

Moderate and increased physical activity is not detrimental to live birth rates among women with unexplained infertility and obesity

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Objective: To determine if moderate physical activity is associated with live birth rates in women with unexplained infertility and obesity.

Design: Secondary analysis of the Improving Reproductive Fitness through Pretreatment with Lifestyle Modification in Obese Women with Unexplained Infertility trial.

Setting: US fertility centers, 2015–2019.

Patient(s): A total of 379 women participated in Improving Reproductive Fitness through Pretreatment with Lifestyle Modification in Obese Women with Unexplained Infertility trial, a lifestyle modification program with increased physical activity (phase I, 16 weeks) and up to three cycles of clomiphene citrate treatment and intrauterine insemination (phase II).

Intervention(s): Participants were instructed to add 500 steps/day weekly until a maximum of 10,000 steps/day was reached and maintained. Participants were stratified as active (top third, N = 125) and less active (lower third, N = 125) on the basis of the average number of steps per day recorded using a FitBit activity tracker.

Main Outcome Measure(s): Live birth rate.

Result(s): Active participants were more physically active at the time of enrollment than less active participants (average baseline steps per day, 8,708 [7,079–10,000] vs. 4,695 [3,844–5,811]; $P \leq 0.001$) and were more likely to reach 10,000 steps/day than less active participants (average steps per day, 10,526 [9,481–11,810] vs. 6,442 [4,644–7,747]; $P \leq 0.001$), although both groups increased their average steps per day by a similar amount (1,818 vs. 1,747; $P = 0.57$). There was no difference in live birth rates (24/125 [19.2%] vs. 25/125 [20%]; $P = 0.87$) between active and less active participants nor were there differences in clinical pregnancy rates ($P = 0.45$) or miscarriage rates ($P = 0.49$) between the two groups.

Conclusion(s): Active participants were more likely to achieve the physical activity goal, although this was not associated with benefit or harm with respect to live birth.

Clinical Trial Registration Number: ClinicalTrials.gov (NCT02432209), first posted: May 4, 2015. (Fertil Steril Rep® 2023;4:308–12. ©2023 by American Society for Reproductive Medicine.)

Key Words: Obesity, physical activity, steps per day, unexplained infertility

Received April 18, 2023; revised and accepted June 20, 2023.

W.S.V. has nothing to disclose. F.S. has nothing to disclose. E.C. has nothing to disclose. K.H. has nothing to disclose. K.R.H. has nothing to disclose. N.S. has nothing to disclose. H.Z. has nothing to disclose. R.S.L. has nothing to disclose.

Supported by CREST (Clinical Research/Reproductive Scientist Training) Program, Eunice Shriver National Institute of Child Health and Human Development R25HD075737, U10HD38992, U10HD077680, and U10HD055925.

The subjects in this secondary analysis were enrolled in the Improving Reproductive Fitness through Pretreatment with Lifestyle Modification in Obese Women with Unexplained Infertility (FIT-PLEASE) trial. Data presented in this manuscript have not been previously published. The initial data analysis was presented as an oral abstract at American Society for Reproductive Medicine Scientific Conference & Expo, Baltimore, MD, October 2021 by V.W., S.F., C.E., N.M., S.N.F., Z.H., L.R.S. Increased physical activity is not detrimental to live birth in women with obesity and infertility.

Data will be made available on request in compliance with the National Institutes of Health Policy for Data Management and Sharing through the NIH DASH Data and Specimen Hub available at: <https://dash.nichd.nih.gov/>.

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Fertil Steril Rep® Vol. 4, No. 3, September 2023 2666-3341

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<https://doi.org/10.1016/j.xfre.2023.06.004>

Regular and moderate physical activity during pregnancy and the postpartum period is associated with lower rates of excess gestational weight gain, gestational diabetes, and postpartum depression (1). Healthy women can safely engage in moderate-intensity activity during pregnancy with no increase in the risk of miscarriage, preterm birth, or low birth weight infant. National physical activity guidelines recommend that pregnant and postpartum women should aim for at least 150 minutes of moderate-intensity physical activity per week. Moving more and sitting less throughout the day appears to be as important for health as regular moderate-intensity physical activity (2). Walking 10,000 steps/day is a common fitness goal that may be reached by engaging in 30 minutes of moderate-intensity activity, such as brisk walking and regular movement throughout the day, and has been associated with enhanced weight loss when paired with a behavioral intervention (3).

