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Cost-effectiveness analysis of lifestyle intervention in obese infertile women

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STUDY QUESTION: What is the cost-effectiveness of lifestyle intervention preceding infertility treatment in obese infertile women?

SUMMARY ANSWER: Lifestyle intervention preceding infertility treatment as compared to prompt infertility treatment in obese infertile women is not a cost-effective strategy in terms of healthy live birth rate within 24 months after randomization, but is more likely to be cost-effective using a longer follow-up period and live birth rate as endpoint.

WHAT IS KNOWN ALREADY: In infertile couples, obesity decreases conception chances. We previously showed that lifestyle intervention prior to infertility treatment in obese infertile women did not increase the healthy singleton vaginal live birth rate at term, but increased natural conceptions, especially in anovulatory women. Cost-effectiveness analyses could provide relevant additional information to guide decisions regarding offering a lifestyle intervention to obese infertile women.

STUDY DESIGN, SIZE, DURATION: The cost-effectiveness of lifestyle intervention preceding infertility treatment compared to prompt infertility treatment was evaluated based on data of a previous RCT, the LIFEstyle study. The primary outcome for effectiveness was the vaginal birth of a healthy singleton at term within 24 months after randomization (the healthy live birth rate). The economic evaluation was performed from a hospital perspective and included direct medical costs of the lifestyle intervention, infertility treatments, medication and pregnancy in the intervention and control group. In addition, we performed exploratory cost-effectiveness analyses of scenarios with additional effectiveness outcomes (overall live birth within 24 months and overall live birth conceived within 24 months) and of subgroups, i.e. of ovulatory and anovulatory women, women <36 years and ≥36 years of age and of completers of the lifestyle intervention. Bootstrap analyses were performed to assess the uncertainty surrounding cost-effectiveness.

PARTICIPANTS/MATERIALS, SETTINGS, METHODS: Infertile women with a BMI of ≥29 kg/m^2 (no upper limit) were allocated to a 6-month lifestyle intervention programme preceding infertility treatment (intervention group, $n = 290$) or to prompt infertility treatment (control group, $n = 287$). After excluding women who withdrew informed consent or who were lost to follow-up we included 280 women in the intervention group and 284 women in the control group in the analysis.

[†]Additional members of the LIFEstyle study group are listed in the 'Acknowledgements' section.

MAIN RESULTS AND THE ROLE OF CHANCE: Total mean costs per woman in the intervention group within 24 months after randomization were €4324 (SD €4276) versus €5603 (SD €4632) in the control group (cost difference of −€1278, $P < 0.05$). Healthy live birth rates were 27 and 35% in the intervention group and the control group, respectively (effect difference of −8.1%, $P < 0.05$), resulting in an incremental cost-effectiveness ratio of €15 845 per additional percentage increase of the healthy live birth rate. Mean costs per healthy live birth event were €15 932 in the intervention group and €15 912 in the control group.

Exploratory scenario analyses showed that after changing the effectiveness outcome to all live births conceived within 24 months, irrespective of delivery within or after 24 months, cost-effectiveness of the lifestyle intervention improved. Using this effectiveness outcome, the probability that lifestyle intervention preceding infertility treatment was cost-effective in anovulatory women was 40%, in completers of the lifestyle intervention 39%, and in women ≥36 years 29%.

LIMITATIONS, REASONS FOR CAUTION: In contrast to the study protocol, we were not able to perform the analysis from a societal perspective. Besides the primary outcome of the LIFEstyle study, we performed exploratory analyses using outcomes observed at longer follow-up times and we evaluated subgroups of women; the trial was not powered on these additional outcomes or subgroup analyses.

WIDER IMPLICATIONS OF THE FINDINGS: Cost-effectiveness of a lifestyle intervention is more likely for longer follow-up times, and with live births conceived within 24 months as the effectiveness outcome. This effect was most profound in anovulatory women, in completers of the lifestyle intervention and in women ≥36 years old. This result indicates that the follow-up period of lifestyle interventions in obese infertile women is important.

The scenario analyses performed in this study suggest that offering and reimbursing lifestyle intervention programmes in certain patient categories may be cost-effective and it provides directions for future research in this field.

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TRIAL REGISTRATION NUMBER: The LIFEstyle RCT was registered at the Dutch trial registry (NTR 1530). http://www.trialregister.nl/trialreg/admin/rctview.asp?TC = 1530.

