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Weight loss improves reproductive outcomes in obese women undergoing fertility treatment: a randomized controlled trial

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What is already known about this subject

- Obesity has many detrimental consequences on reproductive health and fertility treatment.
- Obese women experience a spectrum of complications before conception and throughout gestation, and there are also risks for the future health of mother and child.
- Weight loss produces numerous benefits associated with reproductive health.

What this study adds

- A group weight loss programme, incorporating dietary, exercise and behavioural components, is associated with a significant improvement in pregnancy rates and live births in a group of obese women undergoing fertility treatment.
- Provision of a very-low-energy diet with a suitable refeeding period is efficacious for women prior to fertility treatment.
- Attempts should be made to encourage weight loss prior to pregnancy.

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Summary

For women attempting pregnancy, obesity reduces fertility and is an independent risk factor for obstetric and neonatal complications. The aim of this evaluator-blinded, randomized controlled trial was to evaluate a weight loss intervention on pregnancy rates in obese women undertaking fertility treatment. Forty-nine obese women, aged ≤37 years, presenting for fertility treatment were randomized to either a 12-week intervention ($n = 27$) consisting of a very-low-energy diet for the initial 6 weeks followed by a hypocaloric diet, combined with a weekly group multidisciplinary programme; or a control group ($n = 22$) who received recommendations for weight loss and the same printed material as the intervention. Anthropometric and reproductive parameters were measured at baseline and at 12 weeks. The 22 women who completed the intervention had greater anthropometric changes (-6.6 ± 4.6 kg and -8.7 ± 5.6 cm vs. -1.6 ± 3.6 kg and -0.6 ± 6.3 cm) compared with the control group ($n = 17$; $P < 0.001$). The intervention group achieved a pregnancy rate of 48% compared with 14% ($P = 0.007$), took a mean two fertility treatment cycles to achieve each pregnancy compared with four in the control group ($P = 0.002$), and had a marked increase in the number of live births (44% vs. 14%; $P = 0.02$). A group weight loss programme, incorporating dietary, exercise and behavioural components, is associated with a significant improvement in pregnancy rates and live births in a group of obese women undergoing fertility treatment.

Keywords: Assisted reproductive techniques, *in vitro* fertilization, obesity, pregnancy, weight loss.

Introduction

Obesity is a serious global health issue. Its prevalence is on the rise and it now constitutes a major worldwide epidemic (1). Obesity has many detrimental consequences on general health and also on reproductive health, with a reduced response to fertility treatment (2,3). Obese women experience a spectrum of complications before conception and throughout gestation, and there are also risks for the future health of mother and child (4).

Weight reduction strategies investigated in a preconception population include diet (5–9), very-low-energy diets (VLEDs) (10), surgical interventions (11) and medical procedures (12). In summary, a multidisciplinary approach appears to be of paramount importance. The resultant weight loss from these various interventions translates into benefits related to embryos available for transfer (13), less fertility treatment cycles required to achieve pregnancy (9), regularization of the menstrual pattern (5,6) and a decrease in miscarriage rates (6). However, not all studies reported a positive association with fertilization (10) or a statistically significant difference in pregnancy rates (8,9).

There are very few studies addressing preconception care and as yet no published randomized, controlled studies reporting a significant outcome of a weight loss programme on pregnancy rates. The aim of the study was to evaluate a group weight loss intervention on pregnancy rates, anthropometric measures, fertility treatment outcomes, and maternal and fetal complications in obese women undertaking fertility treatment.

Materials and methods

Study design and participants

This was a single-centre, evaluator-blinded, randomized controlled trial. Medical records of current and potential patients undergoing *in vitro* fertilization (IVF), intracytoplasmic sperm injection (ICSI) cycles or subsequent cryostored embryo transfer cycles at the Royal Prince Alfred Hospital (RPAH) Fertility Unit, Sydney, Australia, were screened for eligibility and participation was discussed. The study was conducted between February 2007 and February 2011.

