


Weight reduction using a formula diet recovers menstruation in obese patients with an ovulatory disorder

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Abstract

Aim: To determine the effectiveness of a formula diet in weight reduction and the recovery of menstruation in obese patients with ovulatory disorders.

Methods: After the enrollment of 39 obese women with ovulatory disorders, they replaced one or two of their three normal meals with a microdiet (MD) (240 kcal/meal) for 24 weeks. Physical, endocrinological, and biochemical tests were conducted before and at 12 and 24 weeks of the study. Of the 39 women enrolled, 26 were not taking clomiphene. They were divided into three groups according to their body weight outcomes and then analyzed for menstruation recovery.

Results: A weight reduction of $\geq 5\%$ was observed in 31 (81.5%) of the 39 women. There were significant decreases in the body weight and Body Mass Index during the study. Menstruation returned in 18 (69%) of the 26 patients without clomiphene treatment, with the recovery being significantly more prevalent in the groups (totally 81.0%) that exhibited a 5%-10% weight reduction and $\geq 10\%$ weight reduction, compared to the group with a $< 5\%$ weight reduction.

Conclusion: The use of a formula diet effectively reduced the patients' body weight and led to the recovery of menstruation in these obese patients with ovulatory disorders.

KEYWORDS

formula diet, obesity, polycystic ovary syndrome, weight reduction

1 | INTRODUCTION

Obesity is rapidly increasing and becoming a major cause of disease and death throughout the world.^{1,2} In 2014, there were 1.9 billion overweight and 600 million obese adults in the world, with this

obesity more common in women, compared to men. Obesity also has been known to be a risk factor for anovulation, ovulatory disorder, lower pregnancy rates in subfertility, and polycystic ovary syndrome (PCOS).^{3,4} Ovulatory disorders in patients with PCOS have been reported to improve in conjunction with the loss of weight.^{5,6} In cases

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where patients are not able to successfully lose weight, the induction of ovulation is usually attempted during infertility treatments. However, in order to achieve ovulation in obese patients, high doses of the ovulation induction drugs are usually required.⁷ It has been reported that a high body mass index (BMI) increases the consumed gonadotropin ampoules and there is a longer treatment duration, together with a decreased number of collected oocytes,^{8,9} which is costly¹⁰ in in vitro fertilization. Furthermore, side-effects such as miscarriage and a low pregnancy rate, cycle cancelation, and/or the ineffectiveness of the treatment option are more prevalent in obese patients.⁹ Thus, scientific evidence has shown that weight loss treatment options are just as effective as any of the high-cost treatments that are normally used when trying to treat patients with infertility and ovulatory disorder. Currently, however, there are only a few good ways that can effectively and successfully reduce body weight. Formula diets are often used for weight loss treatments, as they contain fewer carbohydrate and lipid products while still providing sufficient protein, vitamins, and all of the necessary minerals.^{11,12} The microdiet® (MD, Sunny Health Company, Ltd., Tokyo, Japan) is a formula diet that is used to maintain the normal functions of the living body and suppress the body protein to a minimum level so that the body can lose excess fat by more efficiently burning calories. In 1983, a research group led by Jacqueline Stordy at the University of Surrey in the UK first created MD for use as a hospital diet, which was based on the very-low-calorie diet (LCD) theory, and is an ultra-low-calorie, high-nutrition food. The consumption of MD instead of a normal meal helps to create a greater energy deficit between the energy requirement and the dietary energy intake. Two daily servings of MD supplies all of the nutrients required for 1 day, while only containing 480 kcal. When administered to obese patients with type 2 diabetes who were taking part in a weight reduction program, a high success rate was reported for MD.¹¹ The current study further examined the effectiveness of MD in weight reduction (WR) and in the recovery of menstruation in obese patients with ovulatory disorders.

2 | MATERIALS AND METHODS

2.1 | Study design

This study was conducted in the departments of Obstetrics and Gynecology at Tokushima University, Kagoshima University, Saitama Medical University, St. Marianna University of Medicine, University of Fukui, and Kawano Mika Lady's Clinic. All the procedures were conducted after obtaining approval from the institutional review boards (Approved No. 377). All the patients provided written informed consent prior to the start of the study.

2.2 | Participants

This study enrolled 45 women with ovulatory disorders (including 21 women with PCOS, as diagnosed by the Japanese PCOS criteria,^{13,14} all of which also meet the Rotterdam criteria,¹⁵ and a BMI of ≥ 25). All of them did not have menstruation for at least 2 months. Table 1 presents the baseline characteristics of the patients. Those patients with

severe underlying diseases that prohibited a LCD (600–1200 kcal/d), a known allergy to any of the products, including MD, limited competence for consent under the Civil Code, hyperprolactinemia, ovulation failure associated with high serum follicle stimulating hormone (FSH), and who were pregnant or potentially pregnant women, nursing women, or who were considered to be inappropriate for LCD therapy by the physician were excluded from the study. During the experimental period, one patient withdrew from the study after being confirmed to be pregnant. In addition, all the patients were prohibited from undergoing sex hormone treatments during the study.

