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SHORT REPORT

Women's Health Research and Hormone Replacement Therapy and Menopause

Oral contraceptive pill phase does not influence muscle protein synthesis or myofibrillar proteolysis at rest or in response to resistance exercise

Lauren M. Colenso-Semple,[1] James McKendry,[1,2] Changhyun Lim,[1,3] Philip J. Atherton,[4,5] Daniel J. Wilkinson,[4] Kenneth Smith,[4] and Stuart M. Phillips[1,6]

[1]*Exercise Metabolism Research Group, Department of Kinesiology, McMaster University, Hamilton, Ontario, Canada;* [2]*Food, Nutrition and Health, Faculty of Land and Food Systems, The University of British Columbia, Vancouver, British Columbia, Canada;* [3]*Population Health Sciences Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, United Kingdom;* [4]*MRC/ARUK Centre for Musculoskeletal Ageing Research and National Institute of Health Research, Biomedical Research Centre, School of Medicine, University of Nottingham, Nottingham, United Kingdom;* [5]*Faculty of Sport and Health Science, Ritsumeikan University, Kyoto, Japan; and* [6]*Department of Sport and Exercise Science, Institute of Sport, Manchester Metropolitan University, Manchester, United Kingdom*

Abstract

There is speculation that the use of oral contraceptive pill (OCP) affects skeletal muscle biology and protein turnover in response to resistance exercise; however, research in this area is scarce. We aimed to assess, using stable isotope tracers and skeletal muscle biopsies, how second-generation OCP phase affected muscle protein synthesis and whole body proteolysis. Participants ($n = 12$) completed two 6-day study phases in a randomized order: an active pill phase (active; *week 2* of a monthly active OCP cycle) and an inactive pill phase (inactive; final week of a monthly OCP cycle). They performed unilateral resistance exercise in each study phase, exercising the contralateral leg in the opposite phase in a randomized, counterbalanced order. The active phase myofibrillar protein synthesis (MPS) rates were $1.44 \pm 0.14\%\cdot day^{-1}$ in the control leg and $1.64 \pm 0.15\%\cdot day^{-1}$ in the exercise leg ($P < 0.001$). The inactive phase MPS rates were $1.49 \pm 0.12\%\cdot day^{-1}$ in the control leg and $1.71 \pm 0.16\%\cdot day^{-1}$ in the exercise leg ($P < 0.001$), with no interaction between phases ($P = 0.63$). There was no significant effect of OCP phase on whole body myofibrillar proteolytic rate (active phase $k = 0.018 \pm 0.01$; inactive phase $k = 0.018 \pm 0.006$; $P = 0.55$). Skeletal muscle remains equally as responsive, in terms of stimulation of MPS, during active and inactive OCP phases; hence, our data do not support a proanabolic or catabolic, based on myofibrillar proteolysis, effect of OCP phase on skeletal muscle in females.

NEW & NOTEWORTHY We discovered that women taking a second-generation oral contraceptive pill (OCP) showed no difference in integrated daily muscle protein synthesis or whole body myofibrillar proteolysis in the active or placebo pill phases of the pill cycle. Our data show that OCP phase neither influences skeletal muscle protein turnover in females and nor supports a marked procatabolic or anabolic effect.

anabolism; female; protein turnover; resistance exercise

INTRODUCTION

Premenopausal females are frequently excluded from exercise physiology research, with an often-cited reason being the potential for the effects of menstrual cycle (MC) hormones or oral contraceptive pills (OCP) on the outcomes (1). Although the primary purpose of ovarian hormones [estradiol (E2) and progesterone (P4)] is for reproductive function, it has been proposed that E2 may be proanabolic and involved in pathways and processes that influence muscular adaptations to exercise (2). In contrast, the presence of P4 has been proposed to antagonize the action of E2 (3). Despite this speculation, we recently showed that MC phase does not affect rates of MPS or whole body myofibrillar proteolysis (4). We have also pointed out that P4 is more androgenic than E2, which conflicts with the notion that high P4 in the luteal phase creates a catabolic environment (3, 5, 6).

