Effects of pulsatile intravenous follicle-stimulating hormone treatment on ovarian function in women with obesity

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Objective: To establish conditions for effective hypothalamic suppression in women with normal and high body mass index (BMI) and test the hypothesis that intravenous (IV) administration of pulsatile recombinant follicle-stimulating hormone (rFSH) can overcome the clinically evident dysfunctional pituitary-ovarian axis in women with obesity.
Design: Prospective interventional study.
Setting: Academic medical center.
Patient(s): Twenty-seven normal-weight women and 27 women with obesity, who were eumenorrheic and aged 21–39 years.
Intervention(s): Two-day frequent blood sampling study, in early follicular phase, before and after cetrorelix suppression of gonadotropins and exogenous pulsatile IV rFSH administration.
Main Outcome Measure(s): Serum inhibin B and estradiol (E2) levels (basal and rFSH stimulated).
Result(s): A modified gonadotropin-releasing hormone antagonism protocol effectively suppressed production of endogenous gonadotropins in women with normal and high BMIs, providing a model to address the functional role of FSH in the hypothalamic-pituitary-ovarian axis. The IV rFSH treatment resulted in equivalent serum levels and pharmacodynamics in normal-weight women and those with obesity. However, women with obesity exhibited reduced basal levels of inhibin B and E2 and a significantly decreased response to FSH stimulation. The BMI was inversely correlated with serum inhibin B and E2. In spite of this observed deficit in ovarian function, pulsatile IV rFSH treatment in women with obesity resulted in E2 and inhibin B levels comparable with those in normal-weight women, in the absence of exogenous FSH stimulation.
Conclusion(s): Despite normalization of FSH levels and pulsatility by exogenous IV administration, women with obesity demonstrate ovarian dysfunction with respect to E2 and inhibin B secretion. Pulsatile FSH can partially correct the relative hypogonadotropic hypogonadism of obesity, thereby providing a potential treatment strategy to mitigate some of the adverse effects of high BMI on fertility, assisted reproduction, and pregnancy outcomes.
Clinical Trial Registration Number: ClinicalTrials.gov #NCT02478775. (Fertil Steril® 2023;120:890–8. ©2023 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

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The association between obesity and reduced reproductive fitness is well documented; however, the mechanisms are poorly understood (1, 2). Much less attention has been paid to infertility and poor response to treatment in women with obesity and regular, ovulatory cycles compared with those with obesity and polycystic ovary syndrome. Several studies have documented low gonadotropin and ovarian hormone levels among women with obesity (3–5). Overweight women had lower follicular serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), and inhibin B levels than normal-weight women but no differences were noted in estradiol (E2) levels or follicle counts (3), whereas the Nurses' Health Study observed lower serum E2 levels associated with obesity (5). Similarly, decreased levels of urinary FSH, LH, and progesterone metabolites were observed in women with obesity (4). In women with infertility and obesity, a higher dose of exogenous gonadotropin is needed to achieve adequate ovarian stimulation (6, 7), and an increase in body mass index (BMI) negatively impacts outcomes (oocyte retrieval, clinical pregnancy, live birth, and miscarriage) in women undergoing in vitro fertilization (IVF) (8–10). These findings suggest that both pituitary dysfunction and ovarian dysfunction are implicated in the evident adverse effects of obesity on fertility and fecundity (11).

Follicle-stimulating hormone and LH stimulate ovarian follicular development. Obesity is associated with reduced LH pulse amplitude with no change in frequency; however, less is known regarding FSH secretion and activity (12). Although both FSH and LH are secreted in a pulsatile manner in humans, the role of FSH is not well characterized (13). Transgenic mouse models have demonstrated that rerouted FSH (secreted via the pulsatile LH pathway) enhances ovarian function and fertility (14). Currently, there are no standardized human models to delineate and study the specific effects of FSH, particularly in women with obesity.

Exogenous FSH can be used to investigate its pulsatile effects on the ovary in women with obesity. However, subcutaneous dosing should be individualized on the basis of BMI because of variable absorption rates of FSH (6). Intravenous (IV) administration of exogenous FSH represents a potential strategy to circumvent this limitation by ensuring more predictable systemic delivery. Confounding effects of endogenous gonadotropin secretion, in the context of exogenous FSH, can be suppressed by administration of a gonadotropin-releasing hormone (GnRH) antagonist. Considering the previously reported phenomenon of premature escape from GnRH antagonist suppression in women with obesity (15), we developed and implemented a modified "booster" strategy to enforce endogenous suppression in all study participants.

