

The effect of body mass index on the outcomes of first assisted reproductive technology cycles

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Objective: To provide assisted reproductive technology (ART) outcome rates per body mass index (BMI) category after controlling for potential confounders.

Design: Retrospective cohort study.

Setting: Large university-affiliated infertility practice.

Patient(s): Women undergoing ART.

Intervention(s): None.

Main Outcome Measure(s): The primary outcome was live birth. Analyses were stratified according to BMI category and adjusted for potential confounders, including maternal and paternal age, baseline serum FSH, duration of gonadotropin stimulation, mean daily gonadotropin dose, peak serum E₂, number of oocytes retrieved, use of intracytoplasmic sperm injection, embryo quality and number, transfer day, and number of embryos transferred.

Result(s): We analyzed the first autologous fresh IVF or IVF-ICSI cycle of 4,609 patients. There were no differences in the rates of cycle cancellation, spontaneous abortion, biochemical and ectopic pregnancies, or multiple births. After adjusting for potential confounders, patients with BMI ≥ 30.0 kg/m² had significantly decreased odds of implantation, clinical pregnancy, and live birth. The adjusted odds ratio (95% confidence interval [CI]) of live birth were 0.63 (0.47–0.85) for BMI 30.00–34.99, 0.39 (0.25–0.61) for BMI 35.00–39.99, and 0.32 (0.16–0.64) for BMI ≥ 40.0 compared with normal-weight cohorts.

Conclusion(s): Obesity has a significant negative effect on ART outcomes. Patients with BMI >30 kg/m² have up to 68% lower odds of having a live birth following their first ART cycle compared with women with BMI <30 . (Fertil Steril® 2012;98:102–8. ©2012 by American Society for Reproductive Medicine.)

Key Words: BMI, obesity, infertility, live birth

Obesity is an ongoing epidemic throughout the world, especially within the United States. This disease has significant implications for patient health and wellness. The proportion of the population suffering from obesity has been steadily increasing since the late 1970s. Data from the 2007–2008 National Health and Nutrition Examination Survey (NHANES) estimated that ~64% of American women fell within either the obese or overweight category (body mass index [BMI] >25 kg/m²) and

35.5% were obese (BMI >30 kg/m²) (1). Although there are definite disparities in obesity rates between different ethnic and socioeconomic backgrounds, one of the subpopulations that is mostly affected are women of reproductive age. One study concluded that the prepregnancy obesity rate has increased from 13% in 1993 to 22% in 2003 and that women with the highest prevalence of obesity were among the cohort of 20–29-year-olds (2).

In addition to its association with multiple comorbidities such as coronary

artery disease, hypertension, and diabetes, obesity can negatively affect a woman's reproductive function. Obesity is implicated as a cause of menstrual dysfunction often leading to oligomenorrhea, anovulation, and dysfunctional uterine bleeding. Even among women with regular menstrual cycles, fecundity has been shown to be reduced in both overweight and obese populations (3, 4). Additionally, higher rates of prepregnancy obesity have been associated with increasing rates of pregnancy complications, including increased rates of gestational hypertension, preeclampsia, gestational diabetes, postpartum hemorrhage, and fetal macrosomia. Rates of labor induction and operative delivery are also increased among obese women (5, 6).

Although data suggest that spontaneous pregnancy rates are lower with rising rates of obesity, there remains

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significant debate about the effects of obesity on patients undergoing in vitro fertilization (IVF), specifically regarding response to treatment protocols and success rates. Studies suggest that obese patients require higher stimulation doses of gonadotropins and suffer potentially lower clinical pregnancy (CP) rates compared with patients with normal BMI (7–10). Recent systematic reviews and meta-analyses demonstrated that obese patients using assisted reproductive technologies (ART) require higher doses of gonadotropins, yield a lower number of oocytes per cycle, have higher rates of spontaneous abortions, and exhibit lower CP rates (11, 12). However, there are insufficient data on the effect of obesity on live birth (LB) rates following ART.

The aim of the present study was to investigate the relationship between obesity and ART outcomes in a large cohort of women undergoing their first IVF or IVF–intracytoplasmic sperm injection (ICSI) cycle in a single institution, with specific emphasis on LB outcome data.