2.3 | Interventions and outcomes

Microdiet® (240 kcal/meal, provided by Sunny Health Company, Ltd., Tokyo, Japan) was provided as a replacement for one or two of the three normal meals that were consumed each day for a period of 24 weeks (Figure 1). Throughout the study, all the participants underwent physical examinations, blood pressure measurements, transvaginal ultrasonography (Tv-USG), the testing of the serum concentrations of estradiol (E_2) and progesterone (P_4) at 4 week intervals and the serum concentrations of luteinizing hormone (LH), FSH, and testosterone (T) at 8 week intervals. Each patient's weight, height, and hip and waist circumferences were measured and used to calculate the BMI. At 12 and 24 weeks after the beginning of the study, blood samples were collected after a 12 hours overnight fast and were analyzed by using commercial kits and automated analyzers in order to determine the hormonal changes, kidney function, liver function, and the enzyme and lipid profiles. All the patients recorded their basal body temperature (BBT) throughout the study. The recovery of menstruation was assessed every 4 weeks by the biphasic BBT pattern, which was verified by hormonal data and morphological Tv-USG findings of the endometrium and ovaries. During the study, 13 patients were excluded from the analysis of menstruation due to taking clomiphene. The remaining 26 patients who did not take clomiphene were divided into three groups according to their body WR (<5% WR [$n=5$]; 5%–10% WR [$n=5$], and $\geq 10\%$ WR [$n=16$]) and then were analyzed for menstruation recovery. The recovery of menstruation was defined as an experience of menstruation at least once during the study. Those patients who had or did not have a recovery of menstruation were grouped as "eumenorrheic" or "amenorrheic," respectively.

2.4 | Assays

The serum FSH and LH concentrations were measured by using a chemiluminescent immunoassay kit (Abbott Company, Tokyo, Japan). The E_2 concentration was measured by an electrochemiluminescence immunoassay kit (ECLusys Estradiol II; Roche Diagnostics, K.K., Tokyo, Japan). The serum T concentration was measured by an electrochemiluminescence immunoassay kit (ECLusys TESTO II; Roche Diagnostics, K.K.). The serum prolactin and P_4 were measured by using an enzyme-linked immunosorbent assay kit (Abcam, Tokyo, Japan). The serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase, gamma-glutamyltransferase, alkaline

Characteristic	Unit	N	Mean ± SD	Minimum	Maximum
Age	years	45	29.5±5.5	20.0	38.0
Height	cm	45	158.0±5.0	147.0	170.0
Weight	kg	45	85.1±15.8	60.5	134.8
Body mass index	kg/m ²	45	34.2±5.7	24.9	50.1
Waist (W)	cm	34	101.5±13.7	82.0	128.4
Hip (H)	cm	34	109.4±9.4	93.1	130.0
W-H ratio		34	0.93±0.07	0.82	1.13
Systolic BP	mm Hg	26	131±18	102	162
Diastolic BP	mm Hg	25	84±13	62	116
Serum prolactin	ng/mL	34	6.7±4.5	1.7	21.6
FSH	mIU/mL	45	7.0±3.2	1.2	21.5
LH	mIU/mL	44	8.1±5.3	0.3	24.0
LH-FSH ratio		44	1.2±0.60	0.1	2.8
Estradiol	pg/mL	41	45.0±28.0	10.0	156.0
Progesterone	ng/mL	41	1.2±2.3	0.2	11.9
Testosterone	ng/mL	43	0.7±0.6	0.1	2.8
AST	IU/L	43	29±18	12	114
ALT	IU/L	43	40±26	11	136
LDH	IU/L	43	197±38	138	291
γ-GTP	IU/L	43	46±59	7	324
ALP	IU/L	43	231±62	137	472
Total bilirubin	mg/dL	42	0.6±0.3	0.0	1.2
Total protein	mg/dL	41	7.6±0.5	6.7	8.7
FBS	mg/dL	42	111±38	79	232
IRI	μIU/mL	41	37.4±56.2	4.2	297
Total cholesterol	mg/dL	43	207±33	106	275
Triglyceride	mg/dL	43	182±159	34	1008
HDL-C	mg/dL	40	57±34	34	260
BUN	mg/dL	41	11.8±3.2	4.0	20.0
Uric acid	mg/dL	40	5.7±1.2	3.5	8.0
Creatinine	mg/dL	40	0.60±0.10	0.39	1.00
WBC	/μL	41	7964±1913	4180	11 300
RBC	×10 ⁴ /μL	41	469±85	419	576
Hemoglobin	g/dL	41	14.2±1.1	11.3	16.0
Ht	%	41	42.7±3.1	34.0	47.5
MCV	μm ³	41	89.10±5.1	81.1	102.0
MCH	pg	41	29.70±1.9	26.5	35.0
MCHC	%	41	33.3±0.7	32.0	35.0

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; BUN, blood urea nitrogen; FBS, fasting blood sugar; FSH, follicle stimulating hormone; GTP, glutamyltransferase; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; Ht, hematocrit; IRI, fasting immunoreactive insulin; LDH, lactate dehydrogenase; LH, luteinizing hormone; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RBC, red blood cell; SD, standard deviation; WBC, white blood cell.

phosphatase, total bilirubin, and total protein levels were measured by using an automated clinical analyzer (Hitachi, Tokyo, Japan). The fasting blood sugar (FBS) was measured by a glucose analyzer (GA04; A&T

