



Weight gain after in vitro fertilization: a potential consequence of controlled ovarian stimulation

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Abstract

In the USA, 42% of adult women were estimated to have obesity, and 13% of women of childbearing age similarly have impaired fecundity. Obesity is associated with infertility such that patients with obesity often seek out in vitro fertilization (IVF) services. Here, we report on the case of a woman with childhood-onset class II obesity who had been undergoing treatment with phentermine and topiramate prior to undergoing 3 cycles of IVF. With each cycle, the patient temporarily gained 13–15 lbs. during controlled ovarian stimulation (COS). Weight gain from COS may be clinically relevant and merits further study to optimize weight status across women's reproductive life and to better assist women who gain weight secondary to IVF. Incorporating weight monitoring into IVF protocols may also help better characterize the scope of weight gain from COS.

In the USA, 42% of adult women were estimated to have obesity [1], and 13% of women of childbearing age similarly have impaired fecundity [2]. In addition to being a significant risk factor for type 2 diabetes and hypertension, obesity may contribute to greater infertility, with higher body mass index (BMI) potentially resulting in anovulation, impaired oocyte development, and poorer endometrial receptivity [3]. Indeed, women with obesity have a three times greater risk of infertility than women without obesity [4], and for every unit increase in BMI above 29 kg/m², the probability of pregnancy is decreased by about 5% [5]. As such, many patients with obesity require fertility assistance, including in vitro fertilization (IVF), to conceive [6].

IVF medications, however, can also lead to substantial weight gain during controlled ovarian stimulation (COS)

[7], although there is limited data to support this relationship. Indeed, it is not standard practice in reproductive endocrinology to track a woman's weight status through either stimulation or transfer cycles. As such, published side effects of COS rarely include potential weight gain, and COS medications are not typically included in the category of weight-promoting medications [8]. Given that obesity can often lead to poor IVF outcomes [4, 9], there is a clinical imperative to better assist women who may gain weight secondary to IVF and to optimize weight status across women's reproductive life. With the case report of a woman who gained 13–15 lbs. during COS in each of her 3 IVF cycles, we argue that the impact of COS on obesity merits more significant consideration and further study.

A 33-year-old woman with childhood-onset class II obesity (weight of 228 lbs.) presented in 2011 for a general obesity medicine consultation. The possible contributors to her excess weight are complex and multifactorial but may have included genetic predisposition due to a family history of obesity, early-onset weight gain, decreased physical activity, and prior use of selective serotonin reuptake inhibitors (SSRIs), a known class of weight-promoting medications [8]. Through previous weight loss efforts, including commercial programs, exercise, and diets, the patient would generally lose 15–17 lbs. but subsequently regained the weight.

The patient preferred to avoid metabolic and bariatric surgery, so she was treated with a combination of phentermine (started in late 2011) and topiramate (started in late 2012),

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which resulted in a recorded weight loss of 40 lbs. and a new weight of 188 lbs. (Fig. 1). With a corresponding BMI of 29.4, pharmacotherapy had brought the patient outside the range of a formal obesity diagnosis. The patient experienced no adverse side effects due to the phentermine and topiramate combination. In early 2014, the patient was removed from these weight loss medications because she was trying to conceive, and these medications are contraindicated with pregnancy. Within 6 months, the patient regained her weight and rebounded to her baseline BMI with a weight of 224 lbs.

Given a history of congenital hypothyroidism and her husband's potential infertility, the patient proceeded with 3 IVF cycles between 2015 and 2019 and collected monthly weight data from her home scale for her personal records. Regarding COS, her IVF protocol for each cycle included the initial 3-day use of estradiol patches and cetrorelix before beginning follitropin alfa and mentotropins, as well as dexamethasone. Thirty-six hours prior to egg retrieval, the patient received human chorionic gonadotropin (hCG) with two doses of leuprolide shortly thereafter. The first cycle retrieved 11 eggs, resulted in 2 embryos, and led to the successful delivery of a 40-week, 6-day boy. The second cycle retrieved 11 eggs and resulted in 6 embryos, but all arrested in development before day 5. The third cycle retrieved 13 eggs, resulted in 5 embryos, and led to the successful delivery of a 39-week, 2-day girl.