MATERIALS AND METHODS

Study Population

All patients in this study were evaluated and treated at Boston IVF, a large university-affiliated infertility practice. We conducted a retrospective chart review of all ART cycles performed at the center from January 1, 2004, to December 21, 2010, using the electronic medical record database eIVF (Practice Hwy). Women were included in the study if they were aged 20–47 years, were having their first IVF or IVF–ICSI cycle using autologous oocytes, and had a BMI recorded in their electronic medical chart. Patients were excluded if they used donor oocytes, gestational surrogacy, or cryopreserved embryos or lacked BMI documentation in their medical record. The study was approved by the Institutional Review Board of Beth Israel Deaconess Medical Center.

Patients were selected for IVF with or without ICSI according to standard accepted indications. Controlled ovarian hyperstimulation (COH) was achieved using one of three IVF protocols based on the patient's age, infertility diagnosis, and ovarian reserve assessment. These regimens included pituitary down-regulation with long luteal leuprolide acetate (Lupron; TAP Pharmaceuticals) with or without oral contraceptive (OCP) pretreatment and an OCP/microdose flare using microdose Lupron. An antagonist protocol involved the addition of a GnRH antagonist (Cetrotide, Serono; Antagon, Organon USA; or Ganirelix, Merck) to the standard protocol when a lead dominant follicle measuring ≥ 14 mm in diameter was identified by transvaginal ultrasonography. The dosage of gonadotropins varied according to the patient's ovarian response and ranged from 75 to 300 IU administered twice daily. The gonadotropins that were used included human menopausal gonadotropins (Pergonal, Serono; Hume-gon, Organon USA; or Repronex, Ferring Pharmaceuticals), purified urinary FSH (Fertinex, Serono; or Bravelle, Ferring), recombinant LH (Luveris, Serono), or recombinant FSH (Follistim, Organon; or Gonal-F, Serono).

Cycle monitoring generally consisted of serum estradiol (E_2) measurements and transvaginal ovarian ultrasonography (6.5 MHz probe, GE L200) during days 6–8 of gonadotropin

stimulation. The frequency of patient monitoring was dependent on the ovarian response to COH. The decision to cancel a cycle was determined by the reproductive endocrinologist, and was based on a combination of factors that included the patient age, low peak E_2 levels obtained during COH, and a low follicular response to COH. hCG (Profasi, Serono; Novarel, Ferring; or Pregnyl, Organon USA; 10,000 units subcutaneously) or the equivalent dose of recombinant hCG (Ovidrel, Serono) was administered to those patients who had at least one mature follicle ≥ 14 mm and were offered a continuation of the treatment cycle. Vaginal oocyte retrieval was performed 36 hours after the administration of hCG or recombinant hCG by transvaginal ultrasonography–guided needle aspiration under anesthesia. Each visible and accessible follicle was aspirated. IVF and/or IVF–ICSI were performed by standard techniques, as previously described (13). Embryos were generally transferred to the uterus either 3 days (cleavage stage) or 5 days (blastocyst stage) after oocyte retrieval. The number of embryos transferred was determined by institutional and American Society for Reproductive Medicine guidelines (14) as well as physician/patient discretion. Luteal-phase support was provided by the administration of transvaginal micronized progesterone (Crinone 8%, Serono Labs; Prometrium 200 mg, Solvay Pharmaceuticals; or Endometrin, Ferring).

Data Set

All patients included in the study had a documented BMI before treatment onset. BMI was defined as their weight in kilograms divided by the square of their height in meters (kg/m^2). We used the most recent World Health Organization (WHO) classification of BMI categories to divide our patient population; <18.50 kg/m^2 (underweight), 18.50 – 24.99 kg/m^2 (normal), 25.00 – 29.99 kg/m^2 (overweight), 30.00 – 34.99 kg/m^2 (obese class I), 35.00 – 39.99 kg/m^2 (obese class II), and ≥ 40.00 kg/m^2 (obese class III) (15).

The patient information we collected included the following: ages of both partners, baseline (cycle day 2–3) FSH, duration of stimulation (days), total gonadotropin dose used, peak serum E_2 level, number of oocytes retrieved, use of ICSI, day of embryo transfer, and number of embryos transferred. Serum E_2 concentrations were determined by a solid-phase competitive chemiluminescent enzyme assay with a sensitivity of 15 pg/mL and intrassay and interassay variation $<11\%$.