Key words: cost-effectiveness / infertility / lifestyle intervention / obesity / anovulation / scenario analysis

Introduction

Obesity is a major cost driver in healthcare services (Finkelstein *et al.*, 2009). Since obesity is associated with an increased risk of adverse health outcomes, such as cardiovascular disease and diabetes (World Health Organization June, 2016), obese individuals tend to utilize health services more frequently (Raebel *et al.*, 2004). Furthermore, obesity poses challenges in the area of reproductive medicine and obstetric care. Obese couples have more difficulty to conceive and therefore may require infertility treatment more often (Ramlau-Hansen *et al.*, 2007; van der Steeg *et al.*, 2008).

Whether a woman's increased BMI has an impact on the subsequent costs of infertility investigations and treatment is still under debate. Koning *et al.* (2010) estimated that the reduced probability of achieving a successful pregnancy in obese women was associated with increased infertility treatment costs, as more treatment cycles are necessary. On the other hand, Pandey *et al.* (2014) found higher costs of infertility investigations and treatments in women with a normal weight, as compared to obese women. The latter finding might reflect current practice in some countries, where invasive diagnostic procedures or treatments in obese women are not offered or reimbursed until sufficient weight loss has been achieved (Gillett *et al.*, 2006; Pandey *et al.*, 2010; National Collaborating Centre for Women's and Children's Health (UK), 2013). Furthermore, there is evidence that couples who exhibit less healthy lifestyle behaviours are less likely to seek help for their infertility problems, which could consequently decrease resource use and total costs in this population (Farland *et al.*, 2016).

Besides these obesity-related infertility problems, obese women have an increased risk of pregnancy complications resulting in maternal and neonatal morbidity (Weiss *et al.* 2004; Ovesen *et al.* 2011; Cnattingius *et al.*, 2013; Aune *et al.*, 2014; Denison *et al.*, 2014). Indeed, several studies have shown that increased maternal BMI is associated with an increase in healthcare utilization and costs during pregnancy (Denison *et al.*, 2014; Morgan *et al.*, 2014; Trasande *et al.*, 2009). In the LIFEstyle study, a RCT, we have shown that a 6-month lifestyle intervention in obese infertile women preceding infertility treatment neither increased the rates of vaginal birth of healthy singletons at term nor the rates of live birth, compared to women who received prompt infertility treatment (Mutsaerts *et al.*, 2016). However, there were differences in effectiveness between subgroups of obese infertile women and when secondary outcomes were considered (van Oers *et al.*, 2016).

In general, cost-effectiveness analysis provides relevant additional information regarding the costs and effects of an intervention. Despite the lack of overall effectiveness in our trial, the observed differences in effectiveness and the expected cost savings of the lifestyle intervention in obese infertile women warrant further exploration of its cost-effectiveness.

This paper therefore presents the cost-effectiveness analysis of a lifestyle intervention prior to infertility treatment in obese infertile women, which we performed alongside the LIFEstyle study. In addition, to explore if the cost-effectiveness of a lifestyle intervention preceding infertility treatment is different in subgroups of women or when using longer timeframes, we performed exploratory cost-effectiveness analyses of scenarios with additional effectiveness outcomes and of subgroups, i.e. of ovulatory and anovulatory women, women <36 years old and ≥36 years old and of completers of the lifestyle intervention.

Materials and Methods

The study protocol and primary results of the LIFEstyle study have been reported previously (Mutsaerts *et al.*, 2010, 2016). In short, 577 obese (BMI above 29 kg/m^2, without an upper limit) infertile women between 18 and 39 years old were randomized to either a 6-month lifestyle intervention programme preceding infertility treatment (intervention group, n = 290) or to prompt infertility treatment (control group, n = 287). The 6-month lifestyle intervention consisted of an energy-restricted diet, an increase in physical activity and motivational counselling. It included six outpatient visits of ~30 min and four telephone consultations of 15 min in a 24-week period. Women were considered to have completed the intervention when they did not miss more than two consecutive coaching sessions or finalized the intervention at 6 months independent of the amount of weight loss. When a woman became pregnant or achieved successful weight loss, the intervention was also considered completed. After completion of the lifestyle intervention women continued with infertility treatment as indicated according to the Dutch infertility guidelines (Dutch Society of Obstetrics and Gynaecology (NVOG), 2016). Women in the control group could start their indicated infertility treatment promptly after randomization.

Infertility treatments

Anovulatory women started with ovulation induction, where clomiphene citrate was generally administered first. If no pregnancy occurred in 6–12 cycles or if women were clomiphene resistant, gonadotrophin therapy was started in a low-dose step up regimen for a maximum of 12 cycles. In ovulatory women, treatment depended on the estimated probability of natural conception in the next 12 months using the Hunault prediction model (Hunault *et al.*, 2004). Couples with a good prognosis for natural conception (≥30% in the next 12 months) were counselled for expectant management for 6–12 months.