Of note, with each cycle to induce egg retrieval, there was a sudden increase of the patient's weight that was inconsistent with her past history of weight change. The patient measured her weight before beginning IVF medications and after egg retrieval for each cycle, approximately 1 month apart (Table 1). The first cycle saw a 1-month increase in weight from 224.0 lbs. to 239.0 lbs. (Fig. 2A), the second

Table 1 Increase in patient weight for each of her three in vitro fertilization (IVF) cycles, measured from before the onset of controlled ovarian stimulation (COS) medications to after egg retrieval, approximately 1 month apart

| | Increase in weight | Weight before COS medication onset | Weight after egg retrieval |
|-------------|--------------------|------------------------------------|----------------------------|
| IVF Cycle 1 | 15.0 lbs | 224.0 lbs | 239.0 lbs |
| IVF Cycle 2 | 13.0 lbs | 224.2 lbs | 237.2 lbs |
| IVF Cycle 3 | 15.0 lbs | 222.6 lbs | 237.6 lbs |

cycle saw a 1-month increase in weight from 224.2 to 237.2 lbs., and the third cycle saw a 1-month increase in weight from 222.6 to 237.6 lbs. (Fig. 2B).

Following the birth of her two children, the patient returned for a follow-up obesity medicine appointment. Although she lost some weight during her pregnancies, the patient had been unable to adjust her weight status below 220 lbs. and below her baseline BMI. The patient began on liraglutide, a glucagon-like peptide 1 (GLP-1) agonist, but she was not responsive to the medication, nor did she tolerate it well. As such, liraglutide was withdrawn and phentermine and topiramate were restarted. Within about 10 months, this combination helped bring the patient back down to a weight of 186 lbs.

We describe this patient's case to argue that weight gain from COS may be clinically relevant in some women and as significant as a 13–15-pound increase from the initiation of IVF medications to egg retrieval, even if only temporary. Previous work has examined the impact of ovarian hyperstimulation syndrome (OHSS) on altered thyroid function, myocardial infarction, and acute kidney injury [10–12], but

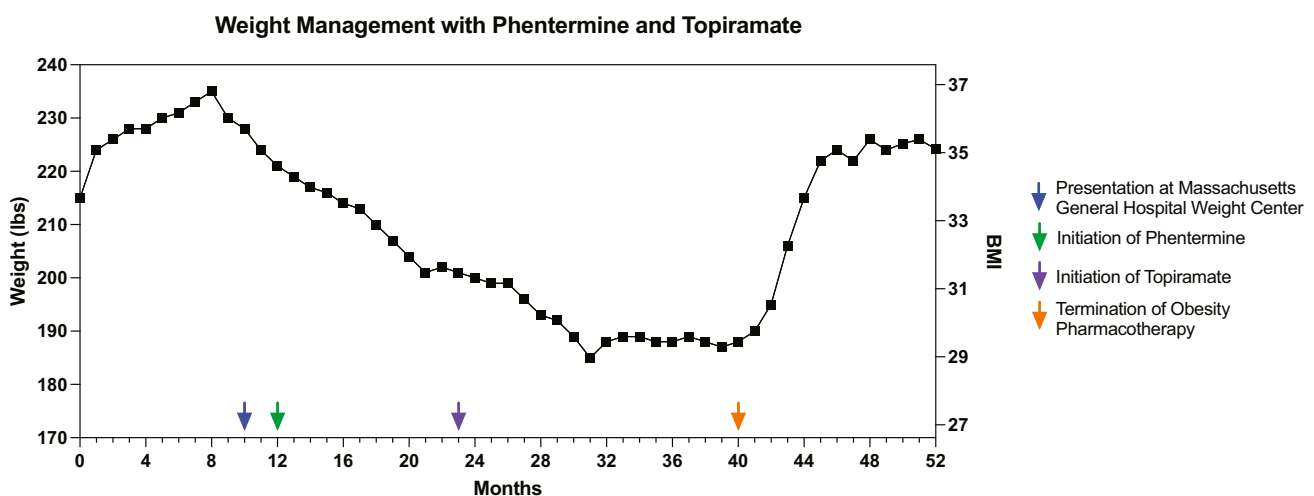


Fig. 1 Weight management following presentation at Massachusetts General Hospital (MGH) Weight Center (blue arrow) in late 2011 with initiation of phentermine (green arrow) and topiramate (purple arrow)

shown. Pharmacotherapy was terminated in early 2014 (orange arrow) due to contraindication with pregnancy