Corporation, Kanagawa, Japan), while the fasting immunoreactive insulin (IRI) was measured by using an enzyme immunoassay (AIA2000; TOSOH Company, Tokyo, Japan). Insulin resistance was calculated by

TABLE 1 Baseline characteristics of the patients

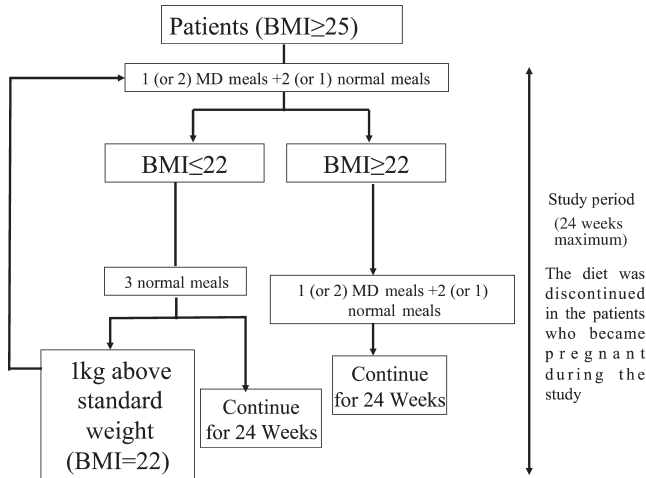


FIGURE 1 Study protocol. The participants with a body mass index (BMI) of ≥ 25 were enrolled in this study for 24 weeks. MD, microdiet[®], which contained 240 kcal/meal

the following formula: homeostasis model assessment of insulin resistance (HOMA-IR) = $\text{IRI} (\mu\text{IU/mL}) \times \text{FBS} (\text{mg/dL}) / 405$. The serum lipid profiles were determined by using total cholesterol (T-Cho), triglycerides (TG), and high-density lipoprotein cholesterol, while the kidney function was determined by using creatinine, blood urea nitrogen, and uric acid. They all were analyzed through the use of automated clinical analyzers (Hitachi, Tokyo, Japan). Additionally, the hematological profiles (white blood cells, red blood cells, hemoglobin, hematocrit (Ht), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV)) were analyzed by an automated analyzer.

2.5 | Statistical analysis

All the data are presented as mean \pm SD values. All the statistical analyses were performed by using a one-way or two-way ANOVA and post-hoc tests. The categorical data analysis was performed by using the chi square test. $P < .05$ was considered to be statistically significant.

3 | RESULTS

Out of the 45 patients who were enrolled in the study, 39 (which included the one patient who became pregnant during the study) completed the study protocol (Figure 2). There were 21 patients who were diagnosed with PCOS. Thirteen of the patients were excluded from the menstruation analysis, as they were found to be using clomiphene for the induction of ovulation. Table 1 presents the baseline characteristics of the patients. They were overweight or obese (BMI ≥ 25).

Of the 39 patients who completed the study, 38 lost weight, while one patient gained weight. After excluding the one patient who became pregnant, the results showed that a WR of $>5\%$ was achieved by 31 (81.5%) out of the 38 patients (Figure 3). Also, the WRs of 10% were achieved by 21 (55.2%) patients.

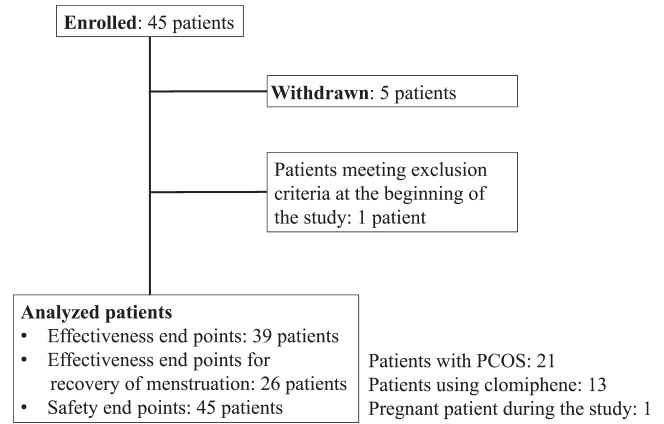


FIGURE 2 Analyzed patients. A total of 45 patients was enrolled in the study, with 39 completing the study and 26 who were not taking clomiphene being analyzed for the recovery of menstruation. PCOS, polycystic ovary syndrome

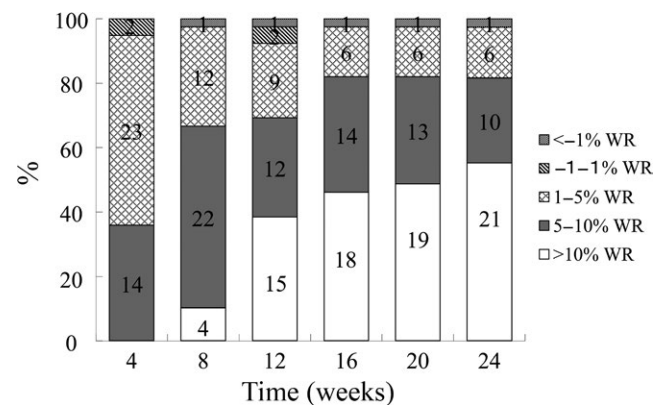


FIGURE 3 Proportion of weight reduction during the study. There was a significant reduction in the body weight of 31 (81.5%) out of 38 patients. At 24 weeks, one patient was excluded from the weight reduction analysis due to pregnancy. WR, weight reduction

