Short title: Lifestyle intervention and IVF

Weight decrease improves live birth rates in obese women undergoing IVF: a pilot study.

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Abstract

Obese women have lower pregnancy rates than normal-weight women undergoing assisted reproductive treatments. We conducted a pilot study **t**o evaluate whether a 12-week diet and exercise intervention prior to an in vitro fertilization (IVF) cycle would influence pregnancy rates in obese women. Forty-one patients were enrolled in this study. They were randomly allocated to two groups: an intervention group (n = 21) who underwent an individually tailored diet and physical exercise program supervised by a dietician and a control group (n = 20) who started IVF with no previous intervention. The primary outcome was clinical pregnancy rate after a single-cycle treatment. Mean weight loss in the study group after the intervention was 5.4 kg (range, 1.1–14.6 kg). The study and control groups had similar results for total follicle stimulating hormone dose, number of oocytes and embryos obtained, and number and quality of embryos transferred. There was a trend towards a higher clinical pregnancy rate after the transfer of fresh embryos (66.7% vs. 41.2%, P = 0.181). The intervention group had a significantly higher cumulative live birth rate (61.9% vs. 30%, P = 0.045)(odds ratio in the intervention group, 3.8; 95% confidence interval, 1.03 to 13.9). The data suggest that the weight loss achieved through a combination of diet and exercise resulted in a significantly increased live birth rate.

KEY WORDS: In vitro fertilization, obesity, diet, physical exercise

Introduction

The prevalence of obesity has increased six fold in the last 50 years, creating a global pandemic affecting both industrialized and developing countries (Mitchell and Shaw, 2015). The situation in Spain is also of concern, as according to the World Health Organization, 56.6 % of women over 20 years of age are overweight and, of these, 26.7 % are obese (WHO, 2013).

There is clear evidence that obesity has negative effects on both general and reproductive health. Natural fertility is reduced in obese couples (ASRM, 2015). In women, hyperandrogenic anovulation, (which is typically associated with central obesity, insulin resistance, and hyperinsulinism) and alterations affecting obesity-related hormones (e.g., adipokines, ghrelin, and endorphins) can affect oocyte quality, fertilization, and embryo implantation and also reduce fertility in women with a normal menstrual cycle (Talmor & Dunphy, 2015; Grodstein et al., 1994; Kuchenbecker et al., 2010; Gosman et al., 2006).

The size of the impact of obesity on IVF outcomes is not known due to the heterogeneity of the studies undertaken in this area, a lack of standardized criteria, and the retrospective nature of most studies (Maheshawari et al., 2007; Metwally et al., 2008; Legge et al., 2014). Obesity has been reported to be associated with an increase in gonadotropin requirements, longer treatments, higher rates of canceled cycles due to inadequate response, lower numbers of total and mature eggs, poor rates of fertilization, and consequently fewer top quality embryos. Obesity has also been linked to endometrial abnormalities associated with implantation failure (Setti et al., 2012; Robker, 2008; Mioni et al., 2004; Rittenberg et al., 2011).

Few studies, however, have analyzed the impact of a weight loss intervention including diet and exercise in obese women wishing to become pregnant (Clark et al., 1995, 1998; Galletly et al., 1996; Awartani et al., 2012; Tsagareli et al., 2006). Furthermore, the findings of these studies have been inconsistent, probably due to methodological shortcomings (Sim et al., 2014a). Three randomized clinical trials have been conducted and only one of them (Sim et al., 2014b) observed differences in clinical pregnancy or live birth rates following different assisted reproductive technique (ART) treatments (Moran et al., 2011, Mutsaerts et al., 2016). The aim of this study was to evaluate the effect of a standardized weight loss intervention on pregnancy rates after a single IVF cycle in obese women with an indication for IVF.

