CHAPTER 6

DROP-OUT IS A PROBLEM IN LIFESTYLE INTERVENTION PROGRAMS FOR OVERWEIGHT AND OBESE INFERTILE WOMEN: A SYSTEMATIC REVIEW


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ABSTRACT

Title: Drop-out is a problem in lifestyle intervention programs (LIPs) for overweight and obese infertile women: a systematic review.

Study question: What are the drop-out rates in LIPs for overweight and obese infertile women and can intervention or patient-related baseline factors associated with drop-out be identified in these women?

Summary answer: Median drop-out rate was 24% in overweight and obese infertile women who participated in a LIP, clinical useful intervention or patient-related factors associated with drop-out could not be identified.

What is known already: Overweight and obese infertile women might improve their chance of conception when they improve their lifestyle and lose weight. Drop-out from LIPs might reduce the chance of losing considerable weight and is therefore considered to be an important limiting factor of the success of LIPs.

Study design: Systematic review of studies investigating the effect of LIPs in overweight and obese infertile women, published between January 1980 and December 2012. From these studies, drop-out rates and intervention and patient-related baseline factors associated with drop-out as well as weight loss and pregnancy rates were recorded.

Participants/materials, setting, methods: Overweight and obese women with infertility participating in LIPs in order to lose weight.

Main results and the role of chance: 15 studies were identified, of which ten reported drop-out rates (median drop-out rate 24% (range: 0-31%). Four studies reported baseline characteristics of drop-outs, but modifiable predictors of drop-out could not be identified. Weight loss and pregnancy rates were lower in women who dropped out than in women who completed the LIPs.

Limitations, reasons for caution: Limited numbers of studies investigated patient-related factors associated with drop-out. The heterogeneity in the studies precluded us from drawing firm conclusions on the relation between the type of intervention and drop-out.

Wider implications of the findings: Drop-out is a major drawback since it predisposes to less weight loss and lower pregnancy rates. Identification of predictors of drop-out is needed to identify overweight and obese infertile women who are prone for drop-out. These women might benefit from extra support and monitoring, potentially increasing adherence rates, weight loss and pregnancy chances.

Study funding/competing interest(s): MM is supported by a research grant from the Dutch Organization for Health Research and Development (ZonMw). There are no competing interests.
INTRODUCTION

Overweight (body mass index (BMI) 25-29.9 kg/m²) and obese (BMI ≥ 30 kg/m²) women have decreased chances of spontaneous conception and lower success rates with fertility treatment (1-5). It has been shown that losing weight might improve the chance of conception in this specific patient category (6-8). Overweight and obese infertile women are therefore advised to participate in lifestyle intervention programs (LIPs) in order to lose weight before entering fertility programs (9).

In LIPs designed for overweight and obese men and women to diminish long-term health risks, drop-out rates have been reported to be up to 77% (10-13). This is considered an important limiting factor in the success of LIPs, since drop-out is related to smaller weight change (12). Hence, identifying patients at risk for drop-out might contribute to the development of strategies to increase adherence rates. In LIPs addressing metabolic health risks of obesity in men and women, research has focused on patient-related factors associated with increased drop-out risk. Socio-demographic factors including full-time employment, psychological factors such as depression and lower quality of life and behavioural factors like smoking were all shown to be associated with increased drop-out rates and might therefore be considered as predictors for drop-out (13-15).

Not only patient-related factors, but also the type of intervention may influence the drop-out risk. In a meta-analysis on the long-term effect of structured weight-loss programs it was demonstrated that very low calorie diets, in which an intake of less than 800 kcal per day was advised, led to higher drop-out rates than diets in which subjects were advised to lower their calorie intake by 600 kcal per day (16).

Due to the emotional and social burden of infertility (17) combined with the short-term goal of conception, it is conceivable that overweight and obese infertile women are more motivated to achieve weight loss than women and men who have to lose weight for long-term health improvement. However, drop-out rates in LIPs for overweight and obese infertile women have not been systematically reported and little is known about intervention and patient-related baseline factors associated with drop-out in this specific patient population. We therefore systematically reviewed the literature on LIPs in overweight and obese infertile women in order to investigate drop-out rates and to identify possible intervention- and patient-related baseline factors associated with drop-out. In addition, we aimed to compare weight loss and pregnancy rates between overweight and obese infertile women who dropped out of the LIPs and women who completed these programs to estimate the effect of drop-out on these important clinical outcome measures.
MATERIALS AND METHODS

We searched PubMed, Embase, and the Cochrane Library for studies published in the English literature between January 1980 and December 2012, investigating the effect of LIPs in overweight and obese infertile women. Women with chronic anovulation or ovulatory women who had tried to conceive for at least one year were defined as infertile. Search terms used included BMI, overweight, obesity, infertility, polycystic ovary syndrome (PCOS), lifestyle, intervention program, diet, exercise, and weight loss (see Appendix I for the full list of key words).

