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ASSISTED REPRODUCTION

Elevated body mass index (BMI) does not adversely affect in vitro fertilization outcome in young women

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Abstract

Objective To determine if elevated body mass index in young women with normal ovarian reserve was associated with poorer ovarian response, difficulty at embryo transfer, and lower clinical pregnancy rates.

Materials and methods Retrospective study of 417 first, fresh in vitro fertilization cycles performed between October 2004 and December 2006. All women were under the age of 35 and had normal cycle day 3 follicle stimulating hormone and estradiol levels. Subjects were divided into groups by BMI: <18.5, 18.5–24.9, 25–29.9, ≥30.

Results Cancellation rates, peak estradiol levels, and mean number of oocytes retrieved were similar in all groups. There was a trend toward increasing difficulty in visualizing the air bubble at time of embryo transfer and lower implantation rates at higher body mass indices. Clinical and ongoing pregnancy rates were similar among groups.

Conclusion Obesity in young women does not adversely affect clinical pregnancy rates in patients treated with in vitro fertilization.

Keywords BMI · Clinical pregnancy · Embryo transfer · IVF

Capsule Obesity does not adversely affect clinical pregnancy rates in young women with normal ovarian reserve undergoing their first in vitro fertilization cycle.

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Introduction

Obese women take longer to conceive [1, 2] primarily due to abnormalities that affect follicular development and ovulation. These patients commonly have altered gonadotropin releasing hormone secretion, elevated circulating insulin levels, decreased sex hormone binding globulin levels [3], and increased ovarian and adrenal androgen production [4]. Many meet the diagnostic criteria for polycystic ovary syndrome and produce increased levels of reactive oxygen species [5] which adversely affects antral follicle development [6]. Adipocytes express the *ob* gene responsible for the production of the weight-regulating protein leptin. Serum leptin levels are four times higher in obese patients versus normal-weight controls [7], and this has an adverse effect on steroid production of theca and granulosa cells [8].

The most recent National Health and Nutrition Examination Survey for 2002–2004 reported that 33.4% of adult women in the USA are obese. Patients presenting for infertility treatment desire conception as quickly as possible, and obese infertile women often find it difficult to comply with recommendations regarding lifestyle changes that will take many months to achieve an effect.

Ovulation induction is more challenging in obese women. There is resistance to clomiphene citrate [9], and as body weight increases, higher doses are required [10, 11]. Despite some early studies suggesting that the addition of the insulin sensitizer metformin might lead to improvement in live birth rates in obese patients, this was not borne out in a recent well-performed large prospective study [12]. When using gonadotropins to stimulate ovulation, obese women require longer stimulations and greater total doses [13].

Most studies to date report decreased success in obese patients treated with in vitro fertilization (IVF). Obese

patients are more likely to have polycystic ovaries, which places them at greater risk of hyperstimulation and the need for cancellation. Monitoring obese patients during stimulations may be more difficult due to the ovaries being located outside the normal sonographic focal plane. Due to body habitus, oocyte retrieval and embryo transfer might also be more difficult. While much data has been collected and analyzed regarding patients with elevated BMI and reproductive outcome, we chose to evaluate details surrounding the embryo transfer as an independent variable in assessing the question.

Because the strongest predictor of IVF success is age, and to decrease the impact of confounding variables, we elected to confine our study to young women with normal ovarian reserve. The aim of this study was to determine if elevated BMI in young patients undergoing IVF adversely impacted response to ovarian stimulation, success of oocyte retrievals and embryo transfers, or implantation and pregnancy rates.

Materials and methods

Our study is a retrospective analysis of 417 patients who underwent their first, fresh, non-donor in vitro fertilization (IVF) cycle at Reproductive Medicine Associates of New York between October 2004 and December 2006. This study was conducted under the auspices of the institutional review board of the Mount Sinai School of Medicine. Inclusion criteria were: age less than or equal to 35, cycle day 3 follicle stimulating hormone levels (FSH) <10 IU/l and cycle day 3 estradiol (E^2) <80 pg/ml. Patient and IVF cycle data were obtained from our electronic medical records database Resource ™(Morristown, NJ).

