ORIGINAL ARTICLE: INFERTILITY

Feasibility of a brief, intensive weight loss intervention to improve reproductive outcomes in obese, subfertile women: a pilot study

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Objective: To evaluate the feasibility of a brief, intensive weight loss intervention (IWL) to improve reproductive outcomes in obese subfertile women.

Design: Pilot study of IWL versus standard-of-care nutrition counseling (SCN).

Setting: Single-site, academic institution.

Patient(s): Obese women (body mass index, 35–45 kg/m^2) with anovulatory subfertility.

Intervention(s): Women were rigorously prescreened to rule out secondary causes of subfertility. Eligible women were randomized to IWL or SCN. IWL consisted of 12 weeks of very-low-energy diet (800 kcal/day) + 4 weeks of a low-calorie conventional food-based diet (CFD) to promote 15% weight loss. SCN consisted of 16 weeks of CFD to promote ≥5% weight loss. Women were transitioned to weight maintenance diets and referred back to reproductive endocrinology for ovulation induction.

Main Outcome Measure(s): Feasibility of recruitment, randomization, intervention implementation, and retention.

Result(s): Thirty-nine women were screened; 25 (64%) were eligible to participate, and 14 of those eligible (56%) agreed to be randomized, seven in each group. One withdrew from the IWL group and two from the SCN group. Percent weight loss was greater in the IWL group than in the SCN group (13% ± 5% vs. 4% ± 4%). Three of six women in the IWL group conceived and delivered term pregnancies. No pregnancies occurred in the SCN group.

Conclusion(s): After rigorous screening, 44% of eligible women completed the study. IWL was associated with greater percentage weight loss and improvements in insulin sensitivity.

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Key Words: Obesity, weight loss, anovulatory, intensive dietary intervention

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I n 2010, 34% of American women 20–39 years of age were obese, including 17% who had a body mass index (BMI) 35.0–39.9 and 8% who had a BMI ≥ 40 kg/m^2 (1). As the prevalence and severity of obesity have increased, so have the number of women who have obesity-related abnormalities in reproductive function including anovulation and infertility (2–7). Obesity is known to contribute to ovulatory dysfunction and to compromise ovarian response to ovulation induction agents such as clomiphene (8). Assisted reproductive technologies are less effective in overweight and obese women (4, 7, 9, 10), and obese women who achieve pregnancy have higher rates of miscarriage and maternal complications associated with pregnancy (3, 11–13). Epigenetic reprogramming of the developing fetus may also have lifelong, adverse health consequences for the offspring of obese

women (1, 14–16). Obesity in the periconceptional period perpetuates an intergenerational cycle of obesity and insulin resistance by its deleterious impact on fat mass, insulin signaling in the liver and muscle, and hepatic fatty acid metabolism (15, 16). These concerns have led to a debate regarding the appropriateness of fertility treatment for obese women (17).

Controversy exists regarding the optimal treatment of obese, subfertile women who have not previously failed ovulation induction. Guidelines from the National Institute for Health and Care Excellence (NICE) recommend that women with a BMI ≥ 30 kg/m^2 be informed about the health benefits of losing weight before becoming pregnant for both themselves and the baby they may conceive; that health professionals advise, encourage, and help women to reduce weight before becoming pregnant using evidence-based behavior change techniques and specific dietary advice; and that health professionals offer weight loss support programs involving diet and physical activity to their obese patients (18). Similarly, in a recent Practice Bulletin on Obesity in Pregnancy, the American College of Obstetricians and Gynecologists recommended that "optimal control of obesity begins before conception" and that motivational interviewing techniques be used to help women move through the stages of dealing with unhealthy behavior to promote weight loss, dietary modifications, and exercise (19). More detailed descriptions of how much weight to lose, how quickly to lose weight, and how to maintain weight loss were, however, lacking. Small studies have demonstrated that weight loss improves some reproductive outcomes (20, 21), but to our knowledge, trials have not been performed to demonstrate the impact of brief, *intensive* weight loss interventions (IWL) on ovulation, conception, or pregnancy outcomes.

There are a number of potential barriers to preconception weight loss. While recognizing the substantial risks associated with obesity in pregnancy, health care providers may be reluctant to recommend weight loss because of their lack of training in obesity management or concerns about the safety of weight loss in the periconception period. Patients are often hesitant to delay fertility treatments to attempt weight loss because of concerns about the limited success and the protracted time necessary to achieve weight loss, the perception that ovulation induction is a faster route to pregnancy, and the belief that the risks of pregnancy associated with obesity are small and manageable (17, 22).

