

Does weight loss in overweight or obese women improve fertility treatment outcomes? A systematic review

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Summary

This systematic review assessed the effect of weight loss in overweight and/or obese women undergoing assisted reproductive technology (ART) on their subsequent pregnancy outcome. Weight losses achieved by diet and lifestyle changes, very-low-energy diets, non-surgical medical interventions and bariatric surgery translated into significantly increased pregnancy rates and/or live birth in overweight and/or obese women undergoing ART in 8 of the 11 studies reviewed. In addition, regularization of the menstrual pattern, a decrease in cancellation rates, an increase in the number of embryos available for transfer, a reduction in the number of ART cycles required to achieve pregnancy and a decrease in miscarriage rates were reported. There were also a number of natural conceptions in five of the six studies that reported this outcome. Non-surgical medical weight loss procedures and bariatric surgery induced the greatest weight losses, but their use, as well as that of very-low-energy diets, for weight loss prior to ART requires careful consideration. While the overall quality of the studies included in this review was poor, these results support the clinical recommendation of advising overweight and/or obese women to lose weight prior to ART. Prospective randomized controlled trials are required to establish efficacious evidence-based guidelines for weight loss interventions in overweight and/or obese women prior to ART treatment.

Introduction

Obesity has numerous health implications relating to fertility and is now the most common clinical risk factor encountered in obstetric practice [1]. Infertility in natural menstrual cycles has been shown to be almost three times higher in obese women (i.e. those with a body mass index [BMI] ≥ 30 kg m⁻²) [2, 3]. The positive relationship between BMI and time to pregnancy has been established in overweight and obese women with anovulation as well as in those with a regular menstrual cycle [4, 5]. With the increasing prevalence of obesity worldwide, the number of obese women who are seeking assisted reproductive technology (ART) as a treatment for infertility is on the rise [6].

Not only is it more difficult for overweight or obese women to conceive, pregnancy in overweight and obese women is associated with an increased risk of complications for both the mother and the fetus [7-9]. In addition to problems apparent during pregnancy or in the perinatal period, pre-pregnancy and gestational obesity may lead to a self-reinforcing vicious cycle of excessive weight gain and adiposity that is passed on from mother to successive offspring [10-12]. While the underlying mechanisms of such maternal obesity-induced programming remain unclear (and are possibly epigenetic), the hypothesis is a potentially important explanation for the rapid rise in obesity [11].

While an increasing number of obese women are seeking ART, it is by no means an optimum solution for infertility in this population. Obesity has been found to impair ART outcomes in most, but not all studies, as recently reviewed [13]. Obese women have been reported to have a 68% lower odds of having a live birth following their first ART cycle compared with non-obese women [14]. Additionally, obesity is related to the requirement for increased doses of ART medications, more frequent cancellation of cycles (when patients stop treatment prior to oocyte retrieval, most commonly due to poor ovarian response) and lower rates of fertilization, embryo transfer, implantation and pregnancy [15]. Furthermore, oocyte retrieval and embryo transfer procedures can be difficult due to obesity itself [15].

Weight loss in overweight and obese women has been shown to increase natural conception rates and to improve the course of pregnancy [16], but there are very few studies investigating the impact of weight reduction in overweight and/or obese women prior to undergoing ART treatment. This question is of utmost clinical significance given the increasing

prevalence of obesity in women of reproductive age. Additionally, access to ART in some countries is restricted, with women of a BMI higher than the upper limit being advised to lose weight, but with limited evidence as to the safety or effectiveness of such a recommendation. Therefore, this systematic review assessed the literature of weight loss interventions on pregnancy rates and/or live births in overweight and/or obese women undergoing ART.

Methods

Identification of studies and eligibility criteria

Electronic databases (Medline, PubMed, Embase, Maternity and Infant Care, and the Cochrane Library) were searched up until February 2014. Only articles published in the English language were considered for eligibility. A search strategy was developed for all databases using the following general search terms: (obesity or overweight) AND (assisted reproductive technology or in vitro fertilisation [IVF] or in vitro fertilization or intracytoplasmic sperm injection) AND (pregnancy or live birth). The complete search strategy used in the electronic database Medline is presented in Table 1. A pregnancy was defined as the presence of one or more gestational sacs diagnosed by ultrasonographic visualization or definitive clinical signs of pregnancy, with multiple gestational sacs counted as one pregnancy [17]. A live birth was defined as the complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of pregnancy, which, after such separation, breathes or shows any other evidence of life, such as a beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles, whether or not the umbilical cord has been cut or the placenta is attached; each a product of such a birth is considered live born [18]. Multiple births were counted as one live birth.

