Lifestyle intervention in obese infertile women

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ORIGINAL ARTICLE

Randomized Trial of a Lifestyle Program in Obese Infertile Women

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ABSTRACT

BACKGROUND

Small lifestyle-intervention studies suggest that modest weight loss increases the chance of conception and may improve perinatal outcomes, but large randomized, controlled trials are lacking.

METHODS

We randomly assigned infertile women with a body-mass index (the weight in kilograms divided by the square of the height in meters) of 29 or higher to a 6-month lifestyle intervention preceding treatment for infertility or to prompt treatment for infertility. The primary outcome was the vaginal birth of a healthy singleton at term within 24 months after randomization.

RESULTS

We assigned women who did not conceive naturally to one of two treatment strategies: 290 women were assigned to a 6-month lifestyle-intervention program preceding 18 months of infertility treatment (intervention group) and 287 were assigned to prompt infertility treatment for 24 months (control group). A total of 3 women withdrew consent, so 289 women in the intervention group and 285 women in the control group were included in the analysis. The discontinuation rate in the intervention group was 21.8%. In intention-to-treat analyses, the mean weight loss was 4.4 kg in the intervention group and 1.1 kg in the control group ($P<0.001$). The primary outcome occurred in 27.1% of the women in the intervention group and 35.2% of those in the control group (rate ratio in the intervention group, 0.77; 95% confidence interval, 0.60 to 0.99).

CONCLUSIONS

In obese infertile women, a lifestyle intervention preceding infertility treatment, as compared with prompt infertility treatment, did not result in higher rates of a vaginal birth of a healthy singleton at term within 24 months after randomization. (Funded by the Netherlands Organization for Health Research and Development; Netherlands Trial Register number, NTR1530.)

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N Engl J Med 2016;374:1942-53.
DOI: 10.1056/NEJMoa1505297

Obesity is a major public health problem.[1] In most developed countries, 14 to 20% of women of reproductive age are obese (body-mass index [BMI; the weight in kilograms divided by the square of the height in meters], ≥30), whereas in some countries, the prevalence of obesity is as high as 60%.[1]

Obesity negatively affects female reproductive health because it is associated with increased risks of menstrual dysfunction, anovulation, and infertility.[2-4] Success rates with ovulation induction and assisted reproductive techniques are lower among obese infertile women than among normal-weight women.[5,6] The risks of miscarriage,[6,7] gestational diabetes, hypertensive disorders, preterm birth, and cesarean section are higher among obese pregnant women than among those who are not obese. Risks of shoulder dystocia and infants with macrosomia are also higher among obese pregnant women,[8-10] and risks of congenital anomalies and perinatal and infant death are also increased.[11,12]

Various guidelines have advocated lifestyle-intervention programs aiming at weight loss of 5 to 10% of body weight as the first step in caring for obese infertile women.[13,14] However, large randomized, controlled trials assessing the effectiveness of lifestyle-intervention programs to support these guidelines are lacking. We therefore performed a multicenter randomized trial involving obese infertile women to assess the effectiveness of a lifestyle intervention preceding infertility treatment.

METHODS

TRIAL DESIGN AND OVERSIGHT

We conducted a multicenter randomized trial at six university medical centers and 17 general hospitals in the Netherlands. The trial protocol (available with the full text of this article at NEJM.org) was approved by the medical ethics committee of the University Medical Center Groningen and the board of directors at each participating center. The last author assumes responsibility for the completeness and accuracy of the data and analyses and for the fidelity of the trial to the protocol. The protocol was published previously.[15]

PARTICIPANTS

Infertile women between 18 and 39 years of age with a BMI of 29 or higher were eligible to participate in the trial. Women were considered to be infertile if they had chronic anovulation (oligomenorrhea or amenorrhea and low levels of gonadotropins and low or undetectable levels of estrogen [World Health Organization (WHO) class I anovulation] or oligomenorrhea or amenorrhea and serum follicle-stimulating hormone and estradiol levels within the normal range [WHO class II anovulation])[16] or if they had an ovulatory cycle and had unsuccessfully tried to conceive for at least 12 months. Women with severe endometriosis, premature ovarian failure, or endocrinopathy (e.g., women with type 1 diabetes or Cushing's syndrome) and those who were eligible for donor insemination because of azoospermia were excluded, as were women with untreated preexisting hypertension and those with hypertension-related complications in a previous pregnancy.[17]

After they provided written informed consent, women were randomly assigned in a 1:1 ratio to one of two treatment strategies: a 6-month lifestyle intervention preceding 18 months of infertility treatment (intervention group) or prompt infertility treatment for 24 months (control group). Randomization was performed online and was stratified according to trial center and ovulatory status. The appropriate infertility treatment was determined and recorded before randomization, since blinding of the treatment assignments was not possible.