At the initial consultation BMI was calculated, and patients were classified into one of four groups: underweight (BMI<18.5), normal weight (BMI 18.5–24.9), overweight (BMI 25–29.9), or obese (BMI≥30). A primary diagnosis of polycystic ovary syndrome (PCOS) was made if patients met at least two out of the following three criteria: (1) oligoovulation or anovulation, (2) clinical and/or biochemical signs of hyperandrogenism, (3) polycystic ovaries. All PCOS patients were screened for thyroid disease, hyperprolactinemia, and when indicated congenital adrenal hyperplasia, androgen-secreting tumors and Cushing's syndrome [14]. Patients underwent controlled ovarian stimulation using one of three protocols: down regulation (78.4%), antagonist (19.2%) or microflare (2.4%) as prescribed by the managing reproductive endocrinologist. Details of these protocols have been described [15].

Oocyte retrieval was performed by transvaginal follicular aspiration under ultrasound guidance 36 h after human chorionic gonadotropin administration. Oocytes were inseminated by either conventional insemination or intracytoplasmic sperm injection (ICSI). Fertilization rate was defined as the number of normally fertilized oocytes (two pronuclei at 18 h postinsemination) divided by the number of metaphase II oocytes retrieved. Day 3 embryos or day 5 blastocysts were transferred using a Wallace catheter (Smiths Medical, Protex Ltd, Kent UK) with transabdominal ultrasound guidance. The presence or absence of visualization of the air bubble at time of transfer was recorded by an embryologist. After transfer, the catheter was examined to insure all embryos had been transferred and to check for the presence of blood in or outside the catheter. All patients received daily intramuscular progesterone (50 mg) for luteal phase support.

Clinical pregnancy was defined as the presence of a gestational sac. Implantation rate was calculated by dividing the number of gestational sacs present by the number of embryos transferred. The ongoing pregnancy rate refers to the presence of fetal heart tones at 8 to 9 weeks gestation at which time patients were discharged to their referring obstetricians.

Statistical analysis was performed using SAS software version 9.1. Student's t test and analysis of variance (ANOVA) were used to compare means of continuous outcomes. Chi square and Fisher's exact tests were used for analysis of categorical outcomes. Analysis of data for trends was performed with the Cochran–Armitage test. Statistical significance was defined as $P<0.05$. Data are reported as mean±standard deviation.

Results

During the 2-year study period, 417 young women underwent their first, fresh IVF cycle (Table 1). Most of the study population had BMIs in the ideal range. Seventy-seven of the patients were overweight (18.5%), and 52 (12.5%) were obese. The mean ages for all four groups were similar. As expected, the prevalence of PCOS was significantly higher in the obese group (26.9%) compared with normal-weight women (12.4%) $P=0.04$. The mean cancellation rate per cycle start was 9.1% and did not differ between the four BMI groups. The indications for cycle cancellation are recorded in Table 2 and were also independent of BMI. There were no cases of ovarian hyperstimulation syndrome (OHSS). Starting gonadotropin doses were significantly lower in PCOS patients $P<0.0001$ (Table 3); however, total gonadotropin doses were similar between all BMI groups and independent of the diagnosis of PCOS (Table 4). The choice of ovarian stimulation regimens was similar across BMI ranges (Table 5).

Table 1 Age, prevalence of PCOS and cancellation rate stratified by BMI

	Body mass index (kg/m^2)				
	<18.5	18.5–24.9	25.0–29.9	≥30	*p*-value
N (%)	21 (5)	267 (63.9)	77 (18.5)	52 (12.5)	
BMI (mean±SD)	17.6±0.8	21.2±1.6	26.6±1.3	34.6±4.0	
Age (mean±SD)	29.7±3.5	31.5±2.6	30.6±3.5	30.8±3.3	0.53
PCOS (%)	2 (9.5)	33 (12.4)	6 (7.7)	14 (26.9)	0.04*
Cancellation rate, *n* (%)	3 (14.3)	22 (8.2)	7 (9.1)	6 (11.5)	0.76

