Lifestyle intervention in obese infertile women

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Effects of periconceptional weight loss on maternal and neonatal outcomes in obese infertile women.

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Submitted

Abstract

Background: Obesity in women of reproductive age has deleterious effects on reproductive and offspring health. In this study, we aimed to evaluate the effects of the magnitude of periconceptional weight loss on maternal and neonatal outcomes in obese infertile women who participated in the LIFEstyle study. The LIFEstyle study was a randomized controlled trial, evaluating if a six-month lifestyle intervention program prior to infertility treatment in obese infertile women improved birth rates, compared to prompt infertility treatment.

Methods and findings: This is an exploratory post hoc analysis of the LIFEstyle study. We recorded periconceptional weight change in women with an ongoing pregnancy, pooling data of all women, regardless of randomization arm. Periconceptional weight change was calculated using weight at randomization and the periconceptional weight (measured 12 weeks before or after conception expressed as BMI change in units BMI (kg/m^2). Subsequently, women were categorized into quartiles according to the magnitude of their periconceptional weight change. The odds of maternal and neonatal outcomes were calculated using logistic regression analysis, comparing women in each of the first three weight change quartiles separately, and combined, to women in the fourth quartile. The fourth quartile was chosen as reference group, since these women had the least weight loss. We adjusted for periconceptional BMI, nulliparity and smoking status. In addition, we performed a subgroup analysis for singleton pregnancies.

In the LIFEstyle study, 321 obese infertile women achieved an ongoing pregnancy which was conceived within 24 months after randomization. Periconceptional weight change was available in 244 of these women (76%). Median BMI at randomization was 35.9 kg/m^2. Women in the first quartile (Q1) had a periconceptional weight change of <-2.1 kg/m^2, women in the second quartile (Q2) -2.1 to -0.9 kg/m^2, women in the third quartile (Q3) -0.9 to 0.1 kg/m^2 and women in the fourth quartile (Q4) gained ≥0.1 units of BMI. There were no significant differences between women in the quartiles regarding rates of excessive gestational weight gain, gestational diabetes, preterm birth, induction of labor, spontaneous vaginal birth and Caesarean section. Compared to women in Q4, the adjusted odds ratios, aOR, and 95% confidence interval for a hypertensive complication were; 0.55 (0.22-1.42) for women in Q1, 0.30 (0.12-0.78) for women in Q2, 0.39 (0.16-0.96) for women in Q3 and 0.39 (0.19-0.82) for women in Q1 to Q3 combined. In the subgroup analysis, investigating singleton pregnancies only, the statistically significant decreased rate of a hypertensive complication remained in women in Q2 (aOR 0.27, 95% CI 0.10-0.72) and Q3 (aOR 0.39, 95%CI 0.16-0.98) and when comparing women in Q1 to Q3 together to women in Q4 (aOR 0.38, 95%CI 0.18-0.80). Furthermore, there was a significantly decreased aOR

(95%CI) of preterm birth in women in Q2 (0.24, 0.06-0.98) and when combining women in Q1 to Q3 (0.37, 0.14-0.97) compared to women in Q4.

Conclusions: These results suggest that specifically modest periconceptional weight loss in obese infertile women could lead to a 2.5 to 4-fold decrease of the rates of hypertensive pregnancy complications and preterm birth. The results are limited by the exploratory nature of the analyses and further evidence is necessary to provide more definitive conclusions.

Introduction

Obesity, defined as a body-mass index (BMI) ≥30kg/m^2, has deleterious effects on women's reproductive health and health of their offspring.[1-4] Obese women are at an increased risk of adverse pregnancy outcomes, such as gestational hypertension, preeclampsia and gestational diabetes.[5,6] Moreover, there is an increased risk of induction of labor, shoulder dystocia, postpartum hemorrhage and Caesarean section.[5,7,8] Maternal obesity is also associated with an increased risk of adverse neonatal outcomes, including an increased rate of preterm birth, large-for-gestational age (LGA) infants, neonatal intensive care unit (NICU) admission, congenital anomalies and perinatal death.[9-12] Furthermore, children born from obese mothers have an increased risk of childhood and adulthood overweight or obesity and increased mortality rate later in life.[3,13-15]

Studies investigating the effect of antenatal lifestyle interventions to prevent excessive gestational weight gain and/or obesity-associated complications in overweight and obese pregnant women report limited clinical risk reduction of maternal and perinatal complications.[16-20] Preconception interventions might have a greater impact on the reduction of obesity-associated complications during pregnancy and in offspring, as is exemplified by studies on the effects of preconception bariatric surgery.[21,22] Even though rates of macrosomia and large-for-gestational age (LGA) are generally decreased after bariatric surgery, rates of small-for-gestational age (SGA) are increased.[22,23]

We conducted a randomized controlled trial (RCT), in which we investigated reproductive outcomes in obese infertile women who were randomized to a six-month lifestyle intervention program preceding infertility treatment, as compared to prompt infertility treatment.[24] The lifestyle intervention did not result in higher rates of the primary outcome, the vaginal births of a healthy singleton at term within 24 months after randomization, while it did result in comparable rates of ongoing pregnancies and more natural conceptions in the intervention group.[25] Rates of maternal and neonatal complications were not different between randomization groups, but the influence of the magnitude of weight loss on these

outcomes was not analyzed separately.