After 24 weeks, there was a significant decrease in the mean body weight of all the patients, with weights decreasing from 84 kg to 75 kg (11%) ($P < .01$) (Figure 4). The BMI decreased from 34.0 kg/m^2 to 30.3 kg/m^2 (10.9%) ($P < .01$). The waist circumference decreased from 101 cm to 92 cm (8.9%) ($P < .05$). The hip circumference decreased from 109 cm to 102 cm (6.4%) ($P < .05$). When compared to the values that had been obtained prior to the study, there were significant decreases in the HOMA-IR, FBS, T-Cho, TG, AST, and ALT after 12 and 24 weeks (Figure 5).

Out of the 26 patients that did not take clomiphene, menstruation recovered in 18 (69%) of the patients without the induction of ovulation (Table 2, Figure 6). Table 2 shows the presence of menstruation before and during the study of each patient with WR data. Menstruation recovered in accordance with the body WR percentages, with the recovery of menstruation observed in one of five patients (20%) who was in the $<5\%$ WR group, in five out of five patients (100%) who had a 5-10% WR, and in 12 of the 16 patients (75%) with $>10\%$ WR (Figure 6), showing as high as 81.0% (17 patients) recovery of menstruation

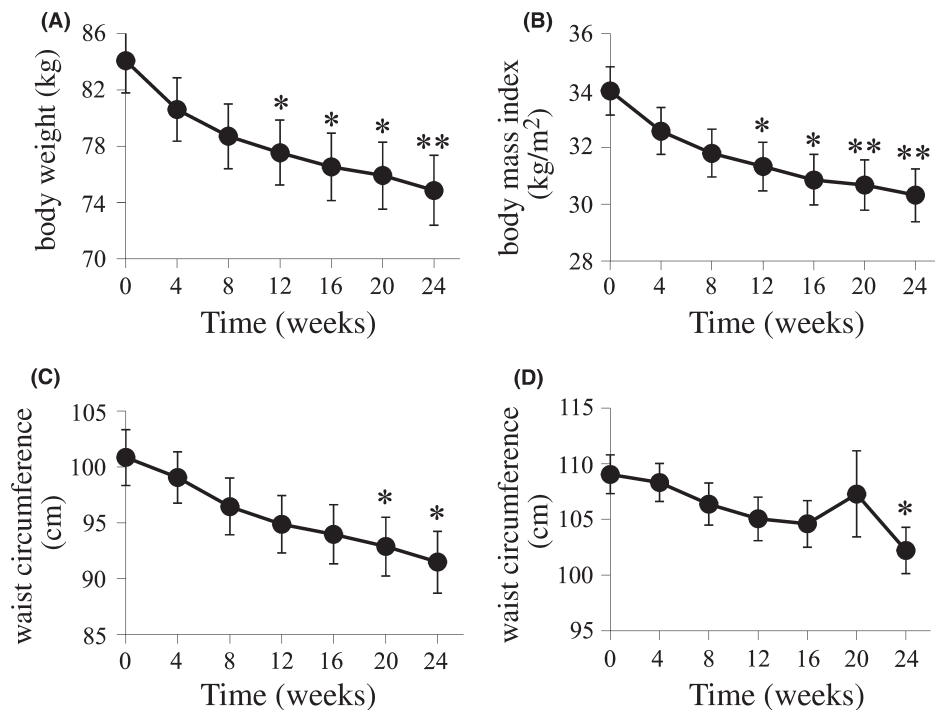


FIGURE 4 Body measurement changes. A, Weight; B, body mass index; C, waist circumference; and D, hip circumference. The data are expressed as the mean \pm SD. * $P < .05$ and ** $P < .01$

