How effective are weight loss interventions for improving fertility in women and men who are overweight or obese? A systematic review and meta-analysis of the evidence.

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Table of Contents

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Abstract

BACKGROUND

The prevalence of obesity is increasing worldwide, with a corresponding increase in overweight and obese patients referred with infertility. This systematic review aimed to determine whether non-surgical weight reduction strategies result in an improvement in reproductive parameters affected by obesity, e.g. delayed time to pregnancy, oligozoospermia and azoospermia. No prior reviews have examined this within the general fertility population, or in both sexes.

OBJECTIVE AND RATIONALE

Our objective was to answer the question: "In overweight and obese women, men and couples seeking fertility treatment, what non-surgical weight loss interventions have been used, and how effective are they at weight loss and improving reproductive outcomes?"

SEARCH METHODS

An electronic search of MEDLINE, EMBASE and the Cochrane Library was performed for studies published between **(AUTHOR**: correct?) January 1966 and March 2016. Text word and MESH search terms used related to infertility, weight, and barriers to weight loss. Inclusion criteria were: an intervention to change lifestyle evaluated in any study design in participants of either gender with an unfulfilled desire to conceive. Studies were excluded if they included participants not attempting pregnancy, with illnesses that might cause weight fluctuations, or studies evaluating bariatric surgery. Two reviewers performed data extraction and quality

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assessment using the Cochrane Risk of Bias Tool for randomised trials, and a ratified checklist (ReBIP) for non-randomised studies.

OUTCOMES

A total of 40 studies were included, of which 14 were RCTs. Primary outcomes were pregnancy, live birth rate and weight change. In women, reduced calorie diets and exercise interventions were more likely than control interventions to result in pregnancy [Risk Ratio 1.59, 95% CI (1.01, 2.50)], and interventions resulted in weight loss and ovulation improvement, where reported. Miscarriage rates were not reduced by any intervention.

WIDER IMPLICATIONS

Overweight and obese persons seeking fertility should be educated on the detrimental effects of fatness and the benefits of weight reduction, including improvement in pregnancy rates. A combination of a reduced calorie diet, by reducing fat and refined carbohydrate intake, and increased aerobic exercise should form the basis of programmes designed for such individuals. A lack of randomised studies in men and couples, and studies evaluating barriers to undertaking weight loss in infertile populations is evident, and future research should examine these issues further.

Key words: infertility, obesity, weight loss, systematic review, diet, exercise

Introduction

Overweight is defined by the World Health Organization (WHO) (World Health Organization, 2016) as a BMI ≥ 25 kg/m², and obesity as ≥ 30 kg/m². The prevalence of obesity is increasing worldwide (World Health Organization, 2016), with more than 600 million obese adults, including 15% of women, in 2014 - double the prevalence reported three decades earlier. Infertility is defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse (Zegers-Hochschild *et al.*, 2009; National Institute for Health and Clinical Excellence, 2013). Using this definition, infertility affects about 1 in 7 couples in the UK, which is similar to an estimate of prevalence in the USA (Thoma *et al.*, 2013). An increasingly overweight and obese population has led to a greater proportion of individuals with high BMI being evaluated in infertility settings (Vahratian and Smith, 2009).

BMI has been associated with delayed conception in women in a dose-dependent fashion (Gesink Law *et al.*, 2007; Wise *et al.*, 2013; Wise *et al.*, 2010). It is thought to produce anovulation (Zain and Norman, 2008; Klenov and Jungheim, 2014), which results in menstrual irregularity (Hartz *et al.*, 1979; Zain and Norman, 2008); impairment of oocyte development (Klenov and Jungheim, 2014) and quality (Carrell *et al.*, 2001; Metwally *et al.*, 2007); and it also has direct effects on the endometrium (Bellver *et al.*, 2011). With ovulation induction (OI) treatment, higher doses of medications (Dickey *et al.*; Balen *et al.*, 2006a) and a longer period of stimulation (Balen *et al.*, 2006b) are required with a higher BMI. With IVF, the chances of achieving a pregnancy decrease with each unit increase in BMI (Ferlitsch *et al.*, 2004), and it is thought that implantation rates are lower in obese women (Bellver *et al.*, 2010; Styne-Gross *et al.*, 2005). An increased risk of miscarriage following IVF has also been reported (Maheshwari *et al.*, 2007).

Obesity may affect male fertility in a dose-dependent manner (Sallmen *et al.*, 2006). Postulated mechanisms include increased testicular temperature with prolonged sitting (Hammoud *et al.*, 2012), and increased oestrogen production in fat with disruption of the hypothalamo-pituitary-gonadal axis (Schneider *et al.*, 1979; Shukla *et al.*, 2014). Some studies have suggested reduced sperm concentration and motility (Hammiche *et al.*, 2012; Hakonsen *et al.*, 2011; Sermondade *et al.*, 2013), and lower clinical pregnancy rates with IVF (Keltz *et al.*, 2010; Umul *et al.*, 2015) with increasing male adiposity. Where both partners are obese, greater difficulty achieving pregnancy is expected (Ramlau-Hansen *et al.*, 2007).

Patients attending for fertility treatments are often advised to optimize their weights to improve outcomes, and in some cases to access assistance with funding (National Institute for Health and Clinical Excellence, 2013; Farquhar and Gillett, 2006; Infertility Network UK, 2015) or to reduce the risks of obstetric complications (The Royal Australian and New Zealand College of Obstetricians and Gynaecologists, 2011).

The purpose of this systematic review was to investigate first whether weight loss interventions for infertile patients achieve their goal in reducing weight, and second whether they result in improved fertility outcomes. A prior systematic review of 11 studies in women (Sim K.A. *et al.*, 2014) focussed on assisted reproduction only and used a much more limited search for studies up until 2014. Our review used an extensive search until 2016 and presents data from 40 studies with women and men with infertility, not just patients requiring assisted reproduction.

Methods

This systematic review was undertaken according to a pre-specified protocol.

Criteria for considering studies for this review

Types of studies

We included intervention studies in overweight or obese participants with any design and any duration of follow-up.

Types of participants

Participants could be of either sex. They were required to have both infertility, defined by an unfulfilled desire to conceive of any duration or attendance for infertility investigations or treatment, and a prescribed period of attempt at weight loss. A BMI ≥ 25 kg/m^2 was used to define overweight, and ≥ 30 kg/m^2 to define obesity (World Health Organization, 2016); participants were required to be at least overweight. Morbid obesity was defined by BMI ≥ 40 kg/m^2. Studies were excluded if participants were not actively attempting pregnancy, or had an illness or eating disorder that might result in weight fluctuation.

Types of interventions

Any intervention for weight loss allowed inclusion, for example prompt for weight reduction, dietary modification, exercise, psychological or behavioural counselling, or the drug orlistat. Bariatric surgery was not included. Alternative or control interventions were included where evaluated in included studies.

Types of outcome measures

Primary outcomes were weight change, achievement of pregnancy, and live birth, the latter defined as the complete expulsion or extraction from its mother of a product of fertilisation, which, after such separation, breathes or shows any other evidence of life such as heart beat, umbilical cord pulsation, or definite movement of voluntary muscles, irrespective of whether the umbilical cord has been cut or the placenta is attached (National Institute for Health and Clinical Excellence, 2013).

Secondary outcomes were BMI change; waist circumference change (North American Association for the Study of Obesity *et al.*, 2000); miscarriage, defined as a loss of pregnancy before 23+6 weeks of gestation (Anonymous , 2012); ovulation improvement, with anovulation defined by suboptimal rise in LH, or a below-threshold serum progesterone level taken in the mid-luteal phase of the menstrual cycle (National Institute for Health and Clinical Excellence, 2013); improvement in menstrual regularity, with irregular cycles defined as outside the range of 26-36 days (National Institute for Health and Clinical Excellence, 2013); and time to conception.

Search methods for identification of studies

The dates searched were 1 January 1966 to 19 March 2016. No restriction was placed on language of origin, ~~or publication status~~and studies could be included regardless of whether they had been published (**AUTHOR:** please would you clarify what you mean by 'status' here?). The electronic databases used were MEDLINE, EMBASE and the Cochrane Library. Additional studies were identified through review of the references of the retrieved papers, contact with study authors, and online searching of Google and Google Scholar (Google Inc., Mountain View, CA, USA). The search strategy used for MEDLINE and EMBASE is given in the Supplementary Data (**AUTHOR:** we tend not to include Appendices, therefore these data have been divided and renamed as supplementary files.).