Only few studies have been performed regarding the effects of periconceptional weight loss on maternal and neonatal outcomes in obese women.[26] It is not known whether periconceptional weight loss, improves pregnancy outcomes in women who did not receive bariatric surgery and what amount of weight loss could do so. Therefore, the purpose of the current analysis is to investigate whether periconceptional weight loss influences maternal and neonatal pregnancy outcomes and to determine what amount of weight loss is required to affect these outcomes.

Materials and methods

We used data from the LIFEstyle study, a multicenter RCT. The study protocol and results of the LIFEstyle study have been reported previously.[24,25] The study protocol of the LIFEstyle study was approved by the Medical Ethics Committee (MEC; 2008.284) of the University Medical Centre Groningen and the board of directors of each participating centre. The study was conducted in adherence to the Declaration of Helsinki and all participants gave written informed consent. In short, obese infertile women were randomly allocated to a lifestyle intervention program preceding infertility treatment (intervention group) or to prompt infertility treatment (control group). Women in the intervention group received a six-month lifestyle intervention, which consisted of an energy-restricted diet, an increase of physical activity and motivational counseling. The lifestyle intervention was aimed at 5-10 % weight loss and the program included six outpatient visits and four telephone consultations. After completion of the six-month lifestyle intervention, women could commence with infertility treatment if they had not conceived naturally during the intervention period. Women in the control group started infertility treatment promptly after randomization. Infertility treatment in both study arms could consist of expectant management, ovulation induction, intrauterine insemination, in vitro fertilization or intracytoplasmic sperm injection including transfers of frozen embryos, depending on the diagnosis. The indicated type of treatment was based on guidelines from the Dutch Society of Obstetrics and Gynecologists.[27] Women were followed for 24 months after randomization. Data on the course of pregnancy and childbirth was also recorded when a woman conceived within 24 months after randomization but childbirth occurred after the 24 months of follow-up. The primary outcome of the LIFEstyle study was the vaginal birth of a healthy singleton at term within 24 months after randomization. A power calculation was performed using the primary outcome of the study.[24] A total of 63 women (21.8%) discontinued the lifestyle intervention. The mean weight loss after 6 months was 4.4kg in 236 non-pregnant women in the intervention group and 1.1 kg in 128 non-pregnant women in the control group ($P < 0.001$).[25]

Periconceptional weight change

For the current analysis we used pooled data, regardless of randomization arm, of women who had an ongoing pregnancy and complete follow-up during the LIFEstyle study. By doing so, we aimed to investigate the effects of weight loss, irrespective of its cause, be it participation in the intervention or possibly a personal initiative to change diet after receiving the information of the deleterious effects of overweight as part of the patient information provided at the start of the study. Furthermore, this is an exploratory post-hoc analysis, which was not described in the study protocol prior to the start of the LIFEstyle study.

Women with an ongoing pregnancy that was conceived within 24 months after randomization, for whom data on periconceptional weight was available, were categorized into quartiles according to their weight change in BMI units (kg/m^2). We used change in BMI since this accurately reflects change in body composition for women with different statures. We calculated weight change using weight at randomization and the periconceptional weight. Periconceptional weight was determined using the weight at the first antenatal visit (which for infertile couples is usually at 7 to 8 weeks gestation). If this was not available the self-reported weight at 12 weeks gestation or weight within 12 weeks of conception was used.

Maternal and neonatal outcomes

Maternal and neonatal outcomes were recorded for all ongoing pregnancies conceived within 24 months after randomization. Maternal adverse outcomes were: excessive gestational weight gain (> 9 kilograms for women with BMI > 30 kg/m^2 or > 11.5 kilograms for women with BMI 25-29.9kg/m^2)[28], gestational diabetes (any form of hyperglycemia during pregnancy)[29], hypertensive complications (pregnancy-induced hypertension, preeclampsia and HELLP syndrome).[30] In addition, we recorded preterm birth (<37 weeks gestational age), induction of labor (induction of labor by artificial means) and mode of delivery (spontaneous vaginal birth, assisted vaginal birth or Caesarean section).

Gestational weight gain was assessed using self-reported weight measurements. Gestational weight gain records were considered complete when weight was measured within four weeks of delivery and when the weight was measured at the start of pregnancy.

Neonatal outcomes were SGA or LGA (defined as birth weight below the 10th or above the 90th percentile according to the Dutch reference curves).[31] Due to low prevalence of the individual complications a composite neonatal outcome was used, consisting of cord pH <7.05, Apgar score <7 at 5 minutes, admission to the NICU and perinatal death (stillbirth

above 24 weeks gestation or early neonatal death within six weeks postpartum).[12] For neonatal outcomes, the number of women was the denominator.

Statistical analysis

Descriptive statistics are given as *n,* %, median and interquartile range (IQR) where appropriate. Baseline characteristics in the weight change quartiles were compared using the non-parametric Kruskall-Wallis test for continuous variables and the chi-square test for categorical variables.