Less is known regarding the benefits and risks of regular moderate-intensity physical activity in the preconception period in women with obesity and infertility (4). The Improving Reproductive Fitness through Pretreatment with Lifestyle Modification in Obese Women with Unexplained Infertility (FIT-PLESE) trial assessed the effect of increased physical activity, with and without weight loss, followed by clomiphene citrate treatment and intrauterine insemination on good birth outcome, defined as delivery of a normal weight term infant without major congenital anomalies (5). All participants were instructed to reach and maintain 10,000 steps/day when the intensive lifestyle modification group underwent caloric restriction and took a weight loss medication to lose weight and the standard lifestyle modification group increased physical activity alone, with the goal of weight maintenance. In the parent trial, there was no difference in good birth outcomes associated with the randomization assignment, with or without weight loss.

The FIT-PLESE trial analyzed good birth outcome using an intent-to-treat approach, with all randomized participants analyzed according to their randomization assignment, regardless of compliance or dropout. We hypothesize that compliance with the physical activity goal will be associated with improved fertility and birth outcomes. We performed a secondary analysis of live birth and fertility outcomes among FIT-PLESE participants who achieved the top tertile of physical activity compared with participants achieving the bottom tertile of physical activity, regardless of randomization assignment.

MATERIALS AND METHODS

The FIT-PLESE trial was approved by the University of Pennsylvania institutional review board, and a summary description of the trial is available at [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT02432209) and the full protocol, with modifications, is available at the PLOS Medicine website (4). In brief, FIT-PLESE was a multicenter, randomized trial of an intensive lifestyle modification (ILM) program compared with a standard lifestyle modification (standard) for 16 weeks, followed by up to three cycles of clomiphene treatment with intrauterine insemination in women with obesity and unexplained infertility. Participants were

women between ages 18 to 40 years, with a body mass index ≥ 30 kg/m², in good health, who had a history of ≥ 1 year of infertility, regular menstrual cycles, normal ovarian reserve, normal uterine cavity, at least one patent fallopian tube, and a male partner with at least 5 million total motile sperm in the ejaculate. In phase I, participants randomized to ILM increased their physical activity, underwent caloric restriction with a daily caloric consumption goal of approximately 1200 kcal, and took a gastric lipase inhibitor (Orlistat) to promote a clinically meaningful weight loss of approximately 7% of total body weight, which has been associated with metabolic benefits (6). Participants randomized to standard group focused on increased physical activity alone with the goal of weight maintenance. All participants received an activity tracking device (Fitbit Wireless Activity Tracker) and established a baseline mean number of steps over a 7-day period. Participants were instructed to increase steps from baseline by 500 steps/day per week until 10,000 steps/day were reached and maintained through phase I and phase II. In phase II, both groups received up to three cycles of ovarian stimulation with clomiphene citrate with intrauterine insemination, unless a spontaneous conception occurred. The dose of clomiphene citrate was increased in a subsequent cycle if no ovulation occurred or only one follicle ≥ 18 mm in average diameter developed or reduced in a subsequent cycle if four follicles ≥ 18 mm in average diameter developed. Blood work for lipid panel, fasting glucose, glycohemoglobin (HgbA1C), thyroid stimulating hormone, and ovarian reserve markers was performed at the screening visit in phase 1, and measurement of waist circumference and administration of the PHQ-9 survey was carried out to assess for metabolic health and depression.

For the secondary analysis, FIT-PLESE participants (N = 379) were stratified as active (top tertile, N = 125) and less active (bottom tertile, N = 125) on the basis of the average number of steps per day recorded at the end of phase I, regardless of their randomized treatment assignment. Conception was defined as a rising serum level of human chorionic gonadotropin for two consecutive tests. Clinical pregnancy was defined as observation of a gestational sac using ultrasound imaging. Miscarriage was defined as loss of a clinical pregnancy. Live birth was defined as the delivery of a live-born infant. Good live birth was defined as the delivery of a live birth of an infant born at ≥ 37 weeks, with a birth weight between 2500 and 4000 g and without a major congenital anomaly. Outcome data were available for all 250 participants for the follow-up interval prescribed in the FIT-PLESE trial.