LIFESTYLE INTERVENTION

The lifestyle intervention consisted of a 6-month structured program with the goal of the loss of 5 to 10% of the woman's body weight at randomization.[18-21] The program was developed according to the recommendations of the National Institutes of Health[22] and was piloted in a single-center study.[23,24] It included six outpatient visits and four telephone consultations during a 24-week period.

Participants were guided by intervention coaches who had a degree in nursing or by dietitians who were trained before the trial. The intervention coaches were supervised on site by one trained nurse, had yearly group training sessions, and used a standardized computerized system to minimize practice variation among coaches. Information that included body weight, menstrual dates, and calorie intake was captured in this system by the coaches.[25] Women were advised to reduce their energy intake by

600 kcal daily with the assistance of an online diet diary[26] while maintaining a minimum caloric intake of 1200 kcal per day. They were also advised to engage in moderate-intensity physical activity, with a target level of 10,000 steps per day (monitored by a step counter), and at least 30 minutes of moderate-intensity exercise two or three times per week.[27] The coaches also provided motivational counseling to promote awareness of a healthy lifestyle and formulate individualized goals.

Women discontinued the intervention if an ongoing pregnancy was achieved, and if a pregnancy ended in a miscarriage, they were allowed to resume the intervention. After women completed the intervention, infertility treatment was initiated according to the Dutch infertility guidelines,[28] irrespective of their BMI. To enhance adherence to the intervention, women who lost 5 to 10% of their initial weight or reached a BMI below 29 in the first 6 months after randomization could proceed with their indicated infertility treatment before the intervention was finished. Women who missed two or more consecutive sessions were considered to have not completed the intervention and received treatment according to local protocols. Local protocols were based on Dutch infertility guidelines,[28] but they differed among infertility clinics; some centers required a BMI below a certain level (ranging from 30 to 40), whereas other centers treated obese women irrespective of their BMI.

Participants were informed in advance that they would not automatically receive infertility treatment if they did not complete the intervention. The follow-up of all women who were randomly assigned to the intervention group (including those who did not complete the intervention) continued until 24 months after randomization.

CONTROL STRATEGY

Women who were assigned to the control group received prompt treatment in accordance with Dutch infertility guidelines, irrespective of their BMI.[28] Treatment of women with anovulatory infertility began with ovulation induction, and clomiphene citrate was generally administered first.[29] The initial dose of clomiphene citrate was 50 mg per day orally, typically for 5 days, starting on the second to the fifth day after the onset of natural or progestin-induced menses. If pregnancy did not occur in 6 to 12 cycles or if clomiphene resistance developed (i.e., ovulation was not induced after the dose was increased to the maximum dose of 150 mg per day), gonadotropin therapy was initiated in a low-dose step-up regimen (starting with 75 IU per day) for a maximum of 12 cycles.[29]

In women who ovulated, treatment depended on the estimated probability of natural conception in the next 12 months according to the Hunault prediction model.[30] If this probability was estimated to be less than 30%, women could undergo up to six cycles of intrauterine insemination with or without ovulation induction.

In vitro fertilization (IVF) was initiated in women with tubal disease or after intrauterine insemination cycles failed. Intracytoplasmic sperm injection (ICSI) was used in couples with severe male-factor infertility (total motile sperm count, <1 million sperm per milliliter or <3 million sperm per milliliter in women in whom intrauterine insemination failed).[28]

Couples with a good prognosis for natural conception (i.e., ≥30% in the next 12 months)[30] received expectant care for 6 to 12 months. Infertility treatment was continued until couples declined further treatment or until further treatment was considered to be ineffective.

During the 24 months after randomization, research nurses recorded data on infertility treatments (e.g., the types of treatment, number of cycles, and types and doses of medication) and reproductive outcomes (including the course and outcomes of pregnancies and complications) in a Web-based digital case-record form. If needed, the general practitioner was contacted to obtain missing information on primary and secondary outcomes. If a woman conceived within 24 months after randomization but the pregnancy ended thereafter, monitoring was continued until the pregnancy ended. These pregnancies were not included in the analysis of the primary outcome.