The probabilities of maternal and neonatal outcomes were calculated as a function of weight change. For each outcome, we performed logistic regression analysis, comparing women in each of the first three weight change quartiles separately, and combined, to women in the fourth quartile. The fourth quartile was chosen as reference group, since these women had the least weight loss. P-values for linear relation of the aOR across the BMI change quartiles were calculated (using the quartiles as a categorical variable). We adjusted for periconceptional BMI, nulliparity and smoking status in the logistic regression analyses. Adjusted odds ratios (aOR) and 95% confidence intervals (CI) are presented. Since pregnancy of multiples affect maternal and neonatal outcomes, we repeated the analyses in singleton pregnancies.

All analyses were performed using SPSS Statistics, version 22 (IBM Corporation, Armonk, USA). Statistical significance was assumed with a $p < 0.05$.

Results

The flowchart of the analysis is shown in Fig 1. Of all 577 women who were randomized and provided informed consent, 290 women were allocated to the lifestyle intervention program preceding infertility treatment (intervention group) and 287 to prompt infertility treatment (control group). Ten women in the intervention group and three women in the control group had incomplete follow-up or withdrawal of informed consent. Of all women in the intervention and control group combined, 321 women conceived within 24 months after randomization and had an ongoing pregnancy. For 244 (76%) of these women the periconceptional weight change was available.

Median BMI at study entry was 36.0 kg/m^2 (IQR 4.7 kg/m^2). Median periconceptional weight change in the 244 women was -0.9 kg/m^2 (IQR -2.1 to 0.1 kg/m^2). Women in the first quartile (Q1) had a periconceptional weight change of < -2.1 kg/m^2, women in the second quartile (Q2) -2.1 to -0.9 kg/m^2, women in the third quartile (Q3) -0.9 to 0.1 kg/m^2 and women in the

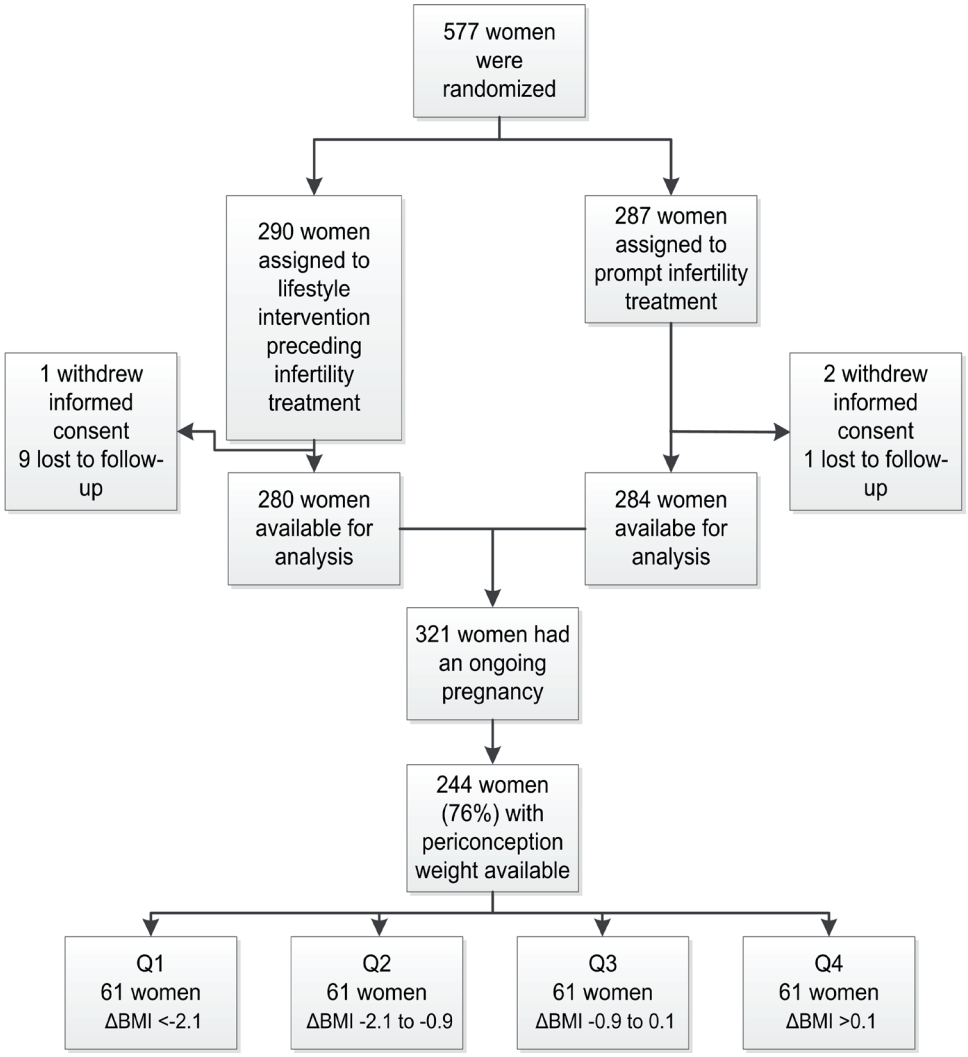

Fig 1. Flowchart of the analysis

fourth quartile (Q4) gained ≥ 0.1 kg/m^2. Baseline characteristics are summarized in Table 1. Women who achieved most weight loss were more often randomized to the intervention group ($P < 0.01$) and had a longer time to pregnancy ($P < 0.01$). Women with a missing periconceptional weight had a significantly longer time to pregnancy compared to women with known periconceptional weight ($P < 0.01$).

