Infertility

Dropout is a problem in lifestyle intervention programs for overweight and obese infertile women: a systematic review

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Submitted on August 30, 2012; resubmitted on December 15, 2012; accepted on January 2, 2013

STUDY QUESTION: What are the dropout rates in lifestyle intervention programs (LIPs) for overweight and obese infertile women and can intervention- or patient-related baseline factors associated with dropout be identified in these women?

SUMMARY ANSWER: The median dropout rate was 24% in overweight and obese infertile women who participated in a LIP; clinical useful intervention or patient-related factors associated with dropout 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. Dropout from LIPs reduces the chance of losing considerable weight and is therefore considered to be an important limiting factor of the success of LIPs.

STUDY DESIGN, SIZE, DURATION: This systematic review included 15 studies published between January 1980 and December 2012.

PARTICIPANTS/MATERIALS, SETTING, METHODS: The included studies investigated the effect of LIPs for overweight and obese infertile women with infertility. From these studies, dropout rates and intervention- and patient-related baseline factors associated with dropout, as well as weight loss and pregnancy rates, were recorded.

MAIN RESULTS AND THE ROLE OF CHANCE: There were 15 studies identified, of which 10 reported dropout rates. The median dropout rate was 24% (range: 0–31%). Four studies reported baseline characteristics of women who dropped out, but modifiable predictors of dropout 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: There were limited numbers of studies investigating patient-related factors associated with dropout. The heterogeneity in the studies precluded us from drawing firm conclusions on the relation between the type of intervention and dropout.

WIDER IMPLICATIONS OF THE FINDINGS: Dropout from LIPs is a major drawback because it predisposes to less weight loss and lower pregnancy rates. Identification of predictors of dropout is needed to identify overweight and obese infertile women who are prone for dropout. These women might benefit from extra support and monitoring, to potentially increasing adherence rates, weight loss and pregnancy chances.

STUDY FUNDING/COMPETING INTEREST(S): M.A.Q.M. was supported by a research grant from the Dutch Organization for Health Research and Development (ZonMw). The department of obstetrics and gynaecology received research grants from Merck Sharpe and Dohme BV, feering pharmaceuticals, Merck Serono, the Netherlands.

Key words: dropout / overweight / infertility / lifestyle program
Introduction

Overweight [body mass index (BMI) 25–29.9 kg/m²] and obese (BMI ≥ 30 kg/m²) women have reduced chances of spontaneous conception and lower success rates with fertility treatment (Gesink Law et al., 2007; Maheshwari et al., 2007; Ramlau-Hansen et al., 2007; van der Steeg et al., 2008; Bellver et al., 2010). It has been shown that losing weight can improve the chance of conception in this specific patient category (Clark et al., 1998; Huber Buchholz et al., 1999; Miller et al., 2008). Overweight and obese infertile women are therefore advised to participate in lifestyle intervention programs (LIPs) to lose weight before entering fertility programs (National Institute for Clinical Excellence, 2004).

In LIPs designed for overweight and obese men and women to diminish long-term health risks, dropout rates have been reported to be up to 77% (Davis and Addis, 1999; Honas et al., 2003; Inelmen et al., 2005; Finley et al., 2007). This is considered as an important limiting factor in the success of LIPs because dropout is related to little weight change (Finley et al., 2007). Hence, identifying patients at risk of dropping 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 dropout risk. Socio-demographic factors including full-time employment, psychological factors such as depression and lower quality of life and behavioral factors like smoking have all been shown to be associated with increased dropout rates and might therefore be considered as predictors for dropout (Clark et al., 1996; Teixeira et al., 2004; Inelmen et al., 2005).

Not only patient-related factors, but also the type of intervention may influence the dropout 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 dropout rates than diets in which subjects were advised to lower their calorie intake by 600 kcal per day (Anderson et al., 2001).

Due to the emotional and social burden of infertility (Greil, 1997), 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, dropout 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 dropout in this specific patient population.

We therefore systematically reviewed the literature on LIPs in overweight and obese infertile women to investigate dropout rates and to identify possible intervention- and patient-related factors associated with dropout. 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 dropout 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 1 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 Supplementary data, Appendix SI for the full list of key words).

Two reviewers independently screened titles and abstracts of all retrieved studies (M.A.Q.M. and W.K.H.K.). 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 dropouts, spontaneous pregnancy rates during the LIP and during follow-up of the LIP, dropout rates and reasons for dropout. Dropout was defined as withdrawal from the program before completing the LIP. Women who discontinued the LIP because of pregnancy were not considered as women who dropped out.