We hypothesized that the relative hypogonadotropic hypogonadism and consequent decreased reproductive fitness characteristic of obesity is due to pituitary dysfunction, which would be rescued by pulsatile exogenous FSH treatment. Herein, we report a novel model to investigate the specific effects of pulsatile IV recombinant FSH (rFSH), in women with normal weight and obesity, after suppression of endogenous LH and FSH secretion with the GnRH antagonist cetrorelix. Specifically, effects of IV rFSH on the relative hypogonadal phenotype characteristic of women with obesity were examined with respect to FSH stimulation of E2 and inhibin secretion.

MATERIALS AND METHODS

Participants

This study was approved by the Colorado Multiple Institutional Review Board (15-0474) and registered on ClinicalTrials.gov (NCT02478775). Informed consent was obtained before enrollment, and participants were compensated.

Fifty-four women with normal (n = 27) and high (n = 27) BMIs were recruited from the Denver Metro area between January 2016 and June 2021. All participants underwent history taking and physical assessment with screening laboratory examinations at the Clinical Translational Research Center. Inclusion criteria were as follows: age of 21–39 years; normal (18.5–24.9 kg/m^2) or high ($\geq$30 kg/m^2) BMI; regular menses (25–40 days); normal prolactin and thyroid-stimulating hormone (TSH) levels, complete metabolic panel result, and blood count; no history or clinical diagnosis of polycystic ovary syndrome; no chronic disease affecting hormone production, metabolism, or clearance; no use of thiazolidinediones or metformin; no current use of medications or supplements containing hormones within 3 months of entry; <4 hours of strenuous exercise per week; not currently pregnant, looking to get pregnant, or breast feeding; and no significant weight loss or gain (>1 kg/week) within 3 months.

Study Design

Study design is summarized in Supplemental Figure 1 (available online). The 26-hour study visit was completed in the early follicular phase (days 2–7) of each participant's menstrual cycle. Visits began at 1:30 PM on study day 1 (baseline) with the placement of an indwelling IV catheter and a serum pregnancy test before the administration of study medications. At 2:00 PM, frequent blood sampling commenced with 3–4 mL of blood being collected every 10 minutes for 10 hours for measurement of LH, FSH, inhibin B and E2. At midnight (10 hours after study initiation), 3 mg of the GnRH antagonist cetrorelix (EMD Serono) was injected subcutaneously in the abdomen, and participants were allowed to sleep for 6 hours. At 6:00 AM on study day 2 (stimulated), a second subcutaneous "booster" dose (0.25 mg) of cetrorelix was administered, and frequent blood sampling (every 10 hours) for hormone measurements resumed. Additionally, beginning at 6:00 AM on study day 2, 30 IU of rFSH was administered IV every hour for 10 hours, for a total dose of 300 IU.

Hormone Assays

The LH, FSH, and E2 levels were measured by competitive immunoassay using direct chemiluminescent technology (Advia Centaur CP, Siemens Healthcare Diagnostic; AB_2895592, AB_28955593, and AB_2895133, respectively). Inter- and intra-assay coefficients of variation were 3.99% and 2.89% for LH, 4.44% and 5.11% for FSH, and 3.25%

TABLE 1

Participant characteristics.

Characteristic	Normal BMI	High BMI	*P* value
N	27	27	
Age (y)	27.3 (4.8)	32.0 (4.1)	< .001
BMI (kg/m^2)	22.5 (1.4)	37.7 (6.2)	< .001
Weight (kg)	61.2 (5.5)	102.0 (19.3)	< .001
Height (cm)	164.9 (6.3)	164.3 (5.6)	.675
Waist/hip ratio	0.84 (0.12)	0.90 (0.12)	.082
TSH (μIU/mL)	1.51 (0.87)	2.15 (1.13)	.024
Prolactin (ng/mL)	8.15 (3.66)	9.74 (4.68)	.172
AMH (ng/mL)	6.16 (5.64)	6.31 (4.31)	.848
Cycle length (days)	28.22 (1.5)	28.39 (1.23)	.67
Cycle day of visit	5.0 (1.5)	4.2 (1.3)	.054

Note: Demographic data were summarized for the 54 participants. Continuous variables were summarized with means (standard deviations), and differences between groups were tested using the 2-sample t-tests. Categorical variables were summarized with frequencies (percentages), and associations were tested using Fisher's exact test. AMH = antimüllerian hormone; BMI = body mass index; TSH = thyroid-stimulating hormone.