Hansen et al. studied the effects of OCP on myofibrillar protein synthesis (MPS) (7) and tendon and muscle connective tissue synthesis (8). These authors reported lower MPS and tendon as well as muscle (and possibly bone based on indirect biomarkers) connective tissue protein synthesis in OCP users (8). When data were split into those taking second- versus third-generation OCP, Hansen et al. (7, 8) concluded

Correspondence: S. M. Phillips (phillis@mcmaster.ca).
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that the lower MPS was predominantly due to third-generation OCP users ($n = 7$) who showed a marked lowering of MPS versus those taking second-generation OCP ($n = 4$). Notably, rates of myofibrillar proteolysis were also determined using microdialysis and reported to be no different between OCP users and controls and were unaffected by OCP generation (7). These were short-term studies lasting several hours, and the exercise used was a high-intensity single-leg kicking (7, 8); thus, the effects over longer periods and with a more anabolic exercise stimulus, such as resistance exercise training (RET), are less well known. Given that the net balance of MPS and muscle protein breakdown (MPB), along with other processes (9), contribute to RET-induced hypertrophy, there is an important research gap.

It is unknown how OCP use may affect RET outcomes such as hypertrophy and strength; however, speculation is that since OCP use downregulates the production of endogenous E2 and P4, this suppression may affect molecular mechanisms that are important in hypertrophy and somehow suppress normal adaptation (2, 10). RET studies involving females taking OCP have produced mixed results (11–15); however, generally, no significant differences were observed between OCP users and nonusers regarding RET-induced muscle hypertrophy. Nolan et al. (10) systematically reviewed how OCP affects RET outcomes and found no consistent effect on hypertrophy, power, or strength.

The purpose of this study was to investigate MPS and myofibrillar proteolysis in response to resistance exercise in females on OCP. Subjects were assessed during their active pill phase and the inactive phase of second-generation OCP. We aimed to test the hypothesis that muscle protein synthesis would increase in response to resistance exercise in both phases but with no differences between phases.

MATERIALS AND METHODS

The study was approved by the Hamilton Integrated Research Ethics Board (project number: 14067) and conformed to the standards for the use of human subjects in research as outlined by the Canadian Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans—TCPS 2, 2022 (https://ethics.gc.ca/eng/policy-politique_tcps2-eptc2_2022.html) and the Declaration of Helsinki (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/). Each participant was informed about the purpose of the study, experimental procedures, and potential risks before written informed consent was obtained. The trial was registered with the National Institutes of Health at http://www.clinicaltrials.gov repository as NCT05347667.

Participants

Healthy young females ($n = 12$) were recruited for the study. Eligible participants were between the ages of 18 and 30 yr and in good health (as determined by a medical screening questionnaire). All participants reported taking second-generation OCP (Allese or Alysena) for at least 6 mo before taking part in the study. Participants were excluded if they: *1*) suffered from an orthopedic, cardiovascular, pulmonary, renal, liver, infectious disease, immune, metabolic, or gastrointestinal disorder likely to impact study outcomes; *2*) took medications known to affect protein metabolism (i.e., corticosteroids, nonsteroidal anti-inflammatory drugs, or high strength acne medication, testosterone replacement); *3*) used tobacco or cannabis or tobacco/cannabis-related products (smoking or vaping); *4*) had been previously diagnosed with a menstrual cycle disorder, polycystic ovarian syndrome, or endometriosis. Participants' characteristics are shown in Table 1.

A sample size of nine subjects, using a crossover design, was determined based on an a priori power analysis calculated using G*power (Version 3.1.9.6, Franz Faul, Kiel University, Germany) based on our previous trial (4) (target alpha of 0.05 and power of 0.80) with a small effect size of 0.2 to be sufficient to detect a change of ~25% in muscle protein synthesis, which we deemed to be physiologically relevant. To protect power and account for any dropouts, we included 12 subjects.

Study Overview

Participants completed two 6-day study phases in a randomized order during each phase of their OCP cycle: active pill phase (*days 9–14*) and inactive pill phase (*days 23–28*). A schematic of the study protocol is shown in Fig. 1.

Participants completed a general health questionnaire to indicate their current health status and medication use to ensure eligibility for the study. Height and body mass were assessed using a calibrated stadiometer and scale. Participants underwent a dual X-ray absorptiometry (DXA; GE-Lunar iDXA; Aymes Medical, Toronto, ON) scan to assess body composition. DXA-derived lean mass was used to determine oral dose of deuterated water (D_2O) dosing. Unilateral knee extension 10 repetition maximum (RM) was assessed for each leg to determine the starting load for subsequent study visits.