Two reviewers independently screened titles and abstracts of all retrieved studies (MM and WK). Full text reports of all studies that were likely to investigate the effect of LIPs in overweight and obese infertile women were obtained. Reviews were excluded. The references of the selected articles were checked for relevant and related publications. We attempted to contact the authors for additional information if deemed necessary. Studies in which it was unclear whether the patient population tried to conceive and studies in which birth-control was advised during the intervention program, were excluded.

We extracted information on study design, number of participants, baseline BMI, design of the LIP, mean weight loss in completers and drop-outs, spontaneous pregnancy rates during the LIP and during follow-up of the LIP, drop-out rates and reasons for drop-out. Drop-out was defined as withdrawal from the program before completing the LIP. Women who discontinued the LIP because of pregnancy were not considered as drop-out.

To evaluate a possible association between the type of intervention and drop-out and pregnancy rates, we extensively mapped the LIP designs of the included studies. Different study arms were compared in order to detect possible relations between a specific type of intervention and drop-out and pregnancy rates. In addition, possible associations between baseline patient characteristics and drop-out reported in all included studies were searched for.

Disagreement was resolved by discussion and consensus. If consensus could not be reached, a third reviewer (AH) was consulted.

Statistics
The weighted average, which corrects for sample size, was used to compare pregnancy and drop-out rates between the different types of intervention of the included studies.
RESULTS

Our initial literature search generated 609 studies (Figure I). After screening the titles and abstracts, 96 articles were identified as potentially eligible. After reading these full-text publications, 81 articles were excluded (see separate reference list in Appendix II), while data of the remaining 15 studies were included and subsequently analysed. Table I summarises the detailed content of the included studies. Data reported in Table I are extracted from the original articles. Of the 15 included studies, 13 were prospective cohort studies and two were randomised controlled trials. The participants were overweight and obese infertile women with a BMI ranging from 27.2 up to 43 kg/m². The median duration of the programs was 24 weeks (range 6-32 weeks). Of the 15 included studies, 14 reported pregnancy rates: median pregnancy rate was 23% (range 1-56%). The amount of weight loss in the included studies could not be summarised, as this was not reported in a consistent way. Ten studies reported drop-out rates: median drop-out rate was 24% (range 0-31%). Three studies provided reasons for drop-out.

Figure I. Flow Chart

<table>
<thead>
<tr>
<th>609 records identified by literature search</th>
<th>513 records excluded after initial assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>96 full-text articles assessed for eligibility</td>
<td>81 full-text articles excluded after further assessment (Appendix II)</td>
</tr>
<tr>
<td>15 studies included in the review</td>
<td></td>
</tr>
</tbody>
</table>

**Type of intervention and drop-out**

We extensively mapped the LIP designs of the included studies; different study arms within the studies were thereby allocated to the different intervention strategies.

- **Dietary regimen alone (n=6):** In total, 118 women participated, of whom 32 women conceived (weighted average 6%, one program did not report pregnancy rates), while 20 dropped out (weighted average 4%, three programs did not report drop-out rates). Median duration of these programs was 24 weeks (range 6-24 weeks) (18-23).

- **Dietary regimen combined with exercise program (n=8):** In total, 310 women participated, of whom 56 women conceived (weighted average 11%), while 96
women dropped out (weighted average 7%; two programs did not report drop-out rates). Median duration of the programs was 24 weeks (range 6-32 weeks) (6-8,24-28).

- **Structured exercise program (n=1):** 20 women participated in this program of whom seven conceived (35%), while 14 women dropped out (15%). Duration of the program was 24 weeks (22).

- **Dietary regimen, exercise program and medication or a placebo (n=3):** In total, 175 women participated, of whom nine conceived (weighted average 3%), while 17 women dropped out (weighted average 7%). Median duration was 24 weeks (range 6-24 weeks) (25,29).

- **Medication only (n=5):** In total, 322 women participated of whom 43 women conceived (weighted average 11%). Only one study reported drop-out rates (no drop-out). Median duration was 18 weeks (range 3-24 weeks) (23-25).