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Data collection and analysis

Selection of studies

The titles and abstracts obtained were screened by one author (DB). To verify the process of selection, the titles and abstracts for the year 2000 were independently screened by DB and AA, with full agreement with respect to papers to be included or excluded. Thus full text versions of all relevant papers were retrieved by DB for further scrutiny by both reviewers. Any disagreement between the two as to which studies to include was resolved by discussion.

Data collection process

Data were extracted by one reviewer (DB), and checked by a second (AA). Discrepancies were resolved by discussion between the reviewers, and a third reviewer (SB) was available for referral as necessary. Study authors were contacted as required for missing data or clarification.

For each included study, the information collected included study design; methods; location, setting and time period; information about the participants (demographics, infertility diagnosis, BMI, eligibility criteria); drop-outs; the types of interventions assessed and their descriptions; and outcomes, including pregnancy, live births, weight or BMI change, miscarriage, ovulation and menstrual change. For men, semen analysis parameters were captured. **(AUTHOR:** please would you re-state those outcomes here, for clarity? Thank you.). Any data on barriers to weight loss were also captured. Data on costs and cost-effectiveness were sought but not found.

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Assessment of risk of bias in individual studies

RCTs were assessed for their methodological quality using the Cochrane Risk of Bias Tool (Higgins *et al.*, 2011).

Non-randomised studies were assessed using a checklist developed for the Review Body for Interventional Procedures (ReBIP) ~~(64)~~(**AUTHOR:** please would you use the correct format of citation?). The ReBIP is an independent review body that carries out systematic reviews for the National Institute for Health and Care Excellence's Interventional Procedures Programme. The checklist was adapted from several sources (Verhagen *et al.*, 1998; Khan *et al.*, 2001; Downs and Black, 1998), and has been used in many systematic reviews. It includes assessment of sample selection; clarity of inclusion and exclusion criteria; baseline comparability of participants; consecutive selection of patients; prospective data collection; clarity of intervention descriptions; experience of person administering the intervention; appropriateness of staff, place and facilities where participants were treated; consideration of important incomes on clinical effectiveness, cost-effectiveness, or learning curves; use of objective outcome measures; blinding of outcome assessment; adequacy of duration of follow-up to detect important effects on outcomes of interest; information provision on dropouts, and their similarity to completers; identification of important prognostic factors; and adjustment of analyses for confounding factors.

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Summary measures

Results were summarised descriptively. In the outcome summary tables, numbered rankings are provided in an effort to demonstrate which study interventions reported more favourable outcomes, with a lower number indicating a better outcome. Meta-analysis was undertaken where possible. Risk ratios (RR) and mean differences with 95% CI between groups are reported.

Synthesis of results

Data were imported into Review Manager Version 5.3.5 (The Cochrane Collaboration, Oxford, UK) for quantitative synthesis. A random effects, rather than a fixed effect model, was used for meta-analysis, owing to unavoidable population and intervention heterogeneity, as anticipated in interventions for weight loss.

Assessment of heterogeneity

Statistical heterogeneity was investigated by visual inspection of forest plots, the Q-test (with $p<0.1$ implying statistical heterogeneity) and by examining the I^2 statistic (Higgins and Thompson, 2002), where a result >50% was taken to indicate substantial statistical heterogeneity.

Sensitivity analyses

Sensitivity analysis was planned to compare randomised trials judged to be at low risk of bias for allocation concealment or randomisation with those judged to be at higher risk of bias; however, the small numbers of trials precluded this.

Results

Outcome of the search

Details of the selection process for studies is summarised in the PRISMA flow diagram (Figure 1) (**AUTHOR**: the quality of this figure still seems poor. If possible, please can you send to me a higher quality file?). Seventeen study authors were contacted for clarification or further information; ten provided helpful further information.

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Full details of all the studies and interventions are provided in Supplementary Table SI. There were 14 RCTs, six non-randomised studies with comparison groups (NRCTs), and twenty cohort studies with interventions. Ten studies took place in Australia, seven in the USA, three each in Italy and the Netherlands, and two in Denmark. One each came from Belgium, Brazil, Canada, Egypt, France, Germany, India, Iran, Jordan, Pakistan, Russia, Saudi Arabia, Slovakia, Turkey and the UK. Three studies were multi-centre.

Enrolment varied from eight participants (Faure *et al.*, 2014) to 577 (Mutsaerts *et al.*, 2016). Attrition rates ranged from 10.6% (Mutsaerts *et al.*, 2016) to 66.7% (Turner-McGrievy *et al.*, 2014).

Description of populations

Mean age of study groups varied from 25 years (Lazurova *et al.*, 2004) to 35.4 years (Chavarro *et al.*, 2012). Ethnicity was reported in six papers, with between 55% (Turner-McGrievy *et al.*, 2014) and 87.5% white (Mutsaerts *et al.*, 2016).

Duration of infertility, where reported, ranged from a mean of 19.5 months (Palomba *et al.*, 2008) to 11 years (Aliyeva *et al.*, 1993). Some studies addressed women with any infertility history. Others centred on women undergoing fertility treatments or planning to start immediately following the intervention. Some were exclusively catered to persons with polycystic ovary syndrome (PCOS), with the syndrome defined by Rotterdam 2004 consensus criteria (ESHRE and Group, ASRM-Sponsored PCOS Consensus Workshop, 2004) in ten cases, National Institutes of Health (NIH) criteria (Zawadzki and Dunaif, 1992) in one case, ultrasound appearance of the ovaries in two cases, and not specified in five cases. One study used PCOS as an exclusion criterion (Moran *et al.*, 2003).

In eight studies, patients were anovulatory, and in seven studies patients had irregular menstrual cycles. Three papers were centred on patients who were resistant to clomiphene citrate for ovulation induction.

The lowest mean BMI was 24.5 kg/m^2 (Chavarro *et al.*, 2012), and the highest was 44 kg/m^2 (Mahoney, 2014; Hakonsen *et al.*, 2011).

Two studies were centred on men. One had participants with sperm DNA fragmentation who were overweight or obese (Faure *et al.*, 2014), while the other examined obese men only (Hakonsen *et al.*, 2011). One study examined a weight loss intervention in couples (Homan *et al.*, 2012).

Description of interventions

Table 1 provides brief details of the types of interventions tested. In general, interventions were poorly described, with insufficient detail to allow their replication. Where described, most reducing diets followed healthy eating principles by reducing fat and refined carbohydrate intake. Where available, studies described calorie intakes ranging from 1000 to 2000kcal/d (depending on body size), apart from three studies that tested very low calorie diets as part of their reducing diets (Tsagereli 2006, Kiddy 1992, van Dam 2004) and one that tested a very low carbohydrate ketogenic diet (Mavroupolos 2005). If physical activity advice or programmes were incorporated into interventions, they were generally for aerobic exercise. There was no clear evidence that any particular regime was more effective for weight loss, providing there was a weight reduction diet prescribed.

Five of the 16 interventions incorporating both a dietary and physical activity component provided some part of the intervention in a group setting. Only two interventions were described involving couples. One study (Chavarro *et al.*, 2012) tracked participants' weights after administering a lifestyle questionnaire. While this is not strictly a weight-loss intervention, we have included it with the other cohort studies, because there is evidence that weight loss occurs with enrolment in studies tracking weight, even with minimal intervention (Waters *et al.*, 2012; Johns *et al.*, 2016).

Quality of studies

The quality of the studies included was variable. For full details of risk of bias assessment for ~~all~~ the randomised studies please see Supplementary Table SII. ~~The quality of the studies included was variable.~~ Three of fourteen RCTs had four or five out of seven domains with low risk of bias, e.g. allocation concealment, incomplete outcome data, but the Lifestyle trial (Mutsaerts *et al.*, 2016) stood out as the one with best quality. All studies were of high risk of bias with respect to blinding of participants to treatment allocation, and all had low risk of bias in at least two domains. Five of 26 non-randomised studies, having eight to nine of 14 domains with low risk of bias, were judged to be good quality. Full details of the risk of bias assessment for the non-randomised studies are given in Supplementary Table SIII.

Studies involving female infertility participants

Pregnancy

Aggregated data from six RCTs show that women who received a combination of a reducing diet and exercise had higher pregnancy rates than those who underwent standard care(**AUTHOR**: is there a word missing? Please would you recheck the sense here? Thank you.), 238/434 (54.8%) versus 221/443 (49.9%); RR 1.59, 95% CI (1.01, 2.50) (Figure 2). The trial by Mutsaerts *et al* (2016)) contributed significantly to the heterogeneity, I^2=71% and its exclusion in a post-hoc sensitivity analysis reduced I^2 to 0%. Although the numbers of participants in other RCTs were too few for any meaningful conclusions to be drawn, a very small trial was unable to demonstrate any advantage of diet alone, while another suggested that orlistat might be beneficial. The results of an NRCT (Clark et al, 1998) support the result of the meta-analysis favouring diet and exercise. The study by Koning et al (2015) did not show any advantage associated with motivational interviewing.