In this pilot study, we assessed the feasibility of recruitment, randomization, intervention implementation, and retention and compared a brief IWL with a brief, standard-of-care nutritional counseling (SCN) intervention in severely obese, subfertile women who had not previously failed ovulation induction.

MATERIALS AND METHODS
Study Design

The objective of this pilot study was to examine whether a brief IWL compared with brief SCN was feasible and whether the approach was acceptable to obese, subfertile women seeking ovulation induction. The study was an open-label, single-site pilot study conducted within the University of Michigan (UM) Health System, Ann Arbor, Michigan. Patients were referred from the UM Center for Reproductive Medicine to the UM Weight Management Program. The study protocol was approved by the Institutional Review Board at the UM Hospital and Health Systems, and all women provided written informed consent. A data safety monitoring board oversaw the study. The trial was registered at Clinicaltrials. gov (NCT01894074). Enrollment began in October 2013 and ended in March 2015. With the exception of the last enrollee, who was followed for 6 months after the intervention, all women were followed for at least 12 months.

Participants

Women were eligible to participate if they were 18–40 years of age, had a BMI 35–45 kg/m^2, had infertility (12 months of unprotected intercourse without conception), had ovulatory dysfunction (amenorrhea, irregular cycles, or progesterone (P) level < 10 ng/mL in the luteal phase), and had evidence of normal uterine anatomy based on prior pregnancy or had at least one patent tube documented by hysterosalpingogram or saline infusion sonogram. In addition, their partner was required to have a semen analysis demonstrating at least 20 million sperm/mL, 50% motility, and normal morphology by Kruger criteria of at least 8%. All women had ovulatory dysfunction as their diagnosis, and for some, the cause of ovulatory dysfunction was polycystic ovarian syndrome (PCOS). Women were diagnosed with PCOS on the basis of having at least two of the three Rotterdam criteria: irregular menstrual cycles, hyperandrogen signs or lab findings, and polycystic ovaries on ultrasound. The medical record was reviewed to confirm these findings.

Women were excluded if they were using donor sperm, had an FSH >10 mIU/mL, had endometriosis American Fertility Society class III or IV; were taking antiobesity drugs or appetite suppressants within the past 2 months; had previous bariatric surgery or gastrointestinal disease; used hormone medications within the past 2 months; had elevated prolactin, type 1 diabetes, uncorrected thyroid disease, or evidence of adrenal disease; or had evidence of conditions that would complicate pregnancy (liver disease, kidney disease, autoimmune disorders such as systemic lupus erythematosus, significant anemia, history of clotting disorder, uncorrected hypertension, heart disease, or cancer). Despite subfertility, all women were required to use an effective method of birth control during the dietary intervention. Recommended methods included oral contraceptive pills and barrier methods.

Age, race, education, employment, cardiovascular risk factors, and comorbidities were assessed at baseline. All women also underwent anthropometric, laboratory, and behavioral testing. These included assessments at baseline and after dietary intervention of height, weight, BMI (calculated), blood pressure, and heart rate; oral glucose tolerance testing with a 75 g oral glucose load and blood samples at 0, 30, 60, 90, and 120 minutes for estimation of insulin sensitivity (homeostatic model assessment or HOMA); and fasting lipid profile. Additionally, we collected information on the number of positive LH kits from baseline and for each month

during the dietary intervention using LH predictor kits supplied to the participant (unless the woman was taking oral contraceptive pills as a method of birth control during the intervention; n = 2).

Depression and health-related quality of life (HRQOL) were assessed at baseline and after the dietary intervention. Depression was assessed with the Inventory of Depressive Symptomatology (Self-Report; IDS-SR). HRQOL was measured with the EuroQol-5D (EQ-5D), a simple and widely used multiattribute utility model that assesses five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression according to three levels: no problems, some problems, and extreme problems. The accompanying visual analog scale (VAS) records the patient's self-reported health on a vertical scale where the endpoints are labeled "best imaginable health state" (score of 100) and "worst imaginable health state" (score of 0). The point selected on the scale provides a quantitative measure of the health outcome as judged by the individual. We have previously reported the relationship between BMI and HRQOL before and after weight loss and found that the degree of improvement in HRQOL was associated with baseline BMI, reduction in BMI, baseline comorbidities, and baseline HRQOL (23).

Eligible, consented subjects were randomized (simple randomization) by the research coordinator using sequentially numbered, opaque, sealed envelopes provided by a biostatistician who was independent of the study team. Participants were randomized 1:1 IWL or SCN.

