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Effects of preconception weight loss after lifestyle intervention on fertility outcomes and pregnancy complications

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It is well documented that obesity decreases natural fertility among men and women as well as pregnancy chances after conventional infertility and assisted reproductive technology (ART)–based treatments. Moreover, pregnancy complications are increased in women with overweight and obesity. General guidelines on the treatment of obesity recommend lifestyle intervention, including diet and exercise as the first-line treatment, coupled with or without medical treatments, such as weight loss medication or bariatric surgery, to reduce complications of obesity in adults. In the context of infertility in various countries and infertility clinics, there is a body mass index limit for public refund of infertility treatment of women with obesity. In this respect, it is important to investigate the evidence of effects of lifestyle intervention preceding infertility treatment on reproductive outcomes. The combined results of 15 randomized controlled trials (RCTs) of the effectiveness of preconception lifestyle intervention on reproductive outcomes documented in the latest systemic review and meta-analysis, together with the most recent RCT performed in 2022 are discussed. The current evidence suggests that greater weight loss and increase in clinical pregnancy, live birth, and natural conception rates after lifestyle intervention compared with no intervention were observed, but it seems no beneficial effect of lifestyle intervention preceding ART was observed on these parameters. With respect to potential harm of lifestyle intervention, there is no significant increased risk of early pregnancy loss, although the most recent RCT (not included in the systematic review and meta-analysis) showed a trend toward an increased risk. Complications during pregnancy, such as early pregnancy loss and maternal as well as fetal and neonatal complications, are underreported in most studies and need further analysis in an individual participant data meta-analysis. Limitations of the studies as well as future perspectives and challenges in this field of research will be highlighted. (Fertil Steril® 2022;118:456–62. ©2022 by American Society for Reproductive Medicine.)

Key Words: Lifestyle intervention, infertility, weight loss, pregnancy complications

It is well documented that obesity decreases natural fertility both in men and women and thus increases the prevalence of infertility (1, 2). In addition, obesity decreases clinical pregnancy rates (CPR) and live birth rates (LBR) after ovulation induction (3) and assisted reproductive technique (ART) (4). Once pregnancy is achieved, obesity increases pregnancy complication rates for both pregnant women and their offspring (5–8). Maternal obesity leads to a vicious cycle in the offspring with a high risk of adult obesity and an increased hazard of all-cause mortality (9).

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The recent published *Canadian clinical practice guideline on obesity in adults* (10) summarizes following key points: first of all, "obesity is a chronic, complex, progressive, relapsing disease that impairs health." "People living with obesity face substantial stigma that contributes to increased morbidity and mortality." The guideline shifts the focus from "weight loss alone to improving patient-centered health outcomes." "Obesity care should be based on evidence-based care, and people with obesity should have access to evidence-based interventions, including medical nutrition therapy, physical activity, psychological interventions, pharmacotherapy, and

surgery." The guideline recommends that, like other obesity guidelines, "all individuals with obesity, would benefit from adopting a healthy, well-balanced eating pattern, engaging in regular aerobic physical activity (e.g., 30–60 minutes on most days of the week)." "They should receive individualized support for behavioral change." "Lifestyle intervention including diet and exercise are the first step that can lead to a small amount of weight loss (3%–5%), and helps weight maintenance after weight loss. It can be combined with or without medical treatments, such as weight loss medication or bariatric surgery."

In several countries and in infertility clinics the body mass index (BMI) limits in women with obesity are used for reimbursement of infertility treatment or gaining access to infertility care (11, 12). Therefore, it is important to investigate the effects of lifestyle intervention aiming at weight loss preceding infertility treatment. To do so, we discuss the most recent systematic review (SR) and meta-analysis (13) that gives a comprehensive overview of the existing literature and aggregates the evidence of the effect of preconception lifestyle intervention in women with infertility on reproductive outcomes and early pregnancy complications. The combined results of the RCTs analyzed in this SR and meta-analysis and the most recent RCT performed in 2022 (14) are discussed in this narrative "view." Moreover, limitations of the studies, the future perspectives, and challenges in this field of research will be highlighted.

