Article

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

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KEY MESSAGE

A diet and exercise programme can lead to a significant reduction in total weight and visceral adiposity and to more favourable IVF outcomes in obese women.

A B S T R A C T

Obese women have lower pregnancy rates than normal-weight women undergoing assisted reproductive treatment. We conducted a pilot study to evaluate whether a 12-week diet and exercise intervention before an 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 individualized diet and physical exercise programme 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 treatment cycle. 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 total FSH consumption, number of oocytes and embryos obtained, and number and quality of embryos transferred. There was a non-significant trend towards a higher clinical pregnancy rate after fresh embryo transfer (66.7% versus 41.2%). The intervention group had a significantly higher cumulative live birth rate (61.9% versus 30%, P = 0.045) (odds ratio for intervention group, 3.8; 95% confidence interval, 1.03 to 13.9) The data suggest that weight loss resulted in a significantly increased cumulative live birth rate.

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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 (Practice Committee of the American Society for Reproductive Medicine, 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 (Gosman et al., 2006; Grodstein et al., 1994; Kuchenbecker et al., 2010; Talmor and Dunphy, 2015).

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 (Legge et al., 2014; Maheshwari et al., 2007; Metwally et al., 2008). Obesity has been reported to be associated with an increase in gonadotrophin requirements, longer treatments, higher rates of cancelled 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 (Mioni et al., 2004; Rittenberg et al., 2011; Robker, 2008; Setti et al., 2012).

Few studies, however, have analysed the impact of a weight loss intervention including diet and exercise in obese women wishing to become pregnant (Awartani et al., 2012; Clark et al., 1995, 1998; Galletly et al., 1996; 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 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 study 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 body mass index (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 FSH levels ≥10 IU/l), undiagnosed irregular uterine bleeding, and known allergy to gonadotrophins.

The study was approved by the ethics committee at our hospital on 26 April 2011 (reference number 11/028/1193), 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 ClinicalTrials.gov of the US National Institutes 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 programme 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 kg of ideal weight a day, and at least 15 g of fibre 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 programme 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 pedalling a stationary bicycle for 60 min three times a week for the duration of the intervention (12 weeks). Trained staff monitored all the exercise sessions.

Controlled ovarian hyperstimulation was performed using a short protocol with gonadotrophin-releasing hormone antagonist (GnRH-ant) (Cetrotide; Merck Serono) and recombinant FSH (Gonal-F filled by mass; Merck Serono). Recombinant FSH was started on the second to third day of the cycle with 225 IU/day. When the antral follicle count in one of the two ovaries was >13, the initial dose was 150 IU/day. On stimulation day 6, a GnRH-ant was initiated at a daily dose of 0.25 mg and continued throughout the stimulation period. Follicle 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 human chorionic gonadotrophin (HCG) (choriogonadotrophin alfa; Ovidrel/Ovitrelle, EMD Serono/Merck Serono). Oocyte retrieval by transvaginal ultrasonographic guidance was performed approximately 36 h after HCG administration. All patients received vaginal micronized progesterone (Utrogestan, SEID) 200 mg every 8 h, 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. In patients with a risk of severe ovarian hyperstimulation syndrome (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 transfer cycles with the available cryopreserved embryos.

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 metres. Waist circumference was measured at the narrowest point between the costal margin and the iliac crest.

Body composition was analysed using a single-frequency impedance analyser (Body Composition Analyser, 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 haemoglobin, insulin, total cholesterol, high-density and low-density lipoprotein cholesterol, triglycerides, LH, FSH, prolactin, sex hormone binding globulin, testosterone, oestradiol, 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. We also 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 $P < 0.05$. Differences in frequencies were tested by the chi-squared test. Statistical analyses were performed using SPSS software (version 22.0; IBM Corp., 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**).

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

Variable	Intervention group (*n* = 21)	Control group (*n* = 20)
Age (years)	32.0 ± 3.2	32.9 ± 3.9
Weight (kg)	91.7 ± 11.8	89.2 ± 1.5
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
Trunk fat (%)	49.1 ± 5.1	50.2 ± 4.7
Visceral fat (%)	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. [%])[a]		
Unexplained	1 (4.8)	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 (42.9)	8 (40)
Mean infertility duration (months)	67.7 ± 37.6	52.5 ± 30.0

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 chi-squared test).
BMI = body mass index; PCO = polycystic ovary.
[a] Some couples had more than one infertility factor.