Eligible participants were obese (body mass index [BMI]) ≥30 kg m^{-2}) female patients aged 18–37 years, intending to commence their IVF, ICSI or cryostored embryo transfer treatment at RPAH Fertility Unit. Participants were excluded if they had a current psychiatric condition (i.e. bulimia nervosa, overt psychosis, severe depression and drug or alcohol abuse); significant physical conditions (i.e. acute cerebrovascular or cardiovascular disease, malignancy, significant hepatic or renal dysfunction, or a musculoskeletal disease); an endocrine condition other than polycystic ovarian syndrome (PCOS) (i.e. type 1 diabetes, uncontrolled thyroid disease, Cushing's syndrome, hyperprolactinaemia [>450 IU L^{-1}]); pancreatitis; porphyria; had recently (within 3 months) partaken in treatment known to affect diet or body weight; were unable to follow both verbal and written English instructions; or who were unwilling to suspend fertility treatment for up to 3 months. The fertility unit had an upper BMI limit of 40 kg m^{-2}.

The study received ethics approval from the Sydney South West Area Health Service Ethics Committee (RPAH Zone). The study is registered with the Australian Clinical Trials Registry, No. 12606000448549.

Allocation

Randomization was done by the sequentially numbered, opaque-sealed envelope method (14) by an individual who was independent of the study team. Participants were allocated to 12 weeks of a group weight loss intervention or standard care. The dietitian, midwives, counsellor, fertility fellow and participants were aware of randomization but fertility specialists were not. The fertility fellow who was aware of randomization was not involved with cycle management and did not perform any assisted conception procedures in these patients.

Treatment components

Participants in the weight loss intervention received weekly dietary, exercise and psychological/behavioural advice relating to both weight loss and infertility in a group environment for 12 weeks (15). The programme, specifically tailored for the ART population and taking into account the dietary and exercise interventions, was developed by a dietitian and fertility fellow. It was run by a multidisciplinary therapeutic team, consisted of a fertility fellow, a midwife with expertise in fertility treatment, a fertility counsellor and a dietitian with experience in the treatment of obesity. The weekly sessions were run by at least one member of the multidisciplinary team, after hours, on a weekday decided by group members. Participants were encouraged to invite their partners to attend the introductory session only. The dietary component of the intervention included the use of a VLED (KicStart, Prima Health Solutions Pty. Ltd, Australia) for the initial 6 weeks. KicStart (which provides 2550 kJ, 65.4 g protein, 11.7 g fat, 54 g carbohydrate daily) was given to all women. This was followed by a refeeding protocol leading to them being on a mildly hypocaloric diet (2500 kJ d^{-1} deficit) prescribed by the dietitian. The individualized dietary plans were based on the participant's initial dietary intake that was obtained by a dietitian immediately after the study had commenced. The TEMplate System™, a dietary modification tool developed to provide individuals with a way to

achieve and maintain long-term weight loss, was used to educate participants. They were also asked to increase their physical activity ultimately to a daily target of 10 000 steps. Each participant was given a pedometer (DIGI-WALKER SW-200, Yamax, Japan) for measurement. Activity targets were gradually increased over 6 weeks to reach the 10 000 step target. This activity was then maintained for the remainder of the study. Both dietary intake and physical activity expenditure were recorded by participants in a daily diary. The dietitian provided weekly feedback and encouragement based on these entries as well as anthropometric changes.

Participants in the standard care group were advised to see their general practitioner for weight loss advice. If their BMI was ≥35 kg m^{-2}, they were offered a referral to the public weight loss service at RPAH. Responsibility for weight loss was placed upon the individual participant. Participants received the same printed material, weekly, as the intervention group.

Fertility treatment was commenced 12 weeks after study enrolment in both groups. All participants were followed up 12 months after the intervention to ascertain what fertility treatments they had undergone, pregnancy outcomes and complications. These were also obtained from their medical records.