Materials and methods

Patients

A prospective pilot randomized controlled trial was performed between November 2013 and December 2015 at the Fertility Unit of Hospital de la Santa Creu i Sant Pau-Fundació Puigvert in Barcelona, Spain. Eligible patients were women with a BMI of 30–40 kg/m^2 presenting for their first IVF cycle. Other inclusion criteria were an age of 18–37 years, primary infertility with an indication for IVF/intracytoplasmic sperm injection (ICSI), and absence of hormonal treatment during the previous 3 months. Exclusion criteria were medical contraindications for IVF/ICSI or specific dietary interventions, diminished ovarian reserve, defined as an antral follicle count of ≤7 or baseline follicle stimulating hormone (FSH) levels ≥10 IU/L, undiagnosed irregular uterine bleeding, and known allergy to gonadotropins.

The study was approved by the ethics committee at our hospital, and written informed consent was obtained from all participants, none of whom was entitled to any financial reimbursement. The study was supported by a grant from FIS-PI11/02816 and was registered at the Clinical Trials.gov of the US National Institute of Health (identifier NCT01952795).

Experimental design and interventions

The participants were randomized into two groups: a study group that underwent a 12-week diet and exercise program before starting an IVF/ICSI cycle and a control group who started with no previous interventions. A physician (A.P.) checked the patients for eligibility and these were then randomly allocated to the study or control group using a computer-generated list. The team of fertility specialists was blinded to the group assignment.

The diet was tailored to each individual under the close supervision of the study dietician. The goal was to reduce total daily calorie intake by at least 500–800 kcal compared with pre-intervention levels, while maintaining a well-balanced diet consisting of the intake of 50% of total calories in the form of carbohydrates, <10% in the form of saturated fat, and 20% in the form of monounsaturated or polyunsaturated fats (or where applicable, 25% in monounsaturated fats). The patients were also advised to consume <300 mg of cholesterol a day, approximately 1 g of protein per kilogram of ideal weight a day, and at least 15 g of fiber per 1000 kcal. A strict schedule of three main meals and two snacks was introduced. Dietary intake was assessed by self-reporting every 15 days and if no weight

loss was observed at the follow-up visit, the diet was re-evaluated by the dietician and adjusted accordingly.

The exercise program was designed to increase physical activity to a moderate level and was tailored to each individual's condition. It consisted of walking on a treadmill or pedaling a stationary bicycle for 60 minutes three times a week for the duration of the intervention (12 weeks). Trained staff monitored all the exercise sessions.

IVF/ICSI cycles

Controlled ovarian hyperstimulation was performed using a short protocol with GnRH antagonist (GnRH-ant; Cetrotide, Merck Serono) and recombinant FSH (Gonal-F filled by mass; Merck Serono). Recombinant FSH was started on the 2nd-3rd day of the cycle with 225 UI/d. When the antral follicular count in one of the two ovaries was>13, the initial dose was 150 UI/d. On stimulation day 6, a GnRH antagonist was initiated at a daily dose of 0.25 mg and continued throughout the stimulation period. Follicular development was assessed by transvaginal ultrasonography. When three or more follicles with a diameter ≥18 mm were observed, final follicular maturation was triggered with 250 mg recombinant hCG (choriogonadotropin alfa; Ovidrel/Ovitrelle, EMD Serono/Merck Serono). Oocyte retrieval by transvaginal ultrasonographic guidance was performed approximately 36 hours after hCG administration. All patients received vaginal micronized progesterone (Utrogestan, SEID) 200 mg every 8 hours, starting on the afternoon of oocyte pickup and continuing up to the day of b-hCG measurement; this treatment was maintained throughout the first trimester if the b-hCG was positive. All adequate oocytes were inseminated by ICSI. The embryos were scored according to the Spanish Association of Reproduction Biology Studies (ASEBIR) scoring system. The embryo transfer was performed with a Labotect transfer catheter (Labor-Tecknik-Göttingen, Rosdorf) 3 days after oocyte recovery under ultrasound guidance. Inpatients with a risk of severe ovarian hyperstimulation (OHSS), the embryos were vitrified and transferred in a subsequent substituted cycle (Cobo et al., 2010). Patients who did not become pregnant after a fresh transfer underwent replacement cycles with the available cryopreserved embryos until pregnancy was achieved.

Measurements

The primary outcome was pregnancy rate, defined as number of clinical pregnancies (ultrasound visualization of a gestational sac), divided by the total number of cycles performed or embryo transfers.

