# Immediate weight loss before ovarian stimulation with intrauterine insemination is associated with a lower risk of preeclampsia in women with obesity and unexplained infertility

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**Objective:** To determine whether successful weight loss before ovarian stimulation with intrauterine insemination (OS-IUI) affects the risk of future pregnancy complications among women with obesity and unexplained infertility after fertility treatment.
**Design:** Secondary analysis of the randomized controlled clinical trial Improving Reproductive Fitness Through Pretreatment With Lifestyle Modification in Obese Women With Unexplained Infertility (FIT-PLESE).
**Setting:** Multiple academic health centers in the United States.
**Patient(s):** Three hundred seventy-nine women with obesity and unexplained infertility who underwent standard infertility treatment after a lifestyle intervention.
**Intervention(s):** The FIT-PLESE trial evaluated whether prepregnancy lifestyle interventions (diet with weight loss medication and exercise vs. exercise alone) before OS-IUI improved the live birth rate among women with obesity and unexplained infertility. Although the primary outcome of FIT-PLESE was live birth rate, we compared the demographics and subsequent pregnancy complications of women who successfully lost some weight with those of women who did not lose any during the interventions.
**Main Outcome Measure(s):** Obstetric complications by groups were compared using $\chi^2$ and Fisher's exact tests, and continuous variables were compared using Student's *t*-tests. Logistic regression was used to assess the odds of preeclampsia after adjustment for the randomized treatment arm in FIT-PLESE.
**Result(s):** There was a nonsignificant trend toward a lower risk of intrauterine growth restriction (4% vs. 16%, $P = .124$) and preterm delivery (6% vs. 15%, $P = .343$) among patients who lost at least some weight. The risk of preeclampsia was significantly lower (6% vs.35%, $P = .002$) in the weight loss group (odds ratio, 0.09; 95% confidence interval, 0.016–0.505; $P = .006$) after adjustment for treatment assignment.
**Conclusion(s):** Among women with obesity and unexplained infertility who had live births after fertility treatment, prepregnancy weight loss due to lifestyle interventions before OS-IUI was associated with a lower risk of preeclampsia. (Fertil Steril Rep® 2022;3: 264–8. ©2022 by American Society for Reproductive Medicine.)

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In addition to the immediate implications of pregnancy complications, increasing evidence has implicated maternal obesity as a significant determinant of offspring health during childhood and later adulthood (1). Its prevalence in the United States approaches 47.8% in some counties (2). Approximately two thirds of women of reproductive age in the United States are currently overweight or obese (3). Approximately 25% of women who become pregnant in the United States are obese (4). Obesity during pregnancy is particularly challenging and leads to significantly increased maternal and fetal risks, including gestational hypertension and preeclampsia, gestational diabetes, congenital structural defects, operative delivery, shoulder dystocia, postdelivery infection, and venous thromboembolism (5, 6).

Studies to examine the effectiveness of lifestyle interventions during pregnancy to avoid excessive weight gain have demonstrated limited success in reducing pregnancy complications (7–9). Cost and noncompliance are the potential limitations of the implementation of dietary and exercise interventions during pregnancy (7), when patients are already feeling the significant burden of healthcare demands. Indeed, most physicians do not recommend initiating weight loss plans in already-pregnant women because weight loss during pregnancy might increase the risk of intrauterine growth restriction (IUGR) or preterm birth. Additionally, many weight loss medications are contraindicated during pregnancy.

Weight loss intervention trials have not observed improved live birth rates among patients pursuing fertility treatments (10–12). However, preconception weight loss among women who are overweight (body mass index [BMI], 25–29.9 kg/m$^2$) or obese (BMI $\geq$ 30 kg/m$^2$) has the potential to reduce the risk of pregnancy complications (13–15). Preconception weight loss to reduce hypertensive disorders during pregnancy has biological plausibility. Remodeling the spiral arteries on the maternal side of the placenta is an essential early step in the pathogenesis of hypertensive disorders during pregnancy (14). Obesity is a chronic state of oxidative stress that predisposes the patient to impaired early placentation, endothelial dysfunction, and reduced vascular dilation. These processes are already occurring during the first trimester in pregnant women with obesity, reducing the benefit of during-pregnancy weight loss in the prevention of hypertensive disorders.