Baseline characteristics, fertility rates, and birth outcomes were compared between the active and less active groups using descriptive statistics, Student's *t* test for quantitative variables and χ^2 test for categorical variables. Fisher's exact test was used to compare differences in categorical variables if the frequency count was < 5 . All hypothesis tests were two-sided, and all analyses were performed using SAS software, version 9.4 (SAS Institute). Statistical significance was defined as a two-sided *P* value < 0.05 .

TABLE 1

Baseline characteristics of women with obesity and unexplained infertility who were active and less active.

Variable	Active* n = 125	Less active* n = 125	P value
Age (y), median (range)	33.0 (30.0, 35.0)	31.0 (28.0, 35.0)	0.042
Race, n (%)			0.284
White	88/123 (71.5)	79/124 (63.7)	
Black	25/123 (20.3)	36/124 (29.0)	
Other	10/123 (8.1)	9/124 (7.3)	
Ethnic group, n (%)			0.367
Not Hispanic or Latino	119/125 (95.2)	116/125 (92.8)	
Hispanic or Latino	2/125 (1.6)	6/125 (4.8)	
Unknown	4/125 (3.2)	3/125 (2.4)	
Duration of infertility (mo), median (range)	27.5 (18.5, 48.0) n = 124	30.0 (16.0, 48.0) n = 123	0.420
Prior conception, n (%)			0.247
No	56/125 (44.8)	47/125 (37.6)	
Yes	69/125 (55.2)	78/125 (62.4)	
Former tobacco user, n (%)	33/125 (26.4)	32/125 (25.6)	0.885
Current tobacco user, n (%)	10/125 (8.0)	11/125 (8.8)	0.820
BMI (kg/m ²) at baseline, median (range)	37.2 (33.1, 41.8)	40.4 (34.9, 45.3)	0.001
Waist circumference (cm) at baseline, median (range)	112.0 (103.0, 120.0)	116.0 (106.0, 130.0)	0.012
Weight (kg) at baseline, median (range)	101.2 (89.5, 116.2)	108.9 (94.3, 128.2)	0.016
Hormone levels at baseline, median (range)			
AMH (ng/mL)	3.6 (2.0, 5.9) n = 124	4.9 (2.6, 7.7) n = 124	0.041
TSH (uIU/mL)	1.7 (1.1, 2.4) n = 123	1.8 (1.1, 2.9) n = 124	0.178
HbA1c (%)	5.4 (5.1, 5.6) n = 111	5.5 (5.3, 5.7) n = 113	0.013
Fasting glucose (mg/dL)	91.8 (85.2, 100.3) n = 124	93.1 (85.9, 103.0) n = 124	0.587
Total cholesterol (mg/dL), mean ± SD	181.5 ± 30.6 n = 119	186.4 ± 35.1 n = 121	0.251
Triglycerides (mg/dL)	115.0 (83.0, 146.0) n = 119	125.0 (92.0, 169.0) n = 121	0.035
HDL cholesterol (mg/dL)	40.0 (34.0, 46.0) n = 119	38.0 (33.0, 44.0) n = 121	0.186
PHQ-9 score at baseline, median (range)	2.0 (0.0, 4.0) n = 124	3.0 (1.0, 6.0) n = 122	0.012

AMH, anti-Mullerian hormone; BMI, body mass index; HbA1c, glycohemoglobin; HDL, high-density lipoprotein; PHQ-9, Patient Health Questionnaire-9; TSH, thyroid-stimulating hormone.
* Active participants were in the top tertile and less active participants were in the bottom tertile of the distribution of the average number of steps per day recorded at the end of phase I.

Vitek. Moderate physical activity and live birth rate. *Fertil Steril Rep* 2023.

RESULTS

More active participants were older (mean age in years, 33 vs. 31; $P = 0.04$), weighed less (101.2 kg vs. 108.9 kg; $P = 0.016$), and had a lower body mass index (37.2 kg/m² vs. 40.4 kg/m²; $P = 0.001$) and waist circumference (112 cm vs. 116 cm; $P = 0.015$) at baseline compared with less active participants (Table 1). Active participants had lower levels of anti-Mullerian hormone ($P = 0.04$) at baseline as well as lower HgbA1C ($P = 0.013$) and triglycerides ($P = 0.035$). In addition, active participants had lower PHQ-9 scores at baseline (2.0 vs. 3.0; $P = 0.01$). There were no differences observed between more active and less active participants with respect to race, ethnicity, number of prior conceptions, duration of infertility, and proportion of former or current smokers.