Each patient was assigned an embryo quality score. Because embryo classification systems vary widely among infertility practices, we decided to use a cumulative all-inclusive score for each individual patient. Currently, our embryologists score day 3 embryos by a 2-numeric scale that refers to the number of cells (blastomere) and the degree of blastomere fragmentation as well as an optional designation of “high implantation potential” (HIP) (16, 17). To calculate the embryo quality score, we first collected retrospective data on all patients at our practice who conceived either singleton gestations following elective single embryo transfer or multiple gestations following transfer of the corresponding number of embryos (two embryos transferred resulting in twins, or three embryos transferred resulting in

triplets). All possible 2-number scores \pm HIP designations were arranged in order of implantation rate (IR) and were assigned a number from 6 to 1, from highest to lowest IR. We then multiplied that number by the number of embryos that were of that quality and calculated the cumulative score for each patient.

Outcome Measures

The primary outcome of interest was LB, which was defined by the delivery of a live infant at >20 weeks of gestation, as documented in the electronic patient medical record. Secondary outcomes included the following: cycle cancellation, implantation, CP, spontaneous abortion, biochemical pregnancy, ectopic pregnancy, and multiple births. Implantation was confirmed by the presence of a positive serum pregnancy test (β -hCG). CP was confirmed by the ultrasonographic presence of an intrauterine sac with a fetal heartbeat at 6–8 weeks of gestation. Spontaneous abortion was defined as loss of a clinical or ongoing pregnancy before 20 weeks of gestation, whereas biochemical pregnancy was defined as a dropping serum β -hCG titer, starting from ≥ 100 mIU/mL, before detection of a gestational sac.

Statistical Analysis

Statistical analysis was performed using Stata v.11.2. Continuous variables are presented as mean \pm SD, whereas categorical variables are presented as frequency and percentage. Baseline characteristics of the six BMI categories were compared with the use of Pearson chi-square test for categorical variables and one-way analysis of variance for continuous variables (Table 1). Cycle outcomes were compared between BMI categories with the use of logistic or Poisson regression to calculate the odds ratio (OR; for categorical variables) or incidence rate ratio (IRR; for count variables), respectively, with their 95% confidence interval (CI). We adjusted for the following potential confounders: maternal age, paternal age, embryo quality score, duration of stimulation, baseline FSH, daily gonadotropin dose, peak serum E_2 , use of ICSI, day of embryo transfer, number of oocytes retrieved, and number of embryos transferred (Table 2). We also included the interaction between age and BMI. We defined statistical significance as $P < .05$ (two sided).

RESULTS

A total of 4,767 patients underwent their first fresh autologous ART cycles at our center from 2004 to 2010. Of those, 4,609 patients had their BMI recorded in the electronic medical chart. These patients were divided into six BMI categories; <18.50 kg/m² ($n = 92$; 2.0%), 18.50–24.99 kg/m² ($n = 2,605$; 56.6%), 25.00–29.99 kg/m² ($n = 1,027$; 22.3%), 30.00–34.99 kg/m² ($n = 477$; 10.3%), 35.00–39.99 kg/m² ($n = 275$; 6.0%), and ≥ 40.00 kg/m² ($n = 133$; 2.9%). Baseline characteristics were compared across BMI groups and are presented in Table 1. There were no statistically significant differences in maternal or paternal age, duration of stimulation, total amount of gonadotropins used, number of oocytes retrieved, embryo quality score, or number of embryos transferred.

Compared with normal-weight women, obese patients had statistically lower baseline serum FSH values (class II and III obesity only), required higher daily gonadotropin doses, and had lower peak serum E_2 levels (class I and II obesity only). ICSI was used with statistically higher frequency in underweight, overweight, and obese patients. Overall, as BMI increased, patients underwent more day 3 versus blastocyst transfers.

The cycle outcomes are summarized in Table 2. There were no statistically significant differences across BMI groups regarding to cycle cancellation, spontaneous abortion, biochemical pregnancy, ectopic pregnancy, or multiple births. After adjusting for maternal and paternal age, baseline serum FSH, duration of stimulation, daily gonadotropin dose, peak serum E_2 , number of oocytes retrieved, use of ICSI, embryo quality score, day of embryo transfer, and number of embryos transferred, we demonstrated that the odds of implantation, CP, and LB were significantly lower for obese patients (class I, II, and III) than their normal-weight cohorts. The odds of global miscarriage (which includes both biochemical pregnancies and spontaneous abortions) were significantly higher only in class III obese patients compared with normal BMI. These findings remained unchanged even after including the interaction between age and BMI (data not shown). The adjusted ORs and 95% CIs of LB for each BMI category compared with normal-weight patients are depicted in Figure 1.