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and 2.67% for E2, respectively. Inhibin B and antimüllerian hormone (AMH) levels were measured using enzyme-linked immunosorbent assay (Ansh Labs; AB_2783661 and AB_2783675). Inter- and intra-assay coefficients of variation were 1.9% and 4.98% for inhibin B and 2.5% and 4.25% for AMH, respectively.

Mass Spectrometry Measurement of Cetrorelix

Serum cetrorelix concentrations were determined by liquid chromatography-mass spectrometry (MS)/MS (Applied Biosystems Sciex 4000) as described (Supplemental Methods). Limit of detection was 1.22 ng/mL.

Pharmacokinetic Analysis of Serum FSH

The FSH concentration-time data were subjected to noncompartmental analysis, by the linear trapezoidal-linear interpolation method with uniform weighting, using Phoenix WinNonlin v8.3.3 (Certara L.P.), to obtain predicted values for total exposure, clearance, and volume of distribution at steady state.

Statistical Analysis

An a priori sample size estimate using the reported difference (30 pg/mL) in inhibin B levels between women with normal weight and those with obesity (3), with an alpha of 0.05, was performed, resulting in 80% power with 27 women in each group. Differences between groups and/or study days were tested using 2-sample paired t-tests for continuous variables and Fisher's exact tests for categorical variables. The 2-sample t-tests and linear regressions were only used because analysis methods when we included 1 observation per person in a model. Linear regression was used to adjust BMI group differences for age, cycle day, and AMH. Outcome distributions and model diagnostic plots confirmed that parametric testing was appropriate. Analyses were conducted in R version 4.2.0 (R Foundation for Statistical Computing).

RESULTS

Participant Characteristics

Fifty-four participants were included in the study, with equal cohorts of women with normal and high BMIs, as outlined in the Consort Diagram (Supplemental Fig. 2). Baseline demographic and hormonal characteristics of participants are shown in Table 1. By design, BMI and weight were statistically different between the 2 cohorts. Women with a normal BMI were younger (age, 27 vs. 32 years; $P < .001$) and had a lower mean TSH level than women with a high BMI. However, all women in the study were euthyroid, with normal TSH levels, and of reproductive age with regular menstrual cycles. There were no significant differences in other parameters, including waist-to-hip ratio, prolactin and AMH levels, or cycle length.

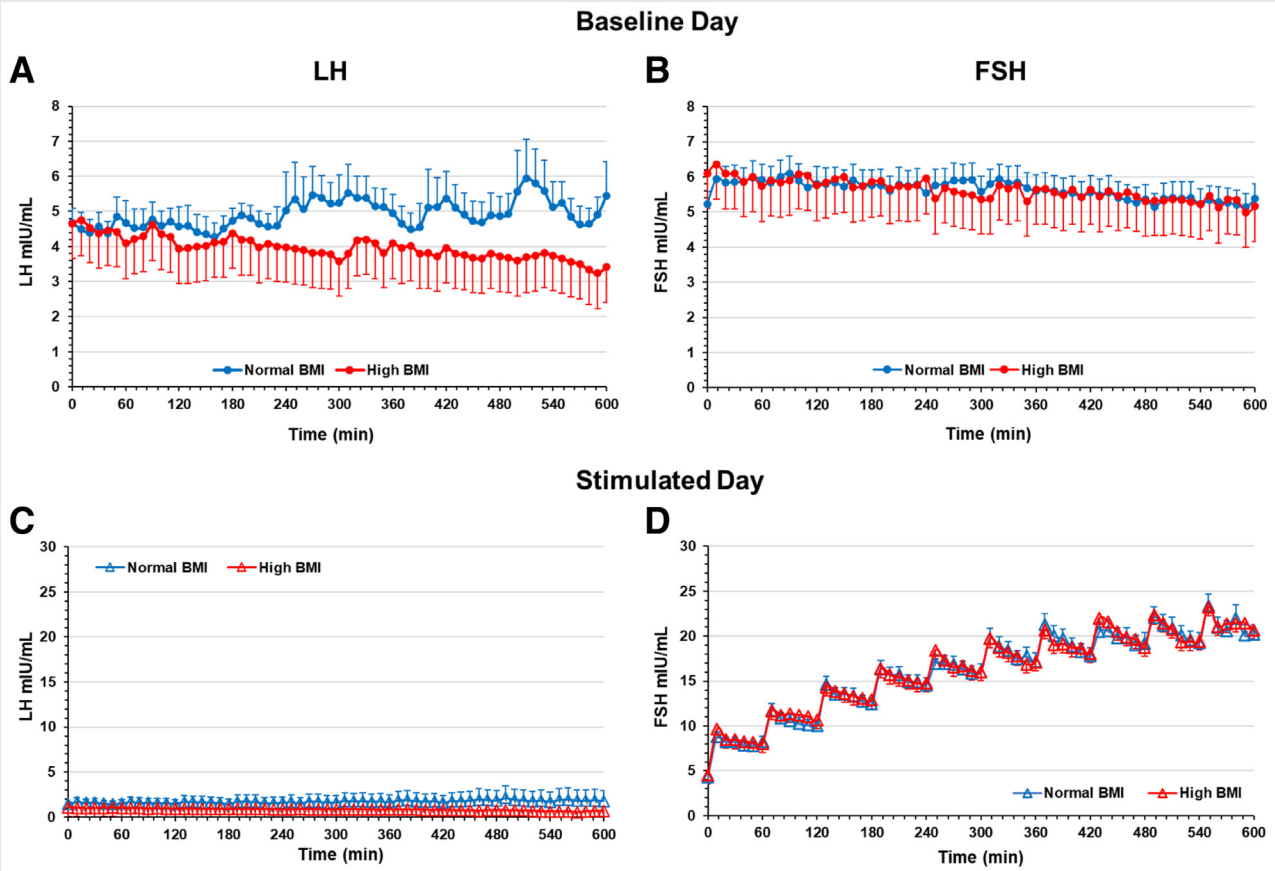
Baseline Endogenous FSH and LH Secretion