Table 1. Baseline characteristics of women according to weight change quartile.

		BMI change quartiles						
	Quartile	Q1	Q2	Q3	Q4	p-value	All women included in the analysis	Women with missing weight change
	ΔBMI (kg/m²)	<-2.1	-2.1 to -0.9	-0.9 to 0.1	>0.1			
	N	n=61	n=61	n=61	n=61		n=244	n=77
Maternal characteristics	unit							
Age	yr	30.0 (5.8)	30.5 (6.4)	28.6 (6.8)	28.6 (6.6)	0.44	29.3 (6.6)	27.9 (6.1)
Body-mass index	kg/m²	36.0 (3.3)	35.4 (6.1)	35.4 (5.5)	36.8 (3.8)	0.27	36.0 (4.7)	35.9 (5.1)
Blood pressure								
– Systolic	mmHg	122 (18)	125 (13)	122 (18)	124 (18)	0.74	125 (19)	129 (19)
– Diastolic	mmHg	80 (10)	80 (10)	80 (6)	80 (15)	0.96	80 (10)	80 (15)
Maternal smoking	N	12 (20)	10 (16)	11 (18)	13 (21)	0.87	46 (19)	22 (29)
Ethnic origin						0.93		
– Caucasian	n	55 (90)	54 (89)	55 (90)	53 (87)		217 (89)	68 (88)
– Other	n	6 (10)	7 (12)	6 (10)	8 (13)		27 (11)	9 (12)
Education						0.20		
– Primary school	n	2 (3.3)	1 (1.6)	3 (4.9)	2 (3.3)		8 (3.3)	2 (2.6)
– Secondary education	n	10 (16)	10 (16)	13 (21)	14 (23)		47 (19)	21 (27)
– Intermediate vocational education	n	26 (43)	27 (44)	33 (54)	33 (54)		119 (49)	33 (43)
– Higher vocational education and university	n	21 (34)	19 (31)	11 (18)	7 (12)		58 (24)	17 (22)
– Unknown	n	2 (3.3)	4 (6.6)	1 (1.6)	5 (8.2)		12 (4.9)	4 (5.2)
Randomized to lifestyle intervention	n	38 (62)	35 (57)	19 (31)	21 (34)	**<0.01**	113 (46)	41 (53)
Duration of infertility	months	21 (23)	17 (13)	19 (14)	19 (23)	0.23	19 (17)	16 (14)
Nulliparous	n	46 (75)	50 (82)	43 (71)	49 (80)	0.43	188 (77)	66 (86)

Table 1. Continued

		BMI change quartiles						
	Quartile	Q1	Q2	Q3	Q4	p-value	All women included in the analysis	Women with missing weight change
	ΔBMI (kg/m²)	<-2.1	-2.1 to -0.9	-0.9 to 0.1	>0.1			
	N	n=61	n=61	n=61	n=61		n=244	n=77
Maternal characteristics	unit							
Time to pregnancy	months	7.8 (4.5)	4.4 (7.8)	3.3 (6.6)	5.2 (7.7)	**<0.01**	6.0 (7.1)	11 (10)[a]
Multiple pregnancy	n	5 (8.1)	1 (1.6)	0	2 (3.3)	0.07	8 (3.3)	8 (10)[a]
Periconceptional weight measured during						0.12		NA
– first antenatal visit	n	41 (67)	40 (66)	37 (61)	44 (72)		162 (66)	NA
– self-reported 12 weeks after gestation	n	11 (18)	13 (21)	9 (15)	14 (23)		47 (19)	NA
– measured within 12 weeks of conception	n	9 (15)	8 (13)	15 (25)	3 (4.9)		35 (14)	NA

Table shows number of women (%) or median (IQR) by quartiles of BMI change between randomization in the LIFEstyle study and the periconception period. Medians were compared using the Kruskal-Wallis test and for categorical data using the Chi-square test.
[a] Women with a missing periconceptional weight change had a significantly longer time to pregnancy, p<0.01 and more often a multiple pregnancy, p=0.01.
BMI, body-mass index NA, not applicable