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Table 2 details the reproductive outcomes for all included studies. Diet and exercise studies without control populations achieved rates that were comparable to those included in the meta-analysis.

Live births

Data from five RCTs (Figure 3) did not favour diet and exercise over standard care in terms of live birth rates which were 48.9% (195/399) versus 46.8% (190/406) respectively; RR 1.54, 95% CI (0.93, 2.56). Mutsaerts et al (Mutsaerts *et al.*, 2016) again contributed significantly to the heterogeneity, I^2=69%. Its exclusion in a post-hoc sensitivity analysis reduced I^2 to 0%, and resulted in diet and exercise having a statistical advantage, RR 1.86, 95% CI (1.25, 2.77). The NRCT (Clark *et al.*, 1995; Clark *et al.*, 1998) also favoured the intervention arm, 45/67 (67.2%) versus no treatment (0/20); RR 28.10, 95% CI (1.81, 436.85). Motivational interviewing was also not associated with an increased live birth rate.

Table 2 details live birth rates for all included studies. Women in studies on diet and exercise without control groups had lower success rates than those included in the meta-analysis. Khaskheli et al (Khaskheli *et al.*, 2013), who did not provide details of their intervention, reported a 37.6% (32/85) livebirth rate, while Crosignani et al, (Crosignani *et al.*, 2003), who administered a 1200 kcal/day diet along with aerobic exercise, achieved a 24.2% (8/33) rate. The numbers of participants in the other studies included in Table 2 were too few for any meaningful conclusions to be drawn.

Spontaneous and IVF conceptions

Pooled data from RCTs (Figures 4 and 5) show that, reducing diets and exercise were not associated with a higher chance of spontaneous conception [28.3% (86/304) versus 15.9% (50/315); RR 2.20, 95% CI (0.98, 4.93)].

Miscarriages

A combination of a reducing diet and exercise was associated with a pooled miscarriage rate of 13.4 per hundred women (48/357) or 23.3% of pregnancies (48/206) (Figures 6 and 7). The control arm had a pooled miscarriage rate of 8.7 per hundred women (31/355) or 15.6% of pregnancies (31/199). This shows no benefit of diet and exercise [combined RR 0.96, 95% CI (0.89, 1.04) per woman and RR 0.91, 95% CI (0.91, 0.82, 1.01) per pregnancy]. Miscarriage rates in the other studies on diet and exercise vary widely (Table 2).

Ovulation

One RCT (Palomba *et al.*, 2010) found a 37.5% (12/32) ovulation improvement with a combination of reducing diet and exercise, while its control group had a 9.3% (3/32) improvement rate; RR 4.00 95% CI (1.25, 12.84) (Figure 8). An NRCT, also using diet and exercise, ~~that~~ had the highest rate of improvement of all included studies in its intervention group (**AUTHOR:** again, does this sentence read correctly? Please would you recheck?), 89.6% (60/67), while none of the participants in the control group saw improvement; RR 37.37, 95% CI (2.41, 578.65).

One RCT (Kumar and Arora, 2014) compared the use of 120mg of orlistat twice daily and a lifestyle modification programme with use of the lifestyle programme alone. The orlistat group had a 50% (15/30) rate of ovulation, while the control group had a 6.7% (2/30) rate; RR 7.50, 95% CI (1.88, 29.99).

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One RCT (Legro *et al.*, 2015) compared the proportions of total clomiphene treatment cycles that were ovulatory in each group. The group whose treatment was preceded by diet and exercise advice and the oral conceptive pill (OCP) had the best ovulation rate, 67.1% (94/140), while the lifestyle alone group and control (OCP alone) group had rates of 60.3% (82/136) and 46.1% (71/154) respectively.

Another RCT (Thomson *et al.*, 2008) randomised its participants, who had PCOS, to receive an energy-restricted high-protein diet alone (DO), combined with aerobic exercise (DA), or combined with both aerobic and resistance exercise (DC). DO saw a 50% (6/12) improvement in ovulation, DA a 50% (3/6) improvement, and DC a 42.8% (3/7) improvement.

Table 2 shows the ovulation rates in cohort studies of diet without controls. One study using a very low calorie diet (van Dam *et al.*, 2004) had a relatively good ovulation improvement rate, 60% (9/15). Other studies had comparatively low rates, including one using a hypocaloric 1434 kcal/day diet (Thomson *et al.*, 2009) which achieved a 19.2% (10/52) rate, and another (Turner-McGrievy *et al.*, 2014) which saw no improvement using either an low-calorie diet (LCD) **(AUTHO**R: please define LCD) or a vegan diet. One study compared a hypocaloric high protein diet to structured exercise training (SET) (Palomba *et al.*, 2008), and achieved a 25% (5/20) improvement rate with diet, and a 65% (13/20) improvement with exercise.

A study comparing ovulation improvement in women receiving acupuncture to those receiving an unspecified diet (Aliyeva *et al.*, 1993) had a 55% (11/20) improvement with the former, and 46.7% (28/60) improvement in the latter; RR 1.18, 95% CI (0.73, 1.90).

Menstrual irregularity

In clomiphene citrate resistant PCOS women, a single trial (Palomba *et al.*, 2010), showed that hypocaloric diet and exercise was significantly more likely to result in menstrual improvement,

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than observation only: 34.4% (11/32) versus 9.3% (3/32); RR 3.67, 95% CI (1.13, 11.92) (Figure 9). Other studies without control groups also suggest that diet and exercise were associated with improvement in menstrual regularity (Table 2). There were no RCTs evaluating the role of dietary interventions alone or motivational interviewing in regulating menstrual cyclicity. Data from observational and often uncontrolled studies of other interventions show variable levels of success (Table 2).

Oocyte retrieval

Data from a single RCT (Figure 10) suggest that a low glycaemic index diet (Becker *et al.*, 2015) could improve oocyte yield in IVF. The mean (SD) number of oocytes in women in the intervention arm was 7.75 (5.39), compared to 4.18 (SD 3.01) in controls; mean difference -3.57, 95% CI (-6.87, -0.27).

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Time to conception

The Lifestyle trial (Mutsaerts *et al.*, 2016) reported that the median time to conception (TTC) resulting in a term live birth was 7.2 months (interquartile range (IQR) 2.6, 12.0) in the intervention group, who underwent a multidisciplinary programme based on diet and exercise, versus 5.2 (IQR 2.4, 10.1) in the control group, who were allowed fertility treatment from the start (P=0.06). An RCT comparing energy-restricted low protein and high protein diet groups who both received exercise instruction (Moran *et al.*, 2003) reported a 4-5 week TTC regardless of group. A cohort study which advised women to lose 10% of their body weight (Kort *et al.*, 2013; Kort *et al.*, 2014) found that those who met the target had a mean TTC of 227 days, while those who had not had a mean of 231 days.

Weight loss

Aggregated data from RCTs suggest that a combination of a reducing diet and exercise resulted in greater weight loss than that achieved in control groups (Figure 11); mean difference -3.98 kg

(95% CI -4.85, -3.12). Diet alone was also shown to be more effective in a small RCT; mean difference -5.23kg (95% CI -7.42, -3.04) (Becker *et al.*, 2015).

In non-randomised trials, Clark et al (Clark *et al.*, 1998) reported significantly greater weight loss from diet and exercise; mean difference -9.00kg (95% CI -10.88, -7.12). Two non-randomised trials testing motivational interviewing also found greater weight loss; mean difference -3.21kg (95% CI -5.93, -0.49kg). Changes in weight, BMI and waist circumference for other studies are provided in Table 3. Generally results are not inconsistent with studies with either randomised or non-randomised control groups.

Comparisons with metformin

Pregnancy

Three small RCTs evaluated lifestyle interventions versus metformin (Figure 12). None was able to show any superiority of metformin over the alternative intervention, but it is difficult to be confident about these outcomes owing to the small sample sizes involved.

Ovulation

Two small RCT of diet or drug treatment (Figure 13) were unable to show any benefit over metformin. Details of other studies are in Table 2.