Mean endogenous serum FSH and LH levels at each sampling interval (study day 1) are shown in Figure 1. Consistent with our previous studies (16–18), participants with high BMI exhibited significantly lower LH levels (Fig. 1A) than their normal-BMI counterparts. Area under the curve (AUC) and mean levels ± standard error of the mean of LH for normal BMI (2,942 ± 180.4 and 4.78 ± 0.21 mIU/mL, respectively) were significantly different from those for high BMI (2,300 ± 164.8 and 3.95 ± 0.16 mIU/mL, respectively; $P < .0001$ for both). Levels of serum FSH (AUC) in women with a normal BMI were not significantly different from those in the high-BMI group ($P = .21$).

Pulsatile Exogenous rFSH Profiles and Pharmacokinetics

Treatment with the GnRH antagonist cetrorelix, using our modified "booster" strategy, effectively suppressed LH levels in both normal-weight women and women with obesity for the duration of study day 2 (Fig. 1C). Subsequent IV administration of hourly boluses of rFSH produced a pulsatile pattern and elevated serum FSH levels in both normal- and high-BMI

FIGURE 1



Serum luteinizing hormone (LH) and follicle-stimulating hormone (FSH) (sampled every 10 hours) on the (**A** and **B**) baseline study day 1 and (**C** and **D**) stimulated study day 2 in the normal– and high–body mass index (BMI) groups. Exogenous intravenous recombinant FSH was administered every 60 minutes for 10 hours as indicated by the observed peaks in the serum FSH levels. Data are the means of 27 participants per group; the error bars are the standard errors of the mean.

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groups (Fig. 1D). There was no statistically significant difference in AUC between the cohorts for LH ($P = .49$) and FSH ($P = .86$). Thus, pulsatile IV rFSH treatment resulted in comparable serum levels, pulse amplitude, and frequency in women with normal and high BMIs.

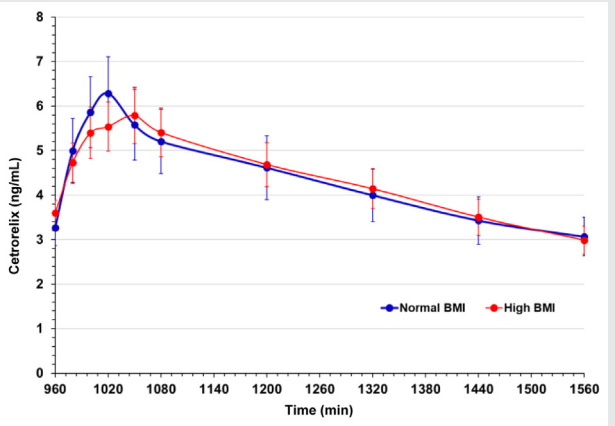
We then examined the pharmacokinetics of serum FSH, during study day 2, using standard noncompartmental methodology. There was no difference in clearance of serum FSH or volume of distribution at steady state between the normal- and high-BMI groups (Supplemental Fig. 3). In addition, there were no significant differences in urinary FSH levels between women with normal and high BMIs, indicating similar FSH clearance (data not shown).