Table 2. Maternal outcomes by quartile of BMI change

	Quartile	Q1	Q2	Q3	Q4		
	ΔBMI	<-2.1	-2.1 to -0.9	-0.9 to 0.1	>0.1	aOR Q1-3 vs Q4	*P*-value linear relation
Rates of ongoing pregnancies within 24 months							
		n=61[a]	n=61	n=61	n=61		
Maternal outcomes							
Excessive gestational weight gain	rate (%)	24/37 (65)	21/32 (66)	12/28 (43)	18/34 (53)		
	aOR	2.28	2.30	0.80	1.00	1.44	0.07
	(95%CI)	(0.71-7.38)	(0.71-7.49)	(0.26-2.40)		(0.55-3.73)	
Gestational diabetes	rate (%)	8 (13)	8 (13)	15 (25)	10 (16)		
	aOR	0.93	0.93	1.69	1.00	1.24	0.61
	(95%CI)	(0.29-2.95)	(0.31-2.74)	(0.65-4.40)		(0.52-2.99)	
Hypertensive complications	rate (%)	14 (23)	9 (15)	10 (16)	21 (34)		
	aOR	0.55	0.30	0.39	1.00	0.39	0.17
	(95%CI)	(0.22-1.42)	(0.12-0.78)	(0.16-0.96)		(0.19-0.82)	
Rates of live births conceived within 24 months							
		n=59	n=60	n=61	n=60		
Preterm birth	rate (%)	10 (17)	4 (6.7)	5 (8.2)	12 (20)		
	aOR	0.88	0.30	0.37	1.00	0.46	0.75
	(95%CI)	(0.30-2.64)	(0.09-1.04)	(0.12-1.19)		(0.19-1.11)	
Induction of labor	rate (%)	25 (42)	20 (33)	25 (41)	30 (50)		
	aOR	0.92	0.59	0.76	1.00	0.73	0.71
	(95%CI)	(0.40-2.10)	(0.27-1.28)	(0.36-1.61)		(0.38-1.39)	
Spontaneous vaginal birth	rate (%)	33 (56)	44 (73)	36 (59)	33 (55)		
	aOR	0.76	1.91	0.95	1.00	1.15	0.94
	(95%CI)	(0.33-1.75)	(0.85-4.29)	(0.45-2.04)		(0.59-2.21)	
Assisted vaginal birth [b]	rate (%)	7 (18)	6 (12)	12 (25)	8 (20)		
	aOR	1.41	0.69	1.88	1.00	1.04	0.85
	(95%CI)	(0.38-5.22)	(0.20-2.33)	(0.63-5.58)		(0.69-1.56)	
Caesarean section	rate (%)	19 (32)	10 (17)	13 (21)	19 (32)		
	aOR	1.15	0.46	0.63	1.00	0.67	0.89
	(95%CI)	(0.47-2.81)	(0.19-1.16)	(0.27-1.48)		(0.33-1.36)	

Table shows rates and % of maternal outcomes by quartiles of BMI change.
Odds ratios are adjusted for periconceptional BMI, nulliparity and smoking.
P-values for the linear relation of quartiles of BMI change were calculated using the quartiles as a categorical variable, with adjustment for confounders.
[a] One woman with an ongoing pregnancy had no follow-up during pregnancy and outcomes were not recorded
[b] The denominator is the total number of vaginal births
BMI, body-mass index, aOR, adjusted odds ratio, CI, confidence interval

Maternal outcomes

There were no significant differences between quartile groups regarding rates of excessive gestational weight gain, gestational diabetes, preterm birth, induction of labor, spontaneous vaginal birth, assisted vaginal birth and Caesarean section (Table 2).

The rate of hypertensive complications was significantly lower among women who lost a moderate amount of periconceptional weight.

Table 3. Neonatal outcomes by quartile of BMI change

	Quartile ΔBMI	Q1 <-2.1 n=61[a]	Q2 -2.1 to -0.9 n=61	Q3 -0.9 to 0.1 n=61	Q4 >0.1 n=61	aOR Q1-3 vs Q4	*P*-value linear relation
Maternal outcomes							
SGA[b]	rate (%)	6 (10)	2 (3.3)	4 (6.6)	4 (6.7)		
	aOR	1.32	0.41	0.91	1.00	0.80	0.87
	(95%CI)	(0.27-6.44)	(0.07-2.56)	(0.20-4.13)		(0.21-3.03)	
LGA[b]	rate (%)	8 (14)	10 (17)	10 (16)	9 (15)		
	aOR	1.31	1.49	1.42	1.00	1.42	0.66
	(95%CI)	(0.41-4.19)	(0.52-4.27)	(0.51-3.99)		(0.58-3.50)	
Composite neonatal outcome	rate (%)	8 (13)	5 (8.2)	4 (6.6)	10 (16)		
	aOR	0.63	0.39	0.34	1.00	0.42	0.51
	(95%CI)	(0.19-2.08)	(0.11-1.33)	(0.10-1.20)		(0.16-1.12)	
Abnormal cord pH	rate (%)	1 (1.7)	1 (1.6)	1 (1.6)	1 (1.6)		
Apgar < 7	rate (%)	4 (6.7)	2 (3.3)	1 (1.6)	2 (3.3)		
Admission to NICU	rate (%)	4 (6.7)	3 (4.9)	3 (4.9)	9 (15)		
Perinatal death	rate (%)	1 (1.7)	2 (3.3)	0	1 (1.6)		

Table shows rates and % of neonatal outcomes by quartiles of BMI change.
Odds ratios are adjusted for periconceptional BMI, nulliparity and smoking.
Composite neonatal outcome consisted of an abnormal cord pH (<7.05), Apgar <7 at 5 minutes, admission to the NICU and perinatal death (stillbirth above 24 weeks gestation or early neonatal death within six weeks postpartum).
P-values for the linear relation of quartiles of BMI change were calculated using the quartiles as a categorical variable, with adjustment for confounders.
a One woman with an ongoing pregnancy had no follow-up during pregnancy and outcomes were not recorded
bThe denominator is the number of live births
BMI, body-mass index, SGA, small-for-gestational age, aOR, adjusted odds ratio, CI, confidence interval, LGA, large-for-gestational age, NICU, neonatal intensive care unit

A hypertensive complication occurred in 23% of women in Q1 (aOR 0.55, 95%CI 0.22-1.42), in 15% of women in Q2 (aOR 0.30, 95%CI 0.12-0.78), in 16% of women in Q3 (aOR 0.39, 0.16-0.96) and 34% of women in Q4 (reference). When women in quartiles 1 to 3 were combined and compared to women in Q4 there was an aOR of 0.39 (95%CI 0.19-0.82) of having a hypertensive complication during pregnancy.