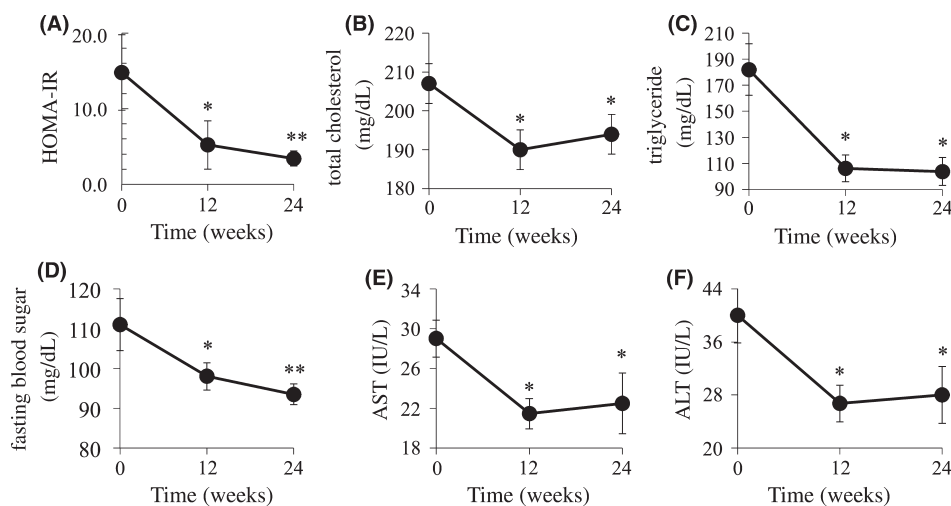


FIGURE 5 Blood biochemistry changes. The (A) homeostasis model assessment of insulin resistance, (B) total cholesterol, (C) triglyceride, (D) fasting blood sugar, (E) aspartate aminotransferase, and (F) alanine aminotransferase all were significantly decreased. The data are expressed as the mean \pm standard deviation. * $P < .05$ and ** $P < .01$

among total 21 patients with $>5\%$ WR. A significantly higher recovery of menstruation (more than twice during the study) was seen in both the 5% - 10% WR group ($P < .05$) and the $>10\%$ WR group ($P < .01$), as compared to the $<5\%$ WR group.

The eumenorrheic patients, who recovered menstruation at least once, exhibited a significantly lower T level at 24 weeks, compared to the amenorrheic patients, who did not recover menstruation during the study ($P < .01$). The T-levels increased from baseline to 12 weeks and then significantly decreased between 12 and 24 weeks in the amenorrheic patients ($P < .05$) (Figure 7). Although the eumenorrheic patients tended to have higher baseline IRI levels, there was no significant difference observed for the IRI between the amenorrheic and eumenorrheic patients in this study. The PCOS-amenorrheic patients exhibited significantly higher T-levels, compared to the non-PCOS-eumenorrheic patients, at 12 and 24 weeks ($P < .01$). The PCOS-amenorrheic patients also had significantly higher T-levels,

compared to the PCOS-eumenorrheic patients, at 12 ($P < .05$) and 24 weeks ($P < .01$).

4 | DISCUSSION

It is well known that obese patients have ovulatory disorders, a low rate of natural cycles, a high rate of miscarriage, and congenital anomalies.^{3,10,16} In women with ovulatory disorders, WR has been shown to improve both menstruation and reproductive parameters. A previous study reported that spontaneous ovulation recovered in obese women at 6 months after WR.¹⁰ These women also had an increased rate of achieving pregnancy and live births and a reduced miscarriage rate, all of which led to a decreased financial cost, as compared to that incurred when undergoing infertility treatments.¹⁰ More recently, a formula diet also was successfully used to achieve WR in obese patients.^{11,12}

TABLE 2 Presence of menstruation in the patients without ovulation induction

No.	PCOS	Weight reduction (%) and recovery of menstruation before and during the study (weeks)						
		-4-0	0-4	4-8	8-12	12-16	16-20	20-24
1	Yes	0.0	-3.9	-5.4	-7.0	-8.2	-7.3	-10.4
2	Yes	0.0	-5.6	-8.1	-8.9	-11.7	-11.1	-12.5
3	Yes	0.0	-1.9	-5.6	-7.2	-7.6	-9.4	-12.0
4	Yes	0.0	-3.1	-3.1	-3.8	-5.0	-5.4	-5.1
5	Yes	0.0	-2.8	-4.2	-2.8	-5.0	-6.1	-7.2
6	Yes	0.0	-3.3	-8.6	-8.7	-10.1	-11.0	-11.3
7	Yes	0.0	-5.8	-9.7	-12.4	-13.6	-16.6	-19.3
8	Yes	0.0	-3.9	-9.5	-14.0	-14.0	-16.4	-17.3
9	Yes	0.0	-2.6	-3.5	-5.6	-3.8	-3.8	-3.5
10	Yes	0.0	-2.9	-4.2	-4.1	-4.3	-4.7	-3.4
11	Yes	0.0	-3.9	-9.5	-10.8	-15.7	-15.8	-16.6
12	No	0.0	-1.8	-4.5	-4.5	-4.9	-5.0	-6.8
13	No	0.0	-5.6	-10.3	-11.0	-13.2	-12.4	-14.5
14	No	0.0	-8.1	-13.0	-15.5	-15.2	-16.9	-19.4
15	No	0.0	-5.8	-8.6	-11.3	-13.3	-16.0	
16	No	0.0	-2.3	-2.7	-3.6	-4.6	-5.0	-7.5
17	No	0.0	-2.3	-7.7	-10.5	-12.4	-12.3	-13.3
18	No	0.0	-1.1	-1.3	-0.4	-1.1	-2.4	-3.2
19	No	0.0	-5.4	-8.2	-10.0	-11.4	-11.7	-11.7
20	No	0.0	-5.5	-6.4	-8.2	-8.5	-10.6	-10.2
21	No	0.0	-5.0	-5.4	-5.8	-5.9	-5.4	-5.9
22	No	0.0	-6.2	-9.8	-12.0	-13.2	-13.6	-15.0
23	No	0.0	0.1	-1.0	-0.8	-1.0	-2.6	-2.0
24	No	0.0	-6.1	-10.8	-14.4	-20.3	-23.2	-26.9
25	No	0.0	-4.6	-7.8	-10.0	-14.3	-13.6	-15.7
26	No	0.0	0.6	1.8	1.8	1.4	1.6	4.1

The shading represents the presence of menstruation. PCOS, polycystic ovary syndrome. Case No.15 conceived during the study due to recovery of ovulation. Therefore, her data of 20-24 weeks was missing and excluded from analysis.