Variables

The primary outcome was clinical pregnancy rate in the 12 months after the 12-week visit. A clinical pregnancy was defined as a fetal heartbeat at 7-week gestation; a preclinical pregnancy was defined as a positive pregnancy result that was spontaneously lost prior to 7 weeks. Secondary outcomes were changes in anthropometric measures of the participant (weight, BMI and waist circumference [WC]); blood pressure and heart rate; cardiometabolic and reproductive parameters; fertility treatment measures (number of stimulated cycles that resulted in an embryo transfer, oocytes fertilized per IVF or ICSI cycle and embryos cryostored per IVF or ICSI cycle); miscarriage rate (calculated as the total number of spontaneous preclinical and clinical pregnancy losses divided by the sum of these pregnancies); antepartum, intrapartum and postpartum outcomes; and compliance to the programme.

Height, weight and WC were measured and BMI calculated. Participants were weighed wearing light clothing and without footwear using a calibrated electronic digital platform scale (Wedderburn DI-160 series). Systolic and diastolic blood pressure and heart rate measures were taken by the same midwife according to the Korotkoff method (16).

Fasting samples were collected for the analysis of glucose, glycated haemoglobin, insulin, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, leptin, adiponectin, ghrelin, lutenizing hormone, follicle-stimulating hormone, prolactin, sex hormone binding globulin, testosterone, dehydroepiandrosterone sulphate, oestradiol, progesterone, the free androgen index and 17-hydroxyprogesterone. Blood and serum analysis was performed in the Clinical Biochemistry, Haematology and/or Endocrinology laboratories at RPAH.

Statistical analysis

Sample size was calculated using PASS 2005 (NCSS Statistical Software; 2005, Kaysville, UT, USA) at a 0.05 level of significance with a power of 80%. The proportions used for the two-sided *t*-test proportion calculation were based on the best available evidence. For the intervention group, Clark and colleagues (6) reported a clinical pregnancy rate of 0.776 for a similar weight loss group. For the control group, we assumed a clinical pregnancy rate of 0.300 pregnancies per embryo transfer, as reported for women less than 38 years of age, irrespective of BMI, at the RPAH Fertility Unit (17). A sample size of 16 in each group was determined. Data from VLED studies in a similar population group (10,18) indicated an attrition rate of up to 30%. As such, a total of 44 patients (22 in each arm) were required.

Intention-to-treat analyses were conducted for primary and secondary outcomes; *P* values ≤0.05 were taken as significant. Student's *t*-tests and mean differences were used for the analysis of continuous variables. Chi-square and odds ratios were calculated for categorical variables; Fisher's exact test was used when there were five or fewer expected case outcomes. Data analyses were done with SPSS 19.0 (SPSS Inc., 2010, Armonk, NY, USA).

Results

Figure 1 shows the trial profile. An estimated 86 patients were identified in consultation at the fertility unit and were approached by the research leader and participation in the study was discussed. Forty-nine were screened for eligibility and 37 chose not to participate. The physicians identifying patients only referred 86 for an initial discussion, it was estimated that a greater number were eligible. All of the 49 participants who entered the trial completed a baseline assessment. There were six separate weight loss intervention programmes run with groups of participants varying in number between 3 and 8. At 12 weeks, 10 (20%) participants had withdrawn or dropped out of the trial (Fig. 1). No participant reported any serious adverse events during the dietary intervention. There were no statistically significant differences between completers and dropouts of both groups in terms of pregnancy rates, fertility treatment outcomes or maternal and fetal complications (results not shown). Demographic and clinical characteristics of