There was no difference in randomization to ILM or standard ($P = 0.61$) among active and less active participants (Table 2). More active participants were more physically active at enrollment than less active participants (average steps per day, 8,708 [7,079–10,000] vs. 4,695 [3,844–5,811]; $P \leq 0.001$). In addition, more active participants were more likely to reach the physical activity goal than less active participants at the end of phase I (average steps per day, 10,526 [9,481–11,810] vs. 6,442 [4,644–7,747]; $P \leq 0.001$), although

both groups increased their average steps per day by a similar amount (1,818 vs. 1,747; $P = 0.57$) and there was a similar percent change in average steps per day from baseline to the end of phase I (21.6% vs. 25.6%; $P = 0.57$). Active participants lost more weight than less active participants (−4.8 kg vs. −2.2 kg; $P \leq 0.001$). Most of the active participants (72.2%) maintained their physical activity level in phase II.

There were no difference in live birth rates (24/125 [19.2%] vs. 25/125 [20%]; $P = 0.87$) between active and less active participants nor were there differences in the conception rates (37/125 [29.6%] vs. 42/125 [33.6%]; $P = 0.49$), clinical pregnancy rates (27/125 [12.6%] vs. 42/125 [25.6%]; $P = 0.45$), miscarriage rates (3/37 [8.1%] vs. 6/42 [14.3%]; $P = 0.49$), ectopic pregnancy rates (2/37 [5.4%] vs. 2/42 [4.8%]; $P = 1.0$), and the rate of good birth outcome (14/125 [11.2%] vs. 16/125 [12.8%]; $P = 0.69$) between the two groups (Table 3). There was no difference in the rate of spontaneous conceptions at the end of phase I (14/125 [11.2%] vs. 12/125 [9.6%]; $P = 0.68$) between the two groups. With respect to fertility treatments, there were no differences in the number of treatment cycles with clomiphene ($P = 0.45$) and maximum dose of clomiphene ($P = 0.089$) between the two groups.

TABLE 2

Treatment characteristics of women with obesity and unexplained infertility who were active and less active.

Treatment characteristic	Active* n = 125	Less active* n = 125	P value
Before treatment, n (%)			0.613
Intensive lifestyle modification	67/125 (53.6)	63/125 (50.4)	
Standard lifestyle modification	58/125 (46.4)	62/125 (49.6)	
Average steps per day at baseline	8708.0 (7079.0, 10000.0)	4695.0 (3844.0, 5811.0) n = 123	<0.001
Average steps per day at end of phase I	10526.0 (9481.0, 11810.0)	6442.0 (4644.0, 7747.0) n = 123	<0.001
Absolute change in average steps per day from baseline to end of phase I	1881.9 ± 3167.5	1441.2 ± 2374.5 n = 122	0.218
Percentage of change in average steps per day from baseline to end of phase I	21.6 (−0.7, 52.1)	25.6 (−9.0, 70.9) n = 122	0.572
Weight change (Kg)	−4.8 (−10.9, −0.8) n = 121	−2.2 (−4.2, 0.6) n = 120	<0.001

* Active participants were in the top tertile and less active participants were in the bottom tertile of the distribution of the average number of steps per day recorded at the end of phase I.

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DISCUSSION

In this secondary analysis of women with obesity and unexplained infertility, we found that women who maintained physical activity in the top tertile of the entire sample did not experience any improvement or detriment in fertility or birth outcomes. More active participants, most of whom reached and maintained the goal of 10,000 steps per day,

were more metabolically fit and reported less mood-related symptoms at baseline than less active participants.

Although several randomized trials have found that preconception weight loss before infertility treatments for women with obesity and infertility have not improved pregnancy outcomes, these trials have been limited by the ability of participants to achieve and maintain weight loss, with

TABLE 3

Fertility, birth outcomes, and treatment characteristics of women with obesity and unexplained infertility who were active and less active.