A secondary analysis of the Improving Reproductive Fitness Through Pretreatment With Lifestyle Modification in Obese Women With Unexplained Infertility (FIT-PLESE) trial was performed to determine the effect of preconception weight loss on the risk of pregnancy complications in women with infertility and obesity. The FIT-PLESE trial (16) was a multicenter, randomized controlled trial sponsored by the Reproductive Medicine Network, National Institute of Child Health and Human Development. Three hundred seventy-nine women with unexplained infertility were randomized in a 1:1 ratio to 2 preconception lifestyle modification groups for 16 weeks before ovarian stimulation with intrauterine insemination (OS-IUI). The primary outcome of FIT-PLESE was the incidence of live birth. In addition to the primary outcome, the trial also tracked the pregnancy outcomes among women with live births. Our objective was to determine whether a difference exists in pregnancy complications among those who achieved weight loss vs. those who did not, regardless of the assigned treatment arm.

## MATERIALS AND METHODS

Institutional review board approval for the study was obtained from the University of Oklahoma Health Sciences Center. In the FIT-PLESE trial, the patients were randomized to 1 of 2 lifestyle intervention treatment arms. Those assigned to the intensive lifestyle intervention group targeted a weight loss goal of 7% through meal replacements, medication (60 mg of orlistat at lunch and dinner), and physical activity. In contrast, the standard lifestyle intervention group increased physical activity alone. The intensive lifestyle intervention group received nutritional counseling, which recommended the consumption of 2 servings of fruits, 3 servings of vegetables, 2 servings of low-fat dairy per day, and meal replacement products (3 Nutrisystem meals/d) to reach a total of 1,100 kcal/d. The macronutrient profile of this diet was 30% protein, 45% carbohydrate, and 25% fat. The last 100 calories could be consumed outside of the planned meals to reach a total of 1,200 kcal/d. The participants were given a multivitamin supplement daily. The physical activity interventions for the standard and intensive lifestyle intervention groups were the same. The baseline physical activity, defined as the number of steps over 7 days, was first determined for each patient using a FitBit (FitBit, San Francisco, CA) physical activity tracker; each patient was then instructed to increase their steps by 500 steps/d each week until 10,000 steps/d was achieved. They were then instructed to maintain this 10,000 steps/d for the duration of the interventions. After 16 weeks of lifestyle interventions, both the treatment groups were then administered standardized empiric infertility treatment consisting of 3 cycles of OS-IUI with clomiphene if unassisted pregnancy had not yet occurred during the lifestyle intervention period. The primary outcome of FIT-PLESE was the incidence of healthy live births (defined as the live birth of a term infant of normal weight without major anomalies). Forty participants dropped out of the study before conception in the exercise-only group, and 31 dropped out of the study in the diet + exercise + orlistat group. There were no significant

**TABLE 1**

**Demographic variables in FIT-PLESE by weight loss status.**

| | Weight loss status | | | |
|---|---|---|---|---|
| **Patient characteristics** | **Weight loss** | **Weight gain** | **No change** | ***P* value** |
| Total (N = 364) | 266 | 96 | 2 | |
| Age (y) | 32 | 31 | 31 | .8407 |
| **Weight change (kg)** | **−5.9 (5.3)** | **+2.5 (2.5)** | | **< .001** |
| Baseline BMI (kg/m$^2$) | 39.4 (7.0) | 38.7 (7.0) | 50 (6.5) | .067 |
| Ethnicity | | | | .993 |
| Non-Hispanic/Latino | 44/266 (17%) | 21/96 (22%) | 1/2 (50%) | .256 |
| Hispanic | 8/266 (3%) | 4/96 (4%) | 0/2 (0%) | .832 |
| White | 186/266 (70%) | 64/96 (67%) | 1/2 (50%) | .709 |
| Black | 59/266 (22%) | 22/96 (23%) | 1/2 (50%) | .640 |
| Asian | 5/266 (2%) | 2/96 (2%) | 0/2 (0%) | .972 |
| Other | 16/266 (6%) | 8/96 (8%) | 0/0 (0%) | .856 |
| Ever smoking history | 85/266 (32%) | 38/96 (40%) | 0/2 (0%) | .196 |
| Current | 18/266 (7%) | 13/96 (14%) | 0/2 (0%) | .114 |
| Former | 68/266 (26%) | 24/96 (25%) | 0/2 (0%) | .707 |
| Never | 180/266 (68%) | 59/96 (60%) | 2/2 (100%) | .323 |
| Alcohol history | | | | |
| Current | 237/266 (89%) | 81/96 (84%) | 2/2 (100%) | .415 |
| Former | 18/266 (7%) | 12/96 (13%) | 0/2 (100%) | .197 |
| Never | 11/266 (4%) | 3/96 (3%) | 0/2 (0%) | .871 |
| Education level | | | | |
| High school | 25/266 (9%) | 14/96 (15%) | 0/2 (0%) | .329 |
| Some college | 197/266 (74%) | 61/96 (64%) | 1/2 (50%) | .120 |
| Graduate school | 44/266 (17%) | 21/96 (22%) | 1/2 (50%) | .306 |