OUTCOMES

The primary outcome was the vaginal birth of a healthy singleton at 37 weeks or more within 24 months after randomization. A child was considered to be healthy if he or she was born alive without major congenital anomalies.[31,32]

Prespecified secondary outcomes included a change in the woman's weight, waist circumference, and blood pressure (measured manually or electronically while she was in a sitting position)

Table 1. Baseline Characteristics, According to Trial Group.*

Characteristic	Intervention Group (N=289)	Control Group (N=285)
Characteristics of woman		
Age — yr	29.7±4.5	29.8±4.6
White race — no. (%)†	256 (88.6)	246 (86.3)
Education level — no. (%)		
Primary school, age 4–12 yr	17 (5.9)	10 (3.5)
Secondary education	68 (23.5)	63 (22.1)
Intermediate vocational education	135 (46.7)	131 (46.0)
Advanced vocational education or university	56 (19.4)	69 (24.2)
Unknown	13 (4.5)	12 (4.2)
Current smoker — no. (%)	76 (26.3)	60 (21.1)
Nulliparous — no. (%)	226 (78.2)	215 (75.4)
Median duration of time attempting to conceive (IQR) — mo	22.0 (14.0–36.0)	19.0 (13.0–32.0)
Median BMI at baseline (IQR)	36.0 (33.4–38.2)	36.0 (33.5–38.2)
Characteristics of male partner		
Age — yr	33.5±6.0	33.6±6.2
Median BMI (IQR)	27.7 (24.4–31.0)	27.2 (24.2–31.0)
Basic subfertility assessment		
Anovulatory infertility — no. (%)	128 (44.3)	141 (49.5)
Polycystic ovary syndrome according to Rotterdam criteria — no./total no. (%)‡	97/128 (75.8)	104/141 (73.8)
Median total motile sperm count (IQR) — million/ml	38.0 (10.2–92.0)	35.0 (9.7–81.8)
Blocked fallopian tubes on both sides — no. (%)	3 (1.0)	2 (0.7)
Infertility diagnosis — no. (%)§		
Anovulation	128 (44.3)	141 (49.5)
Unexplained	86 (29.8)	77 (27.0)
Male factor	67 (23.2)	64 (22.5)
Tubal factor	12 (4.2)	16 (5.6)
Other	8 (2.8)	7 (2.5)
Hunault prognostic score — %¶	31.8±13.0	30.4±13.2

* Plus–minus values are means ±SD. The numbers of women include women who were lost to follow-up. Differences between the groups were compared with the use of Student's t-test for means, the Mann–Whitney U test for medians, and the chi-square test or Fisher's exact test for proportions, where appropriate. There were no significant differences between the groups except for the median duration of time attempting to conceive (P=0.037). BMI denotes body-mass index (the weight in kilograms divided by the square of the height in meters), and IQR interquartile range.
† Race was self-reported.
‡ The denominator is the number of women with anovulatory infertility.
§ A total of 33 couples had two or more reasons for infertility.
¶ The Hunault prognostic score is based on a model assessing the chance of spontaneous pregnancy in infertile couples with unexplained infertility or mild male-factor infertility. Factors in the model are the woman's age, the duration of infertility, primary or secondary infertility, sperm motility, and the referral status (secondary or tertiary care) of the couple. Scores range from 7 to 73%, with higher scores indicating a better chance of natural conception within the next year.[30]

in the first 6 months after randomization. Additional secondary outcomes included an ongoing pregnancy (a viable pregnancy of at least 10 weeks of gestation), a clinical pregnancy (in which the gestational sac was visible on ultrasonography), a miscarriage (loss of a clinical pregnancy at a gestational age of <16 weeks), and a multiple pregnancy. Other secondary outcomes were infertility treatments (ovulation induction, intrauterine insemination, IVF, or ICSI), complications due to infertility treatment (including ectopic pregnancy, ovarian hyperstimu-