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

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

Statistics

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

Results

Our initial literature search generated 609 studies (Fig. 1). 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 Supplementary data, Appendix S2), whereas data of the remaining 15 studies were included and subsequently analyzed. Table 1 summarizes the detailed content of the included studies. Data reported in Table 1 were extracted from the original articles. Of the 15 included studies, 13 were prospective cohort studies and two were RCTs. The participants were overweight and obese infertile women with a BMI ranging from 27 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: the median pregnancy rate was 23% (range 1–56%). The amount of weight loss in the included studies could not be summarized, as this was not reported in a consistent way. Ten studies reported dropout rates: the median dropout rate was 24% (range 0–31%). Three studies provided reasons for dropout.

**Type of intervention and dropout**

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

(i) Dietary regimen alone (n = 6): In total, 118 women participated, of whom 32 women conceived (weighted average 6%, 1 program did not report pregnancy rates), whereas 20 dropped out (weighted average 4%, 3 programs did not report dropout rates). The median duration of these programs was 24 weeks (range 6–24 weeks) (Bates and Whitworth, 1982; Harlass et al., 1984; Bützow et al., 2000; Crosignani et al., 2003; Qublan et al., 2007; Palomba et al., 2008).

(ii) Dietary regimen combined with exercise program (n = 8): In total, 310 women participated, of whom 56 women conceived (weighted average 11%), whereas 96 women dropped out (weighted average 7%; 2 programs did not report dropout rates). The median duration of the programs was 24 weeks (range 6–32 weeks) (Andersen et al., 1995; Hollmann et al., 1996; Clark et al., 1998; Huber Buchholz et al., 1999; Miller et al., 2008; Karimzadeh and Javedani, 2010; Palomba et al., 2010; Kuchenbecker et al., 2011).

(iii) Structured exercise program (n = 1): In total, 20 women participated in this program and 7 conceived (35%), whereas 3 women dropped out (15%). The duration of the program was 24 weeks (Palomba et al., 2008).

(iv) Dietary regimen, exercise program and medication or a placebo (n = 3): In total, 175 women participated, of whom 9 conceived (weighted average 3%), whereas 17 women dropped out (weighted average 7%). The median duration was 24 weeks (range 6–24 weeks) (Tang et al., 2006; Palomba et al., 2010).

(v) Medication only (n = 5): In total, 322 women participated of whom 43 women conceived (weighted average 11%). Only one study reported dropout rates (no dropout). The median duration was 18 weeks (range 3–24 weeks) (Qublan et al., 2007; Karimzadeh and Javedani, 2010; Palomba et al., 2010).

**Baseline characteristics of participants associated with dropout**

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

**Weight loss and pregnancy rates in dropouts**

Three studies reported the amount of weight loss and/or pregnancy rates in women who dropped out (Clark et al., 1998; Crosignani et al., 2003; Kuchenbecker et al., 2011). These studies showed that completers lost more weight than dropouts. In addition, none of the dropouts conceived spontaneously during or within the month after dropout (Table 1).

**Discussion**

We performed a systematic review on dropout rates and intervention and patient-related baseline factors associated with dropout in LIPs for overweight and obese infertile women. We identified 15 studies, of which 10 studies provided data on dropout. In these studies, a median dropout rate of 24% was observed. Lower dropout rates have been reported in studies with a relatively short-time frame (6 weeks) and substantial higher dropout rates are reported in studies with longer lasting LIPs (see Table 1). As adherence to a LIP is associated with increased weight loss and it is essential for a LIP to be successful (Dansinger et al., 2005), dropout rates up to 24% should be considered representative. Four studies reported baseline characteristics of women who dropped out. Although no clinically useful and modifiable predictors for dropout could be identified in these studies, it was shown that dropouts lost less weight than completers and that they did not conceive spontaneously during or within 1 month after dropout.

From these data, it can be concluded that dropout in LIPs for overweight and obese infertile women is a clinically important problem. Therefore, it is important to identify modifiable predictors for dropout, as this might contribute to the development of tailored strategies, thereby improving adherence of participants to LIPs (Fabricatore et al., 2009).

To the best of our knowledge, this systematic review is the first review in which dropout rates and factors leading to dropout from LIPs are investigated in overweight and obese infertile women. A drawback of this 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 dropout, whereas none of the included studies investigated the association between intervention-related factors and dropout.

