Effects of obesity treatment on female reproduction: results do not match expectations

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The adverse effects of obesity of female reproduction have been extensively documented. However, there are few prospective studies that have examined preconception weight loss interventions. There is a need to develop successful interventions with significant weight loss and compliance and most importantly document the effects of preconception interventions on important perinatal outcomes such as live birth and the health of the infant and mother. The existing data from randomized trials that come closest to meeting these criteria have failed to document improved live-birth rates after the intervention compared with control groups. There is a tendency to equate favorable weight change both before and during pregnancy with a direct qualitative improvement in all perinatal outcomes, yet the results from the most successful treatment of morbid obesity, that is, bariatric surgery, with on average 40% weight loss, suggest a mixed risk-benefit ratio on perinatal outcomes. Although interventions to control gestational weight gain have been more completely studied than preconception ones, and have documented successful interventions to achieve appropriate weight gain, there is no clear evidence that controlling gestational weight gain actually improves any important perinatal outcome. Future studies must develop more successful and effective interventions, capture perinatal outcomes instead of weight change as the primary outcomes, use, at least preconception, new antiobesity drugs (in combination with other therapies), and study bariatric surgery in prospective trials to improve our understanding of the effectiveness of obesity treatment before pregnancy. (Fertil Steril® 2017;107:860–7. ©2017 by American Society for Reproductive Medicine.)

Key Words: Infertility, lifestyle modification, bariatric surgery, pharmacotherapy, gestational weight gain

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The adverse effects of female obesity on reproduction have been exhaustively documented (1). The epidemiologic literature provides overwhelming and consistent evidence that female obesity is associated with ovulatory dysfunction; increased time to pregnancy; increased pregnancy loss from first trimester to last, including increased rates of stillbirth; and increased risk of major pregnancy morbidities such as gestational diabetes, preterm labor, and preeclampsia with associated maternal and fetal harm. Higher rates of operative delivery including cesarean section, wound infections, and thromboembolic events characterize the peripartum period. Difficulty initiating and maintaining lactation continue into the puerperium, and the vicious circle continues with higher rates of infant obesity among obese mothers. Never in the field of human reproduction have so many obese women attempted and achieved pregnancy, often with iatrogenic multiple pregnancy further worsening the situation, such that the full scope of female obesity on reproduction is still being described.

Given this mountain of evidence, can we do anything for an obese woman other than strongly advocate weight loss if she is contemplating pregnancy and if she is currently pregnant, to at least slow gestational weight gain (GWG) to some modest margin? Yet as this article will argue, based on level 1 randomized clinical trial evidence, there is little proof that such interventions to control weight before or during pregnancy effectively improve the perinatal outcomes of interest to the patient or clinician, such as improved live-birth rates, term deliveries, appropriate for gestational age babies, and above all the preservation of the health of infant or mother. In fact, there is emerging evidence that such interventions counterintuitively may actually worsen some of these desired outcomes. Potential reasons for the discrepancy between treatment

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and outcome will be explored. This review will focus on the obese reproductive woman, that is, the obese woman who is seeking pregnancy or is pregnant. A disclaimer is also necessary. This article focuses on the effects of weight loss in the obese woman on reproduction. There is no argument that weight loss in an obese woman will improve diabetes or cardiovascular risk and disease, but this review will focus on the shorter term personal and public goal of a healthy baby and a healthy mother.

WEIGHT IS A SURROGATE MARKER FOR REPRODUCTIVE FITNESS

Surrogate markers, which tend to track with a health outcome of interest, are not the end of treatment, but often only a means to a successful outcome. Weight loss preconception or weight maintenance during pregnancy should be sought in the obese reproductive woman only if an outcome of health significance is favorably impacted, that is, the achievement of a healthy normal weight full-term baby with the avoidance of undue harm to the mother and infant (2, 3). Let us explore the first part of this clause: to assume that weight loss will automatically improve the desired outcomes is to make the fundamental flaw of confusing association with cause and effect. Epidemiological studies show that increasing weight, in a dose-response relationship, is associated with increasing reproductive failure in women (4, 5). But that does not necessarily mean that increasing weight loss before pregnancy or controlling weight gain during pregnancy proportionately restores normal outcomes. It is possible that other factors than weight contribute to or cause reproductive failure, which are differentially impacted by therapy. To clearly answer this question, prospective dose-response weight loss studies are needed. They would provide proof of concept not only of increasing weight loss improving perinatal outcomes but also of establishing the optimal amount of weight loss. Without them, we are seeing through a glass darkly.