*$P<0.05$

Table 2 Indication for cycle cancellation

	Body mass index (kg/m^2)				
	<18.5	18.5–24.9	25.0–29.9	≥30	*p*-value
N (%)	21 (5)	267 (63.9)	77 (18.5)	52 (12.5)	
Cancellation rate, *n* (%)	3 (14.3)	22 (8.2)	7 (9.1)	6 (11.5)	0.76
Poor response, *n* (%)	1 (33.3%)	7 (31.8%)	1 (14.3%)	4 (66.7%)	
Poor fertilization, *n* (%)	1 (33.3%)	3 (13.6%)	2 (28.6%)	0 (0%)	0.47
Poor embryo growth, *n* (%)	1 (33.3%)	7 (31.8%)	4 (57.1%)	2 (33.3%)	
Other, *n* (%)	0 (0%)	5 (22.7%)	0 (0%)	0 (0%)	

Table 3 Starting gonadotropin dose in PCOS versus non-PCOS patients

	PCOS	Non-PCOS	*p*-value
275 IU or less	40 (73%)	127 (35%)	
300 to 375 IU	15 (27%)	160 (44%)	<0.0001
450 IU	0 (0%)	75 (21%)	

Table 4 Total gonadotropin dose (IU) stratified by BMI and PCOS Status

	Body mass index (kg/m^2)				
	<18.5	18.5–24.9	25.0–29.9	≥30	*p*-value
N	21	267	77	52	
All patients	2,338	2,519	2,561	2,441	0.84
PCOS	1,649	1,879	2,102	1,844	0.87
Non-PCOS	2,424	2,615	2,603	2,651	0.91

Table 5 Use of protocol correlated with BMI range

Body mass index (kg/m^2)					
	<18.5	18.5–24.9	25.0–29.9	≥30	*p*-value
N	21	267	77	52	
Down reg	18 (86%)	206 (77%)	60 (78%)	43 (83%)	
Antagonist	1 (4%)	57 (21%)	13 (17%)	9 (17%)	0.06
Microflare	2 (10%)	4 (2%)	4 (5%)	0 (0%)	

Response to ovarian stimulation is summarized in Table 6. Ovarian response as measured by peak serum estradiol and mean number of oocytes retrieved was similar between BMI groups and unrelated to the diagnosis of PCOS. Fertilization and clinical pregnancy were also similar in all BMI groups and unrelated to the diagnosis of PCOS.

In PCOS patients there were statistically significant trends in both lower implantation rates and lower ongoing pregnancy rates as BMI increased (Table 7). Among patients who underwent an embryo transfer (ET) the clinical pregnancy rate was 60.7%, and the ongoing pregnancy rate was 51.7%.

The ongoing pregnancy rate at time of discharge was not related to type of ovarian stimulation protocol (Table 8). There was a borderline significant trend that as BMI increased there was greater difficulty in visualizing the air bubble at time of ET. This finding was present in both PCOS and non-PCOS patients. There was also a borderline significant trend in PCOS patients that as BMI increased there was an increased presence of blood in or on the catheter after ET (Table 9).

Discussion

Studies to date have yielded conflicting results as to the effect of elevated BMI on IVF outcome. Our findings add support to the concept that this intensive treatment overcomes whatever endocrinologic abnormalities may be present in obese patients. Monitoring during ovarian stimulation and vaginal oocyte retrieval was successful in our obese patients, and the number of embryos retrieved was identical to that of our normal-weight patients. This may be related to the use of vaginal ultrasound, which avoids imaging through the thick adipose layer of the anterior abdominal wall.