Secondary outcomes were changes in anthropometric variables in the study group (weight, BMI, waist circumference, fat mass) and other fertility treatment measures, namely duration of stimulation, total FSH dose, number of follicles, number of oocytes, fertilization rate, number and quality of embryos, miscarriage rate, live birth rate, OHSS, and adherence to dietary and exercise intervention. Body weight and height were measured in light clothing without shoes. BMI was calculated as weight in kilograms divided by square of height in meters. Waist circumference was measured at the narrowest point between the costal margin and the iliac crest.

Body composition was analyzed using a single-frequency impedance analyzer (Body Composition Analyzer, model BC-420; Tanita). This machine provides estimated values for fat mass. Fat mass is calculated by subtracting fat-free mass from total body water. The other variables were calculated using validated mathematical formulae as already published (García Caballero et al., 2014). We also used the abdominal bioelectrical impedance analysis feature on the TanitaViscan Visceral and Trunk Fat Analyser AB140 to estimate the percentage of visceral fat (Vfat) and trunk fat (Tfat)(Zamrazilová et al., 2010).

Fasting blood samples were collected for the analysis of glucose, glycated hemoglobin, insulin, total cholesterol, high-density and low-density lipoprotein cholesterol, triglycerides, luteinizing hormone, FSH, prolactin, sex hormone binding globulin, testosterone, E_2, progesterone, and reproductive hormones. Blood and serum analysis was performed in the laboratory at our hospital.

Statistical analysis

Primary analyses were performed on an intention-to-treat basis. Data are presented as mean ± SD unless otherwise stated. The significance of differences between groups was determined by an unpaired *t* test for independent variables, analysis of variance (ANOVA) for repeated measures, or the Mann–Whitney *U* test. Normal distribution was assessed using the Kolmogorov–Smirnov test. The differences in pregnancy and live birth rates between the groups were also expressed as odds ratios and 95% confidence intervals. Additionally we built a logistic regression model corrected for age. Correlation coefficients between different variables were obtained using Pearson's and Spearman's methods. Differences and correlations were considered statistically significant at $P < .05$. Differences in frequencies were tested by the χ^2 test. Statistical analyses were performed using SPSS software (version 22.0; SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

Figure 1 shows the study flow chart and patient outcomes. Sixty-five patients were identified on the waiting list of our public hospital fertility unit and were approached by the research leader regarding participation in the study and screened for eligibility. Sixteen failed the screening and eight chose not to participate. Of the 41 participants who entered the trial, 21 were assigned to the study group and 20 to the control group. None of the participants were withdrawn or dropped out from the trial. No serious adverse events were reported.

The baseline characteristics of the women in the two groups did not show statistically significant differences in age, BMI, body composition, menstrual history, infertility factors, duration of infertility, antral follicle count, or prevalence of polycystic ovarian morphology (PCOM) (Table 1).

Effects of changes in lifestyle

Participants assigned to the study group lost a mean of 5.39 kg (range 1.1–14.6 kg), with mean ± SEM weight dropping from 91.7 ± 11.8 to 85.3 ± 11.1 kg ($P < 0.001$); this represented an average weight loss of 6.97% (range 1–15%)(Figure 2). Weight loss following the intervention was <5 kg in 12 (57.1%) of the 21 women, 5–10 kg in four women (19 %), and >10 kg in five women(23.8%)(Figure1). In this last group, there was a significant reduction in waist circumference (from 117.1 ± 10.4 to 110.1 ± 10.8 cm; $P = 0.046$), fat mass (from 39.9 ± 8.5 to 34.5 ± 8.1 kg; $P < 0.001$), Tfat (from 49.1 ± 3.5 to 45.4 ± 5.3%; $P = 0.01$), and Vfat (from 14.1 ± 3.1 to 11.68 ± 2.7; $P = 0.007$). At the end of the intervention, waist circumference ($P = 0.032$), Tfat ($P = 0.004$), and Vfat ($P = 0.002$) were significantly lower in the study group. No differences were observed for BMI or fat mass. Six of 11 anovulatory women resumed regular menstrual cycles during the intervention.

