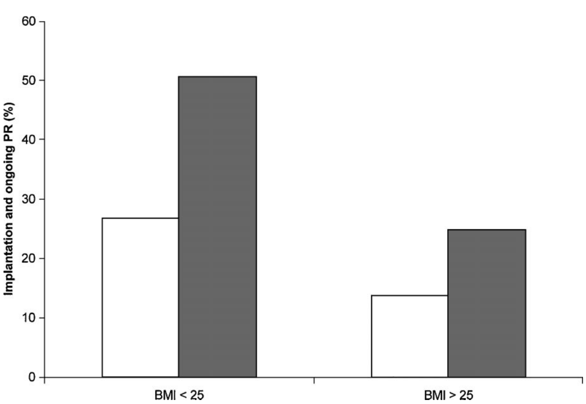

Fig. 1. Implantation rate (open bars) and ongoing pregnancy rate (solid bars) in women with BMI ≤ 25 and >25 kg/m^2.

DISCUSSION

In this study, excess body weight, defined as BMI > 25 kg/m^2, negatively affected IVF outcome. This effect was demonstrated when consideration was limited to initial IVF cycles as well as when all cycles were included. While the association between obesity and infertility has been well documented, studies that have evaluated the effect of body weight on IVF outcome are few in number and reached conflicting conclusions.

Lewis *et al.* published a retrospective study of 368 patients undergoing IVF or GIFT comparing five BMI categories (<19.1 to 27.6 kg/m^2) (10). They found no association between weight and ovarian stimulation outcome, although they did document a decreased number of retrieved oocytes in the highest BMI group and a trend toward higher peak E_2 and PR in the lowest BMI group compared to the highest BMI group (10). Crosignani *et al.* reported IVF results in 111 women comparing outcomes based on three BMI groups ($\leq$20, >20 to 28, and $\geq$28 kg/m^2) (11). These investigators reported significantly fewer follicles on Day 4 of stimulation as well as fewer retrieved oocytes with increasing BMI. The mean number of ampules was similar in the three BMI groups, and all women underwent a standardized stimulation protocol. However, no information was provided regarding cancellation rates, E_2 levels, IR, or PR (11).

Wass *et al.* found a negative association between increased waist to hip ratio (android body fat distribution) and IVF outcome in 220 women undergoing IVF, but no effect with respect to overall body weight or BMI (12). This study may have suffered from a Type II error because the pregnancy rates in the $\leq$25 and >25 kg/m^2 groups were similar (28.9% and 21.0%, respectively, $p = 0.24$), but a trend toward a lower PR was noted in the overweight group (12). Data regarding IR was not provided.

Lashen *et al.* in a retrospective nested case-control study included 333 women undergoing IVF (13). They compared 76 obese patients (BMI > 27.9 kg/m^2) and 35 underweight patients (BMI < 19 kg/m^2) against controls, and demonstrated no adverse effect of extremes of body weight on IVF outcome. However, a Type II error again cannot be excluded given that the IR was 13.2 and 13.4%, and the clinical PR was 23.7% and 20% in the obese group and in normal controls, respectively (13). Another recent retrospective study in 398 women undergoing IVF found significantly higher gonadotropin requirements, and a lower number of collected oocytes in overweight women. However, there were no difference in PR and miscarriage rates compared to the normal BMI group (14). This could again be due to a Type II error (PR were 22.5% in the normal BMI group and 28.6% in the BMI > 25 group).

Most recently, and in agreement with our findings, the largest retrospective study to date using 3,586 women undergoing IVF between 1987 and 1998 have shown a linear decrease in IVF success with increasing BMI (16). Women were stratified by BMI groups: <20, 20–24.9, 25–29.9, 30–34.9, and >30. The odds ratio were 0.81 (95% CI: 0.68–0.97) in the 25–29.9 BMI group, 0.73 (95% CI: 0.57–0.95) in the 30–34.9 BMI group, and 0.50 (95% CI: 0.32–0.77) in the morbidly obese group (16).

Several caveats should be considered when evaluating the body of evidence regarding the effect of excess body weight on IVF outcome. The myriad of definitions of overweight or obese as defined by the BMI values utilized to create study groups renders comparison of the results of these studies difficult. We chose a BMI of 25 for stratifying groups based on multiple epidemiologic studies that define this BMI as overweight (3–5). In addition, the variety of ovulation induction protocols may result in differing effectiveness of stimulation. Halme *et al.* reported a positive correlation between body weight and the dose and duration of gonadotropin stimulation (9). We, too, found a trend toward increased gonadotropin requirements and longer duration of stimulation in the overweight group. These differences may prove to be significant with a larger sample size. It is paramount to ensure that outcomes reflect true population differences, not ability to adequately stimulate patients.

The inclusion of two protocols for stimulation could be seen as a confounding factor in our study. However, patients undergoing the microdose protocol were evenly distributed between the two groups, which should eliminate any bias. In addition, Leondires *et al.* recently published a study comparing the long luteal lupron protocol with a microdose protocol, which demonstrated equivalent ovarian stimulation in a general IVF population (17). Therefore, we do not believe that the inclusion of these protocols confounds the results obtained in our study.

The decreased IR and PR that we found in overweight women in the face of equivalent ovarian stimulation suggest defects in oocyte and/or embryo quality, or perhaps a hostile intrauterine environment, as the cause for the disparate IVF outcomes. While we did not measure androgen and insulin levels, the hormonal milieu is known to be altered in the obese population, and the correction of these changes with weight loss may be instructive regarding what factors enhance or inhibit implantation and continuation of pregnancy. Our findings document an association between excess body weight and worsened outcome with IVF; the underlying cause for this association remains to be defined. While the morbidly obese group (BMI > 35) had a high pregnancy rate and a high early pregnancy loss rate, the small number of women in that group precludes any meaningful interpretation. Prospective studies evaluating the quality of oocytes and embryos from cycles in overweight and normal weight populations may help to elucidate the etiology of the negative impact of increased body weight (BMI) on IVF outcome. Studies evaluating the effect of excess androgen levels or insulin resistance on IVF also may help to determine the mechanism by which excess body fat affects IVF. Until these mechanisms are fully understood, it may be wise to encourage loss of weight prior to initiation of IVF cycles. Not only will this benefit the patient's overall health; it will likely increase the likelihood of success of the IVF cycle.

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