EVIDENCE FROM CURRENT LITERATURE

Hunter et al. (13) summarized the best available evidence in a SR and meta-analysis on the effectiveness of weight loss lifestyle interventions for improving fertility in women and men with overweight or obesity and infertility. This extensive review included 15 RCTs of any duration in women and men with overweight with a BMI of >25 kg/m^2. Studies included any type of lifestyle intervention involving, dietary modification ranging from very low calorie diets (VLCD), liquid formula diet, reduced calorie intake, diet with low glycemic index, and/or exercise modification aimed at reducing weight. Studies on drug treatment and bariatric surgery were excluded. The literature search used in this SR was updated till March 2020, using *Medline, Embase* and *Cochrane Central Register of Controlled Trials* database only including RCTs. Bias was assessed using the *Cochrane risk of bias tool.* They included evidence from 15 RCTs (n = 1,852 women). Reported interventions varied from lifestyle modifications, including combinations of diet, exercise and motivational counseling (n = 11 trials; n = 1,461 women), or any of these interventions alone; diet (n = 2 trials; n = 353 women) and exercise (n = 2 trials; n = 38 women). The duration of lifestyle interventions varied between 4 and 48 weeks. The main outcomes reported were weight loss, CPR, LBR, natural conception rates, recovery of ovulations, and miscarriage rates (defined as a demise of a pregnancy before the fetus reached viability), as shown in Table 1 (13). Aggregated data and main outcomes of the SR and meta-analysis are shown in Table 2 (13, 14).

Overall, the investigators concluded that in the included RCTs a high risk of performance bias was observed because the blinding of participants and personnel was not possible. Only 4 trials were multicenter and reached a low risk of bias in 5 of the 7 domains of bias. Subgroup analysis comparing various intervention strategies were performed to evaluate the effectiveness on weight loss, with an overall conclusion that women who received lifestyle intervention achieved greater weight loss compared with no or minimal intervention. The investigators also performed subgroup analysis of the type of lifestyle intervention (diet and exercise vs. diet alone or exercise alone, or VLCD) on the reproductive outcomes. Diet and exercise increased the LBR, CPR, and ovulation rates compared with no or minimal intervention, whereas diet alone or exercise alone or VLCD did not show this positive effect. Diet only interventions showed increased natural conception rates compared with immediate access to ART-based treatments.

Although this SR and meta-analysis has a high quality and includes various subgroup analysis to evaluate the effect of these various lifestyle intervention strategies, there are also some limitations. Subgroup analysis by recording BMI at baseline in relation to various outcomes was not performed, although BMI might be an important determinant in relation

TABLE 1

Main findings of the systematic review by Hunter et al. (13)

Outcome	No. of trials	No. of participants	Risk ratio (Comparison with no intervention)	95% CI
Weight loss (kg)	13	1,064	−5.24	−7.14 to −3.35
CPR	12	1,313	1.47	1.11–1.94
LBR	9	1,203	1.46	1.04–2.04
CPR in ART	6	1,040	1.05	0.69–1.59
Resumption of ovulation	4	108	4.50	1.84–11.03
Natural conception rate	5	991	2.25	1.42–3.59
Miscarriage rate per participant[b]	5	1,070	0.97[a]	0.94–1.01[a]
Miscarriage rate per pregnancy[b]	5	458	0.94[a]	0.87–1.01[a]

Note: [a]Data are presented as risk ratio of nonevent (no miscarriage) and 95% CI.
[b]Definition of miscarriage: defined as a demise of a pregnancy before the fetus reached viability. CPR = clinical pregnancy rate, LBR = live birth rate, RR = risk ratio, CI = confidence interval, ART = assisted reproductive technology, No. = number.

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to the pregnancy outcomes. Moreover, although there was a large heterogeneity in the type of interventions, they also did not perform subgroup analysis with respect to the length of the interventions, nor the length of follow-up with respect to the pregnancy outcomes. Finally, complications during infertility treatment were not reported, nor during pregnancies or during the neonatal period and dropout rates were not systematically reported. The investigators found no RCTs on the effect of lifestyle intervention and weight loss on fertility outcomes in men, owing to the paucity of trials in men.