Menstrual irregularity

Metformin did not appear to improve menstrual regularity in a number of small trials comparing it to diet and exercise with or without drug treatment, diet alone or acarbose (Figure 14). Details of other studies are in Table 2.

Weight loss

Weight, BMI and waist circumference changes for studies comparing metformin with lifestyle interventions are provided in Table 3.

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Summary of the key findings in infertile women

In overweight and obese infertile women, weight loss is associated with improved chances of becoming pregnant, and possibly spontaneous conception pre-IVF. Ovulation and menstrual irregularity are also aided. There appears to be no significant difference between weight loss interventions and controls with respect to rates of miscarriage and IVF conceptions. The few studies that included metformin showed no significant difference between weight loss interventions and the drug for achieving pregnancy or improvement in ovulation status; similarly there was no difference between the two groups in menstrual improvement.

Barriers to weight loss in infertile women

Very little has been reported regarding the perceived barriers to weight loss in overweight and obese infertile women. Two of the included studies attempted in some way to evaluate these. In the trial by Thomson et al (Thomson *et al.*, 2008), 104 participants were allocated to receive an energy restricted diet only (DO), the same diet combined with five sessions of aerobic walking and jogging exercise per week (DA), or the diet combined with aerobic and resistance training exercises (DC), where resistance exercise replaced two of the aerobic sessions (110) (**AUTHOR:** please would you use the correct format for the citation? Thank you.). Forty-three of the participants in the trial (DO=13, DA=11 and DC=19) completed a validated Exercise Benefits/Barriers Scale at weeks 0, 10 and 20 (Thomson *et al.*, 2016). This was to determine their perceptions of the benefits and barriers to participation in exercise. The scale included 43

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items with statements related to ideas about exercise and a four-point Likert scale, with 4 = strongly agree, 3 = agree, 2 = disagree and 1 = strongly disagree. At baseline, the statements with the highest agreement were: “exercise tires me” [mean (SD), 2.86 (0.71)]; “exercise is hard work for me [2.79 (0.67)], and “I am fatigued by exercise” [2.60 (0.62)]. Those with the lowest agreement were: “my family members do not encourage me to exercise” [1.56 (0.59)], “my spouse does not encourage exercising” [1.63 (0.70)], and “I think people in exercise clothes look funny” [1.72 (0.59)].

Barrier scores were reduced by week 10 in this study, regardless of treatment allocation, with no further reduction by week 20 ($P \leq 0.001$). Time expenditure and physical exertion as perceived barriers saw a significant reduction ($P \leq 0.003$), while family discouragement saw no change ($P=0.6$).

Participants in the study by Galletly et al (Galletly *et al.*, 1996), in addition to completing a 24-week programme with weekly meetings comprising 1 hour of exercise and 1 hour of dietary and psychiatric counselling, completed the Rosenberg Self-Esteem Scale and the General Hospital Anxiety and Depression Scale at the start and end of the study. At baseline, those who dropped out before the end of intervention exhibited higher anxiety ($p<0.02$) and depression scores ($p<0.069$), and lower self-esteem scores ($p<0.056$) than those who completed. Completion was associated with a significant improvement in self-esteem ($p<0.0001$) and depression ($p<0.006$), and a non-significant reduction in anxiety scores.

Based on what little evidence is available, overweight infertile women appear most deterred from exercise by the perception that it causes fatigue and is hard work. These perceptions, as well as depression, seem to decrease with continuation of an exercise programme. Very few women seem to be discouraged from exercise by family members. Those women who discontinue exercise would appear to be more anxious and/or depressed at the outset.

Studies involving male infertility participants

Achievement of pregnancy, live birth rate, and Improvement in sperm DNA integrity

One cohort study (Faure *et al.*, 2014) administered a nutritionist-led personalised dietary programme of an unreported nature coupled with exercise, aimed at reducing intra-abdominal fat over a 3-8 month period, to eight men who had significant abdominal fat and at least 25% sperm DNA fragmentation and unexplained infertility (Table 4). The partners of all eight achieved pregnancy, three naturally and five through IUI, and all went on to have live births. Six who allowed their semen samples to be analysed both before and after the intervention all had an improvement in the degree of sperm DNA fragmentation.

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Improvement in semen analysis parameters

A cohort of 44 men with BMI 33-61 kg/m^2 underwent a programme based on a healthy diet and daily exercise (Hakonsen *et al.*, 2011). Semen analyses before and afterward were compared in 27 men, and the results were as shown in Table 4..

~~The group with 3.5-12.1% weight loss (Group 1, n=9) saw a mean change in sperm concentration of -11 million/ml (95% CI -49, +27). The group with 12.2-17.1% (Group 2, n=9) loss had a mean change of +19 million/ml (95% CI -23, 61). The group with 17.2-25.4% loss (Group 3, n=9) had a mean change of +17million/ml (95% CI -24, 58).~~

~~Group 1 saw a mean change in progressive sperm motility of -2%, 95% CI (-15,11). Group 2 had a mean change +4%, 95% CI (-10, 18). Group 3 had a mean change +11%, 95% CI (-3, 25).~~

~~Group 1 saw a mean change in normal sperm morphology of 0%, 95% CI (-2, 4). Group 2 had~~ a ~~mean change~~ of ~~+1%, 95% CI (-3, 4). Group 3 had~~ s ~~mean change~~ of ~~+4%, 95% CI (1,7).~~

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Change in weight

~~The cohort study by Hakonsen et al (Hakonsen *et al.*, 2011) achieved median weight change -22kg, range -4 to -39 kg. The cohort study by Faure et al (Faure *et al.*, 2014) achieved~~ a ~~mean weight reduction~~ of ~~-4.40 (SD 5.0 kg).~~Table 4 also summarises the weight loss achieved in both studies.

Summary

The relative paucity of studies in overweight and obese men seeking fertility has made it difficult to draw firm conclusions regarding the benefits of weight loss. However, improvements in sperm concentrations, motility and normal morphology have been suggested, though these have not been statistically significant. Improvement in sperm DNA integrity has also been suggested, and this might be linked to an improved live birth rate.

Discussion

Key findings

The present systematic review and meta-analysis found that the weight loss interventions, particularly diet and exercise, improved pregnancy rates and ovulatory status. A trend toward more natural pregnancies, but not IVF pregnancies, occurred. Miscarriage rates were unaffected by weight loss interventions and, as reports of higher oocyte yield and improved menstrual regularity are based on single trials, further research is needed before firm conclusions can be made. A lack of RCTs in men and couples, and of studies evaluating barriers to undertaking weight loss in overweight and obese infertile populations, is evident. The quality of the studies we included was variable, but the one with the lowest risk of bias was the Lifestyle trial (Mutsaerts *et al.*, 2016), whose intervention also ranked highly for both pregnancy and live birth rates.

Women

Pregnancies and live births

Weight loss interventions, particularly those with reducing diets and exercise, were more likely than controls to result in pregnancy. Live births were reported by ~~only a few~~relatively fewer~~er~~ studies **(AUTHOR:** correct?), usually involving women undergoing fertility treatments such as OI or IVF. Data from studies predating the Lifestyle trial in 2016 (Mutsaerts *et al.*, 2016) suggested that diet and exercise combinations were superior to standard care, but inclusion of this trial changed this. Those in the intervention arm underwent a 6-month programme based on diet and exercise, prior to undergoing 18 months of fertility treatments. Those in the control arm commenced fertility treatments immediately. The primary outcome was vaginal birth of a healthy singleton of at least 37 weeks' gestation within 24 months after randomisation. The trial

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was well conducted, with low risk of bias. This was the largest study in the review, and it carried substantial weight during meta-analysis. The results deviated from the trend exhibited by the preceding trials, resulting in marked increase in heterogeneity. It is possible that the results might have been different if the control group underwent 6 months of no intervention observation prior to 18 months of treatment. The trial found that significantly more women in the intervention group had ongoing pregnancies from natural (**AUTHOR:** the term natural' is usually preferred throughout but I leave the final decision to you.) conception than the control group, consistent with our other findings.

Studies reporting the highest pregnancy and live birth rates were not necessarily those with highest weight loss. Clark et al, had a high live birth rate of 67.2% in the diet and exercise arm of their NRCT, while also achieving one of the highest weight changes, mean -10.2kg (SD 4.3) (Clark *et al.*, 1995; Clark *et al.*, 1998). On the other hand, the intervention arm of the Mutsaerts et al (2016) RCT reported a live birth rate of 53.2%, but only achieved a mean weight change of -4.4 kg (SD 5.8).