Table 1 Electronic database search strategy: Medline

Search identification number	Search terms	Results
1	(obesity or overweight).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	183,327
2	Reproductive Techniques, Assisted/ or Fertilization in Vitro/ or Sperm Injections, Intracytoplasmic/	32,506
3	Pregnancy/ or Live Birth/	682,145
4	1 and 2 and 3	155
5	Limit 4 to (English language and humans and year = 1980–current)	138

The titles and abstracts of all studies identified by the search were scanned by two reviewers (KAS and SRP), and the full text of any original research studies that were associated with obesity and/or overweight, weight loss, and ART or related terms were retrieved for further evaluation by both reviewers. Additional studies were identified by examining the titles in the bibliographies of the full-text articles that were assessed for eligibility.

Inclusion criteria

All original research studies (not reviews) about women undergoing various ART procedures were considered for inclusion in the final review. All study types were eligible for inclusion. Studies were included in the review when ART outcomes were reported for overweight and/or obese women who had undergone either lifestyle (dietary management including very-low-energy diets [VLEDs], physical activity and/or behavioural/psychological techniques), pharmacological, a non-surgical medical procedure (the insertion of an intragastric balloon) and/or bariatric surgery, with the intention of weight loss. For study inclusion, overweight and obesity were defined by World Health Organization definitions (BMI \geq 25 kg m⁻² for overweight, BMI \geq 30 kg m⁻² for obesity) [19]. The two reviewers independently identified articles that met the above inclusion criteria. Any disagreement about inclusion of particular research studies was resolved by consensus.

Data extraction

General characteristics of the study (author, year of publication, study design, type of intervention, study period), characteristics of the study population (age, sample size, number of

women undergoing ART, proportion of women who were overweight and/or obese) and the outcomes of weight loss and ART were extracted from all included studies. Both reviewers independently extracted all data. Discrepancies were resolved by consensus.

Outcomes of interest

The primary endpoints were pregnancy or live birth in overweight and/or obese women undergoing ART after a diet and lifestyle intervention, pharmacological means or after a non-surgical medical procedure and/or bariatric surgery designed to produce weight loss.

Quality assessment

Studies were assessed for quality according to the McMaster University quality assessment tool [20]. The six component rating scale was used to evaluate selection bias, study design, confounders, blinding, data collection method, and withdrawals and dropouts. A rating of weak, moderate or strong was allocated to each of the six components, based upon specific, published criteria [20]. Where details of a component were not described in a study, a rating of weak was given for that component. An overall study was rated as weak if it scored two or more weak ratings from the six components, moderate if it scored less than four strong ratings and one weak rating, or strong if it scored four strong ratings with no weak ratings. Two reviewers (KAS and SRP) independently assessed study quality, and any discrepancies in component ratings were resolved through discussion.

Results

Characteristics of included studies and quality assessment

The initial search yielded 715 records. After the removal of duplicates and inclusion of relevant papers identified through perusal of reference lists, there were 45 papers to assess for eligibility, of which 11 were deemed relevant for the current review. Figure 1 outlines the flow of included studies.