To overcome these drawbacks, we aimed to detect associations between intervention-related factors and dropout by comparing the
<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</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>Dropout rates, weight loss and pregnancy rates in dropouts</th>
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<tbody>
<tr>
<td>(Bates and Whitworth, 1982)</td>
<td>Prospective cohort study</td>
<td>18 infertile women with PCOS</td>
<td>28.8 (mean)</td>
<td>Dietary regimen designed to decrease body weight at the rate of 500 g per week Guidance of a therapeutic dietician</td>
<td>Weight loss: 9.6 kg Pregnancy rates: 56% (n = 10)</td>
<td>28% (n = 5) Reasons: not reported Weight loss: not reported Pregnancy rates: not reported</td>
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<td>(Bützow et al., 2000)</td>
<td>Prospective cohort study</td>
<td>10 infertile women</td>
<td>37.1 ± 3.3 (mean, SEM)</td>
<td>6-weeks very low calorie diet consisting of 650 kcal/day followed by a 4-week recovery period (normocaloric diet)</td>
<td>Weight loss: 11% weight reduction (mean BMI − 4.1 kg/m²) Pregnancy rates: not reported</td>
<td>No information on dropout was reported</td>
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<tr>
<td>(Crosignani et al., 2003)</td>
<td>Prospective cohort study</td>
<td>33 infertile women with PCOS</td>
<td>32.1 ± 4.2 (mean, SD)</td>
<td>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</td>
<td>Weight loss: 25 women lost 5% of initial weight Pregnancy rates: 30% (n = 10) within 12 months</td>
<td>24% (n = 8) Reasons: did not reach 5% weight loss within 6 months Weight loss: not reported Pregnancy rates: 0%</td>
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<td>(Harlass et al., 1984)</td>
<td>Prospective cohort study</td>
<td>6 infertile women with irregular or absent menses</td>
<td>43 (mean)</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>Weight loss: 7–12% weight loss (range) Pregnancy rates: 33% (n = 2) within 6 months after study termination</td>
<td>No information on dropout was reported</td>
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<td>(Palomba et al, 2008)</td>
<td>Prospective cohort study 2 study arms</td>
<td>40 infertile women with PCOS: 1. 20 2. 20</td>
<td>1. 33.1 ± 1.3 2. 33.2 ± 1.4 (mean, SD)</td>
<td>1. 24-week structured exercise program (SET): 3 training sessions per week consisting of 30 min exercising on a bicycle ergometer 2. 24-week hypocaloric hyperproteic diet aimed at 800 kcal deficit per day in combination with weekly interactive group education meetings</td>
<td>Weight loss (including dropouts) 1. Ovulatory patients (n = 13): 5.6 ± 1.6 kg, anovulatory patients (n = 7): 2.0 ± 0.2 kg 2. Ovulatory patients (n = 5): 10.5 ± 4.1 kg, anovulatory patients (n = 15): 2.3 ± 3.1 kg (mean ± SD) Pregnancy rates: 1. 20% (n = 7) 2. 10% (n = 2)</td>
<td>1. 15% (n = 3) 2. 35% (n = 7) Reasons: not reported Weight loss: not reported Pregnancy rates: not reported</td>
</tr>
<tr>
<td>(Qublan et al., 2007)</td>
<td>Prospective comparative study 2 study arms</td>
<td>46 infertile women with PCOS: 1. 24 2. 22</td>
<td>1. 32.2 (29–43) 2. 31.9 (29–44) (mean, range)</td>
<td>24 weeks during program consisting of: 1. A diet containing 1200–1400 kcal per day 2. 850 mg metformin twice a day</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>
<td>No information on dropout was reported</td>
</tr>
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</table>
### (Andersen et al., 1995)

**Prospective cohort study**
- **Participants:** 9 women with PCOS (7 women were infertile)
- **Weight loss:** 11% (mean, SD)
  - After 4 weeks (n = 9)
- **Reasons:** not reported

### (Clark et al., 1998)

**Prospective cohort study**
- **Participants:** 87 infertile women
- **Weight loss:** 2.6 kg after 4 weeks (n = 9)
  - Median (range)
- **Reasons:** not reported

### (Hollmann et al., 1996)

**Prospective cohort study**
- **Participants:** 35 infertile women
- **Weight loss:** 6.3 – 4.2 kg
  - Median (range)
- **Reasons:** work and other commitments

### (Huber Buchholz et al., 1999)

**Prospective cohort study**
- **Participants:** 28 infertile women with PCOS:
  - 1. 18 anovulatory
  - 2. 10 ovulatory
- **Weight loss:** 2–5% of starting weight
  - Median (range)
- **Reasons:** not reported

### (Karimzadeh and Javedani, 2010)

**Prospective randomized double-blind study**
- **Participants:** 343 infertile women with PCOS:
  - 1. 90
  - 2. 90
  - 3. 88
  - 4. 75
- **Weight loss:** not reported
  - Median (range)
- **Reasons:** no information on dropout was reported

### (Kuchenbecker et al. 2011)

**Prospective cohort study**
- **Participants:** 32 infertile women with anovulatory cycles
- **Weight loss:** 1.22% (n = 13)
  - Mean, SD
- **Reasons:** not reported