If this probability of a natural conception was estimated to be <30%, up to six cycles of IUI with or without ovarian stimulation were offered. IVF was started in women with tubal pathology or after IUI cycles failed, while ICSI was used in case of severe male factor infertility. Infertility treatment was continued until couples declined further treatment or until further treatment was considered ineffective.

Outcome measures and baseline results of the lifestyle study

The primary outcome of the study was the vaginal birth of a healthy singleton at term within 24 months after randomization, referred to as the healthy live birth rate. A child was considered healthy if it was born alive without any major congenital anomalies. The primary outcome of the RCT was used in the base case analysis of this economic evaluation.

In the intervention group one woman withdrew informed consent and nine women were lost to follow-up, leaving 280 women in the analysis. In the control group two women withdrew informed consent and one case was lost to follow-up, leaving 284 women in the analysis. Baseline characteristics are shown in Table I, and women in the intervention and control groups were comparable at baseline. Of the 289 women randomized to the intervention group, 63 (22%) were non-completers of the lifestyle intervention, mainly due to motivational or relationship problems.

Table I Baseline characteristics of obese infertile women in the intervention and control group

Characteristic	Intervention group (n = 289)	Control group (N = 285)
Age (years), mean (SD)	29.7 (4.5)	29.8 (4.6)
BMI (kg/m^2), median (IQR)	36.0 (33.4–38.2)	36.0 (33.5–38.2)
Nulliparous, N (%)	226 (78)	215 (75)
Infertility diagnosis, N (%)		
Anovulation	128 (44)	141 (50)
Unexplained	86 (30)	77 (27)
Male infertility	67 (23)	64 (23)
Tubal infertility	12 (4)	16 (6)

Baseline characteristics of women who were randomly assigned to either the intervention or control group in the LIFEstyle study. The number of women includes women who were lost to follow-up.
Adapted from Mutsaerts *et al.* (2016).

Economic evaluation

This economic evaluation was performed from a hospital perspective and included direct medical costs of the lifestyle intervention, infertility treatments, medication and pregnancy in the intervention and control group within 24 months after randomization. Resource utilization during the RCT was assessed using individual patient data from the case record forms. For each woman, we recorded number of visits for the lifestyle intervention, number and type of infertility treatment cycles, medication usage and course of pregnancy. Resource use in the initial infertility diagnostic work-up was not taken into account, since patients were randomized after the diagnostic work-up had taken place. Owing to an error in the distribution and collection of cost questionnaires, costs outside the hospital could not be included in the economic evaluation.

Cost items and unit costs

Cost items and unit costs included in the economical evaluation are specified in Table II.

The costs of the lifestyle intervention programme were calculated using costs of dietary advice in an outpatient setting from the Dutch guidelines for cost-effectiveness research, multiplied by 45% overhead costs (Hakkaart-van Roijen *et al.*, 2011). A working group on cost-effectiveness analyses of the Dutch Consortium 2.0 retrieved unit costs of infertility treatments from all university hospitals in The Netherlands and one general hospital. Costs of medications were obtained from the Dutch formulary on medication (Medicijnkosten.nl). Costs of pregnancy and birth were based on a study by Lukassen *et al.* (2004) and indexed to 2014 price levels, in which costs for pregnancy, delivery and admission until 6 weeks postpartum in singleton and multiple pregnancies conceived after IVF were estimated. Since our study included obese women only, we multiplied the unit costs estimated by Lukassen *et al.* by factor 1.23, which is based on previous data on additional costs of pregnancy in obese women (Denison *et al.*, 2014; Morgan *et al.*, 2014). All unit costs were indexed to the price level of 2014 and were expressed in euros.

Exploratory scenario analyses of different effectiveness outcomes and subgroups

To evaluate the impact of varying effectiveness outcomes and subgroups on the cost-effectiveness of the lifestyle intervention we performed 12 exploratory

Table II Cost items and unit costs

Cost item	Unit	Unit costs (€)
Direct medical costs of lifestyle intervention		
Outpatient visit—dietary counselling	30 min	30.71
Telephone consultation—dietary counselling	15 min	15.36
Direct medical costs of infertility treatment		
Ovulation induction with clomiphene citrate with dosage increase [a]	Cycle	289
Ovulation induction with FSH	Cycle	549
IUI ± mild ovarian stimulation	Cycle	321
IVF/ICSI stimulation only	Cycle	502
IVF/ICSI stimulation and follicle aspiration	Cycle	1222
IVF stimulation, follicle aspiration, laboratory and transfer	Cycle	1366
ICSI stimulation, follicle aspiration, laboratory and transfer	Cycle	1699
Frozen embryo transfer monitoring only	Cycle	201
Frozen embryo transfer monitoring, laboratory costs and transfer	Cycle	350
Medication costs		
Clomifene citrate tablets	50 mg	0.53
Gonadotrophins subcutaneous injection	IE	0.42
Triptorelin subcutaneous injection	0.1 mg	10.56
Nafarelin nasal spray	400 ug	2.80
Buserelin nasal spray	0.6 mg	2.50
Cetrorelix subcutaneous injection	0.25 mg	37.77
Ganirelix subcutaneous injection	0.25 mg	34.14
HCG subcutaneous injection	3 × 1500 IU	6.63
HCG subcutaneous injection	5000 IU	5.78
Estradiol tablets	2 mg	0.16
Progesteron suppository	100 mg	0.20
Direct medical costs of pregnancy and birth		
Singleton pregnancy and birth in an obese woman [b]	1	3827
Multiple pregnancy and birth in an obese woman [b]	1	20 220