Intensive Weight Management

Participants randomized to the IWL intervention consumed a very-low-energy diet (VLED) in the form of liquid meal replacements aimed at providing 800 kcal/day (70 g of protein and 100 g of carbohydrate) for a period of up to 12 weeks with a weight loss goal of 15% from baseline weight. Optifast (Nestlé) provided the sachets of 800 meal replacement shakes and soups used in the trial. After the period of VLED, participants were transitioned to a partial meal replacement plan, which they followed for 2 weeks. The partial meal replacement plan provided 1,000–1,200 kcal per day and consisted of three meal replacement products and one 400-kcal conventional food meal with explicitly defined portion sizes. Over the next 2 weeks, women were transitioned to an entirely conventional food–based meal plan with an appropriate calorie intake to promote weight stability. Energy needs were calculated using the Mifflin-St. Jeor equation from the Nutrition Care Manual website. Participants randomized to IWL attended counseling sessions twice per month with a registered dietitian, during which time they discussed any psychosocial stressors, mood, enablers and barriers to weight loss including hunger, cravings, other challenges, and program adherence. They attended appointments with the program physician once per month for medical monitoring at which time the physician provided encouragement, addressed health status and changes, and discussed the biology of weight homeostasis and regulation, some of the physiologic effects due to weight loss, and participant expectations. During the IWL intervention, all participants were encouraged to gradually increase their level and intensity of physical activity to 40 minutes of moderate physical activity per day and to record the number of minutes of physical activity per week on a diet and physical activity tracking sheet provided by the dietitian. They were informed that they could achieve the target number of minutes either in one single bout or divided 10-minute bouts.

Each participant had a urine pregnancy test at baseline and at completion of the study or at any time she reported a menstrual cycle was missed (if the woman had regular menses). Women who did not take oral contraceptive pills were provided ovulation predictor kits and asked if they had a positive test in the interval between their monthly encounters with the physician.

SCN

The SCN group followed a conventional food-based diet for 12 weeks. This treatment reflected usual care provided to obese, subfertile women seen in the UM Center for Reproductive Medicine. Caloric requirements were calculated using the Mifflin-St. Jeor equation to promote weight loss, 0.45–1.8 kg per week. Women met with a registered dietitian for a single 1.5-hour session during which they were provided with counseling and written instructions regarding weight loss calorie requirements and portion sizes using food models. They were instructed to use the "plate" method, that is, a 10-inch plate, three quarters of which was dedicated to nonstarchy vegetables and one quarter to lean protein. They were also provided with weekly meal plans and shopping lists with calculated energy needs. They were advised to track their caloric intake on a daily basis. Suggested caloric intake was usually ~1,200 kcal/day. They were provided general information about energy balance and the neuropsychobiology of weight. Patients were offered three optional monthly follow-up appointments with the registered dietitian. They attended appointments with the program physician at baseline and after 16 weeks. They were provided ovulation predictor kits and asked to report any positive tests.

Postdietary Follow-up

Once participants had completed their dietary intervention and had been transitioned to weight maintenance diets, they were referred back to Center for Reproductive Medicine for ovulation induction or they tried to conceive naturally. A total of three cycles of ovulation induction medication were allowed to each woman who continued to have ovulatory dysfunction, determined by irregular cycles/amenorrhea or midluteal $P<10$ ng/mL. Standard dosing and monitoring included starting clomiphene citrate at 50 mg on cycle days 3–7, use of a urinary LH kit to detect ovulation, and a midluteal P level 8 days after a positive LH surge. If the P level was at least 10 ng/mL, the dose was maintained. If the P level was <10 ng/mL the dose was increased by 50 mg for the subsequent cycle.

Participants' charts were monitored for positive pregnancy tests. The patient's reproductive and obstetrical course was reviewed, and the outcomes recorded for analysis.

Assays

Glucose, insulin, and lipids were measured in the Michigan Diabetes Research Center Chemistry Laboratory. The glucose assay used a hexokinase method and was run on a Randox RX Series Daytona chemistry analyzer (Glucose Assay Product Insert, RX Series GL 3816, Randox Laboratories Limited). The insulin assay was a double-antibody radioimmunoassay using a 125 I-human insulin tracer (Linco Research), a guinea pig anti-porcine insulin first antibody (MDRTC, 68.5% cross-reaction to human proinsulin), and a goat anti-guinea pig gamma globulin (Antibodies Inc.)-PEG second antibody and standardized against the Human Insulin International Reference Preparation (NIBSC). The cholesterol assay was an enzymatic end point method (Cholesterol Assay Product Insert, RX Series CH 3810, Randox Laboratories Limited). The triglyceride assay used a GPO-PAP method, and the high-density lipoprotein (HDL) cholesterol assay used a two-step direct method. All lipid assays were run on a Randox RX Series Daytona chemistry analyzer (Triglyceride Assay Product Insert, RX Series TR 3823; and HDL-Cholesterol Assay Product Insert, RX Series CH 3811, Randox Laboratories Limited). Participants were provided with First Response Ovulation and Pregnancy Test Kits (Church and Dwight).