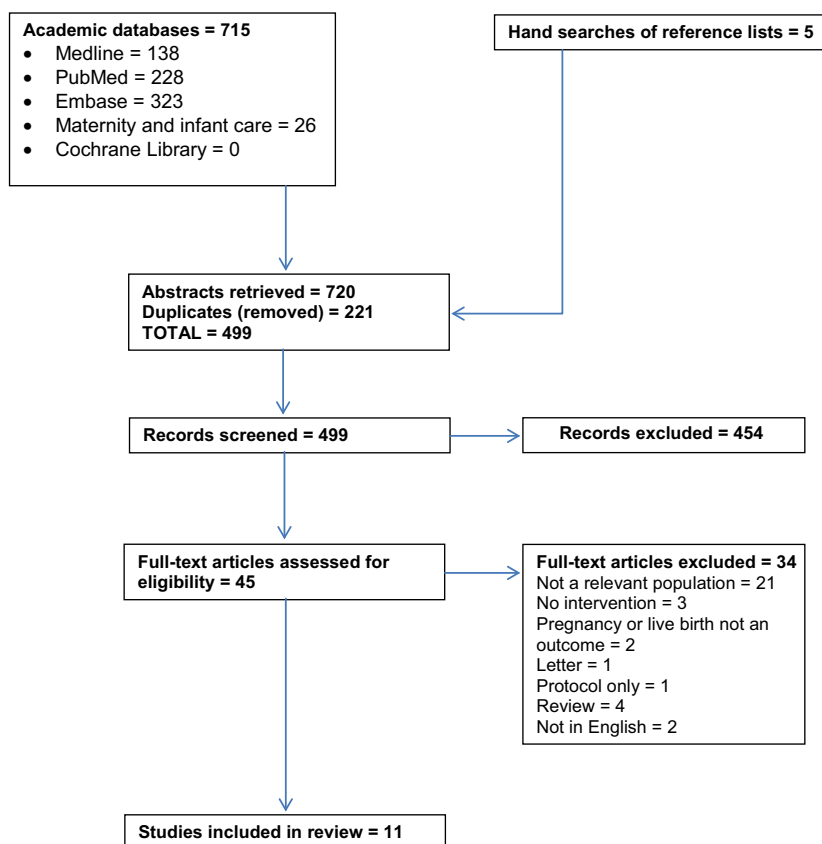


Figure 1 Flow diagram for process of selecting included studies.

Study design, description of the weight loss intervention, participant characteristics, sample size, main outcomes and study quality are presented in Table 2. Two studies were randomized controlled trials (RCTs) [21, 22], there were seven cohort studies [23-29] and two case reports [30, 31]. Two studies were rated as having a moderate overall quality [21, 22], and all the remaining studies [23-31] were rated as being of weak quality despite variations in individual quality criteria. Seven studies implemented a dietary and/or lifestyle intervention programme for weight loss [21-27], with one of these incorporating a VLED regimen [21]. Another exclusively implemented a VLED protocol [28]. Of the lifestyle intervention studies, four included a behavioural component [21, 23-25] and six implemented an exercise regime [21-26]. The remaining three studies reported on a non-surgical medical procedure for weight loss (the insertion of an intragastric balloon) [29] or bariatric surgery (Roux-en-Y gastric bypass surgery and gastric banding) [30, 31]. The number of participants varied between the studies (range: 1–2,896). The duration of interventions ranged from 27 d to 1 year. Follow-up was conducted in four studies, and this ranged from 1 to 3 years. All studies were conducted in adult women aged 18–42 years. No studies corrected for age, only two studies restricted or included participants aged up to and including 37 years [21, 30].

Effect of dietary and lifestyle management in overweight and/or obese women on assisted reproductive technology outcomes

Seven studies were identified as investigating the effect of a dietary intervention (excluding exclusive use of VLED) in overweight and/or obese women prior to ART treatment, as shown in Table 2 [21-27]. Interventions varied between an unspecified programme resulting in weight loss [27] to a 3-h multidisciplinary weekly group session conducted over 6 months [24]. Weight loss from these various interventions was reported via different methods (e.g. weight change, BMI change, percentage of people losing a certain percentage of body weight), so direct comparisons of weight loss are not possible, but it can be seen from Table 2 that all of these interventions resulted in weight loss. Four of these seven studies reported statistically significant improvements in pregnancy rates and/or live births compared with control or comparison groups [21, 23-25]. Of the remaining studies, two reported a non-significant trend to increased pregnancy rates [22, 27] and one study reported a small decrease [26]. Additional clinical benefits of weight loss via dietary and lifestyle management included regularization of the menstrual pattern [23, 24], a reduction in the number of ART cycles required to achieve pregnancy [21, 27] and a decrease in cancellation rates [27]. There was also an increase in the number of natural conceptions in the participants that lost comparatively more weight [21, 23-25], with the exception of one study [26].

Of these seven studies investigating the effects of dietary interventions, four studies – comprising three cohort studies [23-25] and one RCT [21] – implemented a multidisciplinary team programme that incorporated dietary, exercise and behavioural support in a group environment. The weekly sessions varied between 1-h weekly sessions for 3 months [21] and 3-h weekly sessions for 6 months [24]. The other two studies included 2-h weekly sessions [23, 25]. As shown in Table 2, weight loss was similar across all four interventions. Pregnancy rates for participants on these weight loss programmes were also similar between studies, with the exception of the RCT that implemented a VLED for the initial 6 weeks of the programme followed by a hypocaloric diet, which resulted in a comparatively lower pregnancy rate (48%) [21] compared with that in the other three studies (78–85%) [23-25].