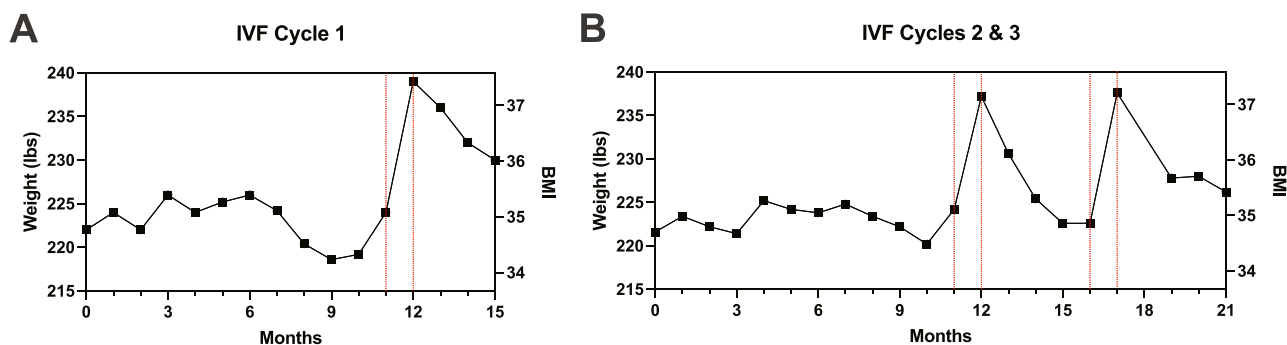


Fig. 2 **A** Weight trends are demonstrated in the 12 months prior to the first cycle, in the month when the first cycle ovarian stimulation medications were received, and in the first trimester of pregnancy of the first cycle. **B** Weight trends are demonstrated in the 12 months prior to the second cycle, in the month when the second cycle ovarian stimulation medications were received, during the 4-month inter-

lude between the second and third cycles, in the month when the third cycle ovarian stimulation medications were received, and in the first trimester of pregnancy of the third cycle. Anti-obesity medications were terminated prior to initiating all the three cycles. Red dotted lines demark the period when ovarian stimulation medications are received

the link between COS and weight gain has not previously been well described. A previous manuscript noted statistically significant weight gain in women undergoing IVF treatment, proportional to the number of oocytes retrieved and independent of age, BMI, stimulation protocol, or gonadotrophin dose. However, the weight gain noted, namely 600 g or 1.3 lbs., was determined to be clinically irrelevant and to be caused by temporary edema [7, 13, 14]. A more recent study noted an average increase of 2.2 kg, or 4.9 lbs., during ovulation induction in patients with polycystic ovary syndrome (PCOS) with increased BMI and three or more IVF cycles associated with greater weight gain [15].

We believe that substantial weight gain following COS is a more significant concern than is presently understood. Recent studies indicate that medications contribute to at least 20% of obesity in the USA [16], and as an obesity-medicine physician, F. C. S. regularly receives anecdotal reports of similar IVF-related weight gain, irrespective of her patients' history of PCOS or other clinical considerations. However, because weight monitoring is not a formal aspect of current IVF protocols, there is a paucity of data in the peer-reviewed literature about weight gain following COS. Given that obesity is associated with infertility and that patients with obesity often require IVF to help conceive [4, 6], it is critical to fully understand the implications of COS on weight gain to optimize patient weight status and better assist women who gain weight secondary to IVF medications.

IVF can be quite stressful for patients [17] because of the economic burden with a median cost of \$19,234 for each cycle [18], the psychological burden with anxiety and depression after failed cycles [19], and the physical burden with some women reporting significant weight gain after COS. Although the economic and psychological burdens of IVF are relatively well-understood, the connections

between IVF treatment and subsequent weight gain are largely not being made by reproductive endocrinologists. Many weight-promoting medications act through metabolic pathways, such as proopiomelanocortin (POMC) and agouti-related protein (AgRP), and further research may examine the specific pathways through which certain COS medications may induce weight gain [20].

Certainly, we recognize the potential for confounding factors beyond COS—stress from the patient's unsuccessful cycle and from her insurance not covering the first IVF cycle—that could have contributed to the observed increase in weight in this case report [21]. However, the patient's sudden, significant weight gain consistently experienced with each IVF cycle suggests that COS may have also played an important role. One explanation for the weight gain may be the patient's receipt of steroid hormone contraceptives, which contain high doses of estrogen and progestin [22–24]. COS induces large increases in estradiol and progesterone, which approach and often exceed levels of estrogen found in pregnancy. The potential for fertility drugs to modify metabolic or hormonal pathways in the short and potentially long term should be further studied.

In conclusion, we describe the case of a patient who saw one-month increases of 13–15 lbs. with COS in each of her three IVF cycles to argue that fertility drugs may modify metabolic or hormonal pathways, potentially inducing rapid weight gain. Obesity medicine specialists and reproductive endocrinologists should collaborate to track weight changes through IVF treatment, formalize regular weight measurements into the protocol, and implement strategies to optimize patient weight status through their reproductive lives. Given that weight gain during COS has not drawn significant attention in the literature, further research is needed

to determine the scope of this phenomenon and to understand the underlying hormonal mechanisms.

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Declarations

Conflict of interest The authors declare no competing interests.

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