Underweight, normal-weight, and overweight patients have similar odds of LB after their first fresh IVF cycle. Compared with normal BMI, the adjusted odds of LB are decreased by 37% in class I obesity, 61% in class II obesity, and 68% in class III obesity.

DISCUSSION

The clinical importance of BMI on the outcome of ART treatments has been the subject of several investigations that have thus far yielded conflicting results. Our findings demonstrate that in patients undergoing their first fresh ART cycle, the odds of implantation, CP, and most importantly LB, are dramatically decreased with increasing BMI. These results remain unchanged even after controlling for numerous statistically and clinically significant confounders.

We used the most recent WHO classification of BMI, which was made possible by the large sample size. Analyzing $>4,600$ ART cycles allowed for an adequate number of patients falling into each BMI category, rendering our results more specific and generalizable. All cycle data were derived from a single large institution, thus increasing the consistency between physician practices, treatment protocols, and patient populations. We analyzed only the first fresh ART cycle of every patient who met the inclusion criteria to minimize additional confounding by a history of repeatedly failed or cryopreserved cycles. Most importantly, the strength of the present study is derived from an analysis that included LB, the most clinically important outcome of ART, as the primary outcome and that also accounted for a large number of potential confounders that could otherwise bias the findings.

Our results showing a decreased LB rate with increasing obesity are in agreement with several published studies. A recent retrospective study of 1,721 first IVF cycles found lower

TABLE 1

Patient characteristics.

Variable	BMI						P value
	< 18.50 (n = 92)	18.50–24.99 (n = 2,605)	25.0–29.99 (n = 1,027)	30.00–34.99 (n = 477)	35.00–39.99 (n = 275)	≥40.00 (n = 133)	
Age of woman (yr)	34.48 ± 4.85	35.16 ± 4.50	35.38 ± 4.59	35.02 ± 4.80	34.71 ± 4.87	34.64 ± 4.48	.11
Age of man (yr)	37.62 ± 7.05	37.19 ± 6.00	37.28 ± 6.07	36.91 ± 6.53	36.71 ± 5.89	36.70 ± 6.05	.56
BMI	18.09 ± 0.61	22.11 ± 1.74	27.19 ± 1.22	32.05 ± 1.46	37.14 ± 1.43	43.30 ± 2.99	n/a
Day 3 FSH (pg/mL)	8.04 ± 3.00	8.19 ± 5.74	7.83 ± 6.38	7.26 ± 5.52	6.55 ± 2.83	6.19 ± 2.59	< .01 ^{b,c}
Duration of stimulation (d)	9.22 ± 1.93	9.38 ± 2.13	9.34 ± 1.91	9.20 ± 1.96	9.36 ± 1.68	6.19 ± 2.59	.04 ^d
Gonadotropin dose (IU)							
Total for cycle	2,556.58 ± 1,971.63	2,844.88 ± 1,918.80	3,014.86 ± 2,044.45	2,908.47 ± 1,478.91	2,913.05 ± 1,561.59	3,232.50 ± 1,770.62	.02 ^d
Average daily	211.66 ± 100.73	234.36 ± 97.59	244.43 ± 92.36	252.64 ± 95.85	256.81 ± 89.28	263.15 ± 86.92	< .01 ^{a,b,c}
E ₂ on hCG day (pg/mL)	2,000.43 ± 1,190.37	2,030.86 ± 1,262.50	2,017.84 ± 1,283.56	1,696.24 ± 1,080.65	1,640.54 ± 1,114.39	1,802.47 ± 1,211.44	< .01 ^{a,b}
No. of oocytes retrieved	11.46 ± 6.62	10.90 ± 7.23	10.80 ± 6.96	9.98 ± 5.89	10.21 ± 7.58	10.48 ± 6.99	.08
ICSI	31 (33.70)	781 (29.98)	353 (34.37)	179 (37.53)	120 (43.64)	52 (39.10)	< .01
Embryo quality score	7.62 ± 5.15	9.00 ± 4.96	9.09 ± 5.00	9.06 ± 5.37	8.53 ± 4.97	9.29 ± 5.03	.10
Day of ET							.04
Day 3	65 (76.47)	2028 (85.71)	786 (86.66)	380 (87.56)	217 (89.67)	106 (89.83)	
Blastocyst	20 (23.53)	338 (14.29)	121 (13.34)	54 (12.44)	25 (10.33)	12 (10.17)	
No. of embryos transferred	1.72 ± 0.96	1.96 ± 1.07	1.97 ± 1.15	2.00 ± 1.11	1.89 ± 1.06	1.93 ± 1.04	.26