Of the seven studies investigating the effects of dietary interventions, two studies investigated weight loss programmes that included only dietary and exercise interventions, without behavioural support. One of these studies was a RCT [22]; the other was a cohort study [26]. The RCT studied the effect of a reduced energy diet, which included replacing one daily meal with a liquid meal replacement formula, combined with a home-based physical conditioning and walking programme in women with a BMI ≥ 28 kg m⁻² who had previously undergone at least one ART cycle [22]. All women received one initial education visit; thereafter, the intervention group also received another face-to-face visit 2 weeks after the initial consultation and an additional follow-up phone call a further 2 weeks later. Despite a significant weight loss in the intervention group (albeit not as great as that induced by studies that also implemented behavioural support), there was no significant effect of the intervention on pregnancy rates or live births. The cohort study [26] investigated weight reduction in women with a BMI ≥ 32 kg m⁻², all with greater than 1 year of sub-fertility and/or oligomenorrhoea (irregular or infrequent menstrual periods with intervals of more than 35 d) or amenorrhoea. The

intervention group received nurse-led personal coaching, where patients were taught to eat more healthily and were informed of the importance of exercise. Participants in the comparison group were advised to reduce weight without further assistance. The personal coaching intervention consisted of a 30-min consultation every 2–3 weeks for an unspecified duration. The proportion of participants losing more than 10% of their body weight was markedly and significantly greater in the coaching intervention group than in the comparison group, but pregnancy rates did not differ significantly between groups (Table 2). Interestingly, more ART procedures were required to achieve pregnancy in the intervention than in the comparison group (Table 2).

Lastly, a retrospective cohort study reported advising morbidly obese women with a BMI ≥ 40 kg m⁻² to reduce their BMI to less than 35 kg m⁻² through unspecified means [27] (Table 2). The intervention group exhibited a lower BMI than the comparison group at the end of the study. There was a trend towards a greater pregnancy rate, a reduction in the number of IVF cycles, ampoules required for stimulation and cancellation rates in the group that was advised to lose weight (Table 2).

Further comparisons between studies could not be made due to variations in study designs.

Effect of very-low-energy diets in overweight and/or obese women on assisted reproductive technology outcomes

Two studies investigated the effect of a VLED prior to ART treatment; results are shown in Table 2. One study [21], a RCT, implemented an exclusive VLED regimen for 6 weeks followed by a hypocaloric diet as part of a multidisciplinary group intervention in obese women. As mentioned in the previous section, the pregnancy rate in the intervention group was significantly greater than that in the comparison group (and included natural conceptions), although not as high as that seen in lifestyle interventions that did not include VLED. The other study using a VLED [28] involved 10 overweight and obese women (BMI ≥ 28 kg m⁻²), of which four withdrew, who followed a partial then complete VLED intervention or solely a complete VLED intervention for 27–41 d immediately before their oocyte pick-up and subsequent IVF procedure. This study reported an unpromising fertility outcome; despite women achieving a sizable average weight loss of 5.6 kg, none of the six participants in this study fell pregnant and half of the participants did not achieve a single fertilization.

Effect of pharmacotherapy in overweight and/or obese women on assisted reproductive technology outcomes

Anti-obesity pharmacological agents are contraindicated in pregnancy [32-34]. No studies were identified in women undergoing a pharmacological weight loss intervention prior to ART.

Effects of non-surgical medical weight loss procedures and bariatric surgery in obese women on assisted reproductive technology outcomes

Of all the interventions used to achieve weight loss, non-surgical medical procedures [29] and bariatric surgery [30, 31] reported the greatest weight losses, as shown in Table 2. In terms of fertility outcomes, 21 (88%) of women in these studies became pregnant and 19 (83%) achieved a live birth. These fertility outcomes are just as good, if not better, than those achieved by women undergoing lifestyle interventions for weight loss.

The use of the endoscopic intragastric balloon procedure was reported in only one study, a retrospective cohort [29]. Not all women proceeded with ART treatment after this procedure and exact numbers were not reported in the study. Of the four women that did proceed with ART treatment, who had unspecified infertility challenges and had previously attempted IVF, all achieved an IVF pregnancy after weight loss. Of the remaining 14 women in the study who were previously unable to achieve a pregnancy but who did not proceed to ART, 11 (73%) achieved a natural conception within 1 year of regular unprotected sexual relations. Two case report studies were identified investigating ART outcomes after bariatric surgery. One case report series recounted five women who had previously undergone bariatric surgery (four cases of Roux-en-Y gastric bypass surgery and one case of gastric banding) and who had various causes of infertility and an average BMI of 31 kg m⁻² at the time of fertility treatment [30]. The average weight loss among these five women was 46 kg and fertility outcomes were positive. The other bariatric surgery case report is on a woman who had previously undergone Roux-en-Y gastric bypass surgery and who had infertility due to empty follicle syndrome and a BMI of

31 kg m⁻² at the time of initial consultation for ART [31]. A live birth was achieved within one subsequent cycle (BMI of 33 kg m⁻²) as the first cycle did not result in a live birth.

