Impact of Body Mass Index on In Vitro Fertilization Outcomes

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Purpose: To determine if body mass index (BMI) impacts IVF outcome.

Methods: Retrospective, cohort study. Main outcome measure was number of oocytes obtained.

Results: BMI did not correlate with the prestimulation parameters. There was a significant positive correlation between BMI and the number of follicles on ultrasound prior to egg retrieval. A threshold analysis revealed a significant change in parameters at a BMI > 24 kg/m². Patients with BMI > 24 kg/m² demonstrated a significant increase in the number of follicles after stimulation ($p = 0.03$) and a comparative decrease in the number ampules of gonadotropins used ($p = 0.04$) and days of stimulation required ($p = 0.01$).

Conclusion: These data demonstrated that an elevated BMI significantly correlates with the number of follicles, days of stimulation, and number of ampules of gonadotropins used. Further correlation to an actual increase in number of oocytes and pregnancy rates may be limited by insufficient power in this study.

KEY WORDS: Body mass index; follicles; gonadotropins; infertility; in vitro fertilization; oocytes; pregnancy.

INTRODUCTION

Body mass index (BMI), defined as weight in kilograms divided by height in meters squared (kg/m²), is a measure commonly used to objectively assess obesity (1). Although obesity is a known contributor to menstrual irregularities, anovulation, and infertility, the effect of obesity on the success of assisted reproductive treatment is less certain. Studies to date have shown mixed results when evaluating the effect of BMI on in vitro fertilization (IVF) success (2–7). The association of BMI and baseline hormone levels has not been consistently demonstrated. The impact of BMI on aspects of controlled ovarian hyperstimulation, such as amount of gonadotropins used, days of

stimulation needed or peak estradiol, and the ability of BMI to predict the number or quality of oocytes and pregnancy success have been evaluated (2–7). While previous studies have suggested no significant impact (2,3), more recently published data suggest that BMI may negatively affect IVF outcome (4–7).

Based on the published data, we have decided to further analyze how BMI impacts IVF. In this study, we have compared BMI to baseline values, stimulation parameters, and IVF outcomes.

MATERIALS AND METHODS

Population

Patients between the ages of 19 and 42 years were included independent of their diagnoses or prior reproductive history. Because of the poor response documented in the literature, patients with elevated FSH levels (≥ 12 mIU/mL) and women >42 years of age

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were excluded (8–10). Data from all women undergoing IVF from January 2000 to January 2001 who met inclusion criteria were included. The study protocol was approved by the human-use committee at Tripler Army Medical Center. Investigators adhered to policies for protection of human subjects as prescribed in 45 CFR 46.

Experimental Design

The main outcome measure was the number of mature oocytes recovered. BMI was calculated on day 3 of the patient's menstrual cycle the month prior to IVF. Transvaginal ultrasound was performed on cycle day 3 after ovarian downregulation and prior to starting gonadotropins to assess basal antral follicle number and ovarian volume. BMI was compared with respect to patient's age, number of stimulated follicles (>12 mm), number of mature oocytes retrieved, basal serum hormone levels (FSH, LH, and estradiol), peak estradiol level (defined as the level of estradiol on the day of human chorionic gonadotropin administration), dehydroepiandrosterone sulfate (DHEAS), ampules of gonadotropins administered, days of stimulation, pregnancy rate, and cancellation rate.

All patients received 35 μ g oral contraceptive pills for 21–35 days. During the last 7 days of the oral contraceptives, the patients were started on a GnRH-a (Lupron, TAP Pharmaceuticals, North Chicago, IL) for a total of 14 days followed by stimulation with exogenous gonadotropins. When the largest cohort of follicles reached the 16–18 mm range, 10,000 units of human chorionic gonadotropin (hCG) were administered. Transvaginal follicular aspiration took place 35–36 h later. Embryos were transferred vaginally with abdominal ultrasound guidance using a Wallace transfer catheter (Cooper Surgical, Shelton, CT) as previously described (11,12).

Pregnancy was confirmed by a rising serum hCG at 4 weeks of gestation followed by sonographic confirmation of cardiac activity at 6 weeks gestation. Patients were cancelled for failing to produce ≥ 3 expanding follicles or failure to respond to gonadotropins with an adequate estradiol response of at least 300 pg/mL.

Laboratory Assays

The LH, FSH, and E_2 assays were all done with the Advia Centaur immunoassay system (Bayer Diagnostics, Tarrytown, New York). The inter- and intra-assay coefficients of variation were 2.9 and 2.7% for

FSH, 3.1 and 2.8% for LH, and 5.2 and 4.9% for E_2 , respectively.