IVF outcomes

Cycle outcomes are summarized in Table 2. The starting dose of rFSH was 150 IU/d in eight women (four in each group); in the remaining cases it was 225 IU/d. Eleven women required a dose adjustment during stimulation. There were no significant differences between the study and control group for total rFSH dose (2.407 ± 513 vs. 2.503 ± 875 IU; $P = 0.669$) or for duration of stimulation. Treatment was cancelled in one woman in each group due to poor response. Similar findings were observed for women in both groups for endometrial thickness, number of follicles, number of total and metaphase II oocytes retrieved, mean number of rapidly progressing spermatozoa, fertilization rate, rate of high-quality embryos, number of embryos transferred, number of cycles cancelled, and E_2 levels on the day of the last ultrasound. Embryo transfer was not performed in four cases (two in each

group). Nonviable embryos were obtained in three of the cases and in the fourth, the embryos were cryopreserved to avoid the risk of OHSS. Although the differences did not reach statistical significance, we observed a trend towards a higher implantation rate (45.5 vs. 34.4%; *P*= 0.534) and a higher clinical pregnancy rate per patient (57.1% vs. 35%; *P* = 0.215) and per transfer cycle (66.7% vs. 41.2%; *P*= 0.181), as well as a non-significant higher live birth rate per attempt and transfer cycle in the study group. We also observed a significantly higher cumulative live birth rate per cycle in the study group (61.1% vs. 30%; *P* = 0.045)(Table 3).

Discussion

Our study shows that a structured program combining a low-calorie diet and physical exercise in obese women prior to a single IVF cycle leads to significant weight loss and higher cumulative live birth rates.

Three prospective randomized controlled studies have addressed this issue. Two of them had a similar design and their findings show the same trend as ours (Sim et al., 2014b; Moran et al., 2011). However, our study is the first to find statistically significant differences in cumulative pregnancy rates after an IVF cycle**.** Possible reasons for the lack of significant differences in the studies by Sim et al. and Moran et al. are the fact that not all women included in the weight loss program finally underwent ART, and the fact that the final weight differences between the groups may not have been sufficiently large to be reflected in reproductive outcomes. One clear difference between our study and these two randomized controlled trials is that our control group did not have to wait for 12 weeks to undergo IVF following inclusion in the study. This could explain why the mean difference in weight loss between the study and control groups in our study was 6.9% compared with the lower rates of 3.3% and 5% in the other two studies. Other possible reasons for the discrepancy in results could be differences in dietary interventions or ethnic profiles.

A third study published recently with a very large sample (n= 564) evaluated the effect of a similar intervention on rates of vaginal birth of a singleton at term within 24 months of randomization (Mutsaerts et al., 2016). The study group had a 6-month intervention preceding the appropriate infertility treatment and the couples received different interventions depending on the infertility diagnosis. The intervention did not result in higher rates of the main outcome. This study is not comparable to ours for several reasons. It was a multicenter study with 23 participating centers, the sample was composed mostly of anovulatory patients, and although the intervention lasted for six months the intensity of monitoring was much lower than in our study and the weight loss was also lower. Finally, the infertility treatments were tailored to the patients' problems and some policies

differed from center to center. Nonetheless, the frequency of spontaneous conceptions and use of infertility treatments to reach the same outcome were significantly lower in the intervention group, providing evidence of a positive effect of the intervention.

The current study has several limitations. The size of the sample was probably too small to detect significant differences in variables such as implantation rate, clinical pregnancy rate, and live birth rate. Very few prospective studies have evaluated the impact of obesity on fertility is very small, preventing the calculation of sample size based on objective data to estimate the influence of an expected weight loss of 5% or higher on reproductive outcomes. There is no explanation for the high interindividual variability in the effectiveness of the intervention on weight loss. The variations suggest that even though all the patients were closely supervised, compliance was probably suboptimal, as almost half of the women experienced a weight loss of <5%, which is also a limiting factor in terms of assessing the potential benefits of the intervention. Due to the high rate of male factor infertility in both groups, all cases were treated with ICSI. We know that this is not an optimal approach but it was included in the design to minimize heterogeneity in treatments. In addition, although the study was blinded to the members of the team, we cannot rule out that some information might have leaked out during the process. The final limitation is related to possible changes in partner weight. Although there were no significant differences in initial BMI values between the partners of women in the study and control groups, we did not monitor weight changes during the intervention period or analyze how these might have influenced sperm quality. We cannot therefore rule out a possible influence on reproductive outcomes.