Table 2 Summary of included studies, showing the effect of various weight loss interventions on weight and fertility outcomes, notably pregnancy and live births, in overweight or obese women undergoing assisted reproductive technology treatments

Authors, year, reference	Study design	Type of weight loss intervention and description	Duration of weight loss intervention (follow-up)	Mean age in years and/or (range)	Sample size (intervention/control or drop-out)	Cause of infertility	Main findings for body mass index and fertility		Quality of study
							Weight loss	Pregnancy rate and live birth outcomes	
Clark <i>et al.</i> , 1995 (23)	Cohort study (prospective)	Diet, exercise and behavioural support	6 months (12 months)	(21–40)	18 (13/5)	Anovulation with previous clomiphene resistance	6.3 ± 4.2 kg (intervention); 1.4 ± 1.8 kg (comparison); <i>P</i> < 0.001. No alteration in waist-to-hip ratio	Pregnancy rate: 85% (11/13), 55% (6/11) were naturally conceived (intervention); no pregnancies (comparison) (intervention); none (comparison) Live births: 77% (10/13)	Weak
Clark <i>et al.</i> , 1998 (24)	Cohort study (prospective)	Diet, exercise behavioural support	6 months (12 months)	(21–40)	87 (67/20)	Various, including anovulation and PCOS	10.2 ± 4.3 kg (intervention); 1.2 ± 3.6 kg (control); <i>P</i> < 0.001	Ovulation: 90% (62/68) of the previously anovulatory women were ovulating spontaneously (intervention); none (comparison) Live births: 67% (45/67)	Weak
Gallaty <i>et al.</i> , 1996 (25)	Cohort study (prospective)	Diet, exercise and behavioural support	6 months (21–36 months)	(22–40)	58 (37/21)	Various	6.2 ± 4.5 kg; <i>P</i> < 0.001. No comparative group data was reported for any parameter	Pregnancy rate: 78% (29/37), 24% (7/29) were naturally conceived (intervention) Live births: not reported	Weak
Sim <i>et al.</i> , 2014 (21)	RCT	Diet (including VLED), exercise and behavioural support	3 months (12 months)	(18–37)	49 (27/22)	Various	6.6 ± 4.6 kg (intervention); 1.8 ± 3.6 kg (control); <i>P</i> = 0.001 WC; 8.7 ± 5.6 cm (intervention); 1.0 ± 6.3 cm (control); <i>P</i> = 0.001	Pregnancy rate: 48% (13/27), 23% (3/13) were naturally conceived (intervention); 14% (3/22), of which none were naturally conceived (control); <i>P</i> = 0.01 Live births: 44% (12/27) (intervention), 14% (3/22) (control); <i>P</i> = 0.02	Moderate
Moran <i>et al.</i> , 2011 (22)	RCT	Diet and exercise	5–9 weeks prior to oocyte pick-up (not reported)	(18–40)	38 (18/20)	Various	3.8 ± 3.0 kg (intervention); 0.5 ± 1.2 kg (control); <i>P</i> < 0.001 WC; 5.3 ± 4.6 cm (intervention); 3.5 ± 3.5 cm (control); <i>P</i> = 0.22	Pregnancy rate: 67% (12/18) (intervention); 40% (8/20) (control); <i>P</i> = 0.12; natural conceptions not reported Live births: 39% (7/18) (intervention), 25% (5/20) (control); <i>P</i> = 0.48	Moderate
van Veen <i>et al.</i> , 2011 (26)	Cohort study (prospective)	Diet and exercise	Not reported (not reported)	Intervention: 30 (21–41) Comparison: 31 (23–41)	2,896 (1,415/1,481)	Oligo-, or amenorrhoea	Weight loss (>10% reduction): 5% (intervention); 72% (comparison); results not reported in kilograms	Pregnancy rate: 68%, 9% naturally conceived (intervention); 69%, 38% naturally conceived (comparison); individual numbers not reported Live births: not reported	Weak