Miscarriages

Studies with some of the lowest rates of weight loss reported fewer miscarriages in their intervention arms, but the data are insufficient to draw conclusions (Tables 2 and 3).

Ovulation

Weight loss interventions, regardless of their nature, were significantly more likely than control interventions to achieve ovulation in anovulatory women. Improvements were not necessarily greatest in those studies achieving the greatest weight loss.

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Menstrual irregularity

A single RCT suggested that diet and exercise were significantly more likely to improve menstrual cycles than a control intervention (Palomba *et al.*, 2010). High rates of menstrual improvement were seen in studies with good weight or BMI reduction. Qublan et al (2007), for example, with a 1200-1400 kcal diet in their RCT, had a 61.9% menstrual improvement and achieved one of the better BMI reductions, with a mean change of -4.8 kg/m^2.

Spontaneous and IVF conceptions

Studies included women expected to proceed to in-vitro treatments after a period of weight loss. Many women were able to conceive without further assistance through weight loss alone. All interventions showed an improved rate of spontaneous conception in comparison to a control. There was however no significant difference between interventions and controls when it came to IVF conceptions. Similar spontaneous conception rates were seen regardless of type of intervention and/or amount of weight lost.

Change in weight, BMI and waist circumference

No class of intervention was consistently better in achieving reduction in weight compared to others. Trials with longer interventions and follow-up sometimes suffered from higher rates of study drop-out, for example 20.4% in the 12-month Sim et al RCT (Sim *et al.*, 2014a) and 10.6% in the 6-month Mutsaerts et al RCT (Mutsaerts *et al.*, 2016), both of which mainly had diet and exercise. Others had no dropout: Karlsen et al after 7-8 months (Karlsen *et al.*, 2013) and Koning et al after 6 months (Koning, 2015), and both included motivational interviewing. This suggests that enhancing motivation plays a key role in compliance. Programmes with strict dietary and exercise modifications may be more likely to see discontinuation. The study with the most weight lost, the cohort study by Mavropoulos et al (Mavropoulos *et al.*, 2005), utilised a very restrictive diet for 6 months, and had very low recruitment (n=11) and a high rate of drop-out (58.5%).

Metformin

The meta-analyses showed that weight loss interventions have a non-significant advantage over metformin with respect to achievement of pregnancy or improvement of ovulation status. There was also no significant difference in menstrual regularity improvement. In light of these findings, and the gastro-intestinal side-effects common with metformin (Kumar and Arora, 2014; Qublan *et al.*, 2007), lifestyle interventions should remain the first line therapy for improvement in ovulation and menstruation.

Interventions in infertile men

There was very little evidence available to judge the effectiveness of weight reduction strategies in men, and this is an area ripe for future research. The two studies both utilised a diet and exercise combination, with neither providing adequate details of the intervention.

Types of diet

As expected, the dietary interventions used were based on caloric restriction, and were usually consistent with weight reduction advice from national guidelines (National Clinical Guideline Centre, 2014; Dietz *et al.*, 2015). It is hard to say, based on the data obtained, whether any particular degree of restriction was superior for achievement of weight loss, particularly given the frequent pairing of diet with exercise. Some of the RCTs used individualized diets, tailoring caloric deficit to baseline weight (Becker *et al.*, 2015; Duval *et al.*, 2015b). Others mentioned a hypocaloric range within which dietary intakes would fall (Kumar and Arora, 2014; Qublan *et al.*, 2007; Thomson *et al.*, 2008; Turner-McGrievy *et al.*, 2014), generally between 1200 and

1800 kcal/day. Dieticians were used to assist with dietary advice in a few cases (Duval *et al.*, 2015b; Turner-McGrievy *et al.*, 2014; Thomson *et al.*, 2008; Mutsaerts *et al.*, 2016). The RCT with the lowest recruitment and highest discontinuation rate used a vegan diet in one of its study arms (Turner-McGrievy *et al.*, 2014), suggesting poor acceptance.

Types of exercise

The majority of exercise interventions sought to increase weekly aerobic activity in participants in order to increase caloric expenditure. The most frequent feature seen in the RCTs was an increase in the number of steps or amount of walking by participants (Duval *et al.*, 2015b; Karimzadeh and Javedani, 2010; Legro *et al.*, 2015; Mutsaerts *et al.*, 2016; Sim *et al.*, 2014a; Thomson *et al.*, 2008). Fewer RCTs (**AUTHOR:** correct, or studies?) included strength or resistance training (Karimzadeh and Javedani, 2010; Moran *et al.*, 2011b; Thomson *et al.*, 2008), and this was always in addition to the basic aerobic approach. Thomson et al found that addition of resistance training did not result in a significantly different weight loss in their RCT of diet alone, diet with aerobic exercise, or diet with aerobic and resistance exercise (Thomson *et al.*, 2008). Physical activity interventions were in some cases individualised (Duval *et al.*, 2015a; Moran *et al.*, 2011a) and in others in the form of group sessions (Moran *et al.*, 2003), with occasional use of a kinesiologist (Duval *et al.*, 2015a) or physiotherapist (Kumar and Arora, 2014).

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Types of weight loss medication

The use of weight loss drugs is contraindicated during pregnancy (Department of Veterans Affairs, 2014), and the studies using them aimed to reduce weight prior to attempting pregnancy. One trial (Legro *et al.*, 2015) recommended barrier contraception during its intervention. Oral medications used in the studies included orlistat, a lipase inhibitor;

sibutramine, a selective serotonin and norepinephrine reuptake inhibitor; and acarbose, an alpha-glucosidase inhibitor shown to induce modest weight loss, though not suitable for weight maintenance (Hauner *et al.*, 2001). Of these, sibutramine, which has been withdrawn in Europe and the USA but is still available on the internet, has been shown in a large study to have a risk of cardiovascular defects in unborn infants (Källén, 2014), while the same study showed no risk of birth defects from orlistat use. The safety of acarbose in pregnancy is not established. Orlistat was shown to be superior to a control with respect to achievement of pregnancy and ovulation in a single study (Kumar and Arora, 2014). Until further evidence is available, lifestyle interventions should still be considered thefirst line therapy, with drug use reserved for monitored trials.

Strengths and limitations of the review

This review has added to the scope of the systematic review by Sim et al (2014b) by going beyond examining overweight and obese women undergoing fertility treatment to encompass individuals of both genders, and couples, from a variety of infertility circumstances undergoing non-surgical weight loss programmes. A wide search strategy meant that we were thus able to capture 40 studies, in comparison to the 11 in that review (Sim *et al.*, 2014b). Author contact, initiated with 17 study authors, was another strength, as this allowed unreported information to be gained, and clarification of unclear information. Nevertheless, we cannot exclude publication bias, where studies with less positive outcomes remain unreported.

Clinical recommendations

Overweight and obese persons seeking fertility should be educated on the effects of being overweight or obese on the ability to achieve pregnancy, and the benefits of weight reduction, including improvement in pregnancy rates, and a reduced need for OI and IVF.

A combination of a reduced calorie diet, which is not overly restrictive, and aerobic exercise, intensified gradually, should form the basis of programmes designed for such individuals. As compliance is key to success, coached sessions of achievable frequency, e.g. weekly, for up to 6 months, should be considered. Motivational interviewing techniques might also be useful. An advantage of fertility care is that couples are catered to, and dual enrolment may result in better adherence, as partners tend to motivate each other.

Research recommendations

Future research would ideally be in the form of large multi-centre RCTs including both women and men, ideally couples, attending fertility clinics and having at least one partner with a BMI within the overweight or obese range. Based on the data from RCTs of diet and exercise examined here, we estimate that a trial would require over 454 participants to detect a difference of 15% in pregnancy rates (90% power, $p < 0.05$, control pregnancy rate 50%, intervention rate 65%). This figure does not take account of losses to follow-up, and would need to be considerably inflated, depending on drop-out rates in feasibility and pilot work.

A reasonable control intervention would be the administration of dietary and exercise advice only~~-~~, to be undertaken for a brief period ~~only~~ (**AUTHOR:** correct?), to reduce persons allocated to this arm feeling as though their fertility treatments were being delayed with no intervention. Similar durations employed between intervention and control groups prior to starting fertility treatments would allow for fair comparisons with respect to weight loss and reproductive outcomes.

