MORE IS NOT BETTER: HIGH STARTING GONADOTROPIN DOSE IS NOT ASSOCIATED WITH INCREASED OOCYTE YIELD IN OVERWEIGHT AND OBESE WOMEN – AN INVERSE PROPENSITY WEIGHT ANALYSIS

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Background
Obesity in infertile women is associated with lower serum AMH, reduced antral follicle count (AFC), and compromised assisted reproduction outcomes. Obese women often need higher total gonadotropin dose during controlled ovarian hyperstimulation (COH) but still produce fewer oocyte and lower live birth rates (LBR). It's uncertain if this reflects physiologic changes or whether obesity further declines ovarian reserve.
Objective
To determine whether increasing the starting gonadotropin dose can improve ovarian stimulation response in obese women and affect pregnancy outcomes.
Materials and Methods
This single-center retrospective cohort study included 402 overweight and obese women (BMI ≥ 25 kg/m2) undergoing their first autologous COH between January 2016 and June 2021. The inverse propensity weight (IPW) analysis was used to simulate randomization of starting gonadotropin dose. Key factors that typically influence this decision, including age (<35 or ≥35 years), AMH (<1.2 or ≥ 1.2 ng/mL), AFC (<5 or ≥ 5), BMI, and pre-cycle follicle stimulating hormone level, were employed to compute inverse propensity weights. Additionally, a multivariable regression model adjusted for covariates of race/ethnicity, gravidity, parity, history of tobacco use, infertility diagnoses, and total gonadotropin dose. Primary outcomes included pre-trigger peak estradiol level, stimulation duration, oocytes retrieved, mature metaphase II (MII) oocytes, fertilized 2-pronuclei (2PN) oocytes, and embryos suitable for transfer/cryopreservation. We also assessed the association with secondary outcomes of implantation, clinical pregnancy, and LBR in subsequent embryo transfer cycles, employing odds ratios. To minimize bias from extreme propensity weights, participants were analyzed in sub-groups based on whether they had a diagnosis of diminished ovarian reserve (DOR). Statistical significance was defined as p-value < 0.05.
Result(s)
The study cohort (mean age: 36.5 years, average BMI: 31.2 kg/m2) was racially diverse (18.4% non-Hispanic White, 28.9% non-Hispanic Black, and 25.9% Hispanic). In obese women without DOR (Table 1), each 100 IU increase in the starting gonadotropin dose raised peak pre-trigger estradiol level by 303.9 pg/mL (95% CI 97.01, 510.8, p-value < 0.01) and correlated with a reduction of 0.48 days (95% CI -0.72, -0.23 days, p-value < 0.01) in length of stimulation. However, this did not result in a higher total oocyte yield (-0.80, 95% CI -2.26, 0.67, p-value 0.29), more mature MII oocytes (-0.27, 95% CI -1.37, 0.82, p-value 0.63), additional 2PN oocytes (0.31, 95% CI -0.55, 1.17, p-value 0.48), or increased quality embryos for transfer/cryopreservation (-0.23, 95% CI -0.81, 0.35, p-value 0.44). No increased odds of implantation, clinical pregnancy, and LBR were observed. Subgroup analyses of women with DOR (Table 2) showed only a slight increase of 14.28 pg/mL in peak pre-trigger estradiol level with each increment of 100 IU higher starting gonadotropin dose (95% CI -172.5, 201.07, p-

value 0.88) and the length of stimulation shortened by –0.76 days (95% CI -1.29, -0.23, p-value 0.01). However, no significant improvement was noted in stimulation outcomes or pregnancy results.

Conclusion(s)

In obese women without DOR, increasing the starting gonadotropin dose is associated with higher pre-trigger peak estradiol level and shorter length of stimulation. However, this does not translate into higher oocyte yield or improved pregnancy outcomes for overweight/obese women.

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Table 1. Inverse propensity weight analysis of controlled ovarian hyperstimulation

	Diminished Ovarian Reserve			No Diminished Ovarian Reserve		
	β^1	95% CI	p-value	β^1	95% CI	p-value
Pre-Trigger Peak Estradiol	303.90	97.01, 510.8	0.00	14.28	-172.5, 201.07	0.88
Length of Stimulation	-0.48	-0.72, -0.23	0.00	-0.76	-1.29, -0.23	0.01
Number of Oocytes	-0.80	-2.26, 0.67	0.29	-0.71	-1.75, 0.33	0.19
Number of Mature MII Oocytes	-0.27	-1.37, 0.82	0.63	-0.95	-1.96, 0.05	0.07
Number of Fertilized 2PN Oocytes	0.31	-0.55, 1.17	0.48	-0.54	-1.45, 0.37	0.25
Number of Good Quality Embryos	-0.23	-0.81, 0.35	0.44	-0.45	-0.96, 0.05	0.09

Additional covariates adjusted for race/ethnicity, gravidity, parity, history of tobacco use, infertility diagnoses, and total gonadotropin dose

References

1. Merhi Z et al. Leptin Suppresses anti-mullerian hormone gene expression through the JAK2/STAT3 pathway in luteinized granulosa cells of women undergoing IVF. Hum Reprod 2013; 28: 1661-9

2. Vitek, Wendy, et al. “Lower Antimüllerian Hormone Is Associated with Lower Oocyte Yield but Not Live-Birth Rate among Women with Obesity.” American Journal of Obstetrics and Gynecology, vol. 222, no. 4, 2020

3. Wang, Jixian. “To Use or Not to Use Propensity Score Matching?” Pharmaceutical Statistics, vol. 20, no. 1, 2020, pp. 15–24.