Table 2 Continued

Authors, year, reference	Study design	Type of weight loss intervention and description	Duration of weight loss intervention (follow-up)	Mean age in years and/or (range)	Sample size (intervention/control or drop-out)	Cause of infertility	Main findings for body mass index and fertility			Quality of study
							Weight loss	Pregnancy rate and live birth outcomes	Other	
Awartani <i>et al.</i> , 2012 (27)	Cohort study (retrospective)	Weight loss via unspecified means	12 months (not reported)	Intervention: 31 Comparison: 35	90 (25/65)	Primary infertility	Final BMI: 33.1 kg m ⁻² (intervention); 37.9 kg m ⁻² (comparison)	Pregnancy rate: 23% (intervention); 19% (comparison); individual numbers and natural conceptions not reported Live births: not reported	Number of IVF cycles: 49 (intervention); 108 (comparison) hMG ampoules for stimulation: 37 (intervention); 44 (comparison) Cancellation rate: 6% (intervention); 21% (comparison); individual numbers not reported	Weak
Tsagareli <i>et al.</i> , 2006 (28)	Cohort study (prospective)	VLED	27–41 d (not reported)	(29–38)	10 (6/4)	Various	5.6 kg (range: 5.3–8.2 kg), 6.3% (range: 2.4–8.8%) BMI: 2.1 kg m ⁻² (range: 1.8–3.2 kg m ⁻²); WC: 10 cm (range: 7–14 cm); 9.7%	Pregnancy rate: no pregnancies Live births: not reported	Fertilization rate: 50% (3/6), half had no fertilization	Weak
Musella <i>et al.</i> , 2011 (29)	Cohort study (retrospective)	Non-surgical medical procedure	N/A	31 ± 5 (22–39)	23 (18/5)	Not reported	7.5 ± 1.1 kg m ⁻² in 18 women, 5 classified as non-responders; results not reported in kilograms	Pregnancy rate: 83% (15/18), 73% (11/15) were naturally conceived Live births: 83% (15/18)		Weak
Doblado <i>et al.</i> , 2010 (30)	Case reports	Bariatric surgery	N/A	31 (20–37)	5	Male factor, fibroids, tubal factor, PCOS	46.3 kg	Pregnancy rate: 100% (5/5) Live births: 80% (4/5)	Number of IVF cycles: 9 Number of failed fertilization: 3 Number of miscarriages: 2	Weak
Hirshfeld-Cytron and Kim, 2008 (31)	Case report	Bariatric surgery	N/A	42	1	Tubal factor, polyps	79.4 kg	Pregnancy rate 100% Live birth: not reported		Weak

ART, assisted reproductive technology; BMI, body mass index; hMG, human menopausal gonadotrophin; IVF, *in vitro* fertilization; N/A, not applicable; PCOS, polycystic ovarian syndrome; RCT, randomized controlled trial; VLED, very-low-energy diet; WC, waist circumference.

Discussion

While the overall quality of studies currently available for review was weak, this systematic review shows that weight loss achieved by diet and lifestyle interventions with or without behavioural support [21-27], VLEDs [21, 28], non-surgical medical interventions [29] and bariatric surgery [30, 31] translated into significantly increased pregnancy rates and/or live births in overweight or obese women undergoing ART in 7 [21, 23-25, 29-31] out of the 11 studies reviewed. Of the remaining four studies, two reported non-significant trends towards improved fertility outcomes [22, 27], one a non-significant trend towards decreased fertility outcomes [26] and the last study, involving partial then exclusive use of a VLED or a complete VLED intervention, suggested a detrimental outcome for fertility in comparison with usual rates of pregnancy and fertilization in response to ART [28]. In addition to the overall significant benefits of weight loss for ART outcomes seen in most but not all studies, regularization of the menstrual pattern [23, 24], a reduction in the number of ART cycles required to achieve pregnancy [21, 27] and a decrease in cancellation rates [27] were reported. Furthermore, weight loss was associated with an increase in natural conceptions in five [21, 23-25, 29] of the six studies [26] that reported this outcome, thus negating the need for fertility treatment. A quantitative comparison of this small number of studies was not possible due to differences in multiple parameters such as causes of infertility, methods used for ART, starting BMI of the women under investigation, as well as duration of weight loss interventions and timing relative to commencement of ART. Nonetheless, this review does suggest some differences in ART outcomes in response to different weight loss interventions. Given that our review provides empirical support for the promotion of weight loss in overweight or obese women as a means of improving ART outcomes, and given that weight loss is frequently recommended for obese women embarking on ART, without knowledge of what types of weight loss methods are most beneficial, further research is required to determine whether any particular methods of weight reduction are more suited for the purpose of promoting positive ART outcomes.

