Weighing the options: a patient-centered approach to timing embryo transfer in women with obesity

In recent decades, the United States has seen a steady increase in obesity rates, defined as having a body mass index (BMI) of ≥ 30 kg/m^2. At present, upwards of 40% of women of reproductive age have obesity, and this group's rate of severe obesity (BMI $\geq$ 40 kg/m^2) has recently exceeded 10% (1). There is a well-established relationship between increasing BMI and poorer reproductive outcomes, including lower implantation and live birth rates, and a higher risk of spontaneous abortion. The etiology of these negative associations is not fully understood. Given that fetal aneuploidy is a common cause of spontaneous abortions, embryonic aneuploidy might be a plausible mechanism to explain the detrimental effects of obesity on reproductive outcomes.

In their study, "Maternal Body Mass Index (BMI) Is Not Associated With Increased Rates of Maternal Embryonic Aneuploidy," Hughes et al. (2) attempted to answer this question by comparing aneuploidy rates in the preimplantation embryos of women with BMIs in the normal range with those in the obese range. They specifically explored whether aneuploidy of maternal origin was associated with maternal BMI. They found that aneuploidy rates were higher in women with obesity, but both overall aneuploidy rates and rates of aneuploidy of maternal origin were not statistically significant when controlling for maternal age. This was true within all classes of obesity, although the numbers of subjects in the subgroups with class 2 and 3 obesity (32 and 36 women) were small. Exploring whether this finding is reproducible in larger cohorts of women with BMI levels >35 and 40 kg/m^2 would be informative, and further studies will help further our understanding of whether embryonic aneuploidy might become a significant factor explaining lower success rates of assisted reproductive technologies in these higher BMI subgroups of patients.

In a recent study, spontaneous abortions in women with obesity had a greater likelihood of being euploid when compared with women without obesity (3). This study was also limited by the small numbers of women with class 3 obesity, thereby limiting the generalizability of the findings to women in the highest weight categories.

If elevated BMI levels are not associated with increased rates of aneuploidy, recommending in vitro fertilization (IVF) before weight loss may be a reasonable option. To be sure, physicians need to be cognizant of the increased complication rates and anesthesia risks and potentially more challenging oocyte retrievals in women with elevated BMIs. However, assuming that these are reasonable risks, the question of whether to proceed with oocyte retrieval but delay transfer in the hopes that weight loss will be achieved becomes a consequential question.

Several studies have examined whether using weight-loss interventions before initiating fertility treatments might improve outcomes. Although these studies have shown a decreased risk of both spontaneous abortions and pregnancy complications in women who achieved weight loss, no compelling evidence supporting the positive impact of weight loss on live birth rates was found (4).

Given that women with obesity do not have an increased risk of aneuploid conceptions, and given that weight loss interventions do not appear to improve live birth rates, is it ethically appropriate to insist on weight loss before either initiating IVF or proceeding with embryo transfer? In making treatment decisions surrounding this issue, it is helpful to approach counseling using a patient-centered approach. Central to this process is ensuring that the patient is fully informed as to the risks and benefits of the timing of IVF. Physicians should share the most up-to-date knowledge with patients regarding immediate vs. delayed transfer, but must not focus on data alone. Each patient undergoing fertility treatment does so within the context of their own personal values and beliefs. Many women, for example, have undergone multiple attempts at weight loss without success. Others are content with their current weight and see discussions regarding weight management as a form of "weight shaming." Some women, fully understanding the increased risks and lower success rates associated with higher BMIs, may be willing to accept these risks. They may choose to pursue treatment in a timely manner as a way of limiting emotional distress and the stress associated with a delay in initiating or continuing treatment.

Entering into a shared decision-making model with patients involves several stages. To start, physicians should discuss what is known, unknown, and as yet uncertain as it relates to each patient's specific situation. This should be done in an unbiased and factual manner. Critical to the process is an attempt by the physician to elicit the patient's values and match the treatment options to these values. For some patients, waiting to transfer an embryo in the hopes that weight loss will be achieved will be the desired course. For others, an immediate transfer may be preferred. There is no one approach that can be applied to all patients. Physicians must look beyond the data and toward a reality in which science and the patient's wishes are intricately intertwined and understood as inextricable. Patients should feel supported in expressing their concerns and their risk acceptance vs. risk aversion, and these elements will help guide the shared decision-making process. Finally, women should be given the opportunity to include their reproductive partners, when available, in decision-making surrounding treatment options.

Women should be given as much information as possible to allow them to weigh the risks and benefits of: 1) IVF and embryo transfer without weight loss, 2) IVF, and cryopreservation of embryos to allow for weight loss and subsequent transfer, and 3) weight loss followed by IVF and embryo transfer. It is unethical to prevent women from undergoing

fertility treatment solely because of increased risks or a lower chance of success (5). When making such judgments, physicians must be careful to avoid discrimination against women with obesity and to be aware of their own potential biases vis a vis patients with elevated BMIs. Additionally, there are already significant societal stigmas surrounding obesity, and care should be taken to avoid further perpetuating these. Counseling should focus on obesity as a medical condition and not as a moral failing. The potential benefit of weight loss should be balanced with the stress of delaying care and the possibility that weight loss will not be achieved. One approach could be to determine a time interval during which weight loss will be attempted, alongside discussion of a plan for moving forward in cases where weight loss has or has not been achieved successfully.

In conclusion, much remains unknown regarding how to best time embryo transfer decisions in women with obesity. Given this uncertainty, it is important to be transparent with patients and to involve them in treatment decisions regarding their reproductive care. Although lowering BMI may both improve outcomes and decrease risks, achieving weight loss will not be possible or desirable for some women. By respecting a woman's wishes and operating within a shared decision-making model, physicians can achieve a higher level of holistic care, taking into account success rates within the context of the woman's value system to best achieve her goals.

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