### (Miller et al. 2008)

**Prospective cohort study**
- **Participants:** 12 infertile women
- **Weight loss:** not reported
  - BMI change: –2.1 kg/m²
- **Reasons:** not reported

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<tr>
<td>(Palomba et al. 2010)</td>
<td>Parallel controlled assessor-blinded RCT 3 study arms</td>
<td>96 CC-resistant infertile women with PCOS: 1. 32 2. 32 3. 32</td>
<td>1. 31.3 ± 2.7 2. 32.3 ± 3.7 3. 31.1 ± 3.0 (mean, SD)</td>
<td>1. 6-weeks during SET: 3 training sessions per week consisting of 30 min cycling and hypocaloric hypoproteic diet aimed at 1000 kcal deficit per day 2. After 2 weeks of observation, 150 mg CC was given daily for 5 days (in absence of ovarian response) 3. 6-week during SET and hypocaloric hypoproteic diet aimed at 1000 kcal deficit per day. After 2 weeks, 150 mg CC was added daily for 5 days (in absence of ovarian response)</td>
<td>Weight loss: not reported BMI change: 1. 2.4 kg/m² 2. −0.06 kg/m² 3. 2.64 kg/m² (mean) Pregnancy rates: 1. 0 2. 0 3. 3% (n = 1)</td>
<td>1. 0 2. 0 3. 0</td>
</tr>
<tr>
<td>(Tang et al. 2006)</td>
<td>Placebo-controlled double-blind RCT 2 study arms</td>
<td>143 infertile women with PCOS: 1. 69 women 2. 74 women</td>
<td>1. 37.6 ± 5.0 2. 38.9 ± 9.5 (mean, SD)</td>
<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>Weight loss: 1. 2.8 kg (1.8–3.9) 2. −1.5 kg (−0.3 to 2.6)(mean, 95% CI) Pregnancy rates: 1. 9% (n = 6) 2. 3% (n = 2)</td>
<td>1. 16% (n = 11) 2. 8% (n = 6) Reasons: side effects Weight loss: not reported Pregnancy rates: not reported</td>
</tr>
</tbody>
</table>

BMI, body mass index; PCOS, polycystic ovarian syndrome; SEM, standard error of the mean; SD, standard deviation; RCT, randomized controlled trial; SET, structured exercise program; CC, clomiphene citrate.
different types of intervention of the included studies. Our comparison showed comparable dropout 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 dropout.

Modifiable predictors for dropout 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 (Ladson et al., 2011). They could not identify any association between dropout and baseline factors such as BMI, hormone levels, lipid parameters, ultrasound parameters and psychosocial baseline factors.

Identifying patients at risk for dropout does not only rely on patient-related baseline factors. In a 6-month weight loss intervention study in 137 post-menopausal obese women, it was suggested that an unsatisfactory or slow rate of weight loss, especially in the beginning of a weight loss program, is also associated with dropout (Messier et al., 2010). Participants who are not losing weight might be discouraged and have increased their risk of dropout. 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 (Messier et al., 2010). Furthermore, weight loss expectations have been shown to be independent cognitive predictors of dropout during weight loss programs: higher expectations at baseline lead to higher dropout rates (Dalle Grave et al., 2005). Self-efficacy, which is faith in oneself, might play a crucial role in this process (Cochrane, 2008). Patients with high self-efficacy may attach themselves to goals that are not realistically achievable that, in turn, might lead to a ‘false hope syndrome’: a phenomenon that is characterized by unrealistic expectations of self-change attempts (Polivy, 2001; Jones et al., 2005). On the other hand, patients with an external locus of control will have low self-efficacy, and it may be hypothesized that these patients are prone for dropout as well (Cochrane, 2008). Studies assessing self-efficacy of participants could help to identify those subjects who are prone for dropout in LIPs for overweight and obese infertile women. Whether initial inadequate weight loss and unrealistic goal setting at baseline can predict dropout should be investigated in this specific population.

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

Supplementary data

Supplementary data are available at http://humrep.oxfordjournals.org/.

Authors’ roles

All authors were involved in the conception and design of the study. M.A.Q.M. contributed to the data acquisition and analysis and the writing of the manuscript. W.K.H.K. contributed to the data acquisition and analysis. All authors critically reviewed and approved the final manuscript.

Funding

M.A.Q.M. and A.H. were supported by a research grant from the Dutch Organization for Health Research and Development (ZonMW; Prevention Program-Health Care Efficiency Research; project number 50-50110-96-518).

Conflict of interest

The department of obstetrics and gynaecology received research grants from Merck Sharpe and Dohme BV, feering pharmaceuticals, Merck Serono, the Netherlands. This is the same research grant as mentioned under funding.

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