Statistical Analysis

The target sample size of 32 (16 subjects per treatment group) for this study was based on a desire to obtain preliminary estimates of the treatment effect. We calculated that with this sample size, there was sufficient ($\geq$80%) power to detect an absolute treatment difference of 50% (i.e., 60% of women in the IWL arm and 10% of the women in the standard-of-care arm would achieve clinical pregnancy) or greater with a two-sided type I error of 5%. This sample size also provided sufficient power to detect large effect sizes (1.02 or greater) for continuous outcomes, such as changes in weight or blood pressure between the treatment groups. Descriptive statistics were used to explore the distribution, central tendency (mean, median), and variation (SD, interquartile range, and range) of each measurement for each group. T-tests and Fisher's exact tests were used for discrete outcomes. $P<.05$ was considered statistically significant with no adjustments for multiplicity.

RESULTS

We screened 39 women, of whom 25 were found to be eligible and 14 agreed to participate (see Fig. 1). Our inability to achieve a target sample size of 32 was due to the extremely restrictive eligibility criteria and reluctance of eligible women to delay ovulation induction. Participants had a mean age of 32 ± 4 years and a mean BMI of $41 \pm 3 \text{ kg/m}^2$. After the baseline oral glucose tolerance test, participants were randomly allocated to their treatments. Seven participants were randomized to each group. One participant withdrew from the IWL intervention after 1 week of starting the dietary intervention and two participants withdrew from SCN group before the dietary intervention. Reasons for withdrawal are given in Figure 1. No participant reported any serious adverse events during the dietary interventions.

Baseline demographics and obstetrical history are shown in Table 1. There were no statistically significant differences between completers and dropouts in baseline measures. There were no differences between groups for marital status, level of education, alcohol consumption, tobacco use, or illicit drug use. Five of 11 of subjects had been having unprotected intercourse for 2 years. Three had been having unprotected intercourse for >2 years. Only two reported having unprotected intercourse for <2 years. The median years of subfertility were slightly greater in the SCN group (median, 2.0 years) than in the IWL group (median, 1.2 years), although women in the IWL group tended to be older (median age, 35) compared with those in the SCN group (median age, 29). Five of six in the IWL group had previous pregnancies and three of five in the SCN group had previous pregnancies (Table 1). At baseline, there were no differences in glycemic indexes (fasting glucose, fasting insulin, glucose tolerance, or HOMA-insulin resistance [IR]; Table 1).