Much of the details of the protocol and methods we used, such as RET protocol and the calculation of the rates of MPS and whole body myofibrillar proteolysis, were reported in our previous paper (4); thus, we provide only relevant details here. The salient difference between our previous protocol (4) and this study was the timing of the study protocols, which was completed within one OCP cycle and took place during the active and inactive pill

Table 1. *Participant characteristics and serum hormone levels*

Age, yr	20 ± 2			
Height, cm	164 ± 2			
Body mass, kg	61.9 ± 8.3			
BMI, kg·m^{-2}	22.9 ± 2.3			
Lean mass, kg*	40.8 ± 4.9			
Muscle mass, kg**	22.3 ± 1.2			
	Inactive phase (OC cycle *days 23–28*)		**Active phase (OC cycle *days 9–14*)**	
	visit 1	*visit 6*	*visit 1*	*visit 6*
E2, pM	97 ± 26	153 ± 47	108 ± 50	101 ± 29
P4, nM	9 ± 3	7 ± 2	8 ± 3	7 ± 3
LH, IU·L^{-1}	3 ± 3	4 ± 3	3 ± 2	2 ± 3

Values are means ± SD. *Derived from DXA. **Derived from D_3-creatine. BMI, body mass index; DXA, dual X-ray absorptiometry; E2, estradiol; OC, oral contraceptive; P4, progesterone; LH, luteinizing hormone.

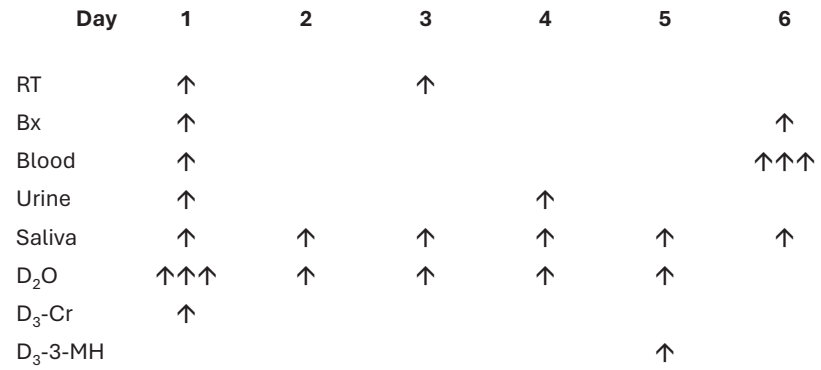

Figure 1. Schematic depiction of the protocol that was repeated in each OCP phase. The exercised limb was randomly selected and switched in a counterbalanced manner, as the phase in which each participant began the protocol. Bx, muscle biopsy; D_2O, oral dose of deuterated water; D_3Cr, oral dose of deuterated creatine; D_3-3-MH, oral dose of deuterated 3-methyl histidine; OCP, oral contraceptive pill; RT, resistance training.

phases. Participants arrived for the first study visit after an overnight fast. Following a pregnancy test, subjects provided a baseline saliva sample (to obtain baseline body water enrichment), a baseline urine sample (to measure D_3-creatinine enrichment for muscle mass; see below), a blood sample (to assess serum hormones), and a baseline muscle biopsy (Bx) from the *vastus lateralis* of the control leg (Fig. 1). The control (nonexercised) leg was randomly determined for *phase 1*, and the contralateral leg served as the control for *phase 2*. On the priming dose day, participants were given three (1.25 mL·kg^{-1} lean mass) aliquots of 70 atom % D_2O to consume 30 min apart. An oral dose of 30 mg D_3-Creatine was included in the third aliquot of D_2O to assess skeletal muscle mass, as previously described in detail (6, 16). Participants performed three sets of 10 unilateral knee extensions to volitional fatigue, defined as an inability to complete a repetition through the full range of motion. If the participant completed >12 or <8 repetitions, the load was adjusted, up or down, accordingly.

Participants returned to the laboratory 48 h after *visit 1* to provide a urine sample and perform three additional sets of unilateral knee extensions, as outlined above. Participants returned to the laboratory 72 h after *visit 1* to provide a urine sample and 18 h prior to the scheduled *visit 5* to consume 10 mg of D_3-3-methylhistidine (3MH) dissolved in water. After an overnight fast, they reported to the laboratory for the final visit. Muscle biopsies were taken from the exercise and control legs. Blood samples were collected hourly for 5 h to assess plasma D_3-3MH and measured whole body myofibrillar proteolysis, as described earlier (4, 6, 16, 17).