Of the studies involving dietary and lifestyle interventions, those studies that implemented multidisciplinary group programmes reported the greatest significant improvements in pregnancy and live birth outcomes from ART. These benefits in ART outcomes could be attributed not only to the greater weight losses seen with such programmes [23-25] compared with those that did not use multidisciplinary group programmes [22, 26, 27] but also to the behavioural and physical activity components of such interventions. In keeping with the latter possibility, reproductive improvements were evident in women who were still classified as obese after the weight loss intervention [21-25, 27, 29-31]. ART is often described as the most stressful event in the lives of a couple [35]. Behavioural therapy may provide benefits in addition to its effects to promote weight loss; three of the four studies that implemented a behavioural support component within the lifestyle intervention [23-25] reported significant improvements in psychological measures, such as self-esteem, and decreases in anxiety and depression. The questionnaire used in the remaining study was not sensitive enough to identify such improvements [21]. It is not clear how psychological improvements may enhance fertility, but it is well established that prolonged psychological stress inhibits activity of the hypothalamo-pituitary-gonadotropic axis (which regulates reproductive hormone functions and thus fertility) [36]. In the currently reviewed studies, it is thus conceivable that improvements in psychological parameters could have induced endocrine changes, which directly affected fertility and contributed to improvements in menstrual function [23, 24] and pregnancy rates in the women [21, 23-25]. Despite these suggestions, it is important to note that no relationship was found between psychological measures and change in weight or BMI between women who became pregnant and those who did not [25]. Moreover, a recent meta-analysis has reported that psychological factors, such as anxiety and depression, may not compromise the chance of getting pregnant through ART [37].

With psychological parameters showing an inconclusive link with ART outcomes in the studies reviewed herein, other factors probably contributed to the apparently greater benefits to ART outcomes seen when weight loss was achieved with a multidisciplinary programme. Two such factors could be social interactions related to the group environment and exercise. Studies investigating the effects of support groups, intended to alleviate psychological distress related to infertility, have confirmed that the use of a support group results in reductions in measures of anxiety, depression, obsessive compulsive symptoms and hostility [38, 39]. These outcomes have translated into an improvement in conception rates for women with unexplained infertility

[38]. Similarly, exercise leading to weight loss in obese women has been shown to enhance psychological well-being, improve self-esteem and maintain motivation [23, 24], and has also been suggested to improve ovulation and subsequent fertility [40].

The currently available data suggest that further research is warranted to investigate the suitability of a VLED as a pre-pregnancy weight loss intervention. VLEDs are being used with increasing frequency because they produce fast and motivating weight losses [41], they provide appetite control [42] and are also cost-effective [43]. Both studies that implemented a VLED achieved a similar weight loss, but one of these studies [21] reported significantly improved pregnancy rates compared with its comparator group, but not as great as the improvements seen with multidisciplinary lifestyle programmes that did not use VLEDs [23-25]. The other study [28] reported particularly poor fertility outcomes, with a 50% fertilization rate and none of the six participants becoming pregnant. The discrepancy in results between these two studies using VLEDs may, in part, be explained by apparent differences in the re-feeding protocols used. The study that reported improvements in ART outcomes [21] implemented a complete VLED full meal replacement regimen for 6 weeks, followed by 6 weeks of re-feeding involving only partial meal replacement prior to commencement of ART, all within the context of a multidisciplinary weight loss programme. By contrast, the study that reported particularly poor fertility outcomes [28] involved 4–6 weeks on a VLED and did not specify any re-feeding period prior to starting ART, nor any multidisciplinary lifestyle support. The hormonal and metabolic milieu resulting from adherence to a VLED, which involves mild ketosis, might be expected to adversely affect ovarian reserve, the quality of developing eggs and/or activity of the hypothalamo–pituitary–gonadal and hypothalamo–pituitary–adrenal axes [44, 45], which regulate reproductive functions and fertility. The use of VLEDs is contraindicated during pregnancy (with no specifications about their use prior to pregnancy) [46]. Further work is required to investigate the safety and efficacy of VLEDs in obese women seeking ART.

This review revealed one cohort study and two case reports showing successful ART outcomes following non-surgical medical weight loss procedures (the insertion of an intragastric balloon) or bariatric surgery [29-31] in participants who had delayed conception for at least 12 months after these obesity treatments. Such procedures or bariatric surgery, when combined with permanent lifestyle change, are the most effective therapies for weight reduction in terms of the extent and duration of weight loss [47-49]. Recent studies have demonstrated that a naturally conceived pregnancy after a bariatric procedure is not only safe but may also be associated with fewer risks or complications in comparison to patients who remain obese during their pregnancy [50]. The incidence of miscarriage rates [51], gestational diabetes, pregnancy-induced hypertension [52], macrosomia, pre-eclampsia and unfavourable fetal outcomes [53-55] in patients who have undergone bariatric surgery are lower than those of gravid obese women and are also similar to those of non-obese women in the general population. It is probable that these benefits would also be applicable to women who conceive via ART. These procedures are however expensive, and there are no long-term follow-up data regarding the progress of offspring. Moreover, women are advised to delay conception for 12 months following weight loss surgery [51, 56, 57]. This may not be a viable option for patients with infertility who have a low ovarian reserve; as such, a delay may be further detrimental to their ability to conceive. Bariatric surgery for reproductive purposes is not currently recommended and further research is required to assess its safety and effectiveness in obese, infertile women seeking ART.