At follow-up, both treatment groups lost weight, but the mean weight loss at 12 weeks was significantly greater in the IWL group (Table 2). Participants assigned to the IWL lost 14 ± 6 kg (13% of initial weight), with a range of 4–21 kg, compared with 5 ± 5 kg (4% of initial weight), with a range of 0–10 kg for participants in the standard group ($P<.05$). BMI changed by 5 ± 2 units in the IWL group compared with 2 ± 2 units in the SCN ($P<.02$). In the IWL group, waist circumference decreased by 10 ± 7 cm ($P<.05$) and hip circumference decreased by 11 cm ($P<.01$; data not shown). Five of the six participants in the IWL group moved from very severely obese to severe or moderately obese. Fasting glucose, fasting insulin, and HOMA-IR (for all measures, $P<.05$) improved in the IWL group relative to the SCN group (Table 2).
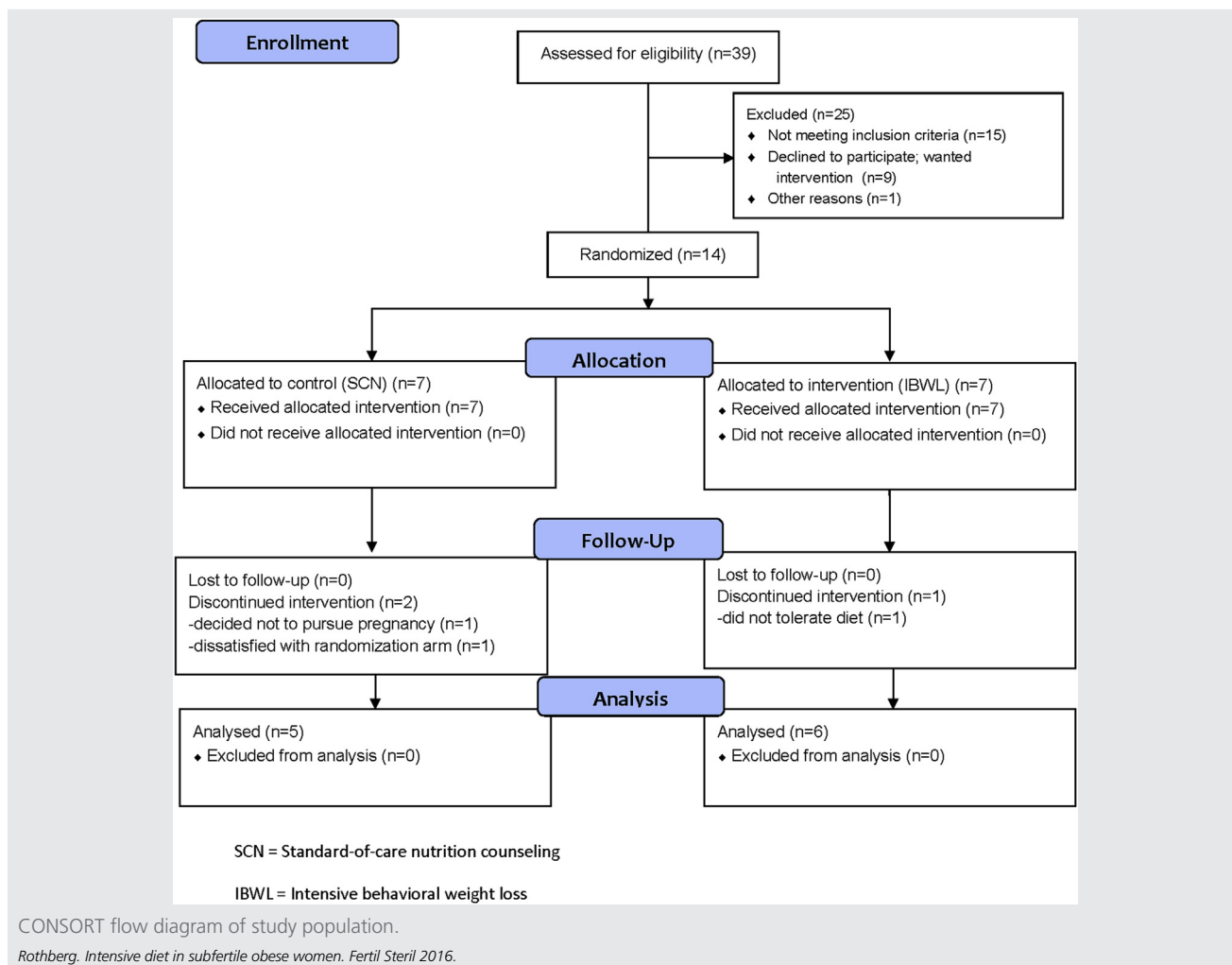
Table 3 shows the number of women reporting positive LH predictor kit tests, the number of medication-induced cycles, pregnancy rates, live births, miscarriages (none), gestational diabetes, hypertensive disorders of pregnancy, and preeclampsia. Women in the IWL group required fewer medication cycles (1 ± 1) compared with those in the SCN group (3 ± 0; $P<.05$).

Women in the IWL group had improvements in measures of HRQOL: mean EQ-5D index increased from 0.87 to 0.92 (0.05 ± 0.08, with a change of +0.03 considered to be clinically significant), whereas there was worsening or no change in the SCN group. HRQOL scores also increased in the IWL group by 13 ± 14, although these were not statistically significant, with worsening in the SCN group with a change of -3 ± 12 (treatment difference of 16 and $P=$NS). There were improvements in depressive symptomatology as measured by the IDS-SR in the IWL group but no improvements in depressive symptomatology for the SCN group.

Weight loss, ovulation, and conception tended to be greater in the IWL group compared with in the SCN group, but neither ovulation nor conception reached statistical significance (three of six women ovulated and conceived in

FIGURE 1

CONSORT flow diagram of study population.

Rothberg. Intensive diet in subfertile obese women. Fertil Steril 2016.

the IWL group vs. zero of five in the SCN group). When these pregnancies were followed, there were three live births in the IWL group. All births were at term.

DISCUSSION

This pilot study demonstrated that a brief IWL in severely obese, subfertile women was feasible and resulted in significant reductions in weight and improvements in metabolic and ovulatory outcomes.