After publication of the SR by Hunter et al. (13), the results of 1 new RCT, the FIT-PLESE study (14) were published. This open-label, multicenter RCT investigated the effect of 2 lifestyle interventions with respect to the primary outcome, a "good birth," defined as an infant (singleton or twin) born at $\geq$37 weeks of gestation, weighing between 2500 and 4000 g, without a major congenital anomaly. The study included 379 women with obesity (BMI >30 kg/m^2) and unexplained infertility. The effect of the 2 interventions were compared: an "intensive" intervention and a "standard" intervention. The intensive intervention aiming at a weight loss of 7% included meal replacements with a VLCD, an increase of physical activity aimed at 10,000 steps per day and Orlistat (Alli, GlaxoSmithKline) 120 mg per day (to reduce fat absorption). The standard intervention consisted of an increase in the physical activity without dietary intervention, but included advice on healthy food choices. Both interventions lasted for 16 weeks after which infertility treatment was started consisting of 3 consecutive cycles of ovarian stimulation and intrauterine insemination. With respect to weight loss, women in the intensive intervention group had significantly more weight loss compared with the women in the standard treatment group; the weight change was -7.3 ± 6.0 kg in the intensive intervention group compared with -0.3 ± 3.4 kg in the standard intervention group. There were no statistically significant differences in the incidence of healthy live births: 12.2% in the intensive intervention group vs. 15.2% in the standard intervention group (risk ratio [RR], 0.81; 95% confidence interval [CI], 0.48–1.34). The cumulative CPR was 27.7% in the intensive intervention group and 24.6% in the standard treatment arm of the study (RR, 1.12; 95% CI, 0.80–1.58). There was a higher, but nonsignificant, first trimester pregnancy loss in the intensive intervention group among women who conceived of 38.1% vs. 23.7% in the standard intervention group (RR, 1.61; 95% CI, 0.92–2.80). In the FIT-PLESE study there were comparable maternal complications during infertility treatment, pregnancies, and childbirth between groups. The same accounts for fetal and neonatal complications. Dropout rate was approximately 20% in both arms of the study.

Legro et al. (14) pointed out that pooling the data of the FIT-PLESE study (14) with the Dutch LIFEstyle RCT (15) and the Swedish lifestyle-ART study (16) suggests an increased risk of miscarriage per participant (RR, 1.79; 95% CI, 1.20–2.67). In this equation 3 other studies on this outcome included in the SR (17–19) of Hunter et al. (13) were not included. Moreover, there is another reason for caution. The search strategy of the SR did not include RCTs using weight loss medication, whereas the FIT-PLESE study did, leaving room for additional analysis in an individual participant data meta-analysis (IPDMA) (PROSPERO CRD42021266201, in which lifestyle RCTs using weight loss medication are also included).

In summary, 16 RCTs (15 full papers and 1 abstract) so far have been published on lifestyle interventions in women with overweight or obesity and infertility. There is a beneficial effect on weight loss, CPR, LBR, and natural conception rates after lifestyle intervention compared with control groups. There seems no effect of lifestyle intervention before ART vs. immediate ART on CPR and LBR. There is no significant increased risk of early pregnancy loss in the latest SR, although the FIT-PLESE study showed a trend toward an increased risk. A limited number of 4 multicenter RCTs investigated maternal and fetal complication rates; and these were not systematically analyzed until now. Does the current available evidence on the effectiveness of lifestyle intervention on fertility outcomes and pregnancy related complications give us definite answers?

LIMITATIONS IN CURRENT LITERATURE

What are the limitations in these RCTs and as a result what limits the evidence in the SR and meta-analyses? Point by point:

- There is heterogeneity in the inclusion criteria of the participants with infertility among the various RCTs, such as women with polycystic ovary syndrome (PCOS) vs. women without PCOS, women indicated for ART with various diagnoses, and indications for treatment thereby making the data collection from these trials problematic because of the clinical heterogeneity.
- There is a large variation in the diet plans of various lifestyle programs with variations in the calorie restrictions ranging from a healthy diet to VLCD and the aid of liquid formula diets, with or without the addition of weight loss medications.
- There is a large variety in the exercise component of the interventions ranging from aerobic exercise to increase in the number of steps per day as well as strength and resistance training.
- The duration of the lifestyle intervention ranges from 4 to 48 weeks adding to the heterogeneity in the interventions that are compared in the SR.
- The follow-up period to assess the reproductive endpoint of RCTs range from 1 cycle to 24 months after randomization.
- The sample size of the trials varies between 12 and 577 participants, with most of the trials being single center studies ($n = 11$) with limited sample size that limit the generalizability of the results (see overview in Table 2).
- Primary and secondary outcome measures also vary between studies from metabolic outcomes, to CPR and LBR and ovulations rates, whereas pregnancy as well as fetal and neonatal complications are frequently not reported (Table 2).
- Unassisted or natural conceptions are not always included as one of the outcomes, despite evidence from large preconception RCTs that indicate an increase in this outcome (15, 16). However, one should keep in mind that in these

TABLE 2

Overview of randomized controlled studies lifestyle intervention in women with infertility and reported main outcomes.

Study	Sample size	Main fertility outcome	Fertility complications	Pregnancy complications	Fetal and neonatal complications	SC/MC RCT	Drop out
Studies included in SR							
Hunter et al (13)							
Guzick (34)	12	Ovulation	-	-	-	SC	-
Hoeger (35)	38	Ovulation	-	-	-	SC	+
Palomba (36)	26	CPR	-	-	-	SC	+
Moran (37)	46	LBR	-	-	-	SC	+
Sim (17)	49	CPR	-	-	-	SC	+
Legro (18)	379	LBR	+	+	+	MC	+
Becker (38)	26	LBR	-	-	-	SC	+
Duval abstract (39)	105	LBR	-	-	-	SC	+
Nasrekani (40)	20	Weight loss	-	-	-	SC	-
Nagelberg (41)	21	CPR	-	-	-	SC	-
Rothberg (42)	14	LBR	-	-	-	SC	+
Mutsaerts (15)	577	LBR	+	+	+	MC	+
Espinos (19)	41	LBR	-	-	-	SC	+
Einarsson (16, 44)	317	LBR	+	+	+	MC	+
Kiel (43)	18	CPR	-	-	-	MC	+
Study published after SR							
Legro (14)	379	LBR	+	+	+	MC	+

CPR = clinical pregnancy rate, LBR = live birth rate, SR = systematic review, SC = single center, MC = multicenter, RCT = randomized controlled trial.

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studies the control group started infertility treatment immediately after randomization, whereas in the intervention arms of the studies, women started infertility treatment after having had the lifestyle intervention, leaving a longer time to attempt a conception by intercourse.

- There is a substantial variability in the quality of the studies with respect to the risk of bias specifically with respect to the blinding of personnel assessing outcomes, incomplete data sets, selective reporting, and allocation concealment.
- Until now only 4 RCTs were adequately powered based on the primary outcome (14–16, 18). However, these 4 RCTs have a large variation in intervention strategies, follow-up time, and included groups of women (PCOS, idiopathic infertility, heterogeneous infertile population, heterogeneous BMI groups before ART).
- Because maternal as well as fetal and neonatal complications are rare outcomes, the question whether lifestyle intervention leads to a low complication rate during pregnancy is not answered yet.

The clinical and statistical heterogeneity and limitations in methodical quality of the studies leads to uncertainties. Which lifestyle intervention strategies are effective in which categories of patients and in which BMI group? What should be the percentage of weight loss to be effective with respect to pregnancy outcomes? Whether there is a potential harm from lifestyle intervention during early pregnancy? All these questions are not answered yet.

VIEW: FUTURE DIRECTIONS

How to proceed? Do we need more studies to get a definite answer whether or not lifestyle intervention preceding infertility treatment is effective in terms of LBR, natural conception rates, and reduction of complication rates, both maternal and neonatal? Our answer is yes! Obesity is defined as a chronic disease (20) and just like in any other chronic disease, patients with overweight and obesity deserve preconception care, based on the best available evidence to optimize their own health, to optimize their chances of pregnancy and LBR with or without infertility treatment, and putatively decrease the risk of pregnancy complications, and to optimize the health of the next generation. Moreover, if there is a potential harm in early pregnancy this should also become clear. New interventions should be designed and adequately powered, good-quality, multicenter studies should be performed to evaluate them. Moreover, to date there are no results of RCTs evaluating the effect of lifestyle intervention in men with obesity in infertile couples, although there is evidence that obesity is correlated with subfertility (2) and adherence to a healthy diet could improve semen quality and fecundity rates (21).