In clinical practice, a wide variety of methods are used to help obese women lose weight prior to ART, not all of which were identified in the current review. These include metformin as well as anti-obesity pharmaceuticals, VLEDs and bariatric surgery. With such interventions, women are generally advised to delay ART for some time after completion of the treatment (several months to up to a year in the case of bariatric surgery). However, the potential benefits of weight loss induced by such methods need to be carefully balanced against the potential adverse effects that the consequent need to delay ART could have on fertility, due to time-sensitive diminishment of ovarian reserves. It is well established that fertility declines with age [58] as well as a BMI in the obese age [8, 9]. When both BMI and age are examined together, BMI has a significant, age-dependent influence on fertility; at younger ages, higher BMIs have a pronounced negative influence on fertility but the effect diminishes at older ages [59]. In fact, BMI has a much less profound effect on fertility in women over the age of 37 years [59]. Therefore, it may be that weight loss methods that require a 'recovery period' prior to attempting conception may be better suited to younger women, notably those who are more obese and who do not have a low ovarian reserve.

Resource allocation for fertility treatment has been extensively debated in countries where ART treatment is publicly funded [60]. There is ongoing debate in relation to cost-effectiveness, risks and benefits, and whether access to ART should be limited only to women who are not overweight or obese [61-63]. Although a high BMI is associated with obstetric and perinatal complications, the BMI thresholds for access to ART that are applied in some countries are not justified by the empirical evidence [64]. In New Zealand, women with a BMI > 32 kg m² are excluded from any fertility treatment. In the United Kingdom, women with a BMI ≥ 30 kg m² are informed that they are likely to take longer to conceive and are encouraged to engage in a weight loss intervention, but there are no explicit BMI cut-off points for treatment [65]. The American College of Obstetricians and Gynaecologists similarly recommends that obstetricians provide preconception counselling and education regarding the specific maternal and fetal risks of obesity in pregnancy, or a referral for further evaluation and treatment [66]. This review provides greater clarity for clinical care by demonstrating that weight loss prior to ART improves fertility outcomes in the majority of studies, even when women still had a BMI in the obese range prior to conception. Further research is required to determine whether specific BMI cut-points should be prescribed via preconception care guidelines for obese women seeking fertility treatment.

Due to the shortage of comparable and high quality study types, there is a necessity for large-scale RCTs investigating weight loss in overweight and/or obese women undergoing ART. In view of the lack of convincing evidence from large intervention studies and the considerable practice variation in many countries, researchers in the Netherlands are undertaking a multi-centre RCT that directly compares a lifestyle intervention ($n = 285$) prior to conventional fertility care ($n = 285$) (including ART) with conventional fertility care in sub-fertile women with a BMI ≥ 29–40 kg m⁻² [67]. The outcomes of this study will potentially provide further evidence for recommending lifestyle intervention for weight loss before ART treatment.

Conclusion

The majority of studies included in this review, albeit being of overall poor quality, demonstrate that weight loss prior to ART is associated with significantly improved pregnancy rates and/or the number of live births, including some naturally conceived pregnancies. Furthermore, a number of additional benefits such as regularization of the menstrual pattern, a reduction in the number of ART cycles required to achieve pregnancy and a decrease in cancellation rates were also reported after weight loss interventions. Non-surgical medical weight loss procedures and bariatric surgery induced the greatest weight losses, but their use, as well as that of VLEDs, for weight loss prior to ART requires careful consideration. Medical weight loss procedures, bariatric surgery and VLEDs may be suitable if an appropriate duration after the procedure or intervention and before commencing ART is abided by. This is a clinical dilemma for obese women of increasing age presenting for ART; a delay in treatment, especially in those with a low ovarian reserve, can compromise the ability to conceive. Weight loss achieved through multidisciplinary group lifestyle interventions, incorporating dietary, exercise and behavioural support components, may provide additional benefits to fertility, such as via psychosocial effects, that are not seen in programmes intervening with diet and exercise only. Overall, these results support the clinical recommendation of advising overweight and/or obese women to lose weight prior to ART. Further prospective RCTs are required to establish which methods of weight loss are most suited to this purpose, as well as determining whether cut-points for BMI need to be recommended prior to accessing ART.

Conflict of interest statement

No conflict of interest was declared.

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