Statistical Analysis

A Wilcoxon-Mann-Whitney rank sum test was used to compare outcomes between two groups. A Kruskal-Wallis one-way analysis of variance was used to compare outcomes among multiple groups. For pairwise multiple comparison, Dunn's method was utilized. Univariate analysis included regression and correlation coefficients examining the association of BMI and linear outcome parameters of ovarian reserve and stimulation response.

Patients were grouped by BMI beginning at the lowest range and extending to highest range at increments of 5 kg/m². The mean number of oocytes retrieved and clinical pregnancy rates were then calculated for each increment. The mean number of oocytes retrieved and clinical pregnancy rates were then evaluated to determine if there was an obvious break point or threshold at which there was a significant change in these values. Contingency table analyses were used to evaluate the mean number of oocytes retrieved and pregnancy rates above and below the selected threshold value. All data were reported as mean values with their associated standard deviations. An alpha error of ≤ 0.05 was considered significant for all calculations.

RESULTS

Forty-one women with a mean age of 32.9 ± 3.6 years (range 27–40 years) undergoing 41 IVF cycles met inclusion criteria and were included in data analysis. Patients enrolled in the IVF program had the following primary etiologies for their infertility: tubal factor (29%), anovulation or polycystic ovarian syndrome (PCOS) (25%), unexplained infertility (21%), male factor (15%), and endometriosis (10%). Table I summarizes the characteristics and the IVF outcomes of the women undergoing IVF.

The BMI for our study group ranged from 19.3 to 36.2 kg/m² with a mean of 26.4 ± 4.1 kg/m². Using linear regression analysis, BMI was compared to prestimulation parameters of day 3 FSH, day 3 LH, day 3 estradiol, ovarian volume, basal antral follicle number, testosterone, DHEAS and age; no correlation was noted for these variables. Likewise, BMI was compared to IVF stimulation parameters of peak estradiol, number of ampules of gonadotropins

Table I. Characteristics and IVF Outcomes

	All patients	BMI ≤ 24 kg/m ²	BMI > 24 kg/m ²	<i>p</i> Value
Day 3 FSH (mIU/mL)	5.8 $\pm$ 1.6	5.7 $\pm$ 1.1	5.8 $\pm$ 1.9	0.81
Day 3 LH (mIU/mL)	6.0 $\pm$ 2.6	6.2 $\pm$ 2.8	5.9 $\pm$ 2.1	0.96
Testosterone (ng/dL)	39.0 $\pm$ 23.2	40.6 $\pm$ 25.2	37.7 $\pm$ 22.0	0.69
DHEAS (ug/dL)	127.4 $\pm$ 53.4	129.6 $\pm$ 67.0	126.0 $\pm$ 40.8	0.82
Number of mature oocytes	15.4 $\pm$ 9.6	13.0 $\pm$ 8.2	17.5 $\pm$ 10.5	0.17
Number of follicles	22.2 $\pm$ 11.1	17.9 $\pm$ 9.3	25.9 $\pm$ 11.4	0.03*
Number of ampules	50.6 $\pm$ 11.9	55.0 $\pm$ 12.0	47.0 $\pm$ 10.8	0.04*
Days of stimulation	9.6 $\pm$ 1.2	10.2 $\pm$ 1.0	9.1 $\pm$ 1.2	0.01*
Pregnancy rate (%)	43.9	38.9	47.8	0.37
Peak estradiol (pg/mL)	3318.9 $\pm$ 1612.4	3066.2 $\pm$ 1601.0	3546.5 $\pm$ 1629.1	0.37
Number of Antral follicles	23.2 $\pm$ 13.1	21.0 $\pm$ 9.9	24.4 $\pm$ 14.9	0.60
Ovarian volume (cm ³)	13.8 $\pm$ 6.5	14.6 $\pm$ 7.5	13.3 $\pm$ 6.0	0.67

Note. Results are given as mean values with their associated standard deviations for all patients in the study, patients with BMI ≤ 24 kg/m², and patients with BMI > 24 kg/m².

* $p \leq 0.05$.

administered, days of stimulation required, number of follicles visualized, and number of mature oocytes obtained. The results demonstrated a statistical significance between BMI and the number of follicles noted by ultrasound prior to egg retrieval ($p = 0.012$), suggesting a positive relationship of increasing number of follicles with increasing BMI ($r = 0.41$, $p < 0.01$) (Fig. 1). Comparison of number of days of stimulation required and the number of ampules of gonadotropins received showed relationships approaching significance with p values of 0.057 and 0.060, respectively. Both comparisons revealed a negative

correlation. Power analysis revealed that 47 patients would be needed to establish statistical significance for days of stimulation and ampules used.