*Note:* Data are mean (standard deviation) or n (proportion of n). Bolded values are statistically significant at $P < .05$ level. BMI = body mass index; FIT-PLESE = Improving Reproductive Fitness Through Pretreatment With Lifestyle Modification in Obese Women With Unexplained Infertility.

*Wild. Weight loss and lower preeclampsia risk. Fertil Steril Rep 2022.*

baseline differences according to the randomized treatment arm for those who continued or dropped out of the study.

The intensive lifestyle intervention group lost more weight than the standard lifestyle intervention group (−6.6% ± 5.4% vs. −0.3% ± 3.2%, respectively). There were no significant differences in the rate of multiple pregnancies, pregnancy loss, or the time to live birth according to the treatment arms. The duration of pregnancy and the delivery weight were also similar between the lifestyle intervention groups. However, there was no significant difference in the incidence of healthy live births between the lifestyle intervention groups, even though most women in each group lost at least some weight.

Weight measurements before and after the lifestyle interventions as well as data regarding pregnancy complication outcomes were available for 74 of 80 women in FIT-PLESE who had a live birth. We compared the baseline demographic variables and major pregnancy complications of women who lost weight with those of women who did not using $\chi^2$ or Fischer's exact and Student's *t*-tests. In subsequent successful pregnancies, the critical complications were IUGR, hyperemesis, gestational diabetes, preterm labor, preeclampsia, and twin gestation. Logistic regression was used to compare the odds of developing preeclampsia for some weight loss after adjustment for the intervention treatment arm in FIT-PLESE. We also compared the odds of developing gestational diabetes and with those of developing preeclampsia for those who were able to lose at least 5% of their body weight.

## RESULTS

Across both the treatment arms, 73% (266) of the participants lost weight, 26% (96) gained weight, and 1% (2 participants) weighed the same as when they entered the trial. Furthermore, 91% of the patients randomized to the intensive lifestyle treatment arm lost at least some weight, as did 55% of the patients in the exercise-alone arm. The demographic variables of each weight loss group are shown in Table 1. The baseline characteristics of the patients in each group did not differ, except for the amount of weight lost after the interventions. The mean age of the participants was 32 years, and the average baseline BMI before any intervention was 39 kg/m$^2$. Age, ethnicity, baseline BMI, smoking history, alcohol history, and the highest level of education were similar between the treatment arms. On average, the weight lost was 5.9 ± 5.3 kg in the weight loss group and the weight gained was 2.5 ± 2.5 kg in the weight gain group. Regardless of whether there was any weight loss, the live birth rate was the same (20%).

The obstetrical complications according to the weight loss group are shown in Table 2. Overall, 49% had at least 1 major pregnancy complication. The 2 persons who weighed the same did not have live births. Complications were frequent. The hyperemesis cases occurred only in patients who lost at least some weight. Although not statistically significant, IUGR and preterm delivery were less frequent in those who lost weight. The risk of preeclampsia was lower in the weight loss group (6% vs. 35%, $P = .002$). The odds ratio for

**TABLE 2**

**Pregnancy complications in FIT-PLESE by weight loss status.**[a]

| | Weight loss status | | |
|---|---|---|---|
| **Pregnancy outcomes** | **Weight loss** | **Weight gain** | ***P* value** |
| Live births (n = 74) | 53 | 21 | |
| Pregnancy complication | | | |
| IUGR | 4% (2/50) | 16% (3/19) | .124 |
| Hyperemesis | 14% (7/50) | 0% (0/17) | .178 |
| Gestational diabetes | 22% (11/51) | 26% (5/19) | .674 |
| Preterm delivery | 6% (3/50) | 15% (3/20) | .343 |
| **Preeclampsia** | **6% (3/50)** | **35% (7/20)** | **.002** |
| Twin gestation | 13% (7/53) | 9.5% (2/21) | .662 |

*Note:* Data are proportion of n (n). Bolded values are statistically significant at $P < .05$ level. FIT-PLESE = Improving Reproductive Fitness Through Pretreatment With Lifestyle Modification in Obese Women With Unexplained Infertility; IUGR = intrauterine growth restriction.
[a] Two persons who weighed the same did not have a clinical pregnancy resulting in a live birth.