**Baseline characteristics of participants associated with drop-out**

In four studies, baseline characteristics of drop-outs were described. Kuchenbecker et al. (2011) found higher free testosterone and total testosterone levels in drop-outs (26). Clark et al. (1998) did not observe different baseline characteristics in drop-outs and completers, but showed that drop-outs underwent significantly less cycles of fertility treatment prior to the LIP, compared with women who completed the LIP (6). Tang et al. (2006) could not demonstrate any differences in baseline characteristics between completers and drop-outs) (29). Crosignani et al. (2003) defined drop-out as not losing weight within six months. They investigated baseline patient characteristics that might predict weight loss and found that the fat mass ratio was the only anthropometric variable which was significantly associated with the probability of losing weight: the lower the basal ratio, the higher the probability of losing weight (20).

**Weight loss and pregnancy rates in drop-outs**

Three studies reported the amount of weight loss and/or pregnancy rates in women who dropped out (6,20,26). These studies showed that completers lost significantly more weight than drop-outs. In addition, none of the drop-outs conceived spontaneously during or within the month after drop-out (Table I).
### Weight loss and spontaneous pregnancy rates in completers

- **Weight loss:** 9.6 kg
  - **Pregnancy rates:** 56% (N=10)

- **Weight loss:** 11% weight reduction (mean BMI -4.1 kg/m²)
  - **Pregnancy rates:** not reported

- **Weight loss:** 25 women lost 5% of initial weight
  - **Pregnancy rates:** 30% (n=10) within 12 months

- **Weight loss:** 7-12% weight loss (range)
  - **Pregnancy rates:** 33% (n=2) within 6 months after study termination.

### Drop-out rates, weight loss and pregnancy rates in drop-outs

#### Study design

- **Prospective cohort study**
- **6-weeks very low calorie diet consisting of 650 kcal/day followed by a 4-week recovery period (normocaloric diet).**
- **16-24-weeks dietary regimen consisting of a diet containing 500 kcal/day.**
- **24-weeks structured exercise program (SET): 3 training sessions per week.**

#### Baseline BMI of all participants (kg/m²)

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Baseline BMI of all participants (kg/m²)</th>
<th>Intervention</th>
<th>Weight loss and spontaneous pregnancy rates in completers</th>
<th>Drop-out rates, weight loss and pregnancy rates in drop-outs</th>
</tr>
</thead>
</table>
| Bates and Whitworth 1962   | 18 infertile women with PCOS | 28.8 (mean)                              | Dietary regimen designed to decrease body weight at the rate of 500 g per week. Guidance of a therapeutic dietician. | Weight loss: 9.6 kg  
  - Pregnancy rates: 56% (N=10) | 28% (n=5)  
  - Reasons: not reported  
  - Weight loss: not reported  
  - Pregnancy rates: not reported |
| Büttow et al. 2000         | 10 obese infertile women | 37.1 ± 3.3 (mean, SEM)                   | 6-weeks very low calorie diet consisting of 650 kcal/day followed by a 4-week recovery period (normocaloric diet). | Weight loss: 11% weight reduction (mean BMI -4.1 kg/m²)  
  - Pregnancy rates: not reported | No information on drop-out reported |
| Crosignani et al. 2003     | 33 anovulatory PCOS women | 32.1 ± 4.2 (mean, SD)                    | 24-weeks dietary regimen consisting of a diet containing 1200 kcal per day. Aerobic exercise was recommended. Regular controls and weight assessment were carried out every 6-8 weeks. | Weight loss: 25 women lost 5% of initial weight  
  - Pregnancy rates: 30% (n=10) within 12 months | 24% (n=8)  
  - Reasons: did not reach 5% weight loss within 6 months  
  - Weight loss: not reported  
  - Pregnancy rates: 0% |
| Harlass et al. 1984        | 6 infertile women with irregular or absent menses | 43 (mean)                                | 16-24-weeks dietary regimen consisting of a calorie-restricted diet of 500 kcal/day. All patients were followed weekly by the authors. | Weight loss: 7-12% weight loss (range)  
  - Pregnancy rates: 3.3% (n=2) within 6 months after study termination. | No information on drop-out reported |
| Kiddy et al. 1992          | 24 PCO women | 34.1 ± 4.9 (mean, SD)                    | 28-weeks dietary regimen: BMI 25-30: low-fat diet consisting of 1000 kcal/day for 28 weeks. BMI > 30: diet consisting of 330 Kcal/day for 4 weeks followed by a low-fat diet consisting of 1000 kcal/day for 24 weeks. Monthly assessment with a dietician. | Weight loss: 6.9 kg (mean)  
  - Pregnancy rates: 18% (n=6) | 17% (n=4)  
  - Reasons: social reasons or noncompliance after 4-6 months  
  - Weight loss: not reported  
  - Pregnancy rates: not reported |
| Palomba et al. 2008        | 40 infertile PCOS women | 1.33 ± 1.3  
  2.32 ± 1.4 | 1. 24-weeks structured exercise program (SET): 3 training sessions per week.  
  2. M. Ovulatory patients (n=3) | Weight loss (including drop-outs)  
  - 1. Ovulatory patients (n=3) | 1. 15% (n=3)  
  2. 35% (n=7) |