Note: Data presented as mean ± SD or n (%). ET = embryo transfer; ICSI = intracytoplasmic sperm injection.

^a Pairwise comparisons revealed a statistically significant difference between the second and fourth BMI categories.

^b Pairwise comparisons revealed a statistically significant difference between the second and fifth BMI categories.

^c Pairwise comparisons revealed a statistically significant difference between the second and sixth BMI categories.

^d Pairwise comparisons failed to detect any statistically significant differences compared with the second BMI category.

Moragianni. BMI effect on ART outcomes. *Fertil Steril* 2012.

TABLE 2

Regression models of IVF outcomes.

Outcome	BMI					
	< 18.50 (n = 92)	18.50–24.99 (n = 2,605)	25.0–29.99 (n = 1,027)	30.00–34.99 (n = 477)	35.00–39.99 (n = 275)	≥ 40.00 (n = 133)
No. of oocytes retrieved ^a	1.01 (0.94–1.09)	Reference	0.98 (0.96–1.01)	0.99 (0.95–1.02)	0.99 (0.94–1.04)	1.02 (0.95–1.09)
No. of embryos transferred ^a	0.96 (0.80–1.16)		1.01 (0.95–1.07)	0.99 (0.91–1.08)	1.00 (0.90–1.11)	1.01 (0.86–1.19)
Implantation ^b	0.92 (0.54–1.58)		0.93 (0.77–1.12)	0.69 (0.53–0.90)	0.52 (0.36–0.74)	0.58 (0.35–0.96)
Clinical pregnancy ^b	0.98 (0.57–1.70)		0.90 (0.74–1.09)	0.70 (0.53–0.92)	0.41 (0.27–0.62)	0.43 (0.24–0.76)
SAb ^b	1.12 (0.39–3.18)		0.75 (0.50–1.14)	1.16 (0.71–1.89)	0.77 (0.36–1.62)	1.27 (0.53–3.05)
Biochemical ^b	0.79 (0.28–2.24)		1.09 (0.78–1.52)	0.88 (0.54–1.43)	1.34 (0.78–2.31)	1.63 (0.78–3.39)
Global miscarriage ^b	0.93 (0.43–2.00)		1.04 (0.83–1.30)	1.22 (0.89–1.66)	1.26 (0.85–1.86)	1.92 (1.14–3.22)
Ectopic pregnancy ^b	—		0.79 (0.25–2.47)	1.02 (0.28–3.69)	1.09 (0.23–5.08)	1.23 (0.15–9.99)
Live birth ^b	0.94 (0.53–1.67)		0.96 (0.78–1.18)	0.63 (0.47–0.85)	0.39 (0.25–0.61)	0.32 (0.16–0.64)
Multiple birth ^b	—		—	—	—	—
Twins	0.83 (0.29–2.39)		0.76 (0.52–1.11)	0.93 (0.53–1.62)	0.85 (0.35–2.06)	0.93 (0.22–3.83)
Triplets	—		1.5 (0.41–2.71)	0.64 (0.11–3.71)	—	4.87 (0.47–50.07)

Note: Data presented as: ^a incidence rate ratio (95% confidence interval [CI]); (Poisson regression); or ^b odds ratio (95% CI) (logistic regression). SAb = spontaneous abortion. Moragiani. BMI effect on ART outcomes. Fertil Steril 2012.