Neonatal outcomes

There were no significant differences in the rates of SGA, LGA or the composite adverse neonatal outcome among women within the weight change quartiles (Table 3).

Subgroup analysis of singleton pregnancies

The results of the subgroup analysis on maternal and neonatal outcomes according to periconceptional weight loss in singleton pregnancies are shown in supplementary tables S1 and S2. In this subgroup analysis, the significantly decreased rate of a hypertensive complication remained in women in Q2 (aOR 0.27, 95% CI 0.10-0.72) and Q3 (aOR 0.39, 95%CI 0.16-0.98) and when comparing women within Q1 to Q3 together to women in Q4 (aOR 0.38, 95%CI 0.18-0.80). In addition, there was a significantly decreased rate of preterm birth in women in Q2 (aOR 0.24, 95% CI 0.06-0.98) compared to women in Q4 and when comparing women in Q1 to Q3 together to women in Q4 (aOR 0.37, 95%CI 0.14-0.97). There were no significant differences in rates of excessive gestational weight gain, gestational diabetes, induction of labor, spontaneous vaginal birth, assisted vaginal birth and Caesarean section between quartiles. The rates of LGA or SGA and the composite neonatal outcome were not different between quartiles.

Discussion

In this exploratory post-hoc analysis of pooled data of both treatment groups of the LIFEstyle RCT, we investigated the effects of the magnitude of periconceptional weight loss on maternal and neonatal outcomes in obese infertile women. Our results show that women who achieved modest periconceptional weight loss have a decreased rate of hypertensive pregnancy complications compared to women who gained weight during the periconceptional period. This was apparent in the total group and in the subgroup analysis including women with a singleton pregnancy. For women with a singleton pregnancy, the rate of preterm birth was significantly decreased in women who lost -2.1 to -0.9 kg/m^2 during the periconceptional period and when combining women in the three quartiles with highest periconceptional weight loss compared to women who gained weight during the periconceptional period. There were no differences in rates of excessive gestational weight gain, gestational diabetes, induction of labor, mode of birth, small for gestational

age or large for gestational age and the composite neonatal outcome among women in the different weight change quartiles.

Interestingly, women with the largest periconceptional weight loss (in Q1) did not have a significantly decreased risk of a hypertensive complication or preterm birth (in the subgroup analysis), while women with more modest periconceptional weight loss did have a significantly decreased risk of these complications. The point estimates of the adjusted odds ratios are well below 1 for all the weight change quartiles 1-3 suggesting that the risk of these complications is lower after weight loss. The fact that this does not reach significance in all quartiles could be the consequence of the relatively small numbers of outcomes in these quartiles, which make the point estimates more susceptible to chance fluctuation. It is also possible that intermediate periconceptional weight loss (as seen in Q2 and Q3) instead of more substantial weight loss (as seen in Q1) is more favorable for decreasing complications, but there is no evidence supporting this hypothesis.

The discrepancy in the incidence of preterm births between the main analysis and subgroup analysis can be explained by the higher risk of preterm birth usually present in multiple pregnancies.[32]

A large body of evidence exists on the negative impact of increased maternal BMI on reproductive, maternal and neonatal outcomes. However, studies on the effects of lifestyle interventions to decrease periconceptional weight to possibly counteract the adverse effects of overweight are limited. This might be due to difficulties providing interventions for women who are planning a pregnancy, as they are generally healthy and have minimal engagement to the healthcare system. Furthermore, most studies focus on interpregnancy weight loss. Villamor and Cnattingius did not find a significant difference in the rate of gestational hypertension or gestational diabetes in overweight women who lost > 1 kg/m^2 before the next pregnancy, but there was a lower rate of LGA.[26] This was also observed by Jain et al., who found that obese women with an interpregnancy weight loss of ≥ 2 kg/m^2 had an aOR 0.61 (95%CI 0.52-0.73) of having an LGA neonate.[33] We did not observe a decreased rate of LGA in obese women who achieved periconceptional weight loss. However, the rate of LGA was relatively low in our study. Our results are in agreement with findings of Mostello et al., who found that women who decreased their BMI between pregnancies were less likely to experience recurrent preeclampsia.[34]