### Table I: Characteristics of the included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Intervention</th>
<th>Baseline BMI of all participants (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bates and Whitworth 1962</td>
<td>18 infertile women with PCOS</td>
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<td>6 infertile women with irregular or absent menses</td>
<td>16-24-weeks dietary regimen consisting of a calorie-restricted diet of 500 kcal/day. All patients were followed weekly by the authors.</td>
<td>43 (mean)</td>
</tr>
<tr>
<td>Kiddy et al. 1992</td>
<td>24 PCO women</td>
<td>28-weeks dietary regimen: BMI 25-30: low-fat diet consisting of 1000 kcal/day for 28 weeks. BMI &gt; 30: diet consisting of 330 Kcal/day for 4 weeks followed by a low-fat diet consisting of 1000 kcal/day for 24 weeks. Monthly assessment with a dietician.</td>
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  2. 35% (n=7) |
<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Study Design</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pasquali et al. 1989</td>
<td>Prospective cohort study</td>
<td>20 women with amenorrhea</td>
<td>2-week period consisting of 30 min exercising on a bicycle ergometer 2.24-weeks hypocaloric hyperproteic diet aimed at 800 kcal deficit per day in combination with weekly interactive group education meetings</td>
<td>Weight loss: 9.8 kg (4.8-15.2 kg); Pregnancy rates: 20% (n=1)</td>
</tr>
<tr>
<td>Qublan et al. 2007</td>
<td>Prospective comparative study, 2 study arms</td>
<td>46 PCOS patients: 1. 32.2 (29-43) (mean, range)</td>
<td>24-weeks dietary regimen: - 3 days 2200 Kcal/day standardized diet containing 250 g carbohydrate followed by - 6-12 months hypocaloric diet of 1000-1500 Kcal/day Duration of treatment period was determined by therapeutic result or the women’s willingness to continue the diet.</td>
<td>Weight loss: not reported BMI change 1.4.8 kg/m² 2.4.1 kg/m² Pregnancy rates: 1.33% (n=8) 2.27% (n=6)</td>
</tr>
<tr>
<td>Stamets et al. 2004</td>
<td>RCT 2 Study arms</td>
<td>35 infertile PCOS women: 1. 36.1 ± 4.8 (mean, SD)</td>
<td>4-weeks during diet consisting of: 1. High protein 2. High carbohydrate Weekly guidance of a dietician.</td>
<td>Weight loss: not reported Pregnancy rates: not reported</td>
</tr>
<tr>
<td>Thomson et al. 2008</td>
<td>RCT 3 study arms</td>
<td>94 PCOS women: 1. 36.1 ± 4.8 (mean, SD)</td>
<td>20-weeks lifestyle intervention consisting of a high-protein diet (1195-1434 kcal/day) combined with: 1. no exercise 2. walking/jogging program 5 times per week 3. walking/jogging program 5 times</td>
<td>Weight loss: Overall: 9.4 kg ± 1.9 (mean ± % of initial weight) 1.8.6 kg ± 6.0 2.10.1 kg ± 5.6 3.8.6 kg ± 5.2 (mean ± SD)</td>
</tr>
</tbody>
</table>