For example, elevated low-density lipoprotein cholesterol (LDL-C) levels are associated with an increased risk for primary and secondary cardiovascular events, and lowering these levels is generally associated with lowering event rates, that is, LDL-C levels are a surrogate marker for cardiovascular events (6). Statin therapy was initially approved by the Food and Drug Administration (FDA) on this basis (LDL-C lowering) without evidence of lowering event rates (which was subsequently demonstrated by the publication of the Scandinavian Simvastatin Survival Study [4S] 7 years later [7]). However, this direct correlation between marker and events is not always the case. There are multiple examples of drugs that significantly lowered LDL-C levels but resulted in increased cardiovascular events in patients, for example, the use of hormone replacement therapy in the Women's Health Initiative (8) or the use of torcetrapib, a potent cholesteryl ester transfer protein, in the ILLUMINATE trial (9). We can argue that the adverse event rates here were likely unrelated to the decline in LDL-C but rather related to the adverse effects of the drug on other organ systems, but it harkens to the importance of capturing all related events to identify collateral benefits and harms.

THE LIMITATIONS OF CURRENT OBESITY THERAPY WITH REGARD TO FEMALE REPRODUCTION

The prevalence of obesity and extreme obesity continues to increase among women in the United States, while it has plateaued in men (10). Currently, 40% of women are obese and 10% have class 3 obesity (body mass index [BMI] $>$ 40 kg/m^2). It is equally as concerning that obesity rates continue to rise among adolescents age 12–19 years (11) in the United States, ensuring a steady pipeline of obese reproductive-age women in the future.

Obesity treatment guidelines adapted by multiple societies advocate that all obese patients should be offered comprehensive lifestyle intervention as a first step; however, additional therapies may also be indicated based on degree of obesity and presence of comorbidities (12). As little as 3%–5% weight loss can reduce circulating triglycerides, blood glucose, hemoglobin A1c, and the risk of developing type 2 diabetes. However greater amounts of weight loss are required to reduce blood pressure, improve LDL-C and high-density lipoprotein cholesterol, and reduce the need for medications to control hypertension and diabetes (12). However, while it is often cited that as little as 5% weight loss can improve fertility (13), there is no clear dose-response relationship between weight loss in an obese patient and fertility, given the lack of published dose-response weight loss studies. Current medical therapies for obesity result in relatively modest weight loss over 6–12 months, ranging from 5%–10% with lifestyle modification to 10%–15% with the combination of lifestyle modification and pharmaceutical agents (12). Currently there are a number of drugs available in the United States for the treatment of obesity, most of which have only limited data on reproductive toxicity in women due to their relatively recent FDA approval (Table 1). Some of the newer drugs such as the combination of phentermine (an appetite suppressant) and topiramate (an antiepileptic adapted to obesity treatment) lack long-term safety data or have a known potential for teratogenicity (topiramate). They have rarely been used in preconception weight loss interventions in women.

Similarly, the most effective therapy for severe obesity, that is, bariatric surgery, is invasive and expensive, with a high initial morbidity related to surgical complications. Additionally, pregnancy is relatively contraindicated during the first 6–12 months after surgery due to the inability of the reconstructed gastrointestinal tract to accommodate the need for the increased nutrition that a developing pregnancy requires. Long-term malabsorption after some procedures may further exacerbate vitamin and specific nutrient needs after surgery. Although bariatric surgery is the recommended weight loss treatment for those with a BMI $>$ 40 kg/m^2 (12, 15), only about 1% of individuals in the United States who meet this BMI criteria elect to undergo surgery (16).

POPULAR MISCONCEPTIONS ABOUT WEIGHT LOSS

The two most popular misconceptions about weight loss are [1] that exercise alone can significantly lead to weight loss