The threshold analysis revealed a break point at a BMI of 24 kg/m². When subdividing the patients into BMI ≤ 24 kg/m² and > 24 kg/m², the number of follicles, number of ampules of gonadotropins used, and days of stimulation all demonstrated a significant difference. Compared to patients with a BMI ≤ 24 kg/m², patients with a BMI > 24 kg/m² demonstrated a higher number of follicles (25.9 $\pm$ 11.4 vs. 17.9 $\pm$ 9.3) ($p = 0.03$), fewer number of ampules (47.0 $\pm$ 10.8 vs.

Fig. 1. Scatter plot demonstrating a significant positive correlation ($r = 0.41$, $p < 0.01$) via linear regression between BMI and the number of ovarian follicles produced during IVF stimulation.

55.0 ± 12.0) ($p = 0.04$) and fewer days of stimulation (9.1 ± 1.2 vs. 10.2 ± 1.0) ($p = 0.01$).

When we examined the data by comparing the BMI of those who were able to achieve the outcome measure of pregnancy compared to those not pregnant, no significant difference in BMI was noted. The data were first studied by including those patients whose IVF was cancelled in the nonpregnant group using a *t*-test, without evidence of a significant difference with a power of only 5%. We further subdivided the patients to create a third group comprised of those cancelled patients, in order to identify any correlation between cycle stimulation and increased BMI; however, using analysis of variance, no significant difference in BMI was noted between the groups. Threshold analysis using contingency tables also failed to reach any significant change in outcome rates between any of the BMI values. Power analysis revealed that 140 patients would be needed in this study to see a statistical significance in pregnancy outcome with an $\alpha = 0.05$ and power of 90%.

DISCUSSION

This study confirms the difficulty in establishing the effect of BMI on in vitro fertilization. We attempted to determine if mean BMI differed between those patients who were successful and those who were not successful with IVF. We also evaluated the correlation of BMI to baseline and stimulation parameters during IVF.

The linear regression analysis of BMI to baseline values of FSH, LH, estradiol, testosterone, DHEAS, antral follicles, and ovarian volume failed to reveal any significant correlation. Since 25% of our infertility patients had the diagnosis of chronic anovulation or PCOS, this was a surprising finding given that features associated with PCOS include obesity, elevated androgens, increased basal antral follicles, and increased ovarian volume.

When we examined stimulation values, a significant positive correlation with BMI was noted only for number of follicles prior to aspiration. Threshold analysis suggested a cutoff BMI value of 24 kg/m^2 . When comparing the groups below and above this cutoff value, we noted a significant difference, not only in follicle number, but also number of days of stimulation and number of ampules used.

Unlike some previous studies, which found it more difficult to stimulate follicular development in pa-

tients with an elevated BMI as demonstrated by an increase in number of days or ampules of gonadotropins required, our data demonstrated that fewer ampules of medication and days of stimulation were needed with increasing BMI (4–7). These results suggest that as BMI increases, the amount of gonadotropins and days of stimulation decrease, while the number of follicles produced increases. If these findings hold true, we would expect an increase in pregnancy rates as well. The mechanism for this finding is uncertain. However, there may be an element of PCOS in the patients studied, which could explain the ease of stimulation and the increase in follicular development seen in the patients with an elevated BMI.

Some possible explanations for the differences seen between the various studies could be the different subdivisions of BMI that have been used in studies to stratify patients. Previous studies have used up to five subdivisions of BMI; likewise, different definitions of obesity have been used ($\text{BMI} > 25 \text{ kg/m}^2$ vs. $\text{BMI} > 27 \text{ kg/m}^2$) and a variety of different IVF induction protocols were used (2,4,5). Unlike the prior studies, we used threshold analysis to define a scientific cutoff point that would be predictive of success or failure. This use of threshold analysis decreases the bias that is found in arbitrarily choosing a BMI at which to study patients.

There are many strengths of this study. The most prominent is the use of threshold analysis. Although this is a retrospective study, the data were collected and placed into a computerized database in a prospective manner. Therefore ascertainment and recall bias were minimized. All patients were accounted for thus there was no loss to follow-up.

In summary, these data demonstrate that an elevated BMI correlates favorably with the number of follicles, days of stimulation, and number of ampules of gonadotropins used in an IVF cycle. The most suggestive data from this study is the strong correlation between increased BMI and number of follicles. In theory, as increased follicles are obtained during gonadotropin stimulation, more mature oocytes and more embryos should be realized ultimately corresponding to a higher pregnancy rate for these patients. Although this has not been noted in this study, a significant limitation to proving this correlation may be the number of participants in the study. Using the data in this study, a post hoc power analysis revealed that at least 140 patients would be needed to show a significant difference in pregnancy rates.

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