In addition, we determined cetrorelix levels, by MS analysis, in serum from baseline and FSH-stimulated days. Serum cetrorelix levels on study day 2 peaked approximately 1 hour after the booster dose and declined slowly thereafter (Fig. 2). No differences in serum cetrorelix profiles were observed between the normal- and high-BMI groups. Thus, using a supplemental booster dose of cetrorelix resulted in similar pharmacokinetics in both women with normal and high BMIs, and effective functional suppression of LH was maintained in both cohorts for the duration of study day 2 (Fig. 1C).

Effects of Obesity on Ovarian Response to Pulsatile IV rFSH

Baseline levels of inhibin B (Fig. 3A) and E2 (Fig. 3B) were significantly lower in women with a high BMI. Inhibin B levels (AUC) were 61,524 ± 10,661 for normal BMI and 43,581 ± 9,088 for high BMI ($P < .0001$). Similarly, E2 AUCs in normal- vs. high-BMI women were 36,932 ± 5,694 and 34,589 ± 3,933, respectively ($P = .008$). Pulsatile administration of rFSH increased serum inhibin B (Fig. 3A) and E2 (Fig. 3B) levels, above the baseline means, for both the normal- and high-BMI groups. However, rFSH induction of both inhibin B and E2 was significantly attenuated in the high-BMI group. Mean and maximum inhibin B and E2 levels increased in response to pulsatile rFSH administration from study days 1 to 2 within each cohort (Fig. 3C and D). The

FIGURE 2



Serum cetrorelix levels determined at the indicated time points by mass spectrometry (Supplemental Methods). Data are the means of 27 participants per group; the error bars are the standard errors of the mean. BMI = body mass index.

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difference in mean E2 was statistically significant for the normal-BMI group ($P = .004$) but not for the high-BMI group ($P = .056$). The increase in maximum E2 between baseline and stimulated day, in response to FSH, was significant for both cohorts (both $P < .001$). Changes in maximum inhibin B response to rFSH were significant in normal- and high-BMI groups (both $P < .001$). In addition, mean inhibin B level increased in both cohorts from study days 1 to 2 but was only significant in women with normal BMI ($P = .007$).

Analysis of the differences in maximum inhibin B and E2 levels (pg/mL) between baseline and stimulated days showed significantly decreased responses to FSH for inhibin B (−62.1 [95% confidence interval {CI}, −94.1 to −30.0], $P < .001$) and E2 (−31.8 [95% CI, −56.5 to −7.1], $P = .013$) in the high-BMI group compared with those in the normal-BMI group. These differences remained significant after adjusting for age, cycle day, and AMH levels (−54.7 [95% CI, −89.1 to −20.3], $P = .002$ for inhibin B and −32.7 [95% CI, −60.7 to −4.7], $P = .023$ for E2). Thus, despite similar FSH levels, pulse amplitude, and frequency in both normal- and high-BMI groups (Fig. 1D), FSH-induced increases in both E2 and inhibin levels were significantly attenuated in women with high BMI. However, we note that in response to pulsatile IV rFSH treatment, day 2 serum E2 (99.1 ± 8) and inhibin B (126.3 ± 10) in the high-BMI women did achieve levels (pg/mL ± standard error of mean) comparable with those observed at baseline (79.3 ± 11.1 and 125.7 ± 11.1, respectively) in the normal-BMI group (Fig. 3).