A recent Cochrane Collaboration Systematic Review of 13 studies highlighted the benefit of ultrasound guidance during embryo transfer. The ongoing pregnancy rate for women randomized to ultrasound-guided embryo transfer was significantly higher than for those managed with clinical touch (OR 1.49, 95% CI 1.29 to 1.72, $P<0.00001$). In addition, the risk of blood on the catheter tip following the transfer procedure was significantly lower for ultrasound-guided embryo transfer than for clinical touch (OR 0.48, 95% CI 0.33–0.70, $P<0.0001$) [16]. The quality of visualization has been reported to correlate with both implantation rate and clinical pregnancy rate. "Excellent/good" visualization led to statistically significantly higher clinical pregnancy rates (41.5%) than did visualization described as "fair/poor" (16.7%) [17]. In our analysis, as BMI increased we noted a trend towards greater difficulty in visualizing the air bubble with transabdominal ultrasound during embryo transfer. There was an associated non-significant decrease in implantation rate. It is possible that as patients' BMIs climb to greater than 35 or 40 they may have less success with IVF. Our study population did not have a large enough number of patients in these groups to allow such analysis.

Most studies to date report decreased success in obese patients treated with in vitro fertilization (IVF). The studies differ as to how the patients were subdivided by body mass index with the cutoffs ranging from 24 kg/mm to 35 kg/mm. Single cycle IVF live birth rates have been reported to be 33% to 50% lower in overweight and obese women [18, 19]. In patients undergoing two treatment cycles, those with normal BMIs had 60% higher pregnancy rates than those with BMIs>35 [20]. Endometrial thickness at the time of retrieval was reported to be greater in obese patients (11.6 mm versus 10.7) and associated with a statistically significantly lower pregnancy rate, 35.2% versus 52.1% [19].

However, a donor oocyte recipient model has clearly demonstrated that endometrial receptivity is not affected by elevated BMI. The study divided 536 women undergoing their first donor oocyte IVF cycle into four BMI groups: underweight, normal, overweight, and obese. They found no statistically significant differences in implantation rate, ongoing pregnancy rate or spontaneous loss rate between groups [21].

Many investigators have found increased cancellation rates in obese women undergoing IVF [22–24]. Others have noted the need for increased total doses of gonadotropins in obese women but found no difference in cancellation, implantation or pregnancy rates [25]. Peak estradiol levels were reported to be lower in obese women, but again this was not associated with a decrease in implantation or clinical pregnancy rate [26]. In our study, no difference was encountered in cancellation rates, peak estradiol levels or total number of retrieved oocytes. In addition, the total gonadotropin doses were similar across BMI groups.

It is not possible to utilize BMI to guide choice of ovarian stimulation regimen. Most patients in our study were managed with a long down-regulation stimulation; however, ongoing pregnancy rate at time of discharge was unrelated to type of stimulation protocol. All PCOS patients were begun

Table 6 Response to ovarian stimulation stratified by BMI and diagnosis of PCOS

Body mass index (kg/m^2)	<18.5		18.5–24.9		25.0–29.9		≥30		*P*-value	
	PCOS	Non-PCOS	PCOS	Non-PCOS	PCOS	Non-PCOS	PCOS	Non-PCOS	PCOS	Non-PCOS
N	2	18	33	223	6	70	12	36		
Peak serum estradiol (pg/ml)	3,142.5	2,540.3	3,133.5	2,535.2	3,284.7	2,566.0	2,452.7	2,381.7	0.41	0.88
Mean number of oocytes retrieved	18.5	18.0	22.6	16.6	21.5	16.8	15.6	16.5	0.12	0.91

Table 7 Fertilization, implantation, clinical and ongoing pregnancy rate stratified by BMI and PCOS status

Body mass index (kg/m^2)	<18.5		18.5–24.9		25.0–29.9		≥30		*P*-value	
	PCOS	Non-PCOS	PCOS	Non-PCOS	PCOS	Non-PCOS	PCOS	Non-PCOS	PCOS	Non-PCOS
N	2	16	32	218	6	64	12	34		
Fertilization rate (%)	84.3	55.0	63.0	59.3	56.3	57.6	61.7	57.9	0.32	0.74
Implantation rate (%)	75.0	42.4	50.7	36.0	57.1	35.8	27.3	38.5	0.016*	0.49
Clinical pregnancy rate [*n*, (%)]	2 (100)	10 (62.5)	23 (71.9)	125 (57.3)	4 (66.7)	40 (62.5)	7 (58.3)	20 (58.8)	0.10	0.41
Ongoing pregnancy rate [*n*, (%)]	2 (100)	10 (62.5)	22 (68.8)	101 (46.3)	4 (66.7)	32 (50)	5 (41.7)	17 (50)	0.039*	0.49