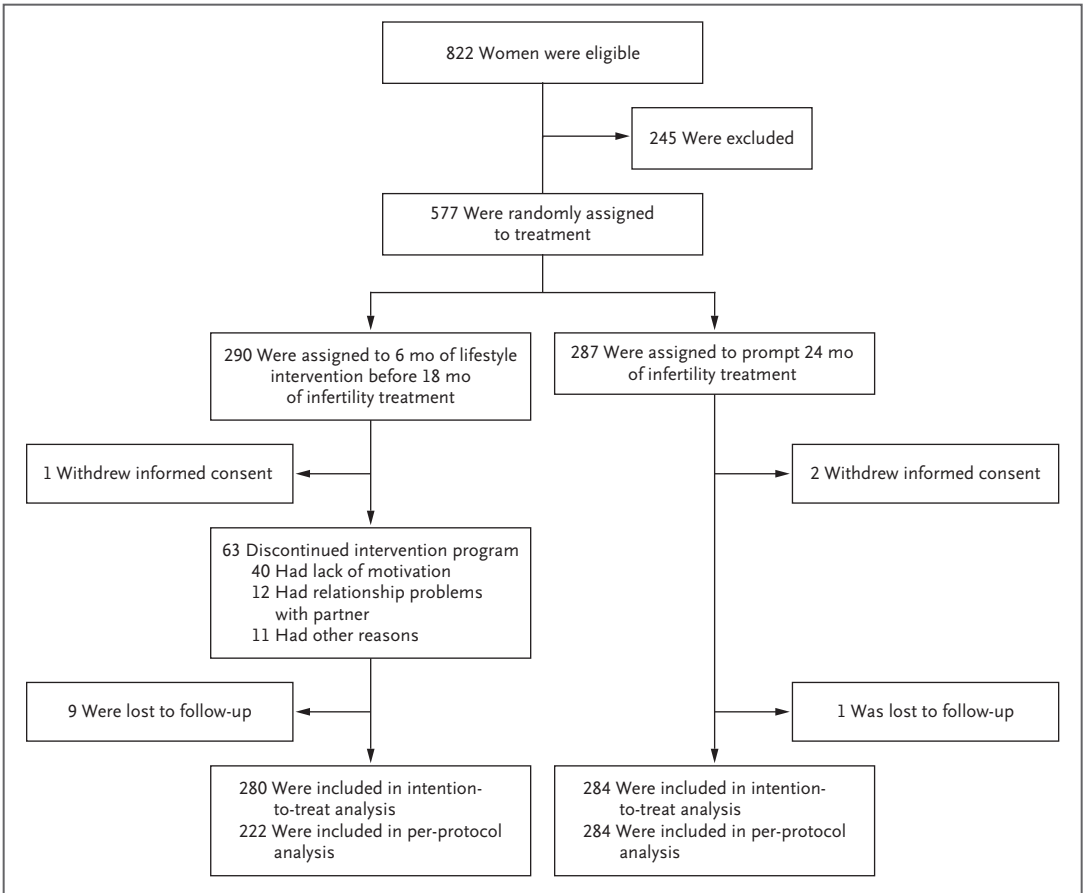

Figure 1. Eligibility, Randomization, and Follow-up.
Five women who discontinued the intervention program were lost to follow-up.

lation syndrome, and an adnexal complication such as torsion, bleeding, or infection after follicle aspiration), gestational diabetes,[33] and hypertension disorders during pregnancy (gestational hypertension, preeclampsia or eclampsia, and the HELLP syndrome, which is characterized by hemolysis, elevated liver-enzyme levels, and a low platelet count[17]).

The secondary outcome of stillbirth was subdivided into antepartum and intrapartum stillbirth[12] after a gestational age of 16 weeks.[12] Related secondary outcomes were the gestational age at delivery, preterm birth (birth before 37 weeks), method of delivery (spontaneous or assisted vaginal birth or emergency or elective cesarean section), and the duration of labor.

Adverse outcomes in women included postpartum hemorrhage (≥1000-ml blood loss). Adverse neonatal outcomes included neonatal death,[12] shoulder dystocia, a 5-minute Apgar score below 7, an arterial pH of less than 7.05, admission to and the duration of stay in a neonatal intensive care unit, and small-for-gestational-age or large-for-gestational-age status, which was defined as a birth weight below the 10th percentile or above the 90th percentile, respectively (according to the Dutch reference curves[34]), within 24 months after randomization. In addition, we assessed the outcomes of live birth (independent of gestational age, method of delivery, and health of the newborn), time to pregnancy, and birth weight within 24 months after randomization.

STATISTICAL ANALYSIS

The power calculations were based on an assumption of an increase in the rate of vaginal birth of a healthy singleton at term from 45% in the control group to 60% in the intervention group,[3,35,36] a 20% discontinuation rate during the lifestyle intervention,[37] and a 5% loss to follow-up. We calculated that a sample of 285

women per group would provide the trial with a power of 80% at a two-sided alpha level of 5%.