We believe that the differences observed in reproductive outcomes between the study and control groups in our study are directly attributable to the diet and exercise program. Women from the study group who became pregnant performed better in terms of anthropometric changes resulting from the weight loss than those who did not, although the differences were not statistically significant (data not shown). One particularly interesting observation was that the weight loss was virtually entirely due to mobilization of abdominal fat, as evidenced by the reductions observed in waist circumference and impedance analyzer results. Clark et al. (1998) suggested that reductions in BMI values of just 5% to 10%, without necessarily reaching normal weight, have positive effects on reproduction. This little weight reduction is not probably beneficial in very obese women and more benefits could be obtained from a higher weight loss. However, greater or more abrupt weight reduction would imply a stricter diet and exercise program or a longer intervention period. Both situations have been shown to

increase the percentage of dropouts considerably, with women returning to their starting weight in a short period of time. So balance is crucial.

Our findings support the original theory that a decrease in BMI results in a reduction in adipocytes in visceral adipose tissue, as these are associated with greater insulin resistance (Barber et al., 2006; Kiddy et al., 1990). There is evidence that insulin resistance and secondary hyperinsulinism are either directly responsible for or are cofactors in many obesity-linked reproductive disorders (Brewer & Balen, 2010).

Based on our data, we cannot pinpoint which changes were responsible for the association observed between weight loss and better reproductive outcomes in the study group, as the two groups showed non significant differences for clinical variables (response to stimulation, number of total and mature oocytes, fertilization rates, and high-quality embryos obtained and transferred) and for biochemical variables (e.g., E_2, progesterone, insulin levels). It has been shown that embryos from nonobese donors are associated with poorer outcomes in obese recipients than in normoweight recipients (Bellver et al., 2011, 2013). The limiting factor might therefore be the endometrium, a theory that finds support in our results, as we observed a tendency towards a lower implantation rate in the control group.

Strengths of our study are the homogeneity in the treatment and the close supervision of the intervention leading to high adherence and weight loss. All couples received the same IVF/ICSI treatment and the intervention was tailored using the same criteria. Success in weight loss programs would therefore appear to be linked to close, personalized follow-up and a multidisciplinary approach including psychological support and reeducation of eating habits, although group therapy has also proven effective (Wadden et al., 2000).

Our study presents the evidence that a 12-week diet and exercise program can lead to a significant reduction in total weight and visceral adiposity and to more favorable IVF outcomes in obese women. This finding encourages us to systematically propose a personalized weight loss program based on diet and exercise before an IVF cycle for all overweight and obese women and to repeat the study with a larger sample to increase our understanding of this growing problem.

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Figures

Figure 1. Study flow diagram and patient outcomes.

Figure 2. Total weight loss in kg (solid column) and % of weight loss relative to the total weight (white column) achieved at 12 weeks following a dietary and exercise program in 21 obese women.

Table 1. Baseline clinical characteristics and anthropometric data in women randomized to the dietary and exercise intervention group or the control group

