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.
Trial Registration: ClinicalTrials.gov NCT01894074. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)
Key Words: Obesity, weight loss, anovulatory, intensive dietary intervention

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In 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

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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 $\geq$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 (DSMB) 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 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 PRL, 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, uncontrolled 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