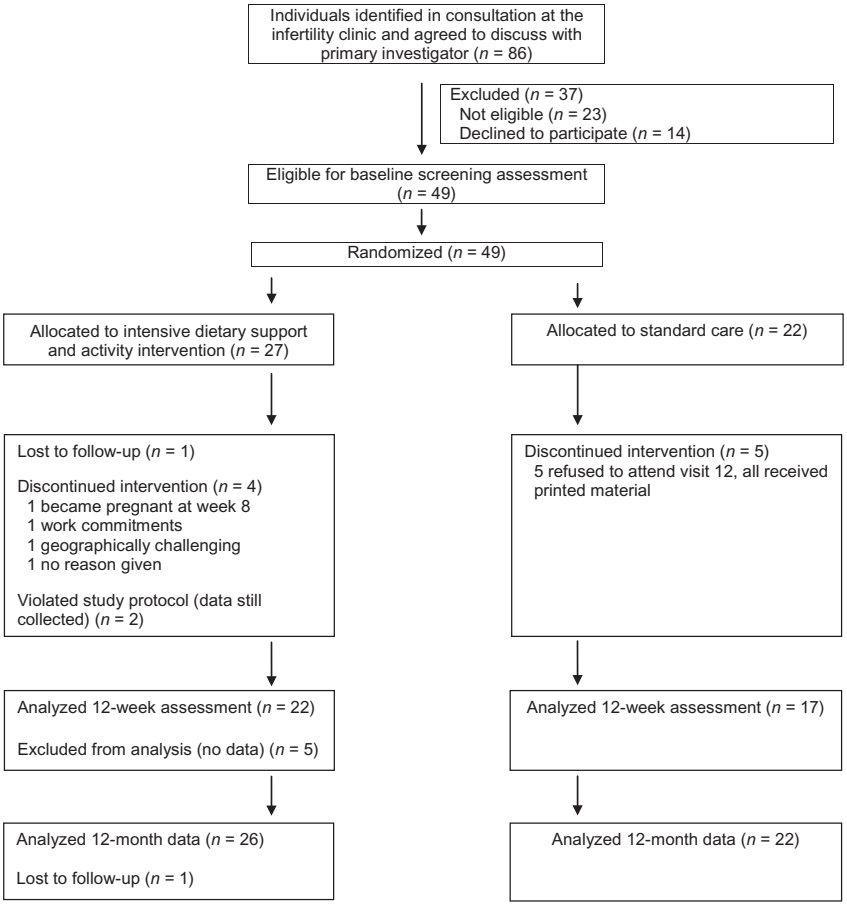

Figure 1 Trial profile.

participants are given in Table 1. Baseline differences were not statistically significant between the groups with the exception of a diagnosis of PCOS. When PCOS diagnosis was included as a covariate, results were unchanged, so unadjusted analyses are reported here. Furthermore, there were no statistically significant differences between the groups for ethnicity, marital status, education level, alcohol consumption, tobacco or marijuana use, or type and number of previous fertility treatments undertaken (results not shown).

Both treatment groups lost weight but the mean loss at 12 weeks was greater for participants in the intervention group (Table 2). Participants assigned to the intervention group lost a mean of 6.6 ± 4.6 kg (6.9% of initial weight; range: −17.4 to +0.7 kg) compared with 1.6 ± 3.6 kg (1.5% of initial weight; range: −9.5 to +5.0 kg) for participants in the standard care group. The greater weight loss in participants assigned to the intervention was accompanied by larger reductions in BMI and WC than those assigned to standard care; $P < 0.001$ for both (Table 2). None of the participant's BMIs returned to within the ideal BMI range. Blood pressure and heart rate were unchanged; $P \geq 0.20$. The intervention group had a large increase in oestradiol levels (236.5 pmol L^{-1} [SD = 448.4]) compared with the

Table 1 Baseline characteristics of women (*n* = 49) allocated to the intervention group (*n* = 27) compared with the control group (*n* = 22)

	Intervention	Control
Age (years)	32.9 ± 3.3	32.8 ± 3.1
Weight (kg)	95.8 ± 12.7	104.0 ± 16.1
Height (m)	1.65 ± 0.1	1.65 ± 0.1
Body mass index (kg m^{-2})	35.1 ± 3.8	38.0 ± 5.2
Waist circumference (cm)	106.1 ± 10.4	108.5 ± 10.4
Menstrual history		
Regular	20 (74%)	13 (59%)
Irregular	6 (22%)	8 (36%)
Anovulatory	1 (4%)	1 (5%)
Obstetric history		
Previous pregnancy	15 (56%)	6 (27%)
Never been pregnant	12 (44%)	16 (73%)
Infertility factors		
Ovulation disorder	8	5
PCOS	3	12
Tubal	5	3
Endometriosis	3	6
Male factor	15	9
Unexplained	2	1
Mean infertility duration (years)	3.4 ± 1.6	3.8 ± 1.6

Data are reported as mean ± SD or number (%).
PCOS, polycystic ovarian syndrome.