A long duration of follow-up, spanning decades, might answer further questions, including whether obstetric problems related to weight such as gestational diabetes or caesarean rates

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might be reduced in imminent or future pregnancies. The permanency of lifestyle changes made while attempting fertility might also be established, as well as their impact on family members, and the maintenance of weight loss in the long term. ~~The role of epigenetic changes might also be explored~~ (**AUTHOR**: although important, and you are discussing possible future research here, this subject has not been mentioned so far and seems a little unrelated to the overall approach here. It is also unclear what particular studies you would perform, therefore I suggest removing it, which would not detract from the discussion. If you agree, please edit accordingly? Thank you.)~~.~~

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Conclusions

Non-surgical weight reduction strategies in the infertile have been shown to improve reproductive outcomes in both men and women. Diet, exercise, a combination of the two, weight-loss medication and motivational interviewing have all been efficacious in reducing obesity. In women, weight loss from diet and exercise is associated with improved chances of becoming pregnant, with a trend toward improved live birth rate. Ovulation and menstrual irregularity are also aided. At present there appears to be no significant difference between weight loss interventions and control interventions with respect to rates of miscarriage and IVF conceptions. Well-designed RCTs should also shed light on the effect of weight loss on numbers of oocytes retrieved and other parameters in IVF cycles, and on TTC, as well as the role of interventions in couples. In men, improvements in sperm concentrations, motility and normal morphology have been suggested, as well as in sperm DNA integrity, but further high quality research is needed to confirm these findings and demonstrate improvement in live birth rates in their partners.

Acknowledgements

Mrs Cynthia Fraser provided useful assistance in the formulation of a search strategy. Authors responding to queries included Gabrielle Turner McGrievy, Ann Van Oers, Kamilla Karlsen, Kyra Sim, Amany Salama, Rebecca Thomson, Cherrie Galletly, and Hanno Pijl.

Authors' roles

Dr Damian Best was involved in design and conduct of the review, data analysis, drafting the manuscript and critical discussion. Professor Alison Avenell was involved in the design and conduct of the review, supervised data analysis, checked data extraction, and was involved in manuscript revision and critical discussion. Professor Siladitya Bhattacharya was involved in the design of the review and contributed to manuscript revision and critical discussion.

Funding

No specific funding was sought. All authors were employed by the University of Aberdeen in a research capacity. The Health Services Research Unit is core funded by the Chief Scientist Office of the Scottish Government Health and Social Care Directorate.

Conflict of interest

None declared.

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Figure legends

AUTHOR: I have files for a Figure 1 (PRISMA chart in tiff format) plus Figures 2-14 in eps format. The legends below are for only 13 figures. Please would you recheck the figure numbering/titles?

Figure 1. PRISMA flow diagram illustrating the process of selection of studies for inclusion in the systematic review. **AUTHOR:** please would you provide a higher quality image for Production?

Figure 2. **AUTHOR:** it may be helpful to also state in all titles that these are Forest plots. Forest plot - Pregnancies associated with diet, diet and exercise, orlistat and motivational interviewing versus control.

Figure 3. Forest plot - Intervention versus control: live births.

Figure 4. Forest plot - Intervention versus control: spontaneous conceptions.

Figure 5. Forest plot - Intervention versus control: IVF conceptions.

Figure 6. Forest plot - Intervention versus control: miscarriages for all participants enrolled.

Figure 7. Forest plot - Intervention versus control: miscarriages for women who became pregnant.

Figure 8. Forest plot - Intervention versus control: ovulation improvement.

Figure 9. Forest plot - Intervention versus control: improvement of menstrual irregularity.

Figure 10. Forest plot - Intervention versus control: oocytes retrieved per female participant.

Figure 11. Forest plot - Intervention versus control: change in weight (kg).

Figure 12. Forest plot - Intervention versus metformin: women who became pregnant.

Figure 13. Forest plot - Intervention versus metformin: improvement in ovulation.

Figure 14. Forest plot – Intervention versus metformin: improvement in menstrual irregularity per irregular menstruating female participant

AUTHOR: we tend not to include Appendices, therefore these data have been divided and renamed as supplementary files. The quality of the file for the

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Supplementary Data (search strategy) is not high enough for Production, therefore please would you send to me a high quality file, eps or tiff format, and preferably at 300dpi? Word and Powerpoint are acceptable if not pixelated or blurry at 400%. Thank you.

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AUTHOR: for accuracy, please could you include *et al* in the references in the tables below, where required? Thank you.

Table 1. Types of interventions evaluated in studies of weight loss interventions and fertility in women and men who are overweight or obese.

Reducing diet/healthy eating and exercise programme or advice	
~~Duval~~Duval *et al* 2015 G	RCT
~~Karimzadeh~~Karimzadeh *et al* 2010	RCT
~~Moran~~Moran *et al* 2011	RCT
~~Mutsaerts~~Mutsaerts *et al* 2016	RCT
~~Palomba~~Palomba *et al* 2010 G	RCT
~~Sim~~Sim *et al* 2014 G	RCT
~~Clark~~Clark *et al* 1998 G	Non-RCT
~~Crosignani~~Crosignani *et al* 2003	Cohort
De Frène 2015	Cohort
~~Faure~~Faure *et al* 2014	Cohort
~~Galletly~~Galletly *et al* 1996a G	Cohort
~~Galletly~~Galletly *et al* 1996b G	Cohort
~~Hakonsen~~Hakonsen *et al* 2011	Cohort
~~Hollman~~Hollman *et al* 1996	Cohort
~~Khaskheli~~Khaskheli *et al* 2013	Cohort
~~Mahoney~~Mahoney *et al* 2014	Cohort
~~Miller~~Miller *et al* 2008 G	Cohort
~~Salama~~Salama *et al* 2015	Cohort
Reducing diet/healthy eating, weight loss drugs, and exercise programme or advice	
~~Legro~~Legro *et al* 2015	RCT
~~Lazurova~~Lazurova *et al* 2004	Non-RCT
~~Kort~~Kort *et al* 2014	Cohort
Reducing diet/health eating, or type of diet	

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~~Becker~~Becker *et al* 2015	RCT
~~Moran~~Moran *et al* 2003	RCT
~~Qublan~~Qublan *et al* 2007	RCT
~~Turner-McGrievy~~Turner-McGrievy *et al* 2014	RCT
~~Aliyeva~~Aliyeva *et al* 1993	Non-RCT
~~Palomba~~Palomba *et al* 2008 G	Non-RCT
~~Awartani~~Awartani *et al* 2012	Cohort
~~Kiddy~~Kiddy *et al* 1992	Cohort
~~Mavropoulos~~Mavropoulos *et al* 2005 G	Cohort
~~Thomson~~Thomson *et al* 2009	Cohort
~~Tsagareli~~Tsagareli *et al* 2006	Cohort
~~Van Dam~~Van Dam *et al* 2004	Cohort
Behavioural therapy, including motivational interviewing	
~~Karlsen~~Karlsen *et al* 2013	Non-RCT
~~Koning~~Koning *et al* 2015 C	Non-RCT
~~Homan~~Homan *et al* 2012	Cohort
Exercise programme	
~~Thomson~~Thomson *et al* 2008 G	RCT
~~Palomba~~Palomba *et al* 2008	Non-RCT
Orlistat	
~~Kumar~~Kumar *et al* 2014	RCT
Metformin	
~~Karimzadeh~~Karimzadeh *et al* 2010	RCT
~~Kumar~~Kumar *et al* 2014	RCT
~~Qublan~~Qublan *et al* 2007	RCT
~~Sonmez~~Sonmez *et al* 2005	RCT
~~Lazurova~~Lazurova *et al* 2004	Non-RCT
Acarbose	
~~Sonmez~~Sonmez *et al* 2005	RCT
Detailed lifestyle questionnaire	

~~Chavarro~~Chavarro *et al* 2012 C	Cohort

G, group intervention; C, couples were able to take part

Table 2. Reproductive outcomes for women (lower numbers for ranking indicate better outcomes).

