Reply of the authors to "Clinical evidence of the relationship between preconception weight reduction and fertility outcomes"

We thank Xu et al. for their interest in our article, "Effectiveness of preconception weight loss interventions on fertility in women: a systematic review and meta-analysis." We welcome their comments and the opportunity to clarify the results and address concerns raised.

Xu et al. requested further discussion of our results because of perceived opposing effects of weight loss intervention length (≤ 12 vs. >12 weeks) on pregnancy and live birth outcomes. Xu et al. report that interventions ≤ 12 weeks had a significantly higher pregnancy risk ratio (RR), whereas interventions >12 weeks had a significantly higher live birth RR. For clarification, the pregnancy RR was significantly higher in interventions ≤ 12 weeks (1.43; 95% confidence interval [CI], 1.13–1.83), indicated by a 95% CI that did not include 1. However, the live birth RR for interventions >12 weeks was not significantly higher (1.11; 95% CI, 0.81–1.53), with a 95% CI that included 1. Furthermore, we report in the original article that women randomized to interventions ≤ 12 weeks had a nonsignificant trend toward more live births (228/768, 29.7%) than those in the control group (192/758, 25.3%) (1.28; 95% CI, 0.99–1.66) (1). The effects in the original article and interpretation stand as reported. The significant *P* value in Figure 2 E corresponds to the test for heterogeneity of the live birth subgroup results. The clinically relevant interpretation of this subgroup analysis is that interventions >12 weeks do not significantly increase the risk of pregnancy or live birth, whereas interventions ≤ 12 weeks were associated with significantly higher pregnancy rates and a trend toward more live births.

Several potential explanations likely contribute to this finding. First, there were more interventions ≤ 12 weeks than those >12 weeks (9 vs. 6). In addition, weight loss intervention research has shown that adherence to dietary modifications is highest in the first few months of an intervention, with lower adherence and less weight loss occurring from that point onward (1). Participants frequently cited discontinuing the prescribed dietary modifications because they were "too hard to follow or not yielding enough weight loss" (1). This is particularly important for women attempting weight loss before pregnancy or accessing fertility treatment. Women should balance delaying fertility treatment to attain a lower body mass index (BMI) as fertility declines with age. Finally, at present, there are no data examining the effects of energy restriction for weight loss on reproductive hormones in women with overweight or obesity. Female mammals, including women, have evolved to adaptively shift energy away from reproduction (lower hormone production) and toward survival during times when energy availability is low (2). However, there is wide variability in women's reproductive endocrine response to energy restriction. This could negatively influence fecundity in women losing weight through energy restriction; however, more data are needed to understand how energy restriction affects reproductive hormone production in women with overweight/obesity.

Second, Xu et al. suggested performing a sensitivity analysis to assess publication bias using the Egger test. Initially, we relied on funnel plots to assess bias. We ran the test proposed by Sterne and Egger (3) on our findings for pregnancy and found that it was significant ($P<.01$). Larger effects were observed in smaller and more variable trials. There are many possible causes of this asymmetry including heterogeneity, publication bias, and chance, and it is not clear which of these factors caused this potential bias in the literature. To assess the sensitivity of our results to publication bias, we used the trim-and-fill method (4), which led to an attenuated pregnancy RR of 1.10 (95% CI, 0.93–1.31). This suggests that if the funnel plot asymmetry is not due to chance, the results are somewhat sensitive to publication bias (the CI now included 1). We did the same sensitivity analysis for the two subgroup analyses we reported a positive effect for (pregnancy: interventions ≤ 12 weeks and BMI of ≥ 35 kg/m^2). The effect for a BMI of ≥ 35 kg/m^2 was attenuated; however, the effect for interventions ≤ 12 weeks was not. Importantly, as raised by Xu et al., these results demonstrate that the small but statistically significant improvement in the pregnancy rates reported for women in weight loss interventions and the effect for higher pregnancy rates among women with a BMI of ≥ 35 kg/m^2 in weight loss interventions should be cautiously interpreted in light of potential publication bias.

Finally, Xu et al. were concerned that we had not assessed risk of bias because the original submitted manuscript mislabeled our Cochrane Collaboration Risk of Bias Table as Table 2, when it is actually Supplemental Table 2. This has been corrected.

In summary, the Eggar test strengthened our conclusions that the data do not support the widely accepted necessity for one-size-fits-all weight loss interventions before pregnancy or infertility treatment among women with obesity. Weight loss interventions >12 weeks in our sample were not associated with higher pregnancy or live birth rates, whereas those ≤ 12 weeks were associated with significantly higher pregnancy rates and a nonsignificant trend toward higher live birth rates.

CRediT Authorship Contribution Statement

Ann E. Caldwell: Writing – review & editing, Writing – original draft. **Anna M. Gorczyca:** Writing – review & editing. **Robert N. Montgomery:** Writing – original draft, Formal analysis. **Nanette Santoro:** Writing – review & editing, Supervision.

A.E.C. and A.M.G. should be considered similar in author order.

Declaration of Interests

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