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%). 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

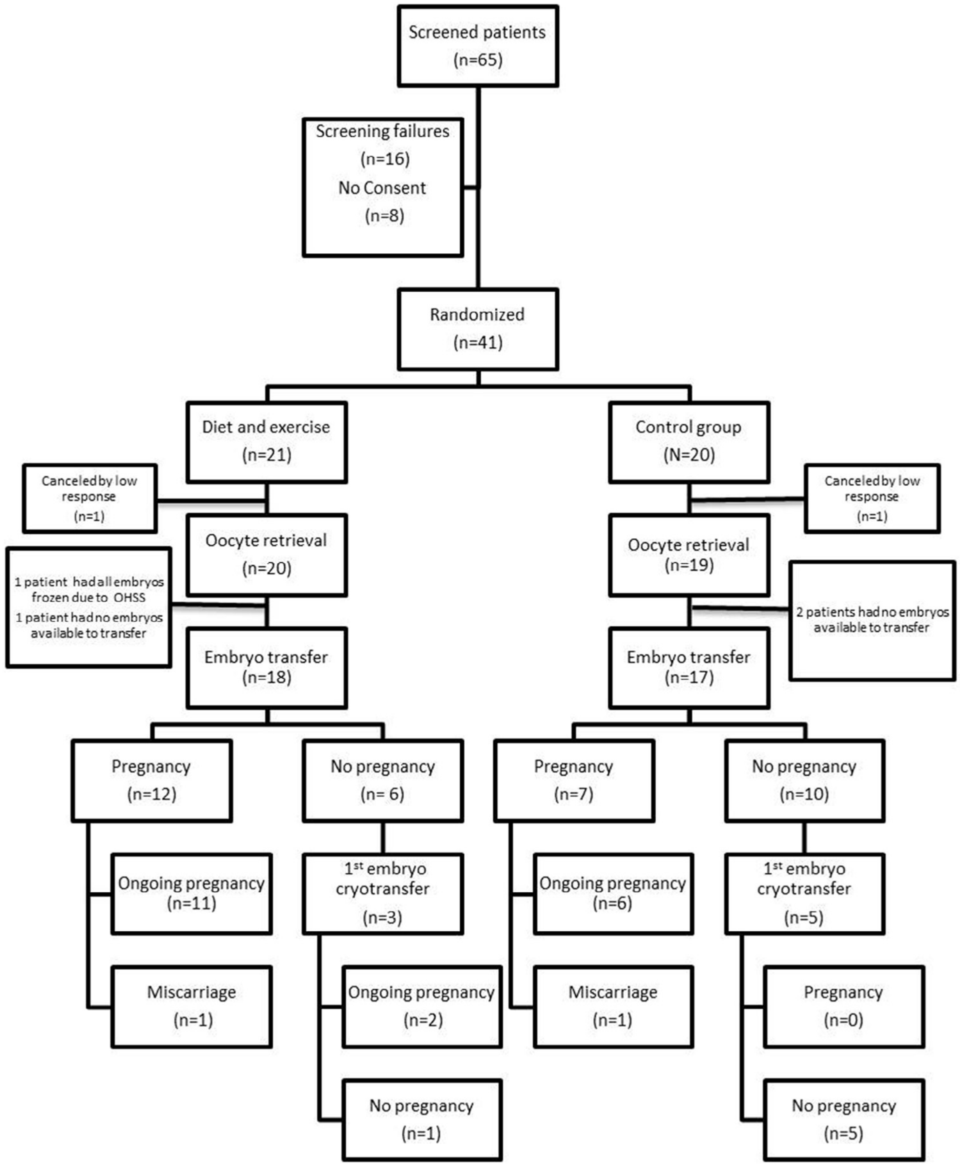

Figure 1 – Study flow diagram and patient outcomes.

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/day in eight women (four in each group); in the remaining cases, it was 225 IU/day. Eleven women required a dose adjustment during stimulation. There were no significant differences between the study and control groups for total rFSH dose (2.407 ± 513 versus 2.503 ± 875 IU) 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 oestradiol levels on the day of the last ultrasound.