*$P<0.05$

Table 8 Status at time of discharge as related to stimulation protocol

	antagonist	down-regulation	microflare	*P*-value
Ongoing pregnancy, *n* (%)	41 (51%)	147 (45%)	5 (50%)	0.57
Not pregnant, *n* (%)	39 (49%)	180 (55%)	5 (50%)	

Table 9 Inability to visualize air bubble at embryo transfer and presence of blood in or on catheter after transfer broken down by BMI and diagnosis of PCOS

Body mass index (kg/m^2)	<18.5		18.5–24.9		25.0–29.9		≥30		*P*-value	
	PCOS	Non-PCOS	PCOS	Non-PCOS	PCOS	Non-PCOS	PCOS	Non-PCOS	PCOS	Non-PCOS
N	2	16	32	218	6	64	12	34		
Inability to visualize air bubble at ET [n, (%)]	0 (0)	0 (0)	1 (3.1)	6 (2.8)	0 (0)	4 (6.3)	2 (16.7)	2 (5.9)	0.07[a]	0.06[a]
Presence of blood in or on catheter after ET [n, (%)]	1 (50)	5 (31.3)	10 (32.3)	63 (28.9)	4 (66.7)	20 (31.3)	6 (50)	8 (23.5)	0.09[a]	0.33

[a] Borderline significance

on an initial gonadotropin dose of 375 IU or less as these patients are at increased risk for OHSS. There were no cases of OHSS in this study.

Technologic advances in modern society have decreased the need for vigorous physical activity and have made high-calorie foods readily available and inexpensive. These factors make weight loss difficult, and best results are reached with a combination of dietary counseling, exercise and physician follow-up and support. Two significant benefits of weight loss for obese infertile patients are greater spontaneous conception rates and healthier pregnancies. Composition of the diet, high protein versus low protein, has been shown to be unimportant in terms of improvement in menstrual cyclicity and ovulation. Weight loss in PCOS patients on either diet leads to increases in sex hormone binding globulin and decreases in free androgen index and testosterone levels [27].

When obese women conceive they have poorer obstetrical outcomes than normal-weight women. Obese patients have increased risk of spontaneous abortion whether they conceive naturally [28] or through infertility treatment [29–31]. They also have increased risk of gestational diabetes, hypertension, preeclampsia and fetal macrosomia [32]. The rate of stillbirth in obese women is double that seen in women of ideal body weight [33]. Obesity is associated with labor complications such as fetal distress, failure to progress, shoulder dystocia, and cesarean section [34–36]. In 2007 the National Birth Defects Prevention Study reported that maternal obesity was significantly associated with increased risk of spina bifida, heart defects, anorectal atresia, hypospadius, limb reduction defects, diaphragmatic hernias and omphalocele [37].

Bariatric surgery is an option for women with BMIs> 35 kg/mm. A prospective study examined obstetrical outcomes in 79 women who had undergone laparoscopic adjustable gastric banding for severe obesity [38]. The incidence of gestational diabetes and pregnancy induced hypertension was comparable with community levels and less than that seen in an obese cohort. Neonatal outcomes were also significantly improved.

In young women undergoing treatment with IVF, BMI in the obese range is not associated with increased cancellation rates, poorer stimulation, lower implantation rates, or decreased clinical and ongoing pregnancy rates. Prior to treating these patients we should counsel them regarding lifestyle changes and advise them that weight loss will improve their fertility and lead to a healthier pregnancy. Visualization of the air bubble at time of embryo transfer is more difficult as BMI increases; however, this is not associated with a decrease in ongoing pregnancy rate. While there are well-known obstetrical and neonatal complications of obesity, young patients with an elevated BMI who are unable to lose weight or desire immediate treatment may be reassured that their IVF outcomes will not differ from that of their normal-weight peers.

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