[a]Only cycles with clomiphene citrate dosage increase were counted, since additional cycles with the same dosage are usually not monitored in the hospital.
[b]Determined using costs of singleton or multiple pregnancy by Lukassen *et al.* (2004) and multiplying this by factor 1.23 (Morgan *et al.*, 2014; Denison *et al.*, 2014).

scenario analyses in addition to the base case analysis. The scenarios consisted of different combinations of effectiveness outcomes, with varying follow-up times and subgroups. In the first scenario we analysed the overall live birth rate within 24 months after randomization as effectiveness outcome; this is a broader endpoint than the primary outcome of the study since it includes all live births irrespective of term, health and mode of delivery. The second scenario had the overall live birth rate for all pregnancies conceived within 24 months after randomization as the effectiveness outcome. This exceeds the timeframe of the RCT but gives a broader perspective on the outcomes of women included in the LIFEstyle study.

All subgroups have been analysed using two different effectiveness outcomes, namely the primary outcome of the study (the vaginal birth of a healthy singleton at term within 24 months after randomization) and the overall live birth rate for all pregnancies conceived within 24 months. Scenarios 3 and 4 include ovulatory women, scenarios 5 and 6 anovulatory women, scenarios 7 and 8 women <36 years old, scenarios 9 and 10 women ≥36 years old and scenarios 11 and 12 include completers of the lifestyle intervention.

In the scenarios using live birth of all pregnancies conceived within 24 months as effectiveness outcome, the costs of these additional pregnancies and births beyond 24 months after randomization were also included. For each scenario we performed bootstrap analysis, using 5000 replications, to evaluate the probability of cost-effectiveness.

Statistical analysis

Resource utilization was determined and multiplied by the unit costs, and subsequently mean costs per woman in the intervention and control group were estimated. The Student's *t*-test was performed to test differences in mean costs between the intervention and control group. We calculated the incremental cost-effectiveness ratio (ICER) for the base case and each scenario and calculated costs per birth event in each scenario. We performed bootstrap analysis with 5000 replications for each scenario to investigate the degree of uncertainty in our estimates. Statistical analyses were performed using SPSS Statistics version 22 (IBM Corporation, Armonk, NY, USA) and all figures were composed using Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA). Bootstrap was performed using R-project software (R Foundation for Statistical Computing, Vienna, Austria).

Ethical approval

The LIFEstyle study was approved by the Medical Ethics Committee (MEC; 2008.284) of the University Medical Center Groningen and the boards of directors of each of the 23 participating centres and was registered at the Dutch trial registry (NTR 1530). Written informed consent was obtained for all women who agreed to participate in the study.

Results

Total resource use and mean costs per woman per cost item and cost category in the intervention and control group are shown in Table III. Mean costs of the lifestyle intervention counselling sessions and lifestyle telephone consultations were €174 (SD €79) per woman (versus €0 in the control group, $P < 0.05$). Total costs for infertility treatment were €1174 (SD €1804) in the intervention group versus €1781 (SD €2161) in the control group ($P < 0.05$), costs for medication were €903 (SD €1899) in the intervention group versus €1227 (SD €1686) in the control group ($P < 0.05$). There were less singleton and multiple births occurring within 24 months after randomization in the intervention group compared to the control group with concordant lower mean costs for pregnancy and childbirth in the intervention group €2073 (SD €3283) versus €2595 (SD €3708) in the control group ($P = 0.08$). In total, mean costs per woman in the intervention group were €4324 (SD €4276) versus €5603 (SD €4632) in the control group (cost difference −€1278, $P < 0.05$). The rate of the primary outcome (vaginal births of healthy singleton at term within 24 months after randomization—the healthy live birth rate) was 76 (27%) in the intervention group and 100 (35%) in the control group (effect difference −8.1%, $P < 0.05$). The ICER is therefore €15 845 per additional percentage healthy live birth rate. Costs per healthy live birth event within 24 months after randomization were €15 932 in the intervention group and €15 912 in the control group.