Therefore, it was decided to investigate further the MD formula diet and to evaluate the ability of this diet to reduce body weight and to recover menstruation in obese patients with ovulatory disorders. Menstruation recovered in 81% (17/21) of the patients who achieved a >5% weight loss. These results demonstrated that the use of the MD formula diet led to a significant weight loss and the achievement of regular menstruation in overweight women, including those with PCOS.

Also, WR and weight maintenance are very important in helping to reduce the morbidity and mortality that are associated with cardiovascular diseases, diabetes, osteoarthritis, and obstructive sleep apnea.¹⁷⁻¹⁹ One study reported a 16% reduction in the incidence of diabetes for each 1 kg of weight loss.²⁰ In the current study, 24 out of the 26 patients showed a WR of at least 1 kg in 4 weeks, which indicated that the diabetic risk was markedly reduced. The National Institute for Clinical Excellence guidelines reported that a 5%-10% weight loss or a 0.5-1 kg weekly reduction is the best range for successful weight loss, as this is associated with large improvements in symptoms and metabolic

parameters.²¹ In this study, 35.8% of the patients achieved a >5% WR in only 4 weeks by using MD; furthermore, as high as 69.2% and 81.5% of the patients did that after 12 and 24 weeks, respectively. The metabolic parameters (HOMA-IR, FBS, T-Cho, TG) and liver function tests (AST, ALT) also were markedly improved after 12 or 24 weeks. A study reported that the FBS, HOMA-IR, and insulin were apparently lower in the formula diet group using MD than in the group using a conventional Japanese low-caloric diet.¹¹ In their report, the metabolic parameters also improved just as in this study. From these results, MD, which contains a rich level of protein and a poor level of carbohydrate, is helpful in order to reduce one's body weight and to improve the metabolic parameters. Although there are many choices for WR treatments, such as exercise, anti-obesity drugs, lifestyle modification, bariatric surgery, and diet, these treatments are not always effective, nor do they always successfully reduce the body weight. Meal replacements or substitution with a LCD can be used to maintain weight loss with no adverse effect, in addition to having a similar efficacy as anti-obesity drugs and

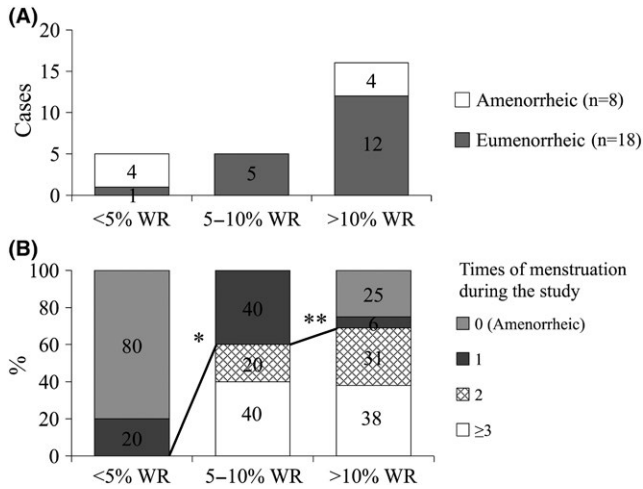


FIGURE 6 Recovery of menstruation in accordance with the level of weight reduction (WR). A, Of the 26 patients not taking clomiphene, 18 recovered menstruation without the induction of ovulation. B, As for the recovery of menstruation more than twice during the study, the percentage was significantly higher in the 5%-10% and in the >10% WR groups. The recovery rate of menstruation was totally 81.0% (17/21) in patients with >5% WR. * $P<.05$ and ** $P<.01$. Amenorrheic, no recovery of menstruation during the study; eumenorrheic, recovery of menstruation at least once during the study; WR, weight reduction

at a lower cost.^{12,22} Studies in many fields have examined reductions in body weight and the maintenance of weight. One reported finding that a protein-sparing, modified fasting (~1.2-1.4 g protein/kg) diet was effective in reducing the body weight as long as the patients also were placed on a full vitamin and mineral supplementation regimen.²³ In recent years, this therapy has become much easier to perform through the use of a formula diet, such as MD, which contains high protein, low carbohydrate, and low fat, while being rich in vitamins and minerals, all of which are required for wellness.¹¹ The MD not only reduces body weight and improves the coronary risk factors in obese patients

with type 2 diabetes, but it also helps to reduce operative risks and to improve postoperative results.²⁴ Additionally, there was no adverse effect during MD treatment in this study, suggesting that MD is a safe method to use to reduce body weight.