Relationship Between Degree of Obesity and Ovarian Response

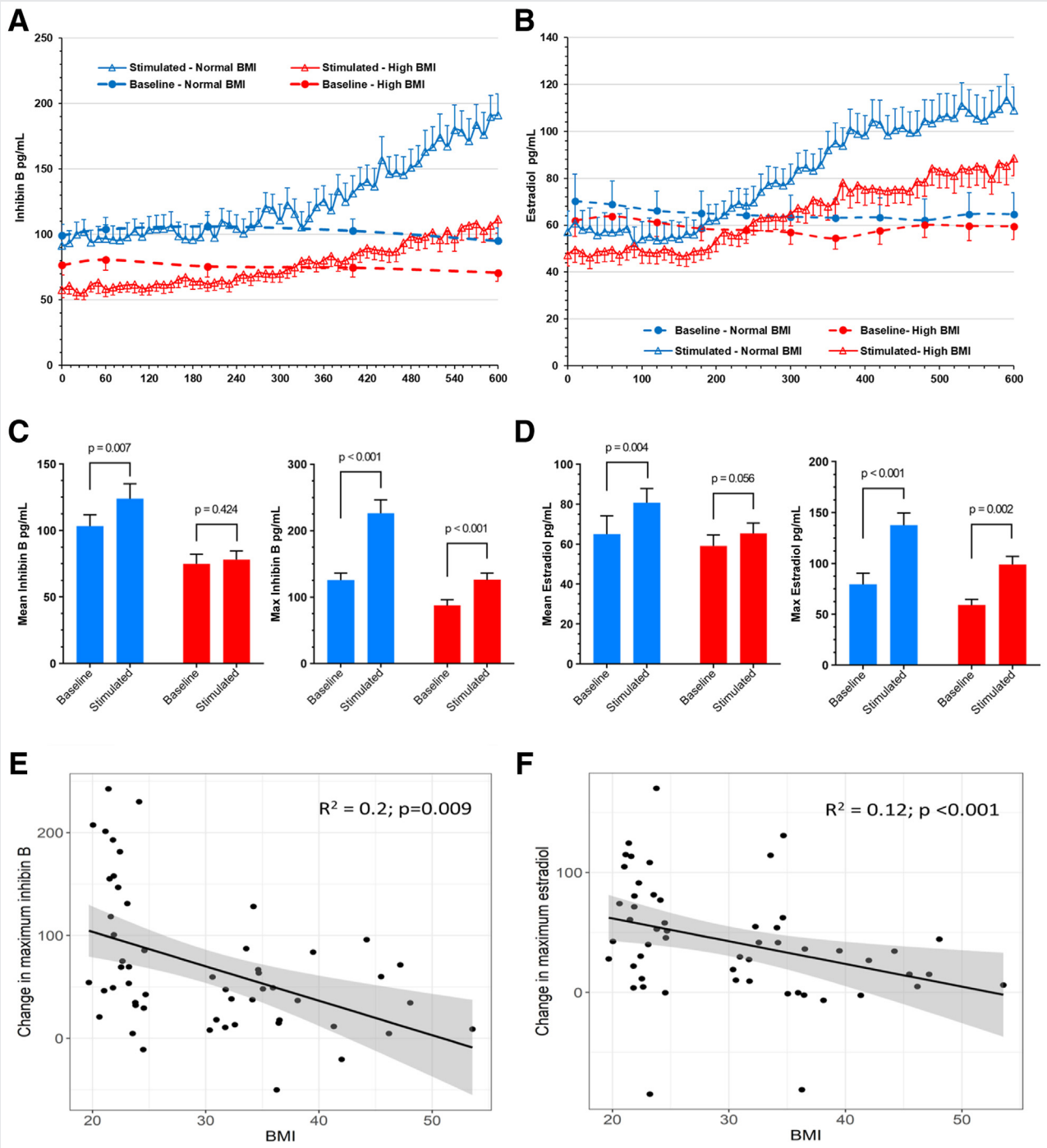
We then examined the relationship between BMI and change in the maximum inhibin B and E2 levels between baseline and the FSH-stimulated days (Fig. 3E and F). A significant correlation was observed between BMI and the change in maximum E2 level (R^2, 0.12; $P < .001$) and inhibin B (R^2, 0.20; $P = .009$). Linear regression demonstrated a 2.82-pg/mL (95% CI, −4.68 to −0.96; $P = .004$) decrease in maximum inhibin B response to FSH (stimulated-baseline) for every unit increase in BMI, adjusted for age, cycle day, and AMH. Similarly, a 1.71-pg/mL (95% CI, −3.21 to −0.20; $P = .027$) adjusted decrease in maximum E2 response to FSH per unit increase in BMI was observed.