However, getting better evidence may not only require more studies. Several of the shortcomings of conventional meta-analysis can be overcome by using the data from existing studies in an IPDMA (22). Such an IPDMA helps to make more robust assumptions about expected effect sizes for primary and subgroup analyses. Moreover, an IPDMA may help to evaluate rare outcomes, such as pregnancy and neonatal complications and miscarriage risk, more robustly and allows adjustment for confounding factors in non-randomized comparisons. An IPDMA, including all RCTs on lifestyle intervention with or without weight loss medications, that is currently performed (PROSPERO CRD42021266201) will give an answer to whether there is any reason for concern for an increased risk of early pregnancy loss after lifestyle intervention.

In the design of the future lifestyle intervention RCTs the following strategies could be applied:

- Patient participation.

  Target groups of women or couples with obesity and infertility should be invited to discuss barriers to achieve weight loss and/or to participate in intervention trials. They could also give input on the issues that make the lifestyle intervention more appealing, to reduce attrition and enhance compliance, e.g., group sessions or couple orientated interventions, vouchers for individual coaching in training centers and incentives that build up over the duration of the trial. Lifestyle RCTs should be performed in men with obesity, because there is a lack of evidence, so far, whether lifestyle interventions lead to better semen quality and more pregnancies. A couple-based approach to weight loss in infertile couples could be explored because there is a concordance between lifestyle in couples (23).

- New eHealth or tele-eHealth approaches.

  A SR and meta-analysis (24) on eHealth interventions for the prevention and treatment of overweight and obesity in adults demonstrated significantly greater weight loss (kg) in eHealth interventions compared with control or minimal interventions and in eHealth weight loss interventions with extra components or technologies compared with standard eHealth programs. Wearables can increase physical activity and are associated with moderate weight loss among the middle or older aged individuals, although with less convincing effects in the long term (>1 year) and in young persons (25). An eHealth lifestyle intervention coaching program "Smarter Pregnancy" RCT (26) showed to be effective in improving the most important nutrition and lifestyle behaviors among couples undergoing in vitro fertilization or intracytoplasmic sperm injection treatment, and significant improvements were especially achieved in men with obesity and overweight and pregnant women. However, this eHealth tool did not show an effect on the pregnancy rates (26). More studies should be performed to assess the added value of eHealth and wearables in these target groups, with or without additional private or group coaching.

- Design of lifestyle RCTs.

  With respect to design of the trials, more efforts should be put toward reduction of risk of bias in RCTs, e.g., assessment bias of outcomes might be reduced by using research nurses, not involved in the lifestyle coaching of the participants, to perform the measurements and follow up of the endpoints defined in the study protocol. The Core Outcome Measure for Infertility Trials (COMMIT) endpoints should be included in the studies on reproductive outcomes (27). Because one of the ultimate goals of weight reduction through lifestyle change before conception is not only LBR, but also a reduction in pregnancy related complications, such as gestational diabetes, preeclampsia, preterm birth, and macrosomia, which affect women and their offspring, these outcomes should be added as secondary outcomes (28). Follow-up time should be long enough to also assess cumulative pregnancy rates over several months or several infertility treatment cycles (e.g., fresh and frozen ART cycles) to assess intervention effect over time and address time to pregnancy as one of the outcome measures. The BMI at randomization may be an important determinant of the outcome of lifestyle intervention; therefore, sufficient numbers of women across the various BMI classes should be included. This could be achieved by using stratification at randomization, so that robust subgroup analyses can be performed. We advocate adequately powered, multicenter studies that increase the generalizability of the results. For the power calculation of the trials, on the basis of experience from previous studies, a dropout rate of at least 20%–25% should be taken into account. The introduction of a "light version" of lifestyle intervention in the control group makes differences in the effect size between groups potentially smaller and hence result in a large sample size for detecting differences.