Primary analyses were performed on an intention-to-treat basis. Differences between groups were expressed as relative risks or odds ratios and 95% confidence intervals. For continuous variables, differences were calculated with the use of the Mann–Whitney U test. No adjustments for multiple comparisons were made.

To estimate the time to pregnancy, including censoring of data in cases of incomplete follow-up, the cumulative rate of vaginal births of healthy singletons at term and rates of live births were compared with the use of Kaplan–Meier analyses and the log-rank test. Neonatal outcomes were compared with the use of multilevel analysis (generalized estimating equations).

We performed a per-protocol analysis in which women who did not complete the intervention were excluded from the intervention group. Two post hoc subgroup analyses (one that involved women with anovulatory infertility and the other that involved women with unexplained infertility) also were performed. All statistical analyses were conducted with the use of SPSS software, version 22.0 (IBM).

RESULTS

Between June 9, 2009, and June 22, 2012, we identified 822 women who were eligible to participate in the trial; 577 of these women provided written informed consent. A total of 290 women were randomly assigned to the intervention group and 287 were assigned to the control group; 3 women withdrew informed consent, for a total of 289 and 285 women, respectively.

Baseline characteristics were similar in the two groups (Table 1). A total of 10 women were lost to follow-up, so data on 280 women in the intervention group and 284 women in the control group were available for the intention-to-treat analysis (Fig. 1).

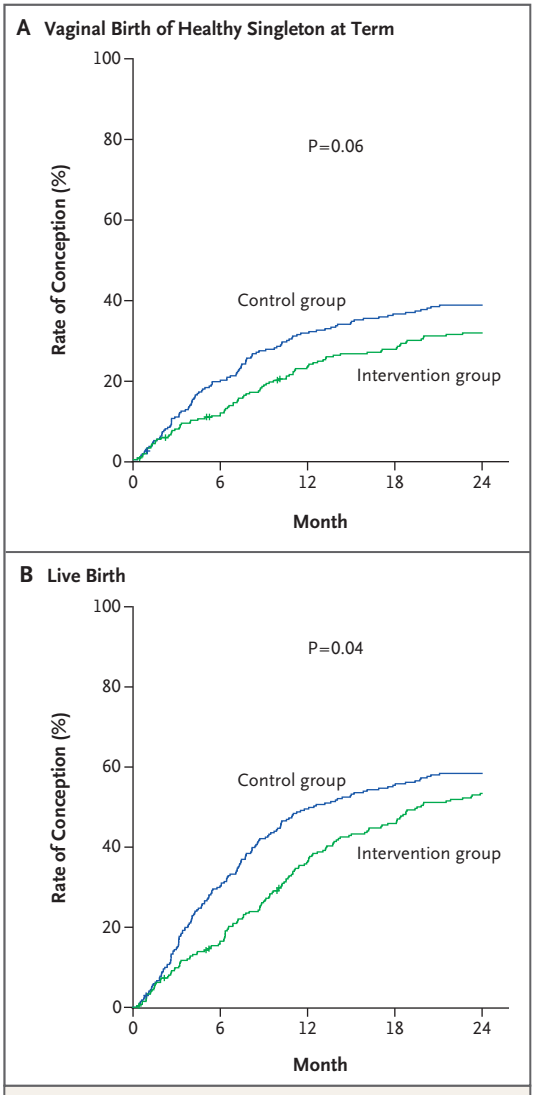

Figure 2. Time to Pregnancy (Intention-to-Treat Analysis).
Kaplan–Meier curves show the time to pregnancy resulting in the vaginal birth of a healthy singleton at term (Panel A) and the time to pregnancy resulting in a live birth (Panel B). Crosses indicate women who were lost to follow-up.

LIFESTYLE INTERVENTION

A total of 63 women (21.8%) discontinued the lifestyle intervention after a median of 2.8 months (interquartile range, 14 days to 3.9 months) (Fig. 1). The mean (±SD) weight loss after 6 months was 4.4±5.8 kg in 236 nonpregnant women and 1.1±4.3 kg in the 128 women in the control group (P<0.001). Among women who were randomly assigned to the lifestyle intervention, 89 (37.7%) lost 5% or more of their original body weight; none of the women in the control group lost 5% or more of their original body weight over the first 6 months. The mean weight loss in the 186 women who completed the intervention program was 5.3±6.1 kg, and 80 of them (43.0%) lost 5% or more of their original body weight.