Table 2 Changes in clinical outcomes mean ± SD between baseline and 12 weeks by treatment group

	Intervention ($n = 26$)*	Control ($n = 17$)	Mean difference (95% CI)	*P* value
Weight (kg)	–6.6 ± 4.6	–1.6 ± 3.6	–5.0 (–7.7 to –2.3)	<0.001
Body mass index (kg m^{-2})	–2.4 ± 1·6	–0.6 ± 1.3	–1.8 (–2.7 to –0.9)	<0.001
Waist circumference (cm)	–8.7 ± 5.6	–0.6 ± 6.3	–8.0 (–11.8 to –4.3)	<0.001
Systolic BP (mmHg)	–2.2 ± 12.7	0.7 ± 11.3	–2.8 (–10.8 to 5.1)	0.29
Diastolic BP (mmHg)	1.1 ± 8.2	–2.4 ± 7.5	4.2 (–1.1 to 9.4)	0.20
Heart rate (bpm)	–2.2 ± 10.9	–0.9 ± 8.8	–0.2 (–7.0 to 6.6)	0.70

*$n = 22$ for systolic BP, diastolic BP and heart rate.
CI, confidence interval; BP, blood pressure.

Table 3 Pregnancy rate, fertility treatment and obstetric-related outcomes at 12 months by treatment group

	Intervention ($n = 27$)	Control ($n = 22$)	Odds ratio or mean difference (95% CI)	*P* value
Clinical pregnancy rate	48.1%	13.6%	5·88 (1·40 to 24·64)	0.007
Assisted pregnancy	10	3	3.73 (0.88 to 15.83)	0.06
Natural conception	3	0	–	0.11
Number of assisted conception cycles undertaken	31	13	0.6 (0.0 to 1.2)	0.04
Fresh transfer (IVF or ICSI)	17	11	0.2 (–0.3 to 0·6)	0.43
Cryostored embryo transfer	14	2	0.4 (0.1 to 0.8)	0.01
Miscarriage rate, %	29.4%	25.0%		0.91
<6 weeks*	4	1		
Weeks 6–12	1	0	–	
Live birth, *n* (%)	12 (44.4%)	3 (13.6%)		0.02
Gestational diabetes	0	1	–	0.12
Hypertensive disorders of pregnancy	0	1	–	0.12
Pre-eclampsia	1	0	–	0.92

*Biochemical pregnancy losses. Data are reported as number (%).
CI, confidence interval; IVF, *in vitro* fertilization; ICSI, intracytoplasmic sperm injection.

control group (18.1 pmol L^{-1} [SD = 151.8]); this was the only significant difference found ($P = 0.04$).

Table 3 shows the fertility treatment procedures undertaken and obstetric outcomes at 12 months. All stimulated cycles resulted in an embryo transfer except for four cycles in four participants, two in each group. This occurred because none of the collected oocytes fertilized in one of the intervention group participant's ICSI cycle and in the other, an IVF cycle, all embryos were cryostored. The two participants in the control group had failed fertilization of all oocytes in their IVF cycle. All embryo transfers were day 5 except one day-3 IVF and three day-3 ICSI transfers in the intervention group; of these, two resulted in pregnancies. Embryo transfers were all single embryo transfers, as per the protocol at the RPAH Fertility Unit. The intervention group underwent more fresh and frozen cycles (mean difference 0.6, 95% CI = –0.0–1.2; $P = 0.04$). Participants in the intervention group had significantly improved fertility treatment outcomes in terms of mean number of treatment cycles required to achieve a pregnancy (2.4) compared with those assigned to standard care (3.7; $P = 0.002$). There was an improvement in the mean percentage of oocytes fertilized per cycle in the intervention group (73% [SD = 20] compared with 49% [SD = 33] in the control group; $P = 0.04$) and the mean number of embryos available to be cryostored per cycle (2.8 [SD = 3.2] and 0.6 [SD = 0.8], respectively; $P = 0.01$). Antepartum complications and methods of delivery did not differ significantly across the groups. There were no other complications reported.