Study ID	Intervention arm		Pregnancies per participant		% Live births per participant		% Miscarriages per participant (fewer = better)		% Miscarriages per pregnancy (fewer = better)		% Improved ovulation per anovulatory participant		% Improved menstrual irregularity / irregular menses per participant		Time to conception per participant (less = better)	
		N	Rank	%	Rank	%	Rank	%	Rank	%	Rank	%	Rank	%	Rank	
~~Duval~~Duval *et al* 2015	Diet & exercise	24	1	79.2	2	62.5										
~~Clark~~Clark *et al* 1998	Diet & exercise	67	2	77.6	1	67.2	13	14.9	9	18.2	1	89.6				
~~Kort~~Kort *et al* 2014	Diet & exercise	52	3	65.4	4	48.1									4	226.57 days for those with 10&% weight loss
~~Mutsaerts~~Mutsaerts *et al* 2016	Diet & exercise	280	4	63.9	3	53.2	12	14.6	12	22.9	17	42.4			3	Median 7.2 months (IQR 2.6, 12.0)
~~Khaskheli~~Khaskheli *et al* 2013	Diet & exercise	85	5	63.5	8	37.6	11	10.6	7	16.7						
~~Galletly~~Galletly *et al* 1996(b)	Diet & exercise	58	6	58.6												
~~Moran~~Moran *et al* 2011	Diet & exercise	18	7	57.1	7	38.9										
~~Koning~~Koning *et al* 2015	Motivational interviewing	102	8	53.9	5	47.1	2	2.0	2	3.6						
~~Chavarro~~Chavarro *et al* 2012	Questionnaire	170	9	51.2												
~~Aliyeva~~Aliyeva *et al* 1993	Acupuncture	20	10	45.0							9	55.0	15	45.0		
~~Sim~~Sim *et al* 2014	Diet & exercise	26	11	44.4	6	44.4	14	18.5	14	41.7						
~~Kumar~~Kumar *et al* 2014	Orlistat	30	11	40.0							10	50.0				
~~Mavropoulos~~Mavropoulos *et al* 2005	Low calorie ketogenic diet	5	13	40.0												

Study ID	Intervention arm		Pregnancies per participant		% Live births per participant		% Miscarriages per participant (fewer = better)		% Miscarriages per pregnancy (fewer = better)		% Improved ovulation per anovulatory participant		% Improved menstrual irregularity / irregular menses per participant		Time to conception per participant (less = better)	
		N	Rank	%	Rank	%	Rank	%	Rank	%	Rank	%	Rank	%	Rank	
~~Palomba~~Palomba *et al* 2008	Exercise	20	14	35.0			7	5.0	5	14.3	5	65.0				
~~Homan~~Homan *et al* 2012	Motivational interviewing	35	15	34.8			5	4.3	3	12.5						
~~Awartani~~Awartani *et al* 2012	Weight reduction advised	90	16	34.4												
~~Qublan~~Qublan *et al* 2007	Diet	24	17	33.3			4	4.2	3	12.5	10	50.0	11	61.9		
~~Legro~~Legro *et al* 2015	Diet & exercise	50	18	32.0	9	26.0	9	6.0	10	18.8	6	60.3				
~~Crosignani~~Crosignani *et al* 2003	Diet & exercise	33	19	30.3	10	24.2					8	55.6	6	66.7		
~~Aliyeva~~Aliyeva *et al* 1993	Diet	60	20	30.0							14	46.7	8	63.3		
~~Kiddy~~Kiddy *et al* 1992	Very low calorie diet/Low calorie diet	24	21	29.2	14	16.7	10	8.3	13	28.6			20	29.4		
~~Hollman~~Hollman *et al* 1996	Diet & exercise	35	22	28.6	12	22.9	8	5.7	11	20.0			3	80.0		
~~Legro~~Legro *et al* 2015	Diet, exercise, oral contraceptive pill	50	23	28.0	11	24.0	3	4.0	5	14.3	4	67.1				
~~Qublan~~Qublan *et al* 2007	Metformin	22	24	27.3			6	4.5	7	16.7	15	45.5	12	61.1		
~~Kumar~~Kumar *et al* 2014	Metformin	30	25	26.7							20	23.3				
~~Becker~~Becker *et al* 2015	Diet	14	26	21.4	13	21.4										
~~Karimzadeh~~Karimzadeh *et al* 2010	Diet & exercise	75	26	20.0									6	66.7		
~~Lazurova~~Lazurova *et al* 2004	Metformin	30	28	20.0									4	70.0		
~~Miller~~Miller *et al* 2008	Diet & exercise	12	29	16.7									1	83.3		
~~Karimzadeh~~Karimzadeh *et al* 2010	Metformin & clomiphene	88	30	14.8									10	62.5		
DeFrene 2015	Diet & exercise	23	31	13.0												
~~Karimzadeh~~Karimzadeh *et al* 2010	Metformin	90	32	12.2									13	55.6		
~~Salama~~Salama *et al* 2015	Mediterranean diet & exercise	58	33	12.1									9	62.8		

Study ID	Intervention arm		Pregnancies per participant		% Live births per participant		% Miscarriages per participant (fewer = better)		% Miscarriages per pregnancy (fewer = better)		% Improved ovulation per anovulatory participant		% Improved menstrual irregularity / irregular menses per participant		Time to conception per participant (less = better)	
		N	Rank	%	Rank	%	Rank	%	Rank	%	Rank	%	Rank	%	Rank	
~~Turner-McGrievy~~Turner-McGrievy *et al* 2014	Low calorie diet	9	34	11.1							22	0.0				
~~Palomba~~Palomba *et al* 2008	Diet	20	35	10.0			1	0.0	1	0.0	19	25.0				
~~Galletly~~Galletly *et al* 1996(a)	Exercise & advice	96	36	9.4												
~~Moran~~Moran *et al* 2003	High protein diet	14	37	8.7									21	26.1	1	4-5 weeks
~~Lazurova~~Lazurova *et al* 2004	Sibutramine, diet, exercise	15	38	6.7									14	53.3		
~~Thomson~~Thomson *et al* 2008	Diet & aerobic exercise	31	39	6.3							10	50.0	17	42.9		
~~Moran~~Moran *et al* 2003	Low protein diet	14	40	4.3									22	22.7	1	4-5 weeks
~~Thomson~~Thomson *et al* 2008	Diet	30	41	3.3							10	50.0	24	21.4		
~~Palomba~~Palomba *et al* 2010	Diet & exercise, Clomiphene	32	42	3.1							18	37.5	19	34.4		
~~Thomson~~Thomson *et al* 2008	Diet & aerobic & resistance exercise	33	43	3.0							16	42.8	16	44.4		
Turner McGrievy 2014	Vegan diet	9	44	0							22	0.0				
~~Sonmez~~Sonmez *et al* 2005	Acarbose	15									2	86.7	5	69.2		
~~Sonmez~~Sonmez *et al* 2005	Metformin	15									3	80.0	2	80.0		
~~Van Dam~~Van Dam *et al* 2004	Very low calorie diet	15									6	60.0				
~~Thomson~~Thomson *et al* 2009	Diet	52									20	19.2	18	42.3		
~~Palomba~~Palomba *et al* 2010	Diet & exercise	32									21	12.5	25	12.5		
~~Mahoney~~Mahoney *et al* 2014	Motivational interviewing, diet, exercise												23	22.2		

Table 3. Weight reduction outcomes for women (lower numbers for ranking indicate better outcomes).

Study ID	Intervention Arm		Mean Weight change (kg) Per Participant		Mean BMI change (kg/m^2) Per Participant		Mean Waist Circumference change (cm) Per Participant	
		N	Rank	Change	Rank	Change	Rank	Change
~~Mavropoulos~~Mavropoulos *et al* 2005	Low calorie ketogenic diet	5	1	-12.34 ± 6.37	8	-4.0		
~~Hollman~~Hollman *et al* 1996	Diet & exercise	35	2	-10.2 ± 7.9	10	-3.4 (median)		
~~Clark~~Clark *et al* 1998	Diet & exercise	67	3	-10.2 ± 4.3	9	-3.7 ± 1.6		
~~Thomson~~Thomson *et al* 2008	Diet & aerobic exercise	31	4	-10.1 ± 5.6			1	-11.7 ± 6.1
~~Karlsen~~Karlsen *et al* 2013	Motivational interviewing	110	5	-9.3	11	-3.3		
~~Thomson~~Thomson *et al* 2009	Diet	52	6	-9.0 ± 0.8 (SEM)			4	-10.4 ± 0.9 (SEM)
~~Thomson~~Thomson *et al* 2008	Diet	30	7	-8.6 ± 6.0			3	-10.8 ± 7.1
~~Thomson~~Thomson *et al* 2008	Diet & aerobic & resistance exercise	3	8	-8.6 ± 5.2			2	-11.0 ± 6.3
~~Moran~~Moran *et al* 2003	High protein diet	14	9	-8.5 ± 1.1				
~~Kumar~~Kumar *et al* 2014	Orlistat	30	10	-7.81 ± 0.66%	4	-8.12 ± 6.71%		
~~Kumar~~Kumar *et al* 2014	Metformin	30	11	-7.78 ± 0.57% (SEM)	3	-8.40 ± 0.65% (SEM)	14	-2.68 ± 0.16% (SEM)
~~Kiddy~~Kiddy *et al* 1992	Very low calorie diet/low calorie diet	24	12	-6.9 ± 6.7				
~~Moran~~Moran *et al* 2003	Low protein diet	14	13	-6.9 ± 0.8 (SEM)				
~~Sim~~Sim *et al* 2014	Diet & exercise	26	14	-6.6 ± 4.6	14	-2.4 ± 1.6	6	-8.7 ± 5.6
~~Salama~~Salama *et al* 2015	Mediterranean diet & exercise	58	15	-6.3 ± 20.8	16	-2.37 ± 7.28	7	-6.45 ± 14.13
~~Legro~~Legro *et al* 2015	Lifestyle	50	16	-6.2, 95% CI (-7.3, -5.3)			8	-6.3, 95% CI (-9.2, -3.4)
~~Galletly~~Galletly *et al* 1996(b)	Diet and exercise	58	17	-6.2 ± 4.5	13	-2.4 ± 1.7		
~~Legro~~Legro *et al* 2015	Diet, exercise, oral contraceptive pill	50	18	-6.1, 95% CI (-7.0, -5.2)			9	-6.2, 95% CI (-9.1, -3.3)
~~Tsagareli~~Tsagareli *et al* 2006	Very low calorie diet	6	19	-5.6; Range -8.2 to -5.3	17	-2.1; Range -1.8 to -3.2	5	-10.0; Range -7 to-14
~~Galletly~~Galletly *et al* 1996(a)	Diet & exercise	96	20	-5.2 ± 5.1				
~~Becker~~Becker *et al* 2015	Diet	14	21	-4.51 ± 0.83 (SEM)			15	-1.31 ± 10.5
~~Palomba~~Palomba *et al* 2010	Diet & exercise, Clomiphene	32	22	-4.42 ± 9.22	12	-2.64 ± 4.26	11	-4.92 ± 5.87