Studies that were performed to investigate the effects of preconception bariatric surgery have shown it to be associated with decreased rates of gestational diabetes, hypertensive disorders, fetal macrosomia and LGA .[21-23] However, the risk of SGA is increased and some

studies report a shorter duration of gestation.[22,23] Average weight loss that can be achieved by obese women of reproductive age after bariatric surgery is on average minus 8 to 15 kg/m^2.[22] This is much greater than weight loss that can be achieved with a lifestyle intervention with a duration of six months, as in our study. However, remarkably, the magnitude of effect in reduction of the rate of hypertensive disorders is comparable to that in our study. A biological explanation for this effect may lie in a reduction in low-grade inflammation after weight loss.[34,35] Obesity is associated with an increase in oxidative stress and inflammatory markers,[36-38] as is seen in preeclampsia.[39] Weight loss is associated with improvement of this low-grade inflammation[35] and the decreased risk of hypertensive disorders could therefore be mediated through a decreased inflammatory state associated with weight loss.[34]

Strengths and limitations

The main strength of this study is that we used data from the largest RCT so far on the effect of a preconception lifestyle intervention program targeted at weight loss in obese infertile women. By taking into account women who had an ongoing pregnancy in both the intervention and control group of the RCT we could create a large cohort with periconceptional data on weight change and a subsequent pregnancy. Women in the control group of the LIFEstyle RCT were also informed about the importance of a healthy weight and lifestyle and on average these women lost -1.1 kg during the first six months after randomization.[25] In addition, due to the prospective data collection inherent to the RCT design of the LIFEstyle study, we were able to adjust for important confounders. While previous studies investigated relations between interpregnancy weight change and maternal or neonatal outcomes, our study provides a unique perspective, in which 77% of women are nulliparous.

A limitation of the current analysis is that the LIFEstyle study was powered on the healthy live birth rate within 24 months, instead of on adverse maternal and neonatal outcomes. Nevertheless, we were able to demonstrate some statistically significant associations between periconceptional weight loss and maternal outcomes. Regarding the neonatal outcomes, our results should not be interpreted as definite proof of absence of an influence of periconceptional weight loss. Secondly, since the LIFEstyle study was a pragmatic RCT in a real care setting, we lack data on body weight during the periconceptional period of 24% of women with an ongoing pregnancy. It is possible that selection bias occurred for women in whom periconceptional body weight measurement was recorded. This could be related to the longer time to pregnancy in women with unknown periconceptional weight change. It is possible that the longer time period between randomization and pregnancy caused women and/or their caregivers to miss or forget the recording of their weight once pregnant. We deem the influence of this possible selection bias as minimal,

since differences in recording of the periconceptional body weight are likely due to practice variations between clinics rather than due to patient preferences. Finally, our results show that 43 to 65% of women gained excessive amounts of weight during pregnancy. This could have increased the rate of various maternal and neonatal complications,[40] confounding the effects of periconceptional weight change. Currently, recording gestational weight gain and measures to prevent excessive gestational weight gain are not part of routine obstetric care in The Netherlands. Since only 54% of women with an ongoing pregnancy in our study provided the self-reported data of their weight change during pregnancy, we could not adjust our analyses for this factor. We recommend that gestational weight gain should be recorded to facilitate research on outcomes of pregnancy in obese women.

These data provide an insight into the possible magnitude of effect of periconceptional weight loss on perinatal outcomes. For the rare outcomes, especially in the neonate, combining our data with similar trials in an individual participant data meta-analysis could provide a more definite answer to the question whether periconceptional weight loss has a beneficial effect on maternal and neonatal outcomes in obese (infertile) women. Since our results show a reduced rate of hypertensive complications and preterm birth in women who achieved a modest amount of periconceptional weight loss, obese women who try to achieve pregnancy should be encouraged and guided to attempt weight reduction.

Conclusions

These results suggest that modest periconceptional weight loss in obese infertile women could lead to a 2.5 to 4-fold decrease in the rate of a hypertensive pregnancy complication and preterm birth. Our study was not powered on adverse pregnancy outcomes and therefore these results should be seen as explorative, indicating the magnitude of effect on maternal and neonatal outcomes that can be achieved by a preconception weight loss program. An individual participant data meta-analysis, combining our data with those from similar trials, would be required to reach more definite conclusions, especially regarding neonatal outcomes. In the meantime, our results support encouragement and guidance for obese women who try to achieve pregnancy to attempt weight reduction. In addition, gestational weight gain during pregnancy should be recorded to facilitate research on outcomes of pregnancy in obese women.

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Table S1. Maternal outcomes by quartile of BMI change in singleton pregnancies.