In PCOS, ~30%-75% of these patients are found to be obese.²⁵ When obesity is present, this induces insulin resistance and hyperinsulinemia. As a result, this inhibits the production of the sex hormone-binding globulin (SHBG) in the liver, thereby causing hyperandrogenism. Subsequently, the increased androgen is converted to estrogen in the adipose tissue and ovary, thereby suppressing gonadotropin secretion.^{3,26} In this study, the IRI decreased but the T-level did not decrease in the patients who recovered menstruation. The recovery of menstruation might be brought about mainly by a reduced free T-concentration through an increased SHBG concentration. In contrast, the amenorrheic patients showed an elevation of the serum T during WR, especially if they had PCOS. Some mechanisms would exist in relation to PCOS pathophysiology; however, further study would be needed to clarify these mechanisms. Moreover, as obesity also reduces serum adiponectin, this can lead to incremental increases in the amount of insulin circulating within the body.²⁷ Thus, in order to achieve the recovery of ovulation in patients with PCOS, they need to consider undergoing potential weight loss treatment. Previous studies have reported that after a WR of at least 5%-10% in patients with PCOS, there were increases in the insulin sensitivity and SHBG levels, normalized reproductive hormone profiles, restored menstrual cyclicity, an improvement in infertility symptoms, and a reduction in cardiovascular risks and comorbidities.^{28,29} One study reported that the use of short-term LCDs improved the reproductive and metabolic parameters, with >50% of the women exhibiting menstruation recovery.³⁰ In this study, the serum insulin level decreased in accordance with PCOS. The patients who recovered menstruation tended to have a higher insulin level at the beginning of the study than those who did not recover menstruation. Higher serum insulin might be a predictor of menstruation recovery in response to WR and might indicate further involvement

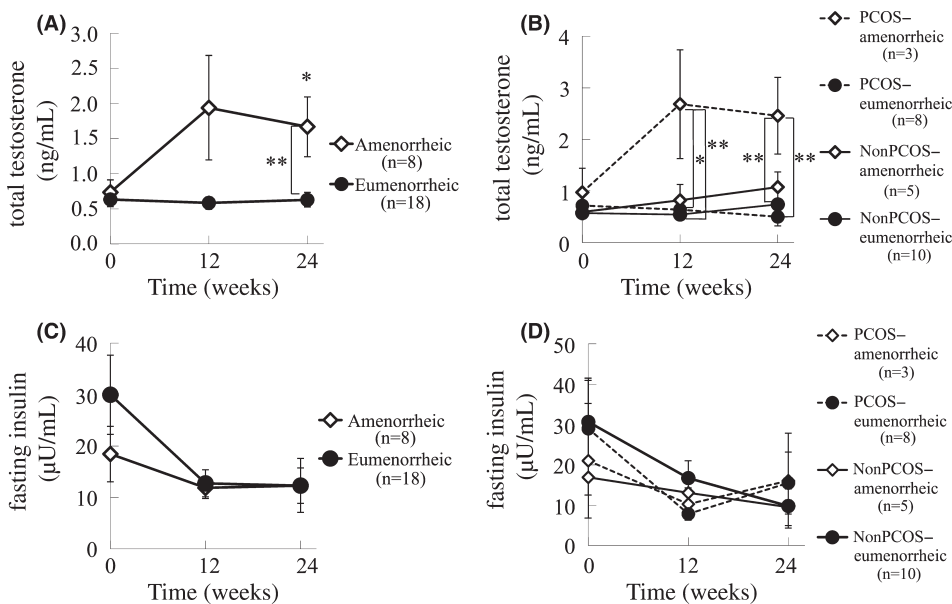


FIGURE 7 (A and B) Serum testosterone and (C and D) fasting immunoreactive insulin level changes. In the 26 patients who were not taking clomiphene, eight were amenorrheic and 18 were eumenorrheic. Considering the background of polycystic ovary syndrome (PCOS), eight were PCOS-eumenorrheic, three were PCOS-amenorrheic, 10 were non-PCOS-eumenorrheic, and five were non-PCOS-amenorrheic. The data are expressed as the mean±SD. * $P<.05$ and ** $P<.01$. Amenorrheic, no recovery of menstruation during the study; eumenorrheic, recovery of menstruation at least once during the study

of hyperinsulinemia for anovulation in this group. Although both the use of a formula diet or a calorie-restricted weight loss regimen can lead to short-term significant reductions in weight, it is important that long-term weight maintenance also be taken into consideration. The results of this study showed that 81.5% of all of the patients exhibited a weight loss of $\geq 5\%$ and 81.0% (17/21 patients) experienced menstruation recovery. As long-term WR also is required to improve reproductive function, the long-term use of MD might be effective for use in patients with reproductive issues. In conclusion, the use of the MD as a WR regimen effectively reduced the body weight of obese patients with ovulatory disorders and assisted them in menstruation recovery.

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DISCLOSURES

Conflict of interest: The authors declare no conflict of interest. **Human and Animal Rights:** All the procedures were followed in accordance with the ethical standards of the responsible committees on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and its later amendments. Informed consent was obtained from all the patients to be included in the study. This article does not contain any study with animal participants that have been performed by any of the authors.