Study ID	Intervention Arm		Mean Weight change (kg) Per Participant		Mean BMI change (kg/m²) Per Participant		Mean Waist Circumference change (cm) Per Participant	
		N	Rank	Change	Rank	Change	Rank	Change
~~Mutsaerts~~Mutsaerts *et al* 2016	Diet & exercise	280	23	-4.4 ± 5.8	21	-1.3 (Median) IQR (-2.5, -0.07)		
~~Koning~~Koning *et al* 2015	Motivational interviewing	102	24	-4.3 ± 0.8 (SEM)	20	-1.4 ± 0.3 (SEM)		
~~Palomba~~Palomba *et al* 2010	Diet & exercise	32	25	-4.21 ± 8.56	15	-2.39 ± 3.54	12	-3.84 ± 6.35
~~Moran~~Moran *et al* 2011	Diet & exercise	18	26	-3.8 ± 3.0	19	-1.4 ± 1.1	10	-5.3 ± 4.6
~~Mahoney~~Mahoney *et al* 2014	Motivational interviewing, diet, exercise	9	27	-3.18 ± 2.27	24	-0.7 ± 7.31		
~~Turner-McGrievy~~Turner-McGrievy *et al* 2014	Vegan diet	9	28	-2.1 ± 3.5				
~~Turner-McGrievy~~Turner-McGrievy *et al* 2014	Low calorie diet	9	29	-0.4 ± 0.9				
~~Chavarro~~Chavarro *et al* 2012	Questionnaire	170	30	&0.3 (Median) IQR (-0.1, 1.8)				
~~Kort~~Kort *et al* 2014	Diet & exercise	52			1	-13.89% ± 3.71% in 17 with 10&% weight loss -3.79% ± 3.98% in 35 with <10% weight loss		
~~Khaskheli~~Khaskheli *et al* 2013	Diet & exercise	85			2	-9.6 ± 1.23		
~~Lazurova~~Lazurova *et al* 2004	Sibutramine, diet, exercise	15			5	-4.6 ± 4.2 (SEM)		
~~Qublan~~Qublan *et al* 2007	Diet	24			6	-4.8		
~~Qublan~~Qublan *et al* 2007	Metformin	22			7	-4.1		
~~Miller~~Miller *et al* 2008	Diet & exercise	12			18	-2.06 ± 0.51 (SEM)		
~~Sonmez~~Sonmez *et al* 2005	Acarbose	15			22	-1.1 ± 2.78		
~~Lazurova~~Lazurova *et al* 2004	Metformin	30			23	-0.85 ± 0.38 (SEM)		
~~Sonmez~~Sonmez *et al* 2005	Metformin	15			25	-0.3 ± 2.47		
~~Homan~~Homan *et al* 2012	Motivational interviewing	35		"47% of the overweight participants had a modest loss of between 1 and 5 kg (not statistically significant)"				-3.8 in ½ of those attending follow-up and not pregnant
~~Duval~~Duval *et al* 2015	Diet & exercise	24		10/24 had ≥ 5% weight loss				12/24 had ≥ 5cm reduction (compared to 11/31 in control group)

Study ID	Intervention Arm		Mean Weight change (kg) Per Participant		Mean BMI change (kg/m^2) Per Participant		Mean Waist Circumference change (cm) Per Participant	
		N	Rank	Change	Rank	Change	Rank	Change
				(compared to 11/31 in control group)				
~~Karimzadeh~~Karimzadeh *et al* 2010	Diet & exercise	75						Significantly lower waist circumference (P=0.001) in the lifestyle group than in the clomiphene, metformin, and clomiphene/metformin groups
~~Aliyeva~~Aliyeva *et al* 1993	Diet	60		"30-40% decrease in body weight in 2-4 months"				
~~Aliyeva~~Aliyeva *et al* 1993	Acupuncture	20		"Slower rate and extent of weight reduction: 7-9 months"				
~~Awartani~~Awartani *et al* 2012	Weight reduction advised	90				23/90 reduced their BMI below 35; 65/90 did not		
~~Crosignani~~Crosignani *et al* 2003	Diet & exercise	33						Those with 5% weight loss had mean waist circumference 94 cm, SD 9 Those with 10% weight loss had mean 86, SD 7
~~Van Dam~~Van Dam *et al* 2004	Very low calorie diet	15		14/15 loss at least 10% of body weight				
~~Palomba~~Palomba *et al* 2008	Exercise	20		Ovulatory (n=13): Mean -5.6%, SD 1.6% Anovulatory (n=7): Mean -2.0% ,SD 0.2%		Ovulatory (n=13): Mean -10.0%, SD 3.7% Anovulatory (n=7): Mean -1.4%, SD 2.1%		Ovulatory (n=13): Mean -9.6%, SD 2.1% Anovulatory (n=7): Mean -2.5%, -SD 2.9%
~~Palomba~~Palomba *et al* 2008	Diet	20		Ovulatory (n=5): Mean -10.5%, SD 4.1% Anovulatory (n=15): Mean -2.3%, SD 3.1%		Ovulatory (n=5): Mean -15.4%, SD 3.9% Anovulatory (n = 15): Mean -4.0%, SD 5.2%		Ovulatory (n=5): Mean -9.4%, SD 2.5% Anovulatory (n=15): Mean -2.8%, SD 3.1%

Table 4. Reproductive and weight outcomes for infertile men.

	~~Faure~~Faure *et al* 2014 N=8	~~Hakonsen~~Hakonsen *et al* 2011 N=27 of 44 at follow-up
Clinical pregnancy rate	8/8	
Live birth rate	8/8	
Improvement in sperm DNA integrity	6/6 consenting to semen analysis upon completion	
Change in sperm concentration (million/ml) Group 1: Weight loss 3.5-12.1% Group 2: Weight loss 12.2-17.1% Group 3: Weight loss 17.2-25.4%		Group 1 (n=9) Mean -11 95% CI -49, 27 Group 2 (n=9) Mean +19 95% CI -23, 61 Group 3 (n=9) Mean +17 95% CI -24, 58
Change in sperm motility (% motile)		Group 1 (n=8) Mean -2 95% CI -15, 11 Group 2 (n=9) Mean +4 95% CI -10, 18 Group 3 (n=9) Mean +11 95% CI -3, 25
Change in normal sperm morphology (% normal forms)		Group 1 (n=9) Mean 0 95% CI -2, 4 Group 2 (n=9) Mean +1 95% CI -3, 4 Group 3 (n=9) Mean +4 95% CI 1, 7
Change in weight (kg)	Mean -4.40 SD 5.00	Median -22 Range -4 to –39
Change in BMI (kg/m^2)	Mean -1.22 SD 1.38	
Change in Waist circumference (cm)	Mean -8.50 SD 7.89	