The pre-specified primary outcome of this randomized trial, pregnancy rate of participants at the 12 months post intervention, was markedly greater in the intervention group compared with the control group (OR = 5·88, 95% CI = 1.40–24.64; Table 3). This included three natural conceptions in the intervention group. This did not differ after adjustment for number of fertility treatment cycles (OR = 5.06, 95% CI = 1.17–21.88). When these pregnancies were followed until birth, there were 12 live births in the intervention group compared with three in the control group ($P = 0.02$). One of the mothers in the control group delivered 24 weeks after preterm labour. Her baby died in the early neonatal period from complications of extreme prematurity. The other 12 births in the intervention group

and two births in the control group were born at full term and within a normal weight range (2500–4499 g).

Discussion

Obesity is associated with a decline in fertility and contributes to many couples seeking assisted reproductive methods to achieve pregnancy. This study showed that a 12-week multidisciplinary group weight loss programme, implemented prior to fertility treatment, was associated with reduced anthropometric measures, a reduction in the number of fertility treatment cycles taken to achieve pregnancy, improved fertilization rates and an increased pregnancy rate compared with participants receiving standard care. The results have major clinical implications given the increasing obesity rates in women of reproductive age. A weight loss of 6.6 ± 4.6 kg resulted in statistically significant tripling of pregnancy rates (48% in the intervention group vs. 14% in the control group). This major difference in pregnancy rates was achieved with a relatively minor degree of weight loss. Despite knowledge of the relationship between obesity and pregnancy, the amount of weight loss required for the resumption of fertility is unclear. This study has shown that a loss of only 6.9% of initial body weight is sufficient to enhance pregnancy rates. Additionally, the results from this current intervention are generalizable as the study showed obese infertile women, irrespective of their infertility diagnosis and duration, benefited from the group weight loss programme.

This is the first randomized controlled trial to demonstrate a significant effect of weight loss on pregnancy rates in obese patients planning assisted conception. Previous studies (5–7,9,11–13), the majority either observational or not truly randomized, have also suggested that weight loss can improve pregnancy rates. They have reported weight losses ranging from 3.8 ± 3.0 kg (8) to 46.3 ± 14.5 kg (11) and pregnancy rates from 22.5% (13) to 100% (11,12). The only other randomized controlled trial is a pilot study and did not report a significant difference in pregnancy or live birth rates (8). The comparatively discrepant pregnancy rates reported in these studies could be attributed to their longer follow-up periods or differences in age. At ages less than 37 years, higher BMIs have a greater pronounced negative influence on fertility but the effect diminishes with age, as age becomes the inimical factor (19).

It may not be just weight change *per se* but a change in body fat distribution that is the critical factor. There was a significant change in the distribution of body fat in the study, evident by the decrease in WC measurements. A study in women undergoing artificial insemination reported a relationship between abdominal adiposity and fertility outcome. One found that a 0.1 unit increase in waist-to-hip ratio was associated with a 30% decrease in probability of conception per cycle, after adjusting for possible confounding factors (20).

It is unknown whether the intervention programme produced a permanent change as the participants' weight and WC were not recorded beyond their final visit at 12 weeks. This is a limiting factor of the study, as weight regain could have confounded the obstetric outcome results obtained in the 12-month follow-up period.

Previous weight loss interventions in similar population groups have reported beneficial changes in endocrine and hormone profiles (6,18). There were no such findings after the weight loss intervention in the current study; however, there was a significant increase in oestradiol levels in the intervention group. The clinical relevance of this finding is questionable as blood samples were taken irrespective of the stage of the participant's menstrual cycle. It does reinforce the need for further investigations to understand the associated biological mechanisms.