The bootstrap analysis reflecting uncertainty of the results on the total costs and healthy live birth rate within 24 months after

Table III Resource use and mean costs per woman within 24 months of randomization in the intervention and control group during the RCT

Cost item	Intervention group (n = 280)*		Control group (n = 284)*	
	N total	Mean costs per woman € (SD)	N total	Mean costs per woman € (SD)
Direct medical costs of lifestyle intervention		174[a] (78.87)		0[a]
Outpatient visit	1216	133 (58.06)	0	–
Telephone consultation	735	40.32 (22.44)	0	–
Direct medical costs of infertility treatment		1174[a] (1804)		1781[a] (2161)
Ovulation induction with clomiphene citrate with dosage increase [b]	104	107 (234)	188	191 (295)
Ovulation induction with FSH	76	149 (646)	125	242 (780)
IUI ± mild ovarian stimulation	225	258 (606)	285	322 (655)
IVF/ICSI stimulation only [b]	15	26.88 (142)	28	49.48 (196)
IVF/ICSI stimulation and follicle aspiration	8	34.90 (251)	7	30.11 (216)
IVF stimulation, follicle aspiration, laboratory and transfer	18	87.80 (408)	50	240 (833)
ICSI stimulation, follicle aspiration, laboratory and transfer	76	461 (1308)	105	628 (1703)
Frozen embryo transfer monitoring only [c]	6	4.31 (29.16)	6	4.25 (33.52)
Frozen embryo transfer monitoring, laboratory costs and transfer	23	45.28 (212)	38	73.76 (280)
Medication costs		903[a] (1899)		1227[a] (1686)
Clomifene citrate	1934	3.66 (9.57)	3539	6.60 (13.61)
Gonadotrophins	534 659	802 (1794)	723 617	1070 (1530)
Triptorelin	1824	68.79 (188)	2553	94.93 (221)
Nafarelin	0	–	17	0.17 (2.82)
Buserelin	0	–	8	0.07 (1.19)
Cetrorelix	92	12.41 (84.48)	255	33.91 (155)
Orgalutran	29	3.54 (37.02)	0	–
HCG (×31500 IU)	12	0.28 (1.75)	23	0.54 (2.81)
HCG (5000 IU)	334	6.89 (11.54)	530	10.79 (13.26)
Estradiol	1068	0.61 (4.35)	1695	0.95 (5.00)
Progesteron	6918	4.94 (14.90)	13 155	9.26 (21.67)
Direct medical costs of pregnancy and birth		2073 (3283)		2595 (3708)
Singleton pregnancy and birth in an obese woman within 24 months	120	1640 (1897)	145	1954 (1916)
Multiple pregnancy and birth in an obese woman within 24 months	6	433 (2933)	9	641 (3548)
Total costs		4324[a] (4276)		5603[a] (4632)

*Number of women with complete follow-up in the LIFEstyle study.
[a]Cost difference $P < 0.05$ using Student's *t*-test.
[b]Only cycles with clomiphene citrate dosage increase were counted, since additional cycles with the same dosage are usually not monitored in the hospital.
[c]These are cancelled cycles, where the follicle aspiration or cryo-embryo transfer was cancelled.

randomization is shown in Figure 1. The majority (98%) of the estimates are located in the south western (SW) quadrant, indicating lower costs in the intervention group, but also lower effectiveness of the lifestyle intervention compared to prompt infertility treatment in terms of vaginal birth rate of healthy singleton at term within 24 months after randomization.

Scenario analyses of subgroups and different follow-up periods

The results of the scenario analyses, with effects and a summary of the costs per scenario, the ICER and mean costs per births event and overall results of the bootstrap analyses are shown in Table IV. The bootstrap figures of the scenarios are shown in Supplementary Figure 1A–L. Specifications of costs in the ovulatory, anovulatory, women <36 years old, women ≥36 years old and completer subgroups are shown in the Supplementary Tables S1–S5, respectively.

Scenario 1, with the overall live birth rate within 24 months as effectiveness outcome, has an equal cost difference as the base case scenario, but lower effectiveness (−9.9%). A total of 99% of the bootstrap estimates are located in the SW quadrant of the cost-effectiveness plane, indicating lower costs, but also lower effectiveness in the intervention group (Supplementary Figure 1A). One percent of bootstrap estimates are located in the south eastern (SE) quadrant. The