**Reasons:** not reported

**Weight loss:** not reported

**Pregnancy rates:** not reported
<table>
<thead>
<tr>
<th>Study Authors</th>
<th>Study Design</th>
<th>Sample Size</th>
<th>Mean BMI (Range)</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolino et al., 2005</td>
<td>Prospective cohort study</td>
<td>144 PCOS women</td>
<td>35 ± 5 (mean, SD)</td>
<td>28-weeks dietary regimen: BMI 25-30: low-fat diet consisting of 1000 kcal/day for 7 months. BMI &gt; 30: diet consisting of 500 kcal/day for 4 weeks followed by a low-fat diet consisting of 1000 kcal/day for 6 months. Results were recorded in a diary.</td>
<td>Pregnancy rates: 1. 3% (n=1) 2. 6% (n=2) 3. 3% (n=1)</td>
</tr>
<tr>
<td>Andersen et al., 1995</td>
<td>Prospective cohort study</td>
<td>9 PCOS women</td>
<td>34.1 (28.7–40.7) median (range)</td>
<td>24-weeks dietary regimen consisting of 4 weeks 421 kcal/day and 20 weeks 1000-1500 kcal/day. Regularly advice to take a daily walk. Monthly examining by a dietician.</td>
<td>Weight loss: 6.0 kg (mean) Pregnancy rates: 25% (n=36)</td>
</tr>
<tr>
<td>Aubuchon et al., 2009</td>
<td>Retrospective chart review</td>
<td>37 PCOS women</td>
<td>36.4 ± 5.3 (mean, SEM)</td>
<td>14-weeks supervised fitness program: Individualized exercise and nutrition assessments. Group exercise (200-300 minutes per week). Group nutrition classes (90 min/wk for 4 weeks). Monthly support groups. Dietary regimen aimed on 500 kcal/day reduction in current diet.</td>
<td>Weight loss: 3.7 kg (mean) Pregnancy rates: 8% (n=3)</td>
</tr>
<tr>
<td>Clark et al., 1998</td>
<td>Prospective cohort study</td>
<td>87 infertile women</td>
<td>Completers: 37.4 ± 6.9 Drop-outs: 35.9 ± 4.1 (mean, SD)</td>
<td>24-weeks group treatment program emphasizing dietary changes and regular exercise containing: - 1hr/wk exercise with fitness instructor - 1hr/wk group session with psychiatrist, dietician or reproductive medicine specialist</td>
<td>Weight loss: 10.2 ± 4.3 kg (mean ± SD) Pregnancy rates: 27% (n=18)</td>
</tr>
<tr>
<td>Hollmann et al., 1996</td>
<td>Prospective cohort study</td>
<td>35 infertile women</td>
<td>Between 30.8-37.3</td>
<td>32-weeks dietary regimen consisting of regularly advice to reduce weekly</td>
<td>Weight loss: 11.6 kg (median) Pregnancy rates: 29% (n=10)</td>
</tr>
<tr>
<td>Study</td>
<td>Study Design</td>
<td>Sample Description</td>
<td>Main Interventions</td>
<td>Weight Loss</td>
<td>Pregnancy Rates</td>
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<tr>
<td>Huber-Buchholz et al. 1999</td>
<td>Prospective cohort study</td>
<td>28 infertile PCOS women 1. 18 anovulatory 2. 10 ovulatory</td>
<td>24-weeks group treatment program emphasizing dietary changes and regular exercise containing: - 1hr/wk exercise with fitness instructor - 1hr/wk group session with psychiatrist, dietician or reproductive medicine specialist</td>
<td>1.7% (n=3) 2.40% (n=4) Reasons: not reported Weight loss: not reported Pregnancy rates: not reported</td>
<td></td>
</tr>
<tr>
<td>Karimzadeh and Javedani 2010</td>
<td>Prospective randomized double-blind study</td>
<td>343 infertile PCOS women 1. 90 2. 90 3. 88 4. 75</td>
<td>1. 100 mg CC on days 3-7 for a maximum of 3-6 cycles 2. 500 mg Metformin® in a step-up dose till 1500 mg/day for 12-24-weeks 3. Combination of CC and Metformin® as described above 4. Lifestyle modification: dietary regimen consisting of a deficit of 500 calories per day as compared to daily requirements in combination with 3-5 times per week 20-60 minutes exercising</td>
<td>Weight loss: not reported Pregnancy rates:</td>
<td></td>
</tr>
<tr>
<td>Kuchenbecker et al. 2011</td>
<td>Prospective cohort study</td>
<td>32 anovulatory infertile women 37.8 ± 5.2 Drop-out: 36.7 ± 4.3 (mean, SD)</td>
<td>24-weeks lifestyle program consisting of - individualized dietary advice (reduction in calorie intake of ≥ 500 kcal/day) - individualized exercise program - behavior modification Guidance of a nurse practitioner every two weeks</td>
<td>Weight loss: Women who resumed ovulation lost 6.3% of body weight. Pregnancy rates: 22% (n=7)</td>
<td></td>
</tr>
<tr>
<td>Miller et al. 2008</td>
<td>Prospective cohort study</td>
<td>12 infertile women  ≥ 30</td>
<td>12-weeks lifestyle program consisting of a 1200-1500 kcal/day individualized diet and three times per week fitness sessions of one hour. Encouraged to exercise independently throughout the week</td>
<td>Weight loss: not reported BMI change: -2.1 kg/m² Pregnancy rates: 8% (n=1)</td>
<td>8% (n=1) Reasons: not reported Weight loss: not reported Pregnancy rates: not reported</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Participants</td>
<td>BMI of completers</td>
<td>Weight loss</td>
<td>Pregnancy rates</td>
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<tr>
<td>Moran et al. 2003</td>
<td>RCT 2 study arms</td>
<td>45 PCOS women</td>
<td>1.37 ± 1.9 (mean, SEM)</td>
<td>-7.7 kg ± 0.7 (mean ± SEM)</td>
<td>-</td>
</tr>
<tr>
<td>Moran et al. 2006</td>
<td>RCT 2 study arms</td>
<td>43 PCOS women</td>
<td>34.9 ± 6.6 (mean, SD)</td>
<td>-6.9 ± 0.8 kg (mean ± SEM)</td>
<td>5% (n=1) 9% (n=2)</td>
</tr>
<tr>
<td>Palomba et al. 2010</td>
<td>Parallel controlled assessor-blinded RCT, 3 study arms</td>
<td>96 CC-resistant infertile PCOS women</td>
<td>31.3 ± 2.7 (mean, SD)</td>
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</tr>
</tbody>
</table>