- Duration of the lifestyle intervention.

  One point of concern is the short duration of preconception lifestyle interventions in some trials, with the LIFEstyle study (15) being the longest multicenter RCT with a maximum of 24 weeks. The obesity guidelines (10) advocate longer interventions to get a sustainable lifestyle change and weight loss in the long term. Preconception interventions should not delay the infertility treatment for too long to decrease dropout rates before the start of infertility treatment. Rebound weight increase during pregnancy is another point of concern. Van Oers et al. (29) showed that weight loss after lifestyle intervention was followed by excessive weight gain during pregnancy, applying the *Institute of Medicine guidelines* of >9 kg weight gain for women with a BMI >30 kg/m^2 or >11.5 kg for women with a BMI ranging between 25 and 29.9 kg/m^2 in a term pregnancy, in >50% of women who got pregnant. It is likely that this might counteract beneficial effects of lifestyle intervention on maternal and pregnancy outcomes. Excessive gestational weight gain is weakly associated with an increased rate of various maternal and neonatal complications and therefore could possibly mask the association between periconceptional weight change and outcomes of pregnancy (30, 31). New forms of interventions continuing during pregnancy could be designed to prevent this rebound effect during pregnancy. Lifestyle intervention strategies could be adapted to different goals during the various phases, e.g., from preconception (weight loss between 5% and 10% and lifestyle change), during infertility treatment (limited weight loss and sustain lifestyle change) and gestation (no excessive weight gain, sustain lifestyle change). Both, a longer duration of the lifestyle intervention program and limiting drop out could be addressed by continuation of lifestyle interventions during infertility treatment. Even prolongation during pregnancy, with the aim to prevent excessive gestational weight gain in this important period of embryonic and fetal development is an interesting avenue to pursue in this respect. However, an IPDMA on the effect of diet and physical activity based interventions in pregnancy on gestational weight gain and pregnancy outcomes showed limited effects with a

mean weight difference of −0.7kg (95% CI, −0.92 to −0.48) (32). There was no reduction in the odds of adverse maternal and offspring composite outcomes, although the odds of cesarean section were reduced. If lifestyle intervention starts in the preconception phase and continues during pregnancy this may alter the effect on weight gain during pregnancy as well as maternal and fetal complications.

- Weight loss medication.

  Whether weight loss medication can be added to lifestyle interventions heavily depends on the safety of the drugs during early pregnancy. The glucagon-like peptide-1 agonists, e.g., are contraindicated during pregnancy because of their potential teratogenic effects (33).

To conclude, the current evidence suggests: more weight loss and an increase in CPR and LBR and more natural conceptions after lifestyle intervention were observed in women with overweight or obesity and infertility. With respect to potential harm of lifestyle intervention; in the current SR and meta-analysis there is no increased risk of miscarriage, although some doubt remains in the latest RCT not included in the SR. An IPDMA will give an opportunity to give an answer whether lifestyle intervention increases the risk of miscarriage. Both maternal and fetal/neonatal complications are underreported in most studies and since these are rare events, it needs further analysis in an IPDMA.

Women and men with infertility and obesity do not attend fertility clinics to lose weight, they want our help to achieve pregnancy and have a healthy infant in the near future. Therefore, we should offer them the treatment (keeping the recent *obesity guideline* in mind (10): "with a shift in focus from weight loss alone to improving patient-centered health outcomes"), using high-quality evidence from robust trials. We invite the research community to invest in this challenging field of research by designing and evaluating optimal lifestyle interventions with or without combining with medical intervention strategies to help this group of women and men and putatively increase their LBR and natural conception rates, reduce complication rates during pregnancy, and improve the health of their offspring. Future studies will benefit from the results of the intended IPDMA to make robust assumptions of effect size for various groups of women with or without PCOS and in various BMI categories. New interventions, using eHealth and wearables with or without private or group or couple-based interventions with a longer duration could be designed comprising the various phases of preconception, phase of infertility treatment, and pregnancy. Consensus is needed regarding relevant minimal effect size, use of COMMIT outcomes with addition of pregnancy as well as fetal and neonatal complications, and highest achievable methodological quality to come to evidence-based conclusions and health care.

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