Blood Analysis

Blood samples were analyzed using the Ortho Vitros MicroWell, using the VITROS 5600 Integrated System that provides enhanced chemiluminescence detection for serum estradiol [E2; pmol·L^{-1}; by competitive immunoassay; interassay coefficient of variation (CV) < 4%], progesterone (P4; nmol·L^{-1}; by competitive immunoassay; interassay CV < 6%), and luteinizing hormone (LH; IU·L^{-1}; by noncompetitive immunometric assay; interassay CV < 5%) by Hamilton Regional Laboratory Medicine and D_3-3-methylhistidine enrichment, as described earlier (4, 6, 16, 17).

Deuterium Oxide

The incorporation of deuterium (as D_2O) into muscle protein-bound alanine was assessed to quantify MPS rates (6, 16–18). The protocol consisted of one loading day and four maintenance days with the goal of enriching and maintaining the body water pool (Fig. 1).

Muscle Biopsies

Muscle biopsy samples were obtained on seven occasions using a 5-mm Bergstrom needle modified for manual suction under 1% xylocaine local anesthesia. The first biopsy site was ~15 cm above the patella, and subsequent biopsy sites were spaced ~3–5 cm apart. Biopsies were taken from the control limb pre-exercise [*phase* (randomized to active or inactive) *1*, *visit 1*] and the control and exercise limbs (*phase 1*, *visit 5*; *phase 2*, *visit 1*; and *phase 2*, *visit 5*). Visible connective and adipose tissue were dissected from each specimen before being snap-frozen in liquid nitrogen and stored at −80°C.

Saliva Analysis

Saliva samples were obtained by gently chewing on a cotton swab for 2–3 min until completely saturated with saliva. Salivates were centrifuged at 1,500 *g* for 10 min and diluted in double distilled water (ddH_2O). Saliva samples were analyzed for ^2H (D) enrichment by cavity ringdown spectroscopy (L2130-i, Picarro Inc., Santa Clara, CA). Measurements were corrected for machine drift and background enrichment, and the ^2H (D) isotopic enrichments for saliva were converted to atom percentage excess using standard equations, as reported earlier (4, 6, 16, 17).

Myofibrillar Extraction

Snap-frozen muscle samples were homogenized using 5-mm stainless steel beads in a 2 mL Eppendorf (2 × 40 s at 20 Hz, TissueLyser, Hilden, Germany) with 500 μL fresh, ice-cold homogenization buffer {25 mM Tris buffer [Tris-HCl, Trizma Base, doubly distilled H_2O (ddH_2O) pH 7.2], one PhosStop Tablet (Roche, Switzerland), one complete (Roche) mini protease inhibitor tab, 100 μL TritonX-100}. Samples were then processed as described in our previous work (4, 17).

Integrated Myofibrillar Protein Synthesis

Ingestion of D_2O was used to label newly synthesized myofibrillar proteins (18). Myofibrillar protein synthesis rates were determined using the standard precursor-product method (19, 20). Total body water (saliva) deuterium (^2H) enrichment (converted to its natural log) was used as a surrogate for plasma alanine labeling (precursor). The change in

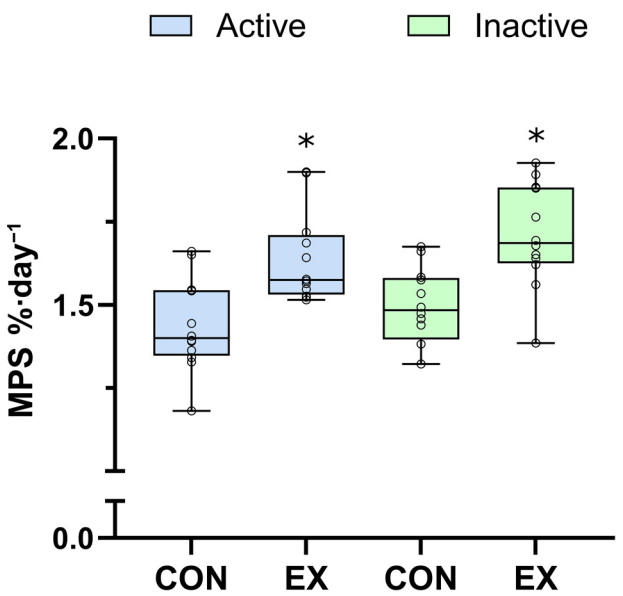

Figure 2. Integrated muscle protein synthesis in active and inactive phases. *Significant ($P < 0.001$) difference (main effect) between EX and CON. There was no significant effect of OCP phase nor an interaction between phases and conditions (all $P > 0.5$). CON, control; EX, exercised; OCP, oral contraceptive pill.