**Weekly educational sessions on obesity and infertility**

16-weeks during program consisting of:
1. A low protein diet (1433 kcal) for 12 wks, followed by a weight maintenance diet for 4 wks in combination with group treatment program containing 1hr/wk exercise with fitness instructor and 1hr/wk group session with psychiatrist, dietician or reproductive medicine specialist.
2. As described above, but with a high protein diet instead.

**BMI change**

1. 2.4 kg/m²
2. -0.06 kg/m²
3. 2.64 kg/m² (mean)

**Pregnancy rates**

1. 5% (n=1)
2. 9% (n=2)
3. 3% (n=1)

**Reasons**

- Illness, personal issues and loss to follow-up
- Weight loss: not reported
- Pregnancy rate: not reported

**Weight loss**

1. 1.24 kg/m²
2. 2.0 kg/m²
3. 3.0 kg/m² (mean)

**Dietary changes**

- Low protein diet (1433 kcal) for 12 wks, followed by a weight maintenance diet for 4 wks.
- High protein diet instead.

**Exercise program**

- 16-weeks program consisting of:
  1. A low protein diet (1433 kcal) for 12 wks, followed by a weight maintenance diet for 4 wks in combination with group treatment program containing 1hr/wk exercise with fitness instructor and 1hr/wk group session with psychiatrist, dietician or reproductive medicine specialist.
  2. As described above, but with a high protein diet instead.

**Weight loss**

1. 6.9 ± 0.8 kg (mean ± SEM)
2. 8.5 ± 1.1 kg (mean ± SEM)

**Pregnancy rates**

1. 5% (n=1)
2. 9% (n=2)
3. 3% (n=1)

**Reasons**

- Illness, personal issues and loss to follow-up
- Weight loss: not reported
- Pregnancy rate: not reported

**Weight loss**

1. 1.32% (n=7)
2. 30% (n=7)