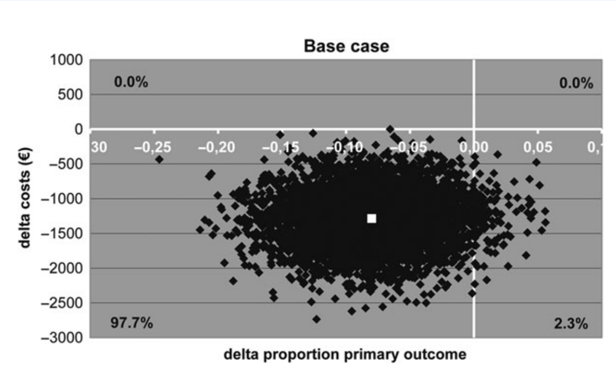

Figure 1 Results of the bootstrap analysis of the base case. Nonparametric bootstrap analysis, using 5000 replications, comparing costs and effects of lifestyle intervention preceding infertility treatment to prompt infertility treatment in the base case using the primary outcome of the LIFEstyle study. Each estimate represents the uncertainty of the additional costs and effects. NW: North Western quadrant, intervention is less effective and more costly. SW: South Western quadrant, intervention is less effective and less costly. NE: North Eastern quadrant, intervention is more effective and more costly. SE: South Eastern quadrant, intervention is more effective and less costly.

estimates in the SE quadrant indicate more effectiveness and lower costs in the intervention group. Mean costs per live birth event within 24 months after randomization were €9844 in the intervention group and €10 400 in the control group.

Scenario 2, with overall live birth rate conceived within 24 months as effectiveness outcome, has higher costs per woman of pregnancy and delivery, since more births occurred due to the longer follow-up time. Eighty-seven percent of the estimates are located in the SW quadrant and 13% in the SE quadrant (Supplementary Figure 1B). Mean costs per live birth event conceived within 24 months after randomization were €8879 in the intervention group and €9800 in the control group.

Scenarios 3 and 4 concerned ovulatory women and showed less favourable cost-effectiveness (Supplementary Figure 1 and D). Results of scenarios 5 and 6, concerning anovulatory women were more favourable, especially with live births conceived within 24 months as effectiveness outcome, with 40% of estimates located in the SE quadrant (Supplementary Figure 1E and F). For women <36 years old (scenarios 7 and 8) only 1% of bootstrap estimates with the primary outcome as effectiveness measure were located in the SE quadrant. This increased to 16% when live births conceived within 24 months were considered (Supplementary Figure 1G and H).

For women ≥36 years old (scenarios 9 and 10) only 2% of bootstrap estimates with the primary outcome as effectiveness measure were located in the SE quadrant. This increased to 29% when live births conceived within 24 months were considered (Supplementary Figure 1I and J). Scenarios 11 and 12 included women who completed the lifestyle intervention. When using the primary outcome of the study as effectiveness outcome 15% of bootstrap estimates were located in the SE quadrant. When using live births conceived within 24 months as effectiveness outcome 39% of estimates were located in the SE quadrant (Supplementary Figure 1K and L).

Discussion

To our knowledge, this economic evaluation including various scenarios using data from a nationwide multicentre RCT is the first to report a robust analysis of the cost-effectiveness of a lifestyle intervention programme preceding infertility treatment compared to prompt infertility treatment in obese infertile women. Our results show that lifestyle intervention preceding infertility treatment is less costly, but not more effective than prompt infertility treatment in terms of vaginal birth rate of healthy singleton at term within 24 months of follow-up.

Scenario analyses showed that in the scenarios using the overall live birth rate of all ongoing pregnancies conceived within 24 months, a lifestyle intervention is more likely to be cost-effective, compared to the scenarios using the primary outcome of the study as effectiveness outcome.

With the overall live birth rate conceived within 24 months as outcome, the probability that lifestyle intervention preceding infertility treatment was cost-effective was higher in anovulatory women, in women who completed the lifestyle intervention program and in women ≥36 years old. Costs per birth event were generally lower in the intervention group compared to the control group using the overall live birth rate conceived within 24 months as effectiveness outcome, but not using the primary outcome as effectiveness outcome.

Recent studies on lifestyle intervention preceding infertility treatment in obese infertile women were mainly focused on anovulatory obese women and did not take costs into account (Legro *et al.*, 2016; Sim *et al.*, 2014). A similar RCT to the LIFEstyle study has been announced in Canada (Duval *et al.*, 2015).

The LIFEstyle study was a pragmatic RCT, investigating infertility treatment as currently offered and therefore this economic analysis gives an accurate and detailed insight into the true costs of infertility treatment in a heterogeneous group of obese infertile women. Furthermore, the unit costs of infertility treatments have been determined within academic and general hospitals in The Netherlands, supporting the reliability of the cost estimates. The scenario analyses increasing the timeframe of the outcome of interest and the analyses investigating different clinically relevant subgroups provide important insight into possible scenarios in which lifestyle intervention preceding infertility treatment can be cost-effective in practice. Moreover, the bootstrap analyses provide information of the robustness of the scenarios.