*Wild. Weight loss and lower preeclampsia risk. Fertil Steril Rep 2022.*

preeclampsia was 0.09 (95% confidence interval [CI], 0.016–0.505; $P = .006$) for the weight loss group after the randomized treatment arm adjustment. For those who lost at least 5% of their weight during the 16-week lifestyle intervention phase before fertility treatment, the odds ratio for the development of gestational diabetes was 0.89 (95% CI, 0.22–3.74; $P = .882$) and that for preeclampsia was 0.544 (95% CI, 0.09–3.28; $P = .507$).

## DISCUSSION

Although losing at least some weight immediately before fertility treatment was not associated with more live births in FIT-PLESE, the subsequent risk of preeclampsia was lower among those who lost at least some weight. After OS-IUI, perinatal complications were common in this high-risk group. We found a nonsignificant trend toward a lower risk of IUGR and preterm delivery among those who lost weight. The risk of the development of gestational diabetes or preeclampsia was lower for those who could lose at least 5% of their body weight; however, this was nonsignificant, likely because of lack of power. The primary outcome of weight loss intervention trials for fertility usually focuses on improving the live birth rate. Our results suggest that the risk of future pregnancy complications is also an important consideration. Preeclampsia is one of the strongest predictors of cardiovascular death during pregnancy (17). It is a significant risk factor for the development of cardiovascular disease (18). Offspring born to women with preeclampsia are at an increased risk of obesity, coronary artery disease, type 2 diabetes, and neurodevelopmental disorders (1). Preeclampsia is hypothesized to originate during the periconceptional period, defined as 14 weeks before conception to 10 weeks after conception (19). This shows the importance of reducing risk factors for preeclampsia during the critical preconception window. For women with infertility and obesity, weight loss can be a challenging conceptual issue. Undergoing an immediate weight loss intervention before treatment may seem burdensome to both the patient and the provider, both of whom are anxious to achieve pregnancy. However, the ability of preconception weight loss to lower the risk of pregnancy complications has long-term implications for both the mother and the fetus.

Our study has some important strengths and limitations. We analyzed a well-defined cohort with strict attention to dropouts and follow-up. The parent study was designed to determine the effects of weight loss on fertility outcomes, not for a comprehensive look at the determinants of pregnancy complications for those who might successfully conceive and carry a pregnancy to viability. We analyzed the weight change measurements and pregnancy complications before and after the lifestyle interventions for 74 of the 80 women with complete data on weight measurements and obstetric complications. The original randomized controlled trial found a nonsignificant trend toward fewer pregnancy complications with weight loss using an intention-to-treat analysis that compared intensive weight loss with exercise alone. Our secondary analysis had more power because we included those who lost some weight in either arm of the trial. We compared persons who adhered to either arm of the study. Cointerventions beyond the interventions described in the trial to affect weight loss cannot be ruled out. Although 379 patients were randomized in FIT-PLESE, only 14% developed preeclampsia. Our study was likely underpowered to detect differences according to successful weight loss for each complication analyzed.

Furthermore, one ethnicity (White, 69%) was predominant in FIT-PLESE. There are known racial differences in the incidence of preeclampsia (20). Well-established clinical risk factors for preeclampsia, such as obesity, diabetes, and chronic hypertension disproportionately, affect non-Hispanic Black, American Indian or Alaskan Native, and Hispanic populations. Despite comparable clinical risk factors for preeclampsia, addressing modifiable risk factors has not had the same protective effect for all women. Outside of this predominantly White study population, other high-risk groups might benefit even more from preconception weight loss.

## CONCLUSION

Although weight loss before fertility treatment did not impact the live birth rate in women with obesity and unexplained infertility, successful weight loss before fertility treatment was associated with less risk of preeclampsia.

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