**Reasons**

- Illness, personal issues and loss to follow-up
- Weight loss: not reported
- Pregnancy rate: not reported
<table>
<thead>
<tr>
<th>Study</th>
<th>Study Type</th>
<th>Participants</th>
<th>Outcome Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jedel et al. 2011</td>
<td>Prospective RCT</td>
<td>84 PCOS women: 1.33, 2.34, 3.17</td>
<td>12-weeks during observation for all participants in which menstrual frequency was established followed by: 1. Western medical acupuncture was given twice per week for 2 weeks followed once a week for 6 weeks followed by once per 2 weeks. 2. 16-weeks of regular exercise consisting of 30 minutes at least 3 days per week. Telephonic guidance once weekly. 3. No intervention. Weight loss: not reported. Change in BMI: 1. 0.06 ± 1.11 2. 0.01 ± 0.70 3. 0.11 ± 0.63 (mean ± SD). Pregnancy rates: 1. 3% (n=1) 2. 6% (n=2) 3. 0. After observation and treatment period: 1. 2.27% (n=9) 2. 3.22% (n=11) 3. 2.44% (n=4). Reasons: moving, personal reasons, diet, depression.</td>
</tr>
<tr>
<td>Gambineri et al. 2005</td>
<td>Single-blind placebo-controlled RCT.</td>
<td>20 PCOS women: 1.10, 2.10</td>
<td>28-weeks dietary regimen consisting of individualized diet (500 kcal/day deficit as compared to usual intake). Maintaining usual physical activity. After 1 month patients received: 1. octreotide-LAR® im injection every 28 days 2. Placebo in injection every 28 days. Weight loss: not reported. Pregnancy rates: 1. 10% (n=1) 2. 0.</td>
</tr>
<tr>
<td>Pasquali et al. 2000</td>
<td>Case control &amp; RCT.</td>
<td>40 women: 1.12 with PCOS, 2.8 with PCOS, 3.8 non-PCOS 4.12 non-PCOS</td>
<td>28-weeks standardized hypocaloric diet (1200-1400 kcal/day) after 4 weeks combined with: 1. Metformin 850mg twice daily 2. Placebo twice daily 3. Metformin 850mg twice daily 4. Placebo twice daily. Weight loss: not reported. Pregnancy rates: 1. 17% (n=2) 2. 0 3. 0 4. 25% (n=3). Reasons: non-compliance with the diet. Weight loss: not reported. Pregnancy rates: not reported.</td>
</tr>
<tr>
<td>Hoeger et al. 2004</td>
<td>Placebo-controlled RCT.</td>
<td>38 PCOS women: 1.9</td>
<td>1. Metformin® 850 mg twice a day (during 48 weeks) Weight loss: 1. 2.6 ± 4.6 after 24 weeks.</td>
</tr>
<tr>
<td>Tang et al. 2006</td>
<td>4 study arms</td>
<td>Placebo-controlled double-blind RCT. 2 study arms</td>
<td>Placebo-controlled double-blind RCT. 2 study arms</td>
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<td>143 infertile PCOS women: 1.69 women 2.74 women</td>
<td>2.11 3.9 4.9 3.417 ± 6.2 4.371 ± 4.6 (mean ± SD)</td>
<td>4.9 2.48-weeks during lifestyle-modification program (consisting of an individualized diet aiming for 500-1000 kcal deficit per day in combination with an individualized exercise program (150 min per week) and weekly interactive group education meetings and progress monitoring) with placebo twice a day 3. Identical lifestyle-modification program with Metformin® 850 mg twice a day 4. Placebo twice a day (during 48-weeks)</td>
<td>6.5 ± 3.7 after 48 weeks 2. 2.8 ± 5.6 after 24 weeks 6.8 ± 3.8 after 48 weeks 3. 6.3 ± 4.4 after 24 weeks 8.9 ± 2.9 after 48 weeks 4. 0.3 ± after 24 weeks -0.2 ± 0.8 after 48 weeks (mean ± SD)</td>
</tr>
<tr>
<td>24-weeks lifestyle modification program consisting of: - Standardized high-carbohydrate low-fat diet aimed at 500 kcal reduction/day - Encouraging to increase daily exercise by 15 min - Monthly visits with a research dietician In combination with: 1. Metformin® 850 mg twice a day 2. placebo medication twice a day</td>
<td>1.376 ± 5.0 2.389 ± 9.5 (mean, SD)</td>
<td>Pregnancy rates: 1. 0.2 2. 18% (n=2) 3. 3.0 4. 4.0</td>
<td></td>
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<tr>
<td>Weight loss: - 1.28 kg (1.8-3.9) 2. -1.5 kg (-0.3-2.6)(mean, 95% CI)</td>
<td>Pregnancy rates: 1.9% (n=6) 2. 3% (n=2)</td>
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<tr>
<td>Pregnancy rates: not reported</td>
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<tr>
<td>Weight loss: not reported</td>
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<td>Pregnancy rates: not reported</td>
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</table>

**Reasons:**
- Time commitment, lost-to-follow-up, adverse effects
- Side-effects
DISCUSSION

We performed a systematic review on drop-out rates and intervention and patient-related baseline factors associated with drop-out in LIPs for overweight and obese infertile women. We identified 15 studies, of which 10 studies provided data on drop-out. In these studies a median drop-out rate of 24% was observed. Lower drop-out rates have been reported in studies with a relatively short time-frame (six weeks) and substantial higher drop-out rates are reported in studies with a longer lasting LIP (see Table I). As adherence to a LIP is associated with increased weight loss and it is essential for a LIP to be successful (30), drop-out rates up to 24% should be considered representative. Four studies reported baseline characteristics of drop-outs. Although no clinically useful and modifiable predictors for drop-out could be identified in these studies, it was shown that drop-outs lost less weight than completers and that they did not conceive spontaneously during or within one month after drop-out.