Outcomes and treatment characteristic	Active* n = 125	Less active* n = 125	P value
Live birth, n (%)	24/125 (19.2)	25/125 (20.0)	0.873
Good live birth**, n (%)	14/125 (11.2)	16/125 (12.8)	0.697
Conception, n (%)	37/125 (29.6)	42/125 (33.6)	0.496
Spontaneous conception in phase 1, n (%)	14/125 (11.2)	12/125 (9.6)	0.679
Clinical pregnancy, n (%)	27/125 (21.6)	32/125 (25.6)	0.456
Pregnancy, n (%)	26/125 (20.8)	31/125 (24.8)	0.451
Miscarriage among women who conceived, n (%)	3/37 (8.1)	6/42 (14.3)	0.490
Ectopic pregnancy among women who conceived, n (%)	2/37 (5.4)	2/42 (4.8)	1.000
Number of treatment cycles, n (%)			0.447
1	20/100 (20.0)	13/89 (14.6)	
2	10/100 (10.0)	13/89 (14.6)	
3	70/100 (70.0)	63/89 (70.8)	
Maximum dose of clomiphene, n (%)			0.089
1 tablet (50 mg)	1/100 (1.0)	4/89 (4.5)	
2 tablets (100 mg)	70/100 (70.0)	50/89 (56.2)	
3 tablets (150 mg)	29/100 (29.0)	35/89 (39.3)	

* Active participants were in the top third and less active participants were in the bottom third of the distribution of the average number of steps per day recorded at the end of phase I.

** Good live birth was defined by the delivery of a live-born infant born who was delivered at a gestational age of 37 weeks or more, with a birth weight ranging between 2500 and 4000g and without a major congenital anomaly.

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<60% of the participants meeting or exceeding the weight loss goal and high dropout rates of up to 30% (7). The FIT-PLESE trial is unique in that most participants were compliant with increased physical activity during the lifestyle modification, regardless of randomized treatment assignment, and the dropout rate was relatively low at <20% and did not differ between groups (5). The high rate of compliance and low dropout rate enabled us to stratify participants into an active group, 72% of whom reached and maintained the physical activity goal of walking 10,000 steps/day and a less active group that did not achieve this physical activity goal. Interestingly, active participants were already relatively active at baseline, with average baseline steps per day that exceeded 7000, and this translated into improved baseline metabolic parameters, such as lower waist circumference, Hgb A1C, and triglycerides, despite being older on average than less active participants. The less active participants increased their average steps per day by a similar amount as the active participants but were relatively sedentary at baseline, with average baseline steps per day <5000, and none of the less active participants recorded baseline steps that exceeded 7000 steps/day, a goal associated with lower mortality rates among middle-aged adults (8). We can use these findings to reassure less active women with obesity that initiating and maintaining moderate physical activity in the preconception period and during ovarian stimulation will not be detrimental to their attempts to conceive, a common misconception among women with infertility. Vigorous exercise may induce anovulation and/or a luteal phase defect in healthy women, but these possible negative effects would be overcome with ovarian stimulation (9).

Several limitations may contribute to our inability to demonstrate a fertility or birth outcome benefit with physical activity, as others have reported (4). First, our population consisted of women with unexplained infertility and obesity who were diagnosed by reproductive endocrinologists using standard diagnostic criteria, including evidence of regular menstrual cycles. Most trials that show a benefit from physical activity are among women with infertility and anovulation or polycystic ovary syndrome and report improved outcomes, such as improved menstrual cycle regularity, increased ovulation, and increased chances of conceptions (10). Second, randomized trials that show a fertility benefit of physical activity often compare the intervention to a control group that received no therapy, whereas nearly all participants in our study increased physical activity so we were unable to compare with a group with persistent sedentary activity levels (11–14). Third, because this is a secondary analysis, we may be underpowered to show a small benefit in live birth rates between the active and less active groups. Finally, we analyzed regular moderate physical activity, defined as averaging 10,000 steps/day, and did not analyze exercise intensity, duration, or strength training. We chose this definition of moderate physical activity because it would meet the current national activity guideline for pregnant and postpartum women, it was accurately recorded by the FitBit activity trackers, and it represents a physical activity

goal that women could achieve outside of a randomized trial if we found a benefit.

CONCLUSION

In conclusion, our secondary analysis did not show benefit or harm with respect to fertility and birth outcomes among active or sedentary women with obesity and unexplained infertility who increased their physical activity in the preconception period. Although physical activity may not improve fertility in this population, active women demonstrated more favorable markers for cardiovascular health and well-being, despite severe obesity. Although reproduction and metabolism are closely intertwined, the optimal lifestyle recommendations for physical activity and weight loss to improve fertility and birth outcomes remain elusive for women with obesity and infertility.

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