Although most obese women are not infertile, obesity has a negative impact on fecundity (2, 4, 13). Obese women are more likely to have subfertility than women of normal body weight. Obese women experience impaired fecundity both in natural and assisted conception cycles (6, 13, 24–26). Studies have shown an increased risk of anovulatory subfertility in obese women (odds ratio, 2–3) (1) by mechanisms that include hyperandrogenism and PCOS (5, 27). In addition, obesity has an impact on psychosocial factors. Obese people may not have sexual intercourse as frequently as thinner people (28). Obese women are more likely to experience sexual

dysfunction (28, 29). A decrease in coital activity may serve to prolong the period to pregnancy. Reduction in weight is likely to augment self-esteem in issues of intimacy and sexual health. Three large retrospective population-based studies have shown lower pregnancy rates in obese women (2, 6, 25). Obesity is associated with a linear reduction in fecundity from the moderately obese to the very obese (7). Obesity induces a state of insulin resistance and compensatory hyperinsulinemia. Weight loss of 5% or more in obese women results in increased insulin sensitivity, an increase in sex hormone–binding globulin, and trends toward normalization of reproductive hormone profiles favoring restoration of menstrual cyclicity in women with and without PCOS (4, 20–21, 27, 30, 31).

Studies in both animals and humans have shown that prepregnancy weight is associated with adverse reproductive, maternal, gestational, and fetal risks and that weight loss can ameliorate or reverse some of these effects. Indeed, surgical approaches have emerged as an effective albeit complex strategy to promote durable weight loss and remission of type 2 diabetes in severely obese women. A number

TABLE 1

Baseline characteristics and obstetrical history.

Characteristic	IWL completers (n = 6)	IWL withdrawn (n = 1)	SCN completers (n = 5)	SCN withdrawn (n = 2)
Age, y	33 ± 5	28	30 ± 4	33 ± 2
Weight, kg	108 ± 10	96.3	107 ± 14	117 ± 5
BMI, kg/m²	41 ± 4	40	41 ± 4	42 ± 0
Waist circumference, cm	118 ± 8	109	117 ± 9	118 ± 21
Hip circumference, cm	126 ± 7	120	126 ± 7	133 ± 3
Systolic blood pressure, mmHg	122 ± 15	110	122 ± 12	126 ± 1
Diastolic blood pressure, mmHg	63 ± 6	64	65 ± 9	72 ± 11
Lipids				
Total cholesterol, mg/dL	158 ± 25	N/A	177 ± 18	235 ± 35
Triglycerides, mg/dL	172 ± 44	N/A	151 ± 95	157 ± 55
HDL, mg/dL	40 ± 12	N/A	42 ± 5	57 ± 1
LDL, mg/dL	87 ± 15	N/A	105 ± 8	147 ± 23
Fasting glucose (mg/dL)	99 ± 6	87	95 ± 9	85 ± 2
Insulin, µU/mL	267 ± 5	N/A	33 ± 3	N/A
HOMA-IR	7 ± 1	N/A	8 ± 1	N/A
EQ-5D Index	0.87 ± 0.06	1	0.89 ± 0.09	1 ± 0
EQ-5D VAS	70 ± 11	100	66 ± 16	65 ± 7
IDS-SR	16 ± 3	15	18 ± 12	12 ± 12
Obstetrical history				
Participants with previous pregnancy, n	5	0	2	1
Total pregnancies, n	7	0	2	1
Participants with spontaneous abortion (Ab) or ectopic pregnancy, n	1	0	2	0
Total Ab or ectopic pregnancies, n	3 (1 subject)	0	2	0
Participants with previous live births, n	4	0	0	1
Total previous live births, n	7	0	0	1
Median years of infertility	1.6	1	2	4.5
Birth control method during intervention				
Condoms	4	NA	2	NA
Hormonal	2	NA	0	NA
Abstinence	0	NA	3	NA

Note: Mean ± SD reported for continuous outcomes. NA = not applicable; LDL = low-density lipoproteins.

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of studies have found a decreased prevalence of obesity in the offspring of mothers who underwent maternal surgical weight loss (32).

Therefore, we hypothesized that a lifestyle intervention that resulted in short-term weight loss similar to the immediate weight loss observed after bariatric surgery (33, 34), but

TABLE 2

Within-group and between-group changes in anthropometric, laboratory, and quality-of-life outcomes.