A possible explanation for the improved fertility outcomes may be psychological factors. Infertility can result in a complex life crisis with attendant psychological distress including grief, depression and marital-sexual discord of varying severity (21–23). The use of a group treatment approach may have been an important factor contributing to the successful outcomes in the intervention group. Group treatment methods tend to be more beneficial than individual treatment programmes because of factors including group support and cohesion, realization that an individual's problems are not unique, the sharing of difficulties with other group members, encouragement from others and a group expectation of a positive outcome (24). Other studies have shown a positive benefit of a group intervention in relation to reproductive outcome (25,26).

The retention rate in this study was greater than that observed in general weight loss trials (27). This could be accounted for by the group environment, the motivation of the patient population or the rapid weight loss methodology. The successful weight loss may have also re-established a sense of achievement as obese infertile women have a perceived sense of failure at both weight maintenance and fecundity (28). Losing weight and its associated achievement might be transferable to fertility.

The rapid weight loss methodology was attributable to the implementation of the VLED. A previous pilot study using a VLED for 27–41 d immediately before fertility treatment resulted in a poor result with half of the participants reporting no fertilization despite achieving a significant mean weight loss (10). The authors concluded that the discrepant results may, in part, be explained by the quality of ovarian reserve or induced ketosis and recommended against the acute use of a VLED. To overcome these adverse outcomes, this study was designed with a 6-week refeeding period and then a return to normal diet constituents. Given there were no statistically significant differences

in fertilization rates or miscarriages, the regimen implemented in this study appears to have overcome this.

The study has several limitations. The sample size in this trial was small, although based on the best available evidence. Given the relatively small sample size, this study was only powered to detect a large, clinically significant difference in reproductive outcomes between the intervention and control groups. No account was taken of the male partner's weight, age or health status, and this too could be a potential limitation. There was the lack of blinding of all staff at the fertility unit. To overcome this, clinicians making treatment decisions and undertaking procedures (oocyte retrieval and embryo transfer) and those who reported pregnancy outcomes were blinded to treatment assignment. Unfortunately, not all participants progressed with fertility treatment. Assisted reproduction is costly, and despite this study being conducted at a partially publicly funded fertility unit, cost is still a limiting factor for many couples considering fertility treatment. Furthermore, the pregnancy rate achieved by participants in the control group was lower than the value predicted based on all patients at the fertility unit. This may be due to lower fertility rates among severely obese women when compared with other women presenting for assisted reproductive treatment.

An understanding of the mechanisms associated with weight loss in this patient population is largely unknown. Research has determined the detrimental effects of maternal obesity on the life trajectory of the infant conclusively (29), but if and how this could be modified in the preconception environment requires further research. Future studies are required to determine whether there is a particular percentage of weight loss that equates to improved fertility outcomes or an upper BMI value beyond which maternal and fetal complications escalate. Despite the various strategies available, there is no conclusive evidence as to which strategy is most advantageous for preconception intervention in obese women. Further research investigating diet quality and duration of the refeeding period, following major weight loss associated with a VLED, would be advantageous. Additionally, there is a distinct shortage of evidence regarding the outcome of pregnancies following weight loss and assisted conception. The area of maternal weight loss in obese women on fetal programming is wide open for future discovery.

Obesity has a significant deleterious effect on fertility in women, on the outcome of fertility treatment interventions, and leads to major maternal and fetal complications. Given this relationship, attempts should be made to encourage weight loss prior to pregnancy. This study demonstrated that a group weight loss programme, incorporating dietary, exercise and behavioural components, was associated with significant improvements in pregnancy rates. The results have a wide-ranging application as participants were recruited into the study irrespective of their obstetric history, and despite this, benefits were evident. Despite the promising findings, these outcomes need to be confirmed by a larger randomized controlled trial, which may also seek to dissect the therapeutic components of this programme.

Conflict of Interest Statement

No conflict of interest was declared.

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