^{2}H enrichment (relative to ^{1}H) of muscle alanine (product) over time was used to calculate the myofibrillar fractional synthesis rates (4, 17).

Creatinine Enrichment

Samples were thawed at room temperature and had 250 μL of ice-cold acetonitrile added, then were vortexed, mixed, and cooled on ice for 30 min. Samples were then centrifuged at 17,000 *g* for 20 min. The supernatant was filtered through a 0.2 μm filter and transferred to vials ready for mass spectrometry analysis, as described earlier (4, 6, 16, 17). The estimated creatine pool size was divided by 4.3 g·kg^{-1}, which reflects the average concentration of creatine found in whole wet muscle tissue (21). Details of the analyses are provided in our previous papers (4, 6, 16, 17).

Plasma D_3-3-Methylhistidine

We have previously described the methods used for this analysis (4, 6, 16, 17). Briefly, plasma samples were defrosted and centrifuged at 1,200 *g* for 3 min. A 0–10% D_3-3-methylhistidine enrichment curve was prepared as a serial dilution. About 100 μL of plasma was deproteinized using 1 mL of MeCN: MeOH (1:1). Samples were vortex mixed and incubated at −20°C for 1 h. Samples were centrifuged at 20,800 *g* for 5 min at 4°C. The supernatant was dried down in a TechneBlock at < 40°C using nitrogen gas. Samples were resuspended using 100 μL MeCN:ddH_2O (65:35) and ready to be analyzed using high-performance liquid chromatography (HPLC; Dionex Ultimate3000, Thermo Scientific) mass spectrometry (MS; Q-Exactive, Thermo Scientific) with a Sequant ZIC-HILIC column (150 mm 200 Å pore size 5 μm particle size; Merck Millipore) using previously described methods (6, 16). The enrichment ratios were log-transformed to determine the decay rates (*k*), representative of the rate of whole body MPB (22).

Statistical Analysis

Data were analyzed using SPSS (IBM Corporation, Released 2023, IBM SPSS Statistics for Windows, Version 29.0.2.0 Armonk, NY: IBM Corporation) using a two-way ANOVA with repeated measures with OCP phase (active or inactive) and leg (exercise or control) as within-subject factors (all factors nested within subject). Significance was set at $P < 0.05$. Data are presented as means ± SD in tables and as box and whisker plots showing interquartile range, median, and upper and lower bounds in figures unless otherwise indicated.

RESULTS

Participants

Participants used daily monophasic pills (Alesse and Alysena) containing 0.02 mg ethinylestradiol and 0.1 mg levonorgestrel (*days 1–21*), with a 7-day inactive week (*days 22–28*). Their characteristics are shown in Table 1.

Hormones

Serum E2, P4, and LH were assessed in both phases. Data are presented in Table 1. There were no differences across any phase in any hormone measured (all $P > 0.4$).

Myofibrillar Protein Synthesis

The mean MPS rates in the active pill phase were 1.44 ± 0.14%·day^{-1} in the control leg and 1.64 ± 0.15%·day^{-1} in the exercise leg ($P < 0.001$). The inactive phase MPS rates were 1.49 ± 0.12%·day^{-1} in the control leg and 1.71 ± 0.16%·day^{-1} in the exercise leg ($P < 0.001$). The two-way ANOVA showed a main effect of condition (leg, $P < 0.001$) but no significant effects of phase ($P = 0.48$; effect size 0.16) or interaction between phases ($P = 0.63$; effect size 0.12). The results are presented in Fig. 2.

Myofibrillar Protein Breakdown

The mean rate (*k*) of whole body myofibrillar proteolysis was 0.018 ± 0.01 in the active phase and 0.018 ± 0.006 in

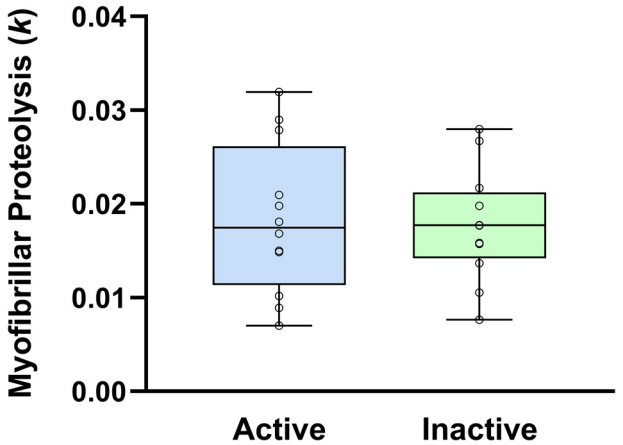

Figure 3. Whole body myofibrillar protein breakdown rate (*k*) in active and inactive OCP phases. OCP, oral contraceptive pill.

the inactive phase ($P = 0.55$). The results are presented in Fig. 3.