Embryo transfer was not performed in four cases (two in each group). Non-viable 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% versus 34.4%). The cycle outcomes are presented in **Table 3**. A non-significantly higher clinical pregnancy rate per patient (57.1% versus 35.0%) and per transfer cycle (66.7% versus 41.2%) were found, as well as a non-significantly higher live birth rate per initial cycle and transfer cycle in the study group. We also observed a significantly higher cumulative pregnancy rate in the study group (61.9% versus 30.0%; P = 0.045) (**Table 3**).

Discussion

Our study shows that a structured programme combining a low-calorie diet and physical exercise in obese women prior to a single

Table 2 – Outcome of IVF cycle in intervention and control groups.

Variable	Intervention group (n = 21)	Control group (n = 20)
Total dose of FSH used (IU)	2407 ± 513	2503 ± 875
Duration of stimulation (days)	11.3 ± 2.23	11.2 ± 2.0
Follicles 12–17 mm on HCG day	9.9 ± 5.2	10.6 ± 5.3
Follicles ≥18 mm on HCG day	5.5 ± 3.3	6.5 ± 4.2
Oestradiol on last US (pmol/l)	1483 ± 935	1562 ± 961
Endometrial thickness on last US (mm)	9.9 ± 1.8	10.2 ± 2.0
No. of oocyte–cumulus complexes	10.1 ± 7.4	10.7 ± 4.3
No. of mature (MII) oocytes	7.8 ± 5.7	7.8 ± 3.6
Mean no. of rapidly progressing spermatozoa (millions)	34.9 ± 21	35.8 ± 20
Fertilization rate (%)	62.2	57.7
No. of embryos	4.8 ± 2.8	4.6 ± 2.5
No. of good-quality embryos (A and B)	2.0 ± 2.1	1.8 ± 1.4
No. of transferred embryos	1.9 ± 0.3	1.9 ± 0.3
Cycles cancelled due to poor ovarian response (%)	4.8	5.0
Cancelled embryo transfers (%)	10.0	10.5
Implantation rate (%)	45.5 (15/33)	34.4 (11/32)
No. of cryopreserved embryos	1.6 ± 2.6	1.1 ± 1.3

Values are means ± SD, unless otherwise stated. There were no statistically significant differences between the two groups.
US = ultrasound.

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 (Moran et al., 2011; Sim et al., 2014b). 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. (2014b) and Moran et al. (2011) are the fact that not all women included in the weight loss programme finally underwent assisted reproductive treatments, 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 6.97% 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 multicentre study with 23 participating centres, the sample was composed mostly of anovulatory patients, and although the intervention lasted for 6 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 centre to centre. 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, 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 inter-individual 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 analyse 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 programme. 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 shown by the reductions observed in waist circumference and impedance analyser results. Clark et al. (1998) suggested that reductions in BMI values of just 5–10%, without necessarily reaching normal weight, have positive effects on reproduction. This small weight reduction is probably not beneficial in very obese women and more benefits could be obtained

Table 3 – Cycle outcomes in both groups.

Variable	Intervention group (n = 21)	Control group (n = 20)	Odds ratio (95% CI)
Pregnancy rate per cycle attempt (%)	57.1 (12/21)	35.0 (7/20)	2.47 (0.7–8.7)
Pregnancy rate per ET (%)	66.7 (12/18)	41.2 (7/17)	2.85 (0.7–11.3)
Live birth rate per initial cycle (%)	52.4 (11/21)	30.0 (6/20)	2.56 (0.71–9.2)
Live birth rate per ET (%)	61.1 (11/18)	35.3 (6/17)	2.9 (0.72–11.4)
Cumulative live birth rate per initial cycle (%)	61.9 (13/21)	30.0 (6/20)	3.8 (1.03–13.9)[a]
Multiple pregnancy rate (%)	14.3 (2/14)	16.7 (1/6)	
Miscarriage rate (%)	7.1 (1/14)	14.3 (1/7)	

Values are means ± SD, unless otherwise stated.
ET = embryo transfer.
[a] P = 0.045.