A limitation of our study is that we were not able to perform an economic evaluation from a societal perspective, in which also direct and indirect costs for the patient and society are taken into account. This deviation from our previously published study protocol (Mutsaerts *et al.*, 2010) was caused by an error in the software module that registered and distributed the questionnaires. Hypothetically, the higher number of infertility treatments and subsequent increased number of hospital visits, travel costs and productivity losses in the control group could further increase the cost difference between the intervention group and control group in favour of the intervention group. Secondly, we recorded basic information on complications during pregnancy (such as diagnosis of complications and information on number of admissions of mother and neonate) and were therefore unable to perform a detailed cost-analysis on the course of pregnancy. Instead, we used a base price of costs of pregnancy, birth and care for neonates up to 6 weeks postpartum in infertile women (Lukassen *et al.*, 2004) and multiplied this by a factor 1.23x to adjust for obesity, which we derived from previous literature

Table IV **Results of the base case and scenario analyses**

Scenario	Subgroup	Effectiveness measure	Effectiveness rate (*n*, %)	RR (95% CI)	ΔEffect (%)	Cost per woman	ΔCost	ICER	Cost per birth event [a]	Cost-effectiveness plane [b] NW	SW	NE	SE
Base case	–	Primary outcome[c]: healthy live birth within 24 months	I: 76/280 (27) C: 100/284 (35)	0.77 (0.60–0.99)	−8.1	I: 4324 C: 5603	−1278[d]	15 845	I:15 932 C:15 912	0%	98%	0%	2%
1	–	Live birth within 24 months	I: 123/280 (44) C: 153/284 (54)	0.82 (0.69–0.97)	−9.9	I: 4324 C: 5603	−1278[d]	12 856	I:9844 C:10 400	0%	99%	0%	1%
2	–	Live birth conceived within 24 months	I: 149/280 (53) C: 165/284 (58)	0.91 (0.79–1.05)	−4.9	I: 4725 C: 5693	−969[d]	19 833	I:8879 C:9800	0%	87%	0%	13%
3	Ovulatory women	Primary outcome: healthy live birth within 24 months	I: 39/157 (25) C: 48/144 (33)	0.75 (0.52–1.06)	−8.5	I: 4721 C: 6227	−1507[d]	17 742	I:19 004 C:18 682	0%	94%	0%	6%
4	Ovulatory women	Live birth conceived within 24 months	I: 77/157 (49) C: 82/144 (57)	0.86 (0.70–1.07)	−7.9	I: 5038 C: 6273	−1236[d]	15 640	I:10 271 C:11 016	1%	91%	0%	8%
5	Anovulatory women	Primary outcome: healthy live birth within 24 months	I: 37/123 (30) C: 52/140 (37)	0.81 (0.57–1.14)	−7.1	I: 3819 C: 4961	−1142[d]	16 169	I:12 695 C:13 355	1%	87%	0%	11%
6	Anovulatory women	Live birth conceived within 24 months	I: 72/123 (59) C: 83/140 (59)	0.99 (0.81–1.21)	−0.8	I: 4325 C: 5097	−772	103 030	I:7389 C:8597	2%	54%	5%	40%
7	<36 years	Primary outcome: healthy live birth within 24 months	I: 75/246 (30) C: 95/255 (37)	0.82′ (0.64–1.05)	−6.8	I: 4358 C: 5574	−1215[d]	17 961	I:14 295 C:14 961	0%	99%	0%	1%
8	<36 years	Live birth conceived within 24 months	I: 139/246 (57) C: 155/255 (61)	0.93 (0.80–1.08)	−4.3	I: 4767 C: 5644	−877[d]	20 498	I:8437 C:9286	1%	82%	1%	16%
9	≥36 years	Primary outcome: healthy live birth within 24 months	I: 1/34 (2.9) C: 5/29 (17)	0.17 (0.02–1.38)	−14	I: 4080 C: 5860	−1780	12 444	I:138 734 C:33 988	6%	92%	0%	2%
10	≥36 years	Live birth conceived within 24 months	I: 10/34 (29) C: 10/29 (34)	0.85 (0.41–1.76)	−5.1	I: 4418 C: 6124	−1706	33 639	I:15 021 C:17 759	3%	64%	4%	29%
11	Completers[e]	Primary outcome: healthy live birth within 24 months	I: 69/222 (31) C: 100/284 (35)	0.88 (0.69–1.14)	−4.1	I: 5112 C: 5603	−491	11 876	I:16 449 C:15 912	10%	74%	1%	15%
12	Completers[e]	Live birth conceived within 24 months	I: 132/222 (59) C: 165/284 (58)	1.02 (0.88–1.19)	1.4	I: 5497 C: 5693	−197	−14 469	I:9244 C:9800	8%	30%	22%	39%

All costs are mean costs expressed in euros. I, intervention group; C, control group; ICER, incremental cost-effectiveness ratio; RR, relative risk.