Parameter	IWL (n = 6)	P value[a]	SCN (n = 5)	P value[a]	Group difference	P value[b]
Weight, kg	−14 ± 6	.00	−5 ± 5	.09	10	.02
Change in weight, %	13 ± 5	.00	4 ± 4	.07	9	.01
BMI, kg/m²	−5 ± 2	.00	−2 ± 2	.09	4	.02
Systolic blood pressure, mmHg	−2 ± 6	.41	−6 ± 6	.08	4	.34
Diastolic blood pressure, mmHg	−5 ± 4	.05	0 ± 11	1.00	5	.39
Lipids						
Total cholesterol, mg/dL	−7 ± 17	.36	9 ± 19	.38	15	.19
Triglycerides, mg/dL	−27 ± 55	.29	31 ± 62	.33	57	.14
HDL, mg/dL	−1 ± 6	.71	2 ± 5	.34	3	.36
LDL, mg/dL	−4 ± 9	.30	1 ± 11	.91	5	.44
Fasting glucose, mg/dL	−9 ± 6	.01	1 ± 9	.83	10	.05
Insulin, µU/mL	−10 ± 4	.00	4 ± 14	.64	14	.05
HOMA-IR	−3 ± 1	.00	1 ± 4	.55	4	.03
EQ-5D Index	0.05 ± 0.08	.21	−0.01 ± 0.07	.84	0.06	.26
EQ-5D Health Score	13 ± 14	.07	−3 ± 12	.63	16	.07
IDS-SR	−5 ± 4	.02	2 ± 7	.60	7	.07

Note: Mean ± SD reported. LDL = low-density lipoproteins.
[a] P value based on paired *t*-test.
[b] P value based on two-sample *t*-test.

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TABLE 3

Obstetrical outcomes by treatment group.

Variable	IWL (n = 6)	SCN (n = 5)	P value[a,b]
Participants with LH surge (nonhormonal users)	3 (out of 4)	1	.21
Ovulation induction	5/6	3/5	.14
Average no. of cycles of ovulation induction medication	1	3	.02
Confirmed pregnancies	3	0	.18
Gestational diabetes	2	NA	NA
Diet controlled	1		
Metformin monotherapy	1		
Hypertension in pregnancy	0	NA	NA
Preeclampsia	0	NA	NA
Singleton live birth	3	0	1.00

Note: NA = not applicable.
[a] P value based on Fisher's exact test.
[b] P value based on two-sample t-test.

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without the costs, potential complications, and long-term nutritional deficiencies associated with bariatric surgery, might be of benefit.

Zhang et al. have demonstrated that energy restriction in the periconceptual period may result in both benefits and adverse consequences. They studied the metabolic and endocrine effects of dietary interventions during the periconceptual period in an animal model. They defined the periconceptual period as including oocyte maturation, follicular development, conception, and embryo/blastocyst growth up until implantation. They suggested that when maternal nutritional interventions extend beyond implantation to include early placentation, the more appropriate description is "early gestation." Nonpregnant ewes were either overnourished or normally nourished for at least 4 months before artificial insemination. In two subgroups of nonpregnant ewes, the investigators imposed a 70% restriction of normal energy intake for 4 weeks before and 1 week after conception and showed ablation of the adverse effects of high maternal prepregnancy weight on offspring adiposity and glucose tolerance. However, this dietary restriction was also associated with enhanced cortisol response to stress in female lambs at 3–4 months of age. The adrenal gland was also bigger at 4 months in the male and female lambs exposed to the dietary restriction, and there was a decrease in the adrenal expression of the insulin-like growth factor 2 (35).

In our study, we imposed a ~40% energy restriction to reduce weight by ~15% and allowed for a period of weight stability on a 1,200–1,500 kcal/day weight maintenance diet before referring participants back to the reproductive endocrinologist. Although participants' energy restriction was less severe and predated ovulation and conception, uncertainty exists with respect to persistence of some of the metabolic costs seen in the study of an animal model.

This pilot study showed that over one third of obese, subfertile women presenting to an academic center for reproductive medicine had secondary causes of subfertility or conditions other than obesity that would represent relative contraindications to pregnancy. Of eligible women, nearly half (44%) declined to be randomized to brief dietary interventions because of concerns related to the time necessary to achieve weight loss, concerns about the limited success of weight loss, a perception that ovulation induction is a faster route to pregnancy, and a belief that the risks of pregnancy associated with obesity are small and manageable. Once enrolled, in the brief weight loss interventions, over one in seven withdrew for reasons including both disappointment at randomization to standard-of-care therapy and inability to adhere to the IWL.

Like us, Phelan et al. reported difficulties recruiting participants, although unlike us, they were studying a low-intensity behavioral intervention (partially mail based) to prevent excessive weight gain during pregnancy, not before pregnancy. Of the 1,499 potential participants approached, only 401 (26%) were ultimately eligible, available, consented and randomized, and only 320 of them (82%) completed the final 6-month postpartum assessment. The intervention reduced excessive weight gain in normal weight but not in overweight or obese women (36).