DISCUSSION

Although there was a strong and consistent effect of RET on MPS in both phases, the response did not differ between the active and inactive OCP phases (Fig. 2). We also observed no difference in whole body myofibrillar proteolysis (Fig. 3), which would include and may be predominantly skeletal muscle-derived (22). Our work shows that females taking OCP derive no specific anabolic advantage, nor are they in a procatabolic state in any particular phase. We also note that compared with our recent data (using an identical design) from naturally cycling women (4), we observed no marked differences between resting or postexercise anabolic and catabolic rates. In fact, combining datasets and running statistical analyses, including a between factor for OCP use and either phase of the MC, showed no pill-by-phase interaction and only main effects for exercise (exercise > rest; data not shown). Thus, our data show, in accordance with meta-analytic analyses of cross-sectional OCP effects (10) and phase-specific effects across the MC (5, 23), that there are no specific differences in terms of muscle anabolism or catabolism in response to RET related to OCP use.

As expected, endogenous ovarian hormones were downregulated, compared with normally cycling females (4), in the OCP cohort across all time points. Our data indicate that a week of inactive pills was insufficient to restore the endogenous hormone profile of a naturally menstruating individual. Despite the lower endogenous hormone concentrations synthetic hormones have a high affinity for andogen receptors, and yet we did not see a change in the muscle protein synthetic or whole body myofibrillar proteolysis responses.

We acknowledge that our data are short-term (days) but propose that they offer new and deeper insight than acute infusions of isotopes taking place over hours (7, 8). Longer-term trials and the use of third- and fourth-generation OCP, as well as intrauterine progesterone-emitting contraception, would be interesting avenues in which to apply similar methods to those we have used here. We note, however, that these methods of contraception have been compared in vascular and cellular physiology and showed statistically significant but physiologically trivial differences (24). We hypothesize that since third- and fourth-generation OCPs have even less androgenic forms of progesterone (25) than second-generation OCPs, it is unlikely that there would be marked anabolic or catabolic effects of these OCPs compared with earlier generations (5).

Our results are largely in line with those of Hansen et al. (7), who assessed MPS in a group of naturally cycling participants compared with a group of habitual OCP users, reporting that MPS and MPB did not differ between groups. However, MPS was significantly lower in a subgroup ($n = 7$) of third generation but not second generation ($n = 4$) OCP users compared with the naturally cycling group ($n = 9$). Further investigations into other forms of contraception, including intrauterine devices, would be an interesting avenue to pursue.

We conclude that second-generation OCP phase does not alter muscle anabolic capacity or influence myofibrillar proteolysis in response to RET. Our results concur with reviews and meta-analyses showing no influence of OCP or MC-related changes in sex hormones on muscle propensity for anabolism (3, 5, 10, 23). Longer-term trials and studies of other contraceptive methods will be needed to confirm whether our findings on day-to-day protein turnover are generalizable and align with RET phenotypes.

DATA AVAILABILITY

Data will be made available upon reasonable request.

GRANTS

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DISCLOSURES

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Stuart Phillips is an editor of *Journal of Applied Physiology* and was not involved and did not have access to information regarding the peer-review process or final disposition of this article. An alternate editor oversaw the peer-review and decision-making process for this article.

AUTHOR CONTRIBUTIONS

L.M.C.-S. and S.M.P. conceived and designed research; L.M.C.-S., J.M., and C.L. performed experiments; L.M.C.-S., J.M., C.L., P.J.A., D.J.W., K.S., and S.M.P. analyzed data; L.M.C.-S. and J.M. interpreted results of experiments; L.M.C.-S. prepared figures; L.M.C.-S. and S.M.P. drafted manuscript; L.M.C.-S., J.M., C.L., P.J.A., D.J.W., K.S., and S.M.P. edited and revised manuscript; L.M.C.-S., J.M., C.L., P.J.A., D.J.W., K.S., and S.M.P. approved final version of manuscript.

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