CP rates in class I–III obese patients and a lower LB rate in class III obese patients only (18). Those results were not adjusted for any confounders. Another retrospective study of 6,500 IVF cycles, that separated patients into four, instead of six, BMI categories (lean, normal, overweight, and obese), also demonstrated decreased implantation, CP, and LB rates in obese patients, which persisted after controlling for cycle number, gonadotropin dose, maternal age and peak serum E₂ levels (19). A larger retrospective study of 8,457 first IVF cycles found a significantly lower LB rate per cycle in women with BMI >27 (20). Similarly, a study of 5,019 IVF cycles found increased cumulative odds of LB after three cycles in patients with BMI ≥30, after adjusting for age and infertility diagnosis (21). However, when analyzing only the first IVF cycles (n = 2,660), they failed to replicate statistical significance regarding to LB. Similar results of significantly lower LB were found in patients with BMI ≥25 (22) as well as in those with BMI >36 (23) compared with normal-weight cohorts. Finally, a Society for Assisted Reproductive Technology Writing Group study of 45,163 embryo transfers demonstrated significantly increased odds of fetal loss or stillbirth in overweight and obese patients, after adjusting for age, race, infertility diagnosis, day of embryo transfer, and number of embryos transferred (24).

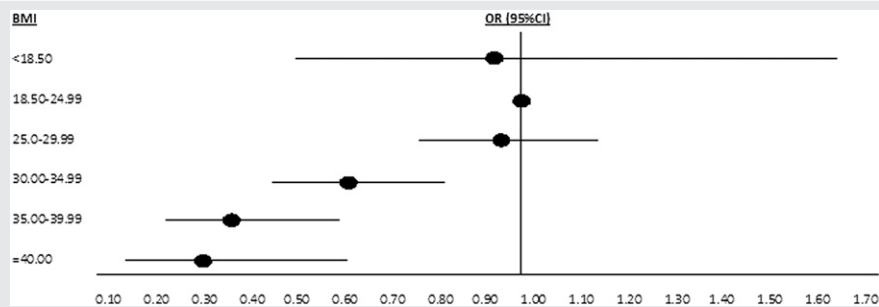
Conversely, several studies have demonstrated no statistically significant difference in LB between normal-weight and obese patients. The majority of those studies had much smaller sample sizes, ranging from 72 to 278, and used binomial BMI classifications (10, 25–27). Two other studies included only Asian patients and three BMI categories (28, 29), and Dokras et al. analyzed data only from patients <38 years old (30).

Despite LB being the optimal ART outcome to be studied, the majority of studies use CP as their primary outcome owing to relative ease of data collection. Several studies have demonstrated decreased odds of CP in patients with higher BMI (9, 10, 16, 31). However, many more studies have failed to identify a statistically significant difference (7, 8, 20, 25–30), including two meta-analyses of 21 and 13 studies that demonstrated a lower chance of CP with obesity (32, 33).

The present results are limited mainly by the retrospective nature of the study, which prevented controlling for confounders such as smoking and lifestyle characteristics. However, compared with the only other large study that controlled for a substantial number of confounders (24), our study offers significant advantages. Specifically, Luke et al. analyzed data from 345 clinics, in cycles that resulted in embryo transfer and included more than just the first ART cycle. In contrast, the present findings were derived from a single institution, where practice consistency can be assured, and included all first-time cycling patients, which enabled us to evaluate cancellation rates and decreased the overrepresentation of patients with repeated failures.

Our decision to include only the first ART cycle, albeit meant to minimize confounding by multiple failed cycles or prolonged treatment, might confer a potential limitation. Earlier studies have demonstrated that obese patients require higher doses of medications and more ART cycles than their normal-weight counterparts to achieve optimal dosing

FIGURE 1



Forest plot of adjusted live birth rate according to body mass index (BMI, kg/m²) category (circle represents odds ratio [OR], horizontal line represents 95% confidence interval [CI]).

Moragianni. BMI effect on ART outcomes. *Fertil Steril* 2012.

regimens (34). Therefore, the lower LB seen in these obese patients may be partly the result of conservative dosing associated with their first ART cycles. This would warrant further investigation.

In summary, our findings indicate that obesity decreases the odds of LB, as well as implantation and CP, in patients undergoing their first IVF or IVF-ICSI cycle, and this decrease persists after controlling for a variety of potential confounders. Our results, especially the schematic of Figure 1, can be used when counseling and educating patients regarding the beneficial lifestyle changes and weight loss required to optimize the success of their ART treatment.

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