Variable	Intervention group (n=21)	Control group (n=20)
Age (years)	32±3.2	32.9±3.9
Weight (kg)	91.7±11.8	89.2±11.5
Height (cm)	163.3 ± 7.3	162.2 ± 6.5
BMI (kg/m^2)	34.6 ± 3.0	34.0 ± 4.1
Waist circumference (cm)	117.1 ± 10.4	117.5 ± 10.0
Fat mass (kg)	43.1 ± 4.2	42.0 ± 4.0
Fat mass (%)	39.9 ± 8.5	37.8 ± 7.8
Tfat (%)	49.1 ± 5.1	50.2 ± 4.7
Vfat (%)	14.1 ± 3.1	14.8 ± 3.2
Partner's BMI (kg/m^2)	28.5 ± 4.3	29.6 ± 4.9
Menstrual history (No. [%])		
Regular	10 (47.6%)	10 (50%)
Irregular	11 (52.4%)	6 (30%)
Amenorrhea	0	4 (20%)
Infertility factors (No. [%])*		
Unexplained	1 (5%)	4(20%)
Male factor	16(76.2%)	10 (50%)
Tubal	5 (23.8%)	5 (25%)
Ovulatory	11(52.4%)	10(50%)
Antral follicle count	17.6 ± 6.6	17.3 ± 6.5
PCO morphology	9 (42.8%)	8 (40%)
Mean infertility duration (months)	67.7 ± 37.6	52.5 ± 30

Note: Values are means ± SD, unless otherwise stated. There were no statistically significant differences between the two groups with respect to patient characteristics (Mann–Whitney *U*- or χ^2test). BMI = body mass index; IUI = intrauterine insemination; PCO =polycystic ovary; Tfat = trunk fat; Vfat = visceral fat. * Some couples had more than one infertility factor

Table 2. Outcome of in vitro fertilization cycle in intervention and control groups

Variable	Intervention group (n=21)	Control group (n=20)	P-value
Total dose of FSH used (IU)	2,407 ± 513	2,503 ± 875	NS
Duration of stimulation (days)	11.3 ± 2.23	11.2 ± 2.0	NS
Follicles 12-17 mm on hCG	9.9 ± 5.2	10.6 ± 5.3	NS
Follicles ≥18 mm on hCG	5.5 ± 3.3	6.5 ± 4.2	NS
E_2 on last US (pmol/L)	1,483 ± 935	1,562 ± 961	NS
Endometrial thickness on last US (mm)	9.9 ± 1.8	10.2 ± 2.0	NS
No. of oocyte-cumulus complexes	10.1 ± 7.4	10.7 ± 4.3	NS
No. of mature (MII) oocytes	7.8 ± 5.7	7.8 ± 3.6	NS
Mean N. of rapidly progressing spermatozoa (millions)	34.9+/-21	35.8 +/- 20	NS
Fertility rate (%)	62.2	57.7	NS
No. of embryos	4.8 ± 2.8	4.6 ± 2.5	NS
No. of good quality embryos (A and B)	2 ± 2.1	1.8 ± 1.4	NS
No. of transferred embryos	1.9 ± 0.3	1.9 ± 0.3	NS
% of cancelled cycles due to poor ovarian response	4.8	5	NS
% of cancelled ETs	10	10.5	NS
Implantation rate (%)	45.5 (15/33)	34.4 (11/32)	NS
No. of cyropreserved embryos	1.6 ± 2.6	1.1 ± 1.3	NS

Note: Values are means ± SD, unless otherwise stated. ET = embryo transfer; FSH = follicle-stimulating hormone; US = ultrasound.

Table 3. Pregnancy outcome in both groups

Variable	Intervention group (n=21)	Control group (n=20)	P-value	Odds ratio (95% CI)
Pregnancy rate per cycle attempt (%)	57.1 (12/21)	35 (7/20)	NS	2.47 (0.7-8.7)
Pregnancy rate per ET (%)	66.7 (12/18)	41.2 (7/17)	NS	2.85 (0.7-11.3)
Live birth rate per cycle initial cyle (%)	52.4 (11/21)	30 (6/20)	NS	2.56 (0.71-9.2)
Live birth rate per ET (%)	61.1 (11/18)	35.3 (6/17)	NS	2.9 (0.72-11.4)
Cumulative live birth rate per cycle initial cycle (%)	61.9 (13/21)	30 (6/20)	0.045	3.8 (1.03-13.9)
Multiple pregnancy rate (%)	14.3 (2/14)	16.6 (1/6)	NS	
Miscarriage rate (%)	7.1	14.3	NS	

Note: Values are means ± SD, unless otherwise stated. ET = embryo transfer.