REFERENCES

- Haslam DW, James WP. Obesity. *Lancet*. 2005;366:1197-1209.
- Obesity and overweight. World Health Organization Web site. <http://www.who.int/mediacentre/factsheets/fs311/en/>. Accessed October 5, 2016.
- Metwally M, Li TC, Ledger WL. The impact of obesity on female reproductive function. *Obes Rev*. 2007;8:515-523.
- Van der Steeg JW, Steures O, Eijkemans MJ, et al. Obesity affects spontaneous pregnancy chances in sub-fertile, ovulatory women. *Hum Reprod*. 2008;23:324-328.
- Pasquali R, Gambineri A. Role of changes in dietary habits in polycystic ovary syndrome. *Reprod Biomed Online*. 2004;8:431-439.
- Diamanti-Kandarakis E. Role of obesity and adiposity in polycystic ovary syndrome. *Int J Obes (Lond)*. 2007;31:S8-S13.
- Dickey RP, Taylor SN, Curole DN, Rye PH, Lu PY, Pyrzak R. Relationship of clomiphene dose and patient weight to successful treatment. *Hum Reprod*. 1997;12:449-453.
- Wittermer C, Ohl J, Bailly M, Bettahar-Lebugle K, Nisand I. Does body mass index of infertile women have an impact on IVF procedure and outcome? *J Assist Reprod Genet*. 2000;17:547-552.
- Maheshwari A, Stoffberg L, Bhattacharya S. Effect of overweight and obesity on assisted reproductive technology – systematic review. *Hum Reprod Update*. 2007;13:433-444.
- Clark AM, Thornley B, Tomlinson L, Galletley C, Norman RJ. Weight loss in obese infertile women results in improvement in reproductive outcome for all forms of fertility treatment. *Hum Reprod*. 1998;13:1502-1505.
- Shirai K, Saika A, Oikawa S, et al. The effects of partial use of formula diet on weight reduction and metabolic variables in obese type 2 diabetic patients – multicenter trial. *Obes Res Clin Pract*. 2013;7:e43-e54.
- Leeds AR. Formula food-reducing diets: a new evidence-based addition to the weight management tool box. *Nutr Bull*. 2014;39:238-246.
- Kubota T. Update in polycystic ovary syndrome: new criteria of diagnosis and treatment in Japan. *Reprod Med Biol*. 2013;12:71-77.
- Niki H, Matsuzaki T, Kinouchi R, et al. Improvement in diagnostic performance of the revised total testosterone measuring system in Japanese women with polycystic ovary syndrome. *J Med Invest*. 2014;64:65-71.
- RotterdamESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertil Steril*. 2004;81:19-25.
- Pandey S, Maheshwari A, Bhattacharya S. The impact of female obesity on the outcome of fertility treatment. *J Hum Reprod Sci*. 2010;3:62-67.
- Wood PD, Stefanick ML, Dreon DM, et al. Changes in plasma lipids and lipoproteins in overweight men during weight loss through dieting as compared with exercise. *N Engl J Med*. 1988;319:1173-1179.
- Jung RT. Obesity as a disease. *Br Med Bull*. 1997;53:307-321.
- Stevens VJ, Obarzanek E, Cook NR, et al. Long-term weight loss and changes in blood pressure: results of the Trials of Hypertension Prevention, phase II. *Ann Intern Med*. 2001;134:1-11.
- Hamman RF, Wing RR, Edelstein SL, et al. Effect of weight loss with lifestyle intervention on risk of diabetes. *Diabetes Care*. 2006;29:2102-2107.
- Obesity prevention. Clinical guideline. National Institute for Clinical Excellence Web site. <https://www.nice.org.uk/Guidance/cg43>. Accessed September 8, 2016.
- Vázquez C, Montagna C, Alcaraz F, et al. Meal replacement with a low-calorie diet formula in weight loss maintenance after weight loss induction with diet alone. *Eur J Clin Nutr*. 2009;63:1226-1232.
- Bistrian BR. Clinical use of a protein-sparing modified fast. *JAMA*. 1978;240:2299-2302.
- Carbajo MA, Castro MJ, Kleinfinger S, et al. Effects of a balanced energy and high protein formula diet (Vegestart complet®) vs. low-calorie regular diet in morbid obese patients prior to bariatric surgery (laparoscopic single anastomosis gastric bypass): a prospective, double-blind randomized study. *Nutr Hosp*. 2010;25:939-948.
- Ehrmann DA. Polycystic ovary syndrome. *N Engl J Med*. 2005;352:1223-1236.
- Sakamoto T, Tokunaga Y, Tanaka H, et al. Insulin resistance/hyperinsulinemia and reproductive disorders in infertile women. *Reprod Med Biol*. 2010;9:185-190.
- Gil-Campos M, Cañete RR, Gil A. Adiponectin, the missing link in insulin resistance and obesity. *Clin Nutr*. 2004;23:963-974.
- Clark AM, Ledger W, Galletley C, et al. Weight loss results in significant improvement in pregnancy and ovulation rates in anovulatory obese women. *Hum Reprod*. 1995;10:2705-2712.
- Hollmann M, Runnebaum B, Gerhard I. Effects of weight loss on the hormonal profile in obese, infertile women. *Hum Reprod*. 1996;11:1884-1891.
- Stamets K, Taylor DS, Kunselman A, Demers LM, Pelkman CL, Legro RS. A randomized trial of the effects of two types of short-term hypocaloric diets on weight loss in women with polycystic ovary syndrome. *Fertil Steril*. 2004;81:630-637.

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