[a]Mean costs per birth event are mean costs per healthy vaginal birth within 24 months when the primary outcome is used and mean costs per live birth conceived within 24 months when the outcome live birth conceived within 24 months is used.

[b]NW: North Western quadrant, intervention is less effective and more costly. SW: South Western quadrant, intervention is less effective and less costly. NE: North Eastern quadrant, intervention is more effective and more costly. SE: South Eastern quadrant, intervention is more effective and less costly.

[c]Vaginal birth of a healthy singleton at term within 24 months after randomization.

[d]Difference in costs $P < 0.05$ using Student's *t*-test.NE: North Eastern quadrant, intervention is more effective and more costly. SE: South Eastern quadrant, intervention is more effective and less costly.

[e]Completers are women who completed the LIFEstyle intervention. Women were considered to have completed the intervention when they did not miss ≥two consecutive coaching sessions or finalized the intervention at 6 months independent of the amount of weight loss. When a woman became pregnant or achieved successful weight loss, the intervention was also considered completed.

(Denison *et al.*, 2014, Morgan *et al.*, 2014). By doing so, we hoped to avoid underestimation of the costs of pregnancy in obese infertile women. Since our conclusions are based on scenarios with both primary outcomes and exploratory subgroup analyses of one RCT, additional similar studies are needed in order to give a definite answer to the question if lifestyle intervention preceding infertility treatment is a cost-effective strategy for specific groups of obese infertile women.

We have chosen to emphasize the bootstrap results instead of the ICER, since the base case results show that the intervention studied is less effective, but also less costly. The resulting ICER, which is the slope of the line through average cost difference and effect difference in the cost-effectiveness plane, is a positive number, which cannot be distinguished from a situation with an intervention that is more effective and more costly. This also means that changes in the ICER for the scenarios that we investigated should be interpreted in a mirror-image fashion from what is generally the case in cost-effectiveness studies. To avoid confusion we have focussed on the distribution of the bootstrap results in the cost-effectiveness plane to indicate the probability of cost-effectiveness (SE quadrant) or effectiveness (SE and NE quadrants).

Our analyses show that increasing the timeframe in which the outcomes are allowed to occur, improves the cost-effectiveness of lifestyle intervention preceding infertility treatment. The 6-month delay of the start of infertility treatment in the lifestyle intervention group might have led to less infertility treatments, less pregnancies and lower costs. This was inherent to the design of our study and the time horizon of 24 months. Our analysis of subgroups shows that in anovulatory women a lifestyle intervention preceding infertility treatment is equally effective and in most cases less costly than prompt infertility treatment. Moreover, we have previously shown that lifestyle intervention increases natural conception rates in this subgroup, leading to less medicalization of reproduction (van Oers *et al.*, 2016). The scenario including completers of the lifestyle intervention suggests that lifestyle intervention preceding infertility treatment becomes increasingly cost-effective, if the intervention could be optimized so that the number of women who complete the lifestyle intervention increases.

In daily practice, effectiveness of treatment, patient preference and, in some countries, reimbursement policies of insurance companies, governments or clinical guidelines determine choices in infertility treatment. The balance between effectiveness, costs, risks of treatment and the likelihood of a subsequent pregnancy should be based on robust estimates in order to direct choices of patients and direct policies for reimbursement. The scenario analyses performed in this study could support choices for offering and reimbursing lifestyle intervention programmes in certain patient categories and it provides directions for future research in this field.

In conclusion, lifestyle intervention preceding infertility treatment in obese infertile women is less effective and less costly as compared to prompt infertility treatment and therefore not cost-effective. A lifestyle intervention preceding infertility treatment is more likely to be cost-effective using a longer follow-up period and a broader endpoint. This indicates that the follow-up period of lifestyle interventions in obese infertile women is an important factor.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

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Authors' roles

A.H., J.A.L., B.W.J.M., M.A.Q.M. and H.G. conceived the LIFEstyle study and developed the study protocol. A.M.v.O., and M.A.Q.M. were responsible for data collection and daily management of the trial. A.H., was principal investigator. A.H., J.M.B., W.K.H.K., D.A.M.P., C.A.M.K., R.v.G., E.M.K., J.M.S., N.F.K. and Y.M.v.K. were responsible for enrolling subjects and managing the project at their hospital. A.v.O. carried out the analyses under supervision of H.G. and wrote the article. All authors were responsible for interpreting the data and critically revising the article.

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