From baseline to 6 months, the change in waist circumference was significantly greater in women in the intervention group than in women in the control group. Changes in blood pressure

Table 2. Pregnancy Outcomes within 24 Months after Randomization, According to Trial Group.*

Outcome	Intervention Group (N=280)	Control Group (N=284)	Rate Ratio (95% CI)
Fetal or neonatal outcomes			
Primary outcome: vaginal birth of healthy singleton at term — no. (%)	76 (27.1)	100 (35.2)	0.77 (0.60 to 0.99)
Live birth — no. (%)	123 (43.9)	153 (53.9)	0.82 (0.69 to 0.97)
Ongoing pregnancy — no. (%)	150 (53.6)	167 (58.8)	0.91 (0.79 to 1.05)
Clinical pregnancy — no. (%)	175 (62.5)	186 (65.5)	0.95 (0.84 to 1.08)
Ectopic pregnancy — no. (%)†	4 (1.4)	7 (2.5)	0.58 (0.17 to 1.96)
Miscarriage — no. (%)	41 (14.6)	27 (9.5)	1.54 (0.98 to 2.43)
Multiple gestation — no. (%)	6 (2.1)	9 (3.2)	0.68 (0.24 to 1.87)
Twins	5 (1.8)	9 (3.2)	0.56 (0.19 to 1.66)
Triplets	1 (0.4)	0	NA
Stillbirth — no./total no. (%)†‡			
Antepartum	1/150 (0.7)	0/167	NA
Intrapartum	2/150 (1.3)	1/167 (0.6)	2.23 (0.20 to 24.31)
Median gestational age at delivery (IQR) — wk§	39.7 (38.0 to 40.6)	39.0 (37.8 to 40.4)	
Premature birth — no./total no. (%)§	17/123 (13.8)	22/153 (14.4)	0.96 (0.54 to 1.73)
Method of delivery — no./total no. (%)§			
Vaginal birth			
Spontaneous	71/123 (57.7)	89/153 (58.2)	0.99 (0.81 to 1.22)
Instrument-assisted	13/123 (10.6)	24/153 (15.7)	0.67 (0.36 to 1.27)
Cesarean section			
Emergency	25/123 (20.3)	19/153 (12.4)	1.64 (0.95 to 2.83)
Elective	14/123 (11.4)	21/153 (13.7)	0.83 (0.44 to 1.56)
Median duration of labor after onset (IQR) — hr§	10.7 (5.7 to 18.7)	11.5 (6.3 to 20.8)	
Median birth weight (IQR) — g¶‖	3312 (3198 to 3426)	3341 (3234 to 3448)	−29 (−185 to 27)
Small for gestational age — no./total no. (%)¶**	10/130 (7.7)	8/161 (5.0)	1.59 (0.60 to 4.02)
Large for gestational age — no./total no. (%)¶**	16/130 (12.3)	23/161 (14.3)	0.84 (0.42 to 1.67)
Adverse neonatal outcomes — no./total no. (%)¶**			
Death†	0	2/161 (1.2)	NA
Shoulder dystocia	3/122 (2.5)	4/153 (2.6)	1.07 (0.24 to 4.89)
Apgar score <7 after 5 min	3/129 (2.3)	5/161 (3.1)	0.74 (0.17 to 3.13)
Arterial pH <7.05	1/104 (1.0)	0/86	NA
Major congenital anomaly†	4/129 (3.1)	5/161 (3.1)	0.69 (0.17 to 2.88)
Admission to NICU	17/130 (13.1)	16/161 (9.9)	1.27 (0.56 to 2.91)
Median duration of NICU stay (IQR) — days††	19 (7.25 to 29)	8.5 (5.25 to 38)	−0.08 (−1.70 to 1.50)
Outcomes in woman			
Gestational complications — no./total no. (%)‡			
Diabetes	23/150 (15.3)	33/167 (19.8)	0.78 (0.48 to 1.26)
Hypertension	26/150 (17.3)	27/167 (16.2)	1.07 (0.66 to 1.75)
Preeclampsia†	10/150 (6.7)	12/167 (7.2)	0.93 (0.41 to 2.09)
HELLP syndrome†	3/150 (2.0)	2/167 (1.2)	1.67 (0.28 to 9.86)

Table 2. (Continued.)