DISCUSSION

We have developed an in vivo model to address the specific role of FSH in the female hypothalamic-pituitary-ovarian axis and examined the effects of pulsatile exogenous FSH on reproductive hormones in obese compared with those in normal-weight women. Multiple prior studies have characterized obesity as a state of relative hypogonadotropic hypogonadism with decreased gonadotropin levels, an attenuated response to GnRH stimulation (16–19), and lower levels of progesterone, E2, and their urinary metabolites (3, 12, 20). In addition, women with obesity undergoing IVF require higher gonadotropin doses and longer stimulation time yet still exhibit lower oocyte yield and quality (21) and adverse changes in the follicular environment (22). Similarly, animal models of obesity have shown smaller oocyte size, ovarian mitochondrial dysfunction, increased endoplasmic reticulum stress markers, and elevated relative oxygen species levels (21). Our study demonstrates that although pulsatile IV rFSH can compensate for the deficit in pituitary gonadotropin secretion and improve ovarian response in women with obesity, there remains a state of relative ovarian dysfunction that is exacerbated by increasing BMI in this model.

Lower exogenous FSH absorption in obese women is well documented for subcutaneous and intramuscular administration (23, 24). We attempted to correct these abnormal FSH pharmacodynamics in obese women and the observed deficit in FSH secretion (3, 12, 17, 18) by superimposing pulsatile exogenous IV rFSH, postulating that it would restore normal inhibin B and E2 levels. We found that despite achieving equal FSH serum levels and identical pulse amplitude and frequency, women with obesity exhibited lower E2 and inhibin B serum levels than normal-weight women. These effects were observed in linear regression models even after adjusting for differences in age, cycle day of study, and AMH. Further, inhibin B and E2 responses to pulsatile exogenous rFSH were inversely related to BMI. Analysis of the pharmacokinetics of FSH in our study cohort did not find a difference in clearance or volume of distribution that could explain the decreased ovarian response. Thus, our data show that short-term pulsatile rFSH does not fully correct the relative hypogonadism characteristic of obesity, indicating a deficit in ovarian response to gonadotropins, in addition to the previously reported pituitary dysfunction (12, 16, 18). Although women with obesity exhibited a significantly attenuated ovarian response, exogenous IV rFSH administration did result in an increase in inhibin B and E2 levels comparable with those of normal-weight women at baseline. This suggests that

FIGURE 3



Serum (**A**) inhibin B and (**B**) estradiol levels in normal and high body mass indices (BMIs) during the baseline (dashed lines) and the stimulated days (solid lines). The inhibin B and estradiol levels were measured at the indicated 5 time points on study day 1 and every 10 minutes on study day 2. The mean and maximum levels of (**C**) inhibin B and (**D**) estradiol at baseline and the follicle-stimulating hormone–stimulated days, in the normal- and high-BMI groups. Data are the means of 27 participants per group; the error bars are the standard errors of the mean. Change in the difference between the baseline and follicle-stimulating hormone–stimulated maximum (**E**) estradiol and (**F**) inhibin B plotted against the participant's BMI. The shaded area indicates the 95% confidence intervals.

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pulsatile rFSH can partially compensate for the observed relative hypogonadotropism of obesity (12, 13, 18) and potentially mitigate for ovarian dysfunction that may underlie the decreased IVF success rates and adverse pregnancy outcomes (6–11).

In considering limitations of our study, we note that the women with obesity were older than their normal-weight counterparts. However, both cohorts were of reproductive age and had regular cycling, and serum AMH levels were not different. The study protocol was identical for normal- and high-BMI groups but we acknowledge that diurnal variation in hormones could contribute to observed differences within groups. However, reports of circadian regulation of E2 and gonadotropins are inconsistent, and diurnal variation appears minimal in the early follicular phase (25, 26). Although small declines in nocturnal LH and FSH secretion have been reported (27), these occurred primarily after midnight, outside of our sampling window. We found no reports of diurnal inhibin variation in women. Although we observed increased inhibin B and E2 levels in response to IV rFSH administration in women with obesity, the levels only reached those of baseline of normal-weight women. Thus, there remains a significant impairment in ovarian responsiveness, indicating that acute pulsatile IV FSH cannot fully compensate for the chronic ovarian suppression characteristic of women with obesity under these study conditions. Future studies should consider increasing the duration of rFSH treatment and correlating responses with age, AMH, and antral follicle counts (AFCs) as indicators of ovarian functional status. In addition, it is possible that higher-amplitude gonadotropin pulses and total exposure (in the form of higher IV doses of rFSH, stratified by BMI) may further improve ovarian responsiveness in women with obesity (28). We did not measure AFC; however, it was shown previously that although women with obesity exhibited lower inhibin B levels, AFC was not significantly different compared with that in normal-weight women. This suggests that ovarian reserve is not impaired in obesity and that the apparent ovarian endocrine dysfunction is not attributable to decreased follicle number. Finally, our study design isolated the effect of FSH on ovarian function by suppressing endogenous gonadotropins, and although LH levels are typically low during the early follicular phase and FSH is primarily responsible for follicular growth and estrogen production, we cannot exclude a complementary, contributory role for LH (29).