Despite a 21% attrition rate in the present study, the IWL appeared to be both effective and safe in the short term. With IWL, substantial weight loss was achieved in a short period of time with significant improvements in diastolic blood pressure, HOMA-IR, and emotional health. None of these improvements were manifest in the SCN group. Mean weight loss among the IWL group was 14 ± 6 kg from baseline. Participants' insulin sensitivity improved in the IWL group as shown by the change in HOMA-IR of -3 ± 1 versus 1 ± 4 ($P < .05$).

Three of six (50%) participants in the IWL group became pregnant within 6 months after completion of the IWL intervention. Two conceived after one cycle of clomiphene, and one conceived without ovulation induction. None of the participants from the SCN group conceived with the opportunity of three cycles of clomiphene.

Our findings suggest that a brief, 16-week, IWL for women with prepregnancy BMI of 35–45 kg/m^2, with a goal or reducing initial body weight by 15% may be more effective than SCN. Our findings differ from those of a previous pilot study conducted in Australia using VLED for 27–41 days immediately before IVF as opposed to ovulation induction. That study found that half of participants reported no fertilization despite significant weight loss. However, four of 10 women withdrew from the study after only 2 weeks and the percentage weight loss was only 6% in the remaining six participants as compared with the 13% weight loss observed in our study. The authors reported that IVF treatment outcomes were not assessed definitively because the study was underpowered given the small sample size, low percentage of weight loss, and the large number of dropouts (37).

Trials of intensive lifestyle management in at-risk populations have shown prevention and control of diabetes and cardiovascular risk factors (38, 39). There are compelling reasons to undergo more intensive weight loss particularly in motivated and more severely obese patients. VLED programs are used when rapid weight loss is necessary because of an obesity-related disease. In other patients with

obesity, it is an alternative to other conservative approaches for treatment of obesity. In type 2 diabetes it may improve long-term glucose metabolism better than conventional weight-reducing diets. Further, VLEDs have no serious harmful effects and can safely be used in patients with various chronic diseases (40, 41). Nackers et al. showed that middle-aged, moderately to severely obese women who lost weight rapidly compared with moderately or slowly were no more susceptible to weight regain than in the other two groups. Indeed, the women who were "fast" losers were more motivated and had better short- and long-term weight loss (42). In our study, we imposed a ∼40% energy restriction to reduce weight and allowed for a period of weight stability on a 1,200–1,500 kcal/day weight maintenance diet before referring participants back to the reproductive endocrinologist. Although participants' energy restriction was less severe and predated ovulation and conception, uncertainty exists as to the potential adverse effects seen in the neonate as seen in the animal model.

Our results show a relatively high rate of ineligibility for IWL, a reluctance to be randomized, and a high initial dropout rate. At the same time, individuals undertaking IWL demonstrated greater absolute weight loss and percentage change from baseline weight, positive changes in metabolic parameters and HRQOL, and a short interval to ovulation and conception. Limitations to our study include its small sample size, baseline imbalance in obstetrical histories, lack of a direct measure of resting metabolic rate or use of more sophisticated tool for calculating energy requirements, and lack of quantitative assessment of dietary intake and physical activity.

Given the small sample size, there is uncertainty around the point estimates of the percentage of pregnancies in the IWL and SCN groups. We reviewed a number of hypothetical pregnancy estimates supported by the pilot study. Using a conservative estimate of the IWL effect, the 80% lower confidence bound of 20% and 0% for IWL and SCN, respectively, a future similar study would require 63 subjects who were eligible and willing to be randomized. However, if we use the upper confidence bound of 80% and 37% for IWL and SCN, respectively, we would require only 34 subjects who were eligible and willing to be randomized (similar to our projected sample recruitment; total sample size to achieve at least 80% power with two-sided type I error of 5% (East 6, Cytel Corporation; two-sample test of proportions).

Finally, a strength of our study was that non-obesity-related causes of infertility were ruled out. Based on the promising results of this pilot study, we believe that the brief intervention that we tested will be acceptable to women concerned about delaying fertility therapy, especially in light of the increased risk of pregnancy-related complications that may be improved and the emerging evidence of adverse epigenetic effects of obesity on offspring.

A larger, multisite trial comparing these interventions that includes following women through delivery, obtaining hormone measures, and quantifiable dietary assessment in parallel with high throughput metabolite profiling may help to identify women who will respond to aggressive weight loss with improved conception and pregnancy and provide greater understanding of the interactions among diet, metabolites, and clinical outcomes to provide greater precision and tailoring to our patients.

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