From these data it can be concluded that drop-out in LIPs for overweight and obese infertile women is a clinically important problem. Therefore, it is important to identify modifiable predictors for drop-out, as they might contribute to the development of tailored strategies, thereby improving adherence of participants to LIPs (31).

To the best of our knowledge, this systematic review is the first review in which drop-out rates and factors leading to drop-out from LIPs are investigated in overweight and obese infertile woman. A drawback of the current review is the difficulty of comparing the LIPs due to the heterogeneity of the available studies. Another drawback is the limited numbers of studies that investigated the association between patient-related baseline factors and drop-out, while none of the included studies investigated the association between intervention-related factors and drop-out.

In order to overcome these drawbacks, we aimed to detect associations between intervention-related factors and drop-out by comparing the different types of intervention of the included studies. Our comparison showed comparable drop-out rates in LIPs consisting of a dietary regimen only and in LIPs in which a dietary regimen was combined with an exercise program (weighted average 4% and 7%, respectively). However, the large heterogeneity in study design, duration of the LIPs and heterogeneous description of the results in the studies precluded us from drawing firm conclusions on the association between the type of intervention and risk of drop-out.

Modifiable predictors for drop-out could not be identified. This is in concordance with the findings in a large cohort of 114 obese women with PCOS in which Ladson et al. (2011) investigated whether the combination of a LIP and Metformin® was better in improving the PCOS phenotype than a LIP in combination with placebo (32). They could not identify any association between baseline factors such as BMI, hormone levels, lipid parameters, ultrasound parameters and psychosocial baseline factors and drop-out.

Identifying patients at risk for drop-out does not only rely on patient-related baseline factors. In a six-month weight loss intervention study in 137 postmenopausal obese women it was suggested that unsatisfactory or slow rate of weight loss, especially in the beginning of a weight loss program, is also associated with drop-out (33). Participants that are not losing
weight might be discouraged and increasing their risk of drop-out. Understanding the possible reasons for the slower rate of weight loss may help to improve the support of these subjects, especially during the start of the LIP (33). Furthermore, weight loss expectations have been shown to be independent cognitive predictors of drop-out during weight loss programs: higher expectations at baseline lead to higher drop-out rates (34). Self-efficacy, which is the faith in oneself, might play a crucial role in this process (35). Patients with high self-efficacy may attach themselves to goals which are not realistically achievable, which, in turn, might lead to the ‘false hope syndrome’: a phenomenon which is characterised by unrealistic expectations of self-change attempts (36,37). On the other hand, patients with an external locus of control will have low self-efficacy and it may be hypothesised that these patients are prone for drop-out as well (35). Studies assessing self-efficacy of participants could help to identify those subjects that are prone for drop-out in LIPs for overweight and obese infertile women. Whether initial inadequate weight loss and unrealistic goal setting at baseline can predict drop-out should be investigated in this specific population.

In conclusion, our review shows a median drop-out rate of 24% in overweight and obese infertile women participating in LIPs. Our data also indicate that drop-outs lose less weight and have lower spontaneous pregnancy chances than completers. We could not identify intervention or patient-related baseline factors associated with drop-out. Future studies should focus on predictors of drop-out in this patient population. This will enable the identification of patients who are prone for drop-out and who might benefit from extra support and monitoring in order to increase adherence rates, weight loss and pregnancy chances.
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APPENDIX I

Full list of key words used in database searches is as follows:
Body mass index
BMI
Overweight
Obesity
Lifestyle
Intervention
Intervention program
Diet
Exercise
Weight loss
Infertility
Ovulation
Anovulation
PCOS
Polycystic ovarian syndrome
Live birth
Pregnancy


APPENDIX II

Excluded studies

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Vanky E, Salvesen KA and Carlsen SM. Six-month treatment with low-dose dexamethasone further reduces androgen levels in PCOS women treated with diet and lifestyle advice, and metformin. Human reproduction 2004:19:529-533.d


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a Not an infertile population
b Due to overlapping data
c No lifestyle intervention program without medication
d Birth-control was advised
e Full-text article never published in peer-reviewed journal