Outcome	Intervention Group (N=280)	Control Group (N=284)	Rate Ratio (95% CI)
Adverse postpartum outcomes — no./total no. (%)§			
Hemorrhage†	8/123 (6.5)	10/153 (6.5)	1.00 (0.41 to 2.45)
Total perineal rupture	1/153 (0.7)	5/153 (3.3)	0.25 (0.03 to 2.10)

* Differences between the groups were assessed with the use of the Mann–Whitney U test for gestational age and the duration of labor, generalized estimating equations for birth weight and size for gestational age, and logistic regressions for shoulder dystocia. There were no significant differences between the two groups. CI denotes confidence interval; HELLP hemolysis, elevated liver-enzyme levels, and low platelet count; NA not applicable; and NICU neonatal intensive care unit.
† Additional information is provided in Table S5 in the Supplementary Appendix.
‡ The denominator is the number of women with an ongoing pregnancy.
§ The denominator is the number of live births.
¶ The denominator is the number of newborns. Small for gestational age was defined as a birth weight below the 10th percentile and large for gestational age was defined as a birth weight above the 90th percentile derived from the Dutch reference curves.[34]
‖ The mean difference and 95% CI are shown.
** Comparisons of size for gestational age and adverse neonatal outcomes are presented as odds ratios.
†† A Poisson regression contrast estimate (rate difference) and 95% CI are shown.

did not differ significantly between the groups (Table S1 in the Supplementary Appendix, available at NEJM.org).

PREGNANCY OUTCOMES

Within 24 months after randomization, the frequency of vaginal births of healthy singletons at term was significantly lower in the intervention group than in the control group: 76 (27.1%) versus 100 (35.2%) (rate ratio in the intervention group, 0.77; 95% confidence interval [CI], 0.60 to 0.99) (Fig. 2A and Table 2); rates of live births within 24 months after randomization followed a similar pattern (Fig. 2B and Table 2). Rates of ongoing pregnancy and clinical pregnancy were not significantly different between the groups. After the inclusion of data from pregnancies that were conceived within 24 months after randomization but ended following that period, there were no significant between-group differences in the rates of vaginal births of healthy singletons at term or in the rates of live births (Table S2 in the Supplementary Appendix).

The median time to pregnancy resulting in the vaginal birth of a healthy singleton at term was 7.2 months in the intervention group (interquartile range, 2.6 to 12.0) versus 5.2 months in the control group (interquartile range, 2.4 to 10.1; P=0.06) (Fig. 2A). The median times to pregnancy resulting in a live birth were 8.8 months (interquartile range, 3.5 to 13.2) in the intervention group and 5.2 months (interquartile range, 2.6 to 9.4) in the control group (P=0.04) (Fig. 2B).

INFERTILITY TREATMENT

Overall, significantly more women in the intervention group than in the control group had ongoing pregnancies that resulted from natural conception (Table 3). In the intervention group, 90% of the women who completed the intervention program, as compared with 87% of the women in the control group, received treatment according to the Dutch infertility guidelines.

The number of treatment cycles was lower in the intervention group than in the control group (679 vs. 1067). In the intervention group, women who did not complete the intervention program had fewer natural conceptions and fewer received infertility treatment than those who did complete the program (Tables S3 and S4 and Fig. S1 in the Supplementary Appendix).

COMPLICATIONS AND ADVERSE EVENTS

The frequencies of complications related to pregnancy and labor in women and neonates did not differ significantly between the groups (Tables 2 and 3). There were no significant between-group differences in neonatal outcomes, mean birth weight, or the number of small-for-gestational-age infants.

PER-PROTOCOL AND POST HOC ANALYSES

The per-protocol analysis showed no significant differences in the rates of the primary outcome or in live-birth rates between the groups. The rate of natural conception was significantly higher and the percentage of women who received

Table 3. Method of Conception and Outcome of Infertility Treatment within 24 Months after Randomization.*