Our model used a modified cetrorelix protocol because a prior study using the typical 3-mg subcutaneous dose to suppress gonadotropins observed a rebound in LH in approximately half of women with obesity but not in normal-weight women within 14 hours after cetrorelix administration (15). The obese group exhibited significantly decreased distributional half-life and increased clearance of cetrorelix. Herein, we demonstrate that an additional booster dose to augment cetrorelix levels successfully circumvented this possible escape from cetrorelix suppression in women with a high BMI. Our results show comparable cetrorelix levels in both normal- and high-BMI groups with sustained endogenous LH suppression for the duration of the study. Serum FSH levels were reduced equally in both cohorts to levels consistent with previous observations (30). These data demonstrate that endogenous gonadotropins can be effectively suppressed, in both women with normal and high BMIs, with appropriate cetrorelix dosing.

In summary, our results demonstrate a significant decrease in ovarian response to FSH in obesity. However, we also show that pulsatile IV rFSH administration can circumvent issues with pharmacokinetics of subcutaneous injection in women with obesity, thereby partially compensating for this intrinsic deficit, resulting in FSH-induced E2 and inhibin levels comparable with those of normal-weight women at baseline. The use of FSH pumps to deliver IV pulses over extended periods with dosing on the basis of BMI merits further exploration. Such approaches hold promise for assisted reproductive technology procedures for women with obesity and infertility to improve oocyte yield, quality, and pregnancy outcomes.

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Efectos del tratamiento hormonal folículo estimulante intravenoso pulsátil en la función ovárica en mujeres con obesidad

Objetivo: Establecer condiciones para la supresión hipotalámica efectiva en mujeres con índice de masa corporal (BMI) normal y alto y probar la hipótesis de que la administración intravenosa (IV) de hormona folículo estimulante recombinante (rFSH) pulsátil puede superar la evidencia clínicamente disfuncional del eje pituitario-ovárico en mujeres con obesidad.

Diseño: Estudio intervencional prospectivo.

Lugar: Centro médico académico.

Paciente(s): Veintisiete mujeres con peso normal y 27 mujeres con obesidad, que eran eumenorréicas y de 21-39 años.

Intervención(es): Estudio de muestra de sangre frecuente de dos días, en fase folicular temprana, antes y después de la supresión de gonadotropinas con cetrorelix y la administración IV de rFSH pulsátil exógena.

Principal(es) Medida(s) de Resultado(s): Niveles de inhibina B sérica y estradiol (E2) (basal y estimulados por rFSH).

Resultado(s): Un protocolo antagonista modificado de hormona liberadora de gonadotrofina suprimió efectivamente la producción de gonadotrofina endógena en mujeres con BMIs normal y alto, brindando un modelo para direccionar el rol funcional de FSH en el eje hopotalámico-pituitario-ovárico. El tratamiento IV rFSH resultó en niveles séricos equivalentes y farmacodinámicos en mujeres con peso normal y aquellas con obesidad. Sin embargo, las mujeres con obesidad mostraron niveles basales reducidos de inhibina B y E2 y una respuesta significativamente disminuida a la estimulación FSH. A pesar de este déficit observado en la función ovárica, el tratamiento IV rFSH pulsátil en mujeres con obesidad resultó en niveles de E2 y inhibina B comparable con aquellos en mujeres con peso normal, en ausencia de estimulación de FSH exógena.

Conclusión(es): A pesar de la normalización de los niveles y pulsatilidad de FSH, por su administración IV exógena, mujeres con obesidad demostraron disfunción ovárica con respecto a la secreción de E2 e inhibina B. FSH pulsátil puede corregir parcialmente el hipogonadismo hipogonadotrópico relativo de obesidad, de este modo brindando una estrategia potencial de tratamiento para mitigar algunos de los efectos adversos de BMI alto en fertilidad, reproducción asistida, y resultados de embarazos.