	Quartile	Q1	Q2	Q3	Q4		
	ΔBMI	<-2.1	-2.1 to -0.9	-0.9 to 0.1	>0.1	aOR Q1-3 vs Q4	*P*-value linear relation
Rates of ongoing pregnancies within 24 months							
		n=56[a]	n=60	n=61	n=59		
Maternal outcomes							
Excessive gestational weight gain	rate (%)	23/36 (64)	21/32 (66)	12/28 (43)	17/33 (52)		
	aOR	2.28	2.42	0.83	1.00	1.49	0.71
	(95%CI)	(0.70-7.43)	(0.74-7.91)	(0.28-2.52)		(0.57-3.88)	
Gestational diabetes	rate (%)	8 (15)	8 (13)	15 (25)	10 (17)		
	aOR	1.01	0.91	1.63	1.00	1.24	0.71
	(95%CI)	(0.32-3.21)	(0.31-2.70)	(0.62-4.25)		(0.51-2.97)	
Hypertensive complications	rate (%)	13 (24)	8 (13)	10 (16)	20 (34)		
	aOR	0.55	0.27	0.39	1.00	0.38	0.15
	(95%CI)	(0.21-1.45)	(0.10-0.72)	(0.16-0.98)		(0.18-0.80)	
Rates of live births conceived within 24 months							
		n=54	n=59	n=61	n=58		
Preterm birth	rate (%)	5 (9.3)	3 (5.1)	5 (8.2)	11 (19)		
	aOR	0.49	0.24	0.41	1.00	0.37	0.16
	(95%CI)	(0.14-1.79)	(0.06-0.98)	(0.13-1.34)		(0.14-0.97)	
Induction of labour	rate (%)	24 (44)	20 (34)	25 (41)	29 (50)		
	aOR	0.99	0.60	0.76	1.00	0.74	0.83
	(95%CI)	(0.43-2.30)	(0.27-1.32)	(0.36-1.61)		(0.38-1.43)	
Spontaneous vaginal birth	rate (%)	32 (59)	44 (75)	36 (59)	33 (57)		
	aOR	0.81	1.87	0.88	1.00	1.12	0.88
	(95%CI)	(0.34-1.91)	(0.81-4.28)	(0.41-1.90)		(0.57-2.18)	
Assisted vaginal birth [b]	rate (%)	7 (18)	6 (12)	12 (25)	8 (20)		
	aOR	1.43	0.69	1.88	1.00	1.25	0.87
	(95%CI)	(0.39-5.29)	(0.20-2.34)	(0.63-5.57)		(0.47-3.34)	
Caesarean section	rate (%)	15 (28)	9 (15)	13 (21)	17 (29)		
	aOR	1.05	0.47	0.71	1.00	0.68	0.87
	(95%CI)	(0.41-2.69)	(0.18-1.23)	(0.30-1.68)		(0.33-1.44)	

Table shows rates and % of maternal outcomes by quartiles of BMI change in women with an ongoing pregnancy. Odds ratios are adjusted for periconception BMI, nulliparity and smoking.
P-values for the linear relation of quartiles of BMI change were calculated using the quartiles as a categorical variable, with adjustment for confounders
[a] One woman with an ongoing pregnancy had no follow-up during pregnancy and outcomes were not recorded
[b] The denominator is the total number of vaginal births
BMI, body-mass index, aOR, adjusted odds ratio, CI, confidence interval

Table S2. Neonatal outcomes by quartile of BMI change in singleton pregnancies.

	Quartile	Q1	Q2	Q3	Q4		
	ΔBMI	<-2.1	-2.1 to -0.9	-0.9 to 0.1	>0.1	aOR Q1-3 vs Q4	*P*-value linear relation
		n=56[a]	n=60	n=61	n=59		
Maternal outcomes							
SGA[b]	rate (%)	4 (7.4)	1 (1.7)	4 (6.6)	3 (5.2)		
	aOR	0.94	0.23	1.09	1.00	0.73	0.68
	(95%CI)	(0.15-6.09)	(0.02-2.52)	(0.21-5.60)		(0.16-3.34)	
LGA[b]	rate (%)	8 (15)	10 (17)	10 (16)	8 (14)		
	aOR	1.63	1.71	1.58	1.00	1.64	0.42
	(95%CI)	(0.50-5.35)	(0.58-5.05)	(0.55-4.58)		(0.65-4.16)	
Composite neonatal outcome	rate (%)	6 (11)[a]	4 (6.7)	4 (6.6)	9 (15)		
	aOR	0.55	0.34	0.36	1.00	0.40	0.35
	(95%CI)	(0.15-2.00)	(0.09-1.29)	(0.10-1.32)		(0.14-1.11)	
– Abnormal cord pH	rate (%)	1 (1.8)	1 (1.7)	1 (1.6)	1 (1.7)		
– Apgar < 7	rate (%)	4 (7.3)	2 (3.3)	1 (1.6)	2 (3.4)		
– Admission to NICU	rate (%)	2 (3.6)	2 (3.3)	3 (4.9)	8 (14)		
– Perinatal death	rate (%)	1 (1.8)	1 (1.7)	0	1 (1.7)		

Table shows rates and % of neonatal outcomes by quartiles of BMI change in women with an ongoing pregnancy. Odds ratios are adjusted for periconception BMI, nulliparity and smoking.
Composite neonatal outcome consisted of an abnormal cord pH (<7.05), Apgar <7 at 5 minutes, admission to the NICU and perinatal death (stillbirth above 24 weeks gestation or early neonatal death within six weeks postpartum). P-values for the linear relation of quartiles of BMI change were calculated using the quartiles as a categorical variable, with adjustment for confounders [a] One woman with an ongoing pregnancy had no follow-up during pregnancy and outcomes were not recorded
[b] The denominator is the number of live births.
BMI, body-mass index, SGA, small-for-gestational age, aOR, adjusted odds ratio, CI, confidence interval, LGA, large-for-gestational age, NICU, neonatal intensive care unit