Outcome	Intervention Group (N=280)	Control Group (N=284)	Rate Ratio (95% CI)
Method of conception leading to ongoing pregnancy — no. (%)			
Natural	73 (26.1)	46 (16.2)	1.61 (1.16–2.24)
Ovulation induction	34 (12.1)	64 (22.5)	0.54 (0.37–0.79)
Intrauterine insemination	21 (7.5)	25 (8.8)	0.85 (0.49–1.48)
IVF or ICSI	22 (7.9)	32 (11.3)	0.70 (0.42–1.17)
Infertility treatment — no. (%)			
Any infertility treatment	177 (63.2)	231 (81.3)	0.78 (0.70–0.86)
Ovulation induction	73 (26.1)	114 (40.1)	0.65 (0.51–0.83)
Intrauterine insemination	68 (24.3)	74 (26.1)	0.93 (0.70–1.24)
IVF or ICSI	58 (20.7)	79 (27.8)	0.75 (0.55–1.00)
Infertility treatment cycles — no.			
Ovulation induction	308	548	NA
Intrauterine insemination	225	285	NA
IVF or ICSI†	146	234	NA
Cycles per woman — no.‡			
Ovulation induction	4.2	4.8	
Intrauterine insemination	3.3	3.9	
IVF or ICSI†	2.5	3.0	
Complications related to infertility treatment — no./total no. (%)§			
Ovarian hyperstimulation syndrome¶	0	4/231 (1.7)	NA
Adnexal complication after retrieval of oocytes¶			
Torsion	1/177 (0.6)	0	NA
Bleeding	0	1/231 (0.4)	NA
Infection	0	2/231(0.9)	NA
Triplet gravidity	2/177 (1.1)	0	NA

* ICSI denotes intracytoplasmic sperm injection, and IVF in vitro fertilization.
† These numbers include cryopreserved embryo–transfer cycles.
‡ The difference between the groups in the total randomized population was calculated with the use of the Mann–Whitney U test. There were significant between-group differences with respect to ovulation induction ($P<0.001$) and IVF or ICSI ($P=0.03$).
§ The percentages shown are ratios of women who received infertility treatment.
¶ Additional information is provided in Table S5 in the Supplementary Appendix.

infertility treatment was significantly lower in the intervention group than in the control group (Table S4 in the Supplementary Appendix). The times to pregnancy resulting in the vaginal birth of a healthy singleton at term within 24 months after randomization or in a live birth were similar in the two groups (Fig. S2 in the Supplementary Appendix).

In addition, post hoc subgroup analyses that were limited to women with anovulatory infertility or to women with unexplained infertility showed no significant differences between the groups with respect to the rates of the primary outcome or of live births. Additional information is provided in Tables S6 and S7 in the Supplementary Appendix.

DISCUSSION

In this multicenter, randomized trial involving obese infertile women, a 6-month structured lifestyle intervention preceding infertility treatment did not result in higher rates of term births of vaginally delivered healthy singletons at 24 months than rates of these births among women who received prompt infertility treatment. The rates of pregnancy-related, labor-related, and neonatal complications and neonatal outcomes were similar in the two groups. The frequency of natural conception was significantly higher and the number of infertility treatments was significantly lower in the intervention group than in the control group. After exclusion of women who did not complete the intervention program from the intervention group, birth rates and the time to pregnancy were similar in the two groups.

We chose the primary outcome to take into account the ways in which preconception weight loss may be advantageous during pregnancy and labor (i.e., reduced risks of pregnancy complications and cesarean delivery). This choice was in line with recent recommendations emphasizing that live birth should be the outcome in infertility trials.[38]

Limitations of the trial should be noted. For one, blinding was not possible. However, we specified the type of infertility treatment before randomization in order to minimize differences in treatment assignments; this led to similar distributions of infertility treatment in both groups. Moreover, bias was unlikely in the assessment of the prespecified primary and secondary outcomes.

We compared two treatment strategies of equal duration; the 6-month lifestyle intervention was an integrated part of the intervention strategy. Since any comparison between the groups had to be performed at the same time after randomization, women in the intervention group were generally able to access infertility treatment for only 18 months, as compared with 24 months in the control group. This led to an increased time to pregnancy and to lower birth rates within the follow-up period of 24 months. However, there were no significant between-group differences in birth rates after we took into account pregnancies that were conceived within but ended after the follow-up period.

Only 38% of the participants reached their target weight loss of 5 to 10% of the original body weight. The discontinuation rate of 22% was similar to that in similar intervention programs involving infertile women.[37]

A more intensive program or one involving better strategies to enhance adherence might have resulted in more weight loss, but it is unknown whether more weight loss would have led to a higher birth rate than the rate in our trial.[20] Moreover, excessive weight loss in a short period of time was discouraged, since such a reduction in weight has been reported to have a negative effect on the outcome of assisted reproductive technology[39] and to be associated with an increased risk of adverse pregnancy outcomes such as low birth weight or miscarriage.[40] In conclusion, this randomized trial showed that a 6-month structured intervention program to facilitate weight loss preceding infertility treatment, as compared with prompt infertility treatment, did not improve rates of vaginal birth of healthy singletons at term during 24 months of follow-up.

Supported by a grant (50-50110-96-518) from the Netherlands Organization for Health Research and Development.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

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