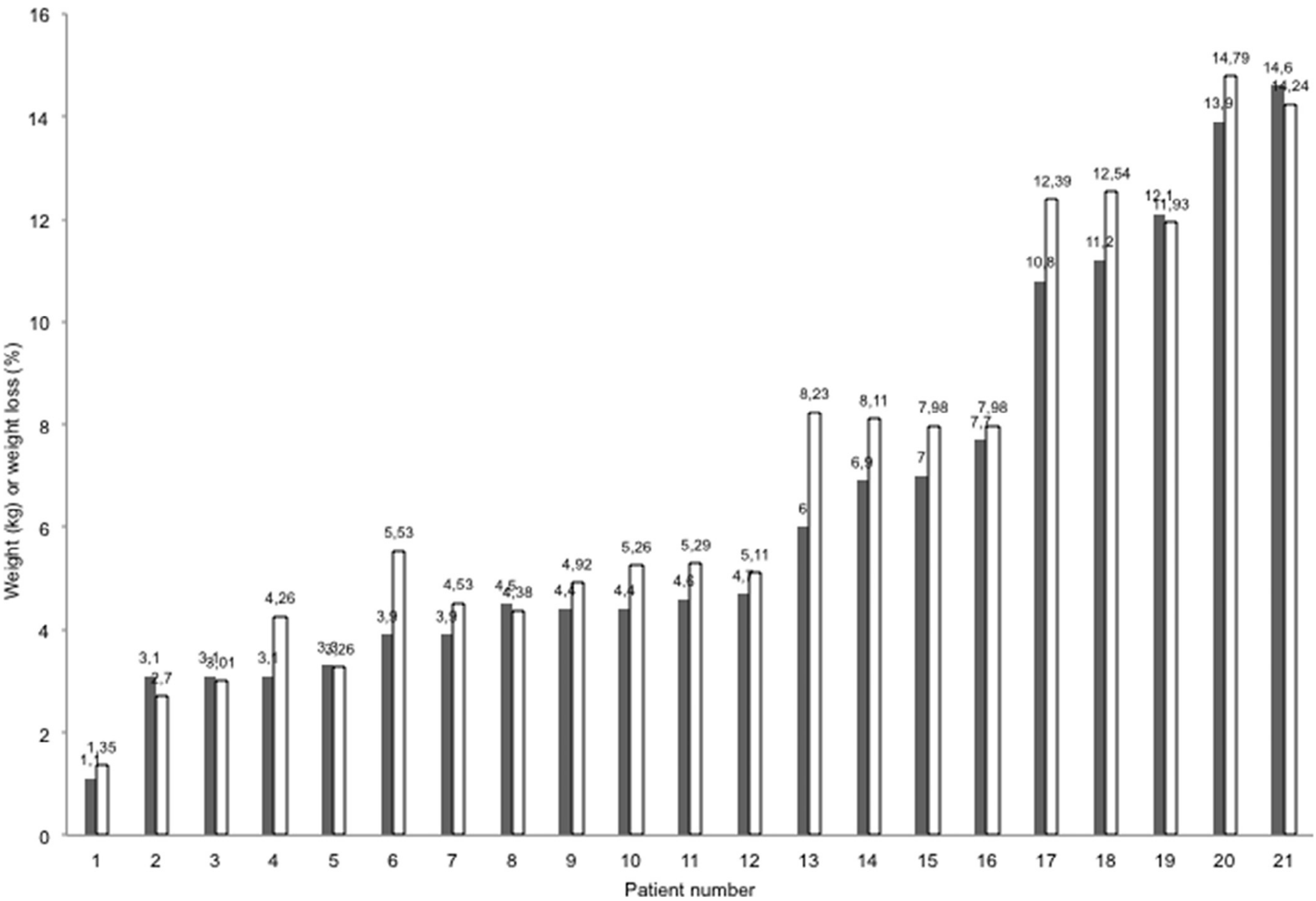

Figure 2 – Total weight loss in kg (solid column) and % of weight loss relative to the total weight (white column) achieved at 12 weeks following a diet and exercise programme in 21 obese women.

from a greater weight loss. However, greater or more abrupt weight reduction would imply a stricter diet and exercise programme 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 (Naude et al., 2014).

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 and 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. oestradiol, progesterone, insulin levels). It has been shown that embryos from non-obese donors are associated with poorer outcomes in obese recipients than in normal-weight 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 programmes would therefore appear to be linked to close, personalized follow-up and a multidisciplinary approach including psychological support and re-education of eating habits, although group therapy has also proven effective (Wadden and Foster, 2000).

Our study presents the evidence that a 12-week diet and exercise programme can lead to a significant reduction in total weight and visceral adiposity and to more favourable IVF outcomes in obese women. This finding encourages us to systematically propose a personalized weight loss programme 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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