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Oral contraceptive use and menstrual cycle influence acute cerebrovascular response to standing

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ABSTRACT

Purpose: To determine if the menstrual cycle and oral contraceptives (OC) influence responses to acute orthostatic stress and if these factors are clinically relevant to the diagnosis of initial orthostatic hypotension (iOH).
Methods: Young, healthy women were recruited, including OC users (n = 12) and non-users (NOC; n = 9). Women were tested during the low hormone (LH; placebo pills; days 2–5 natural cycle) and high hormone (HH; active dose; days 18–24 natural cycle) menstrual phases. Changes in mean arterial pressure, cardiac output, heart rate, the 30:15 heart rate ratio and cerebrovascular resistance indices within 30 s of standing were examined.
Results: There were no effects of OC or menstrual cycle on hemodynamic responses during standing (all $p>0.05$). In the LH phase, OC users had a greater fall in mean middle cerebral artery blood velocity (MCA_V) compared to NOC ($p<0.05$). However, this was reversed in the HH phase, where OC users had a reduced fall in mean MCA_V ($p<0.05$). Interestingly, 8 women (OC and NOC) had drops in systolic/diastolic blood pressure meeting the criteria for iOH, and 7 of those 8 women displayed this drop in a single phase of the menstrual cycle.
Conclusion: Our results indicate that chronic versus acute OC use (i.e., long-term use observed via LH phase versus short-term use observed via HH phase) have opposing effects on cerebral blood velocity during standing. Further, our results highlight that multiple assessments across the cycle may be necessary to accurately diagnose iOH, as most women met the diagnostic criteria during a single menstrual phase.

1. Introduction

Orthostatic stress causes a caudal fluid shift, and in those with intolerance, normal physiological responses are insufficient to maintain blood pressure. This large fluid shift redistributes blood from central and cerebral circulation to the periphery, thus, cerebral blood flow is diminished, and individuals may experience symptoms of cerebral hypoperfusion, such as lightheadedness, dizziness or nausea (Madsen et al., 1998), and this could ultimately result in syncope. The incidence of syncope or postural orthostatic hypotension (POTS) peaks during puberty (ages 15–19) and is more prevalent in females (Driscoll et al., 1997; Low et al., 2009; Shaw et al., 2019). The fact that women are more likely to experience orthostatic intolerance (OI) and that onset generally peaks around puberty suggests that sex hormones such as estrogen and progesterone may play a role. Since these hormones dramatically decrease during menopause, and younger aged post-menopausal women (<60 years) have a greater blood pressure response to orthostatic stress (Edgell et al., 2012), this potentially suggests that female sex hormones may influence their experience of syncope or OI.

Estrogen is a potent vasodilator where acute estradiol infusion increases nitric oxide bioavailability, promoting smooth muscle relaxation or vasodilation (Guetta et al., 1997; Sudhir et al., 1996). Further, sympathetic vasoconstriction is attenuated by enhanced β2-adrenergic receptor activity in young women compared to men and post-menopausal women (Hart et al., 2011). In fact, blunted peripheral vasoconstriction contributes to OI in women (Wenner et al., 2013). Interestingly, oral contraceptive (OC) users experience even greater β2-adrenergic receptor-mediated vasodilation than non-users (Limberg et al., 2016), potentially indicating a role in orthostatic tolerance. OC exposes users to greater hormone levels than that of endogenous hormones in naturally cycling women (e.g., 1/16–8 times greater progestin exposure than endogenous progesterone and similar – 1.5 times greater ethinyl estradiol exposure depending on OC formulation) (Lovett et al., 2017). Due to the increased hormone exposure in OC users, this may exacerbate the

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experience of hormone-related factors that influence orthostatic tolerance. In OC users and naturally cycling women, estrogen and progesterone levels fluctuate throughout the menstrual cycle, and previous studies indicate that women with and without OI have greater feelings of lightheadedness during the low hormone (LH; days 1–5) phase of the menstrual cycle compared to the high hormone (HH; days 15–22) phase (Muppa et al., 2013; Heggs et al., 2012). However, these studies were completed via survey and consisted of a combination of women taking/not taking hormonal contraceptives. It is worth considering that the chronic influence of estrogen and progesterone via pharmaceutical exposure could have a different influence than the acute monthly influence during the HH phase.

The vasodilatory effects of estrogen may be countered by increased total sympathetic activity during orthostatic stress in the HH phase (Carter et al., 2009; Fu et al., 2009) and could contribute to why women are more likely to faint during the LH phase. OC users do not have cyclical fluctuations in sympathetic activity (Carter et al., 2010); thus, their elevated vasodilatory capacity may be unopposed and could contribute to OI. We previously found minimal influences of both OC use and menstrual cycle on the cardiovascular, cerebrovascular and autonomic responses after 10 min of standing (Abidi et al., 2017); however, we did not investigate the acute response to the first 30 s of standing when symptoms of initial orthostatic hypotension (iOH) may be evident. iOH is characterized by a drop in systolic blood pressure (BP) by >40 mmHg or in diastolic BP by >20 mmHg that occurs within the first 30 s following a postural transition (Freeman et al., 2011). Therefore, the current study aimed to determine the effects of the menstrual cycle and OC use on the cardiovascular and cerebrovascular response to initial postural transition. We hypothesized that during acute standing, women in the LH phase of the menstrual cycle would display a greater drop in mean arterial pressure (MAP) and cerebral blood flow indices compared to the HH phase. Furthermore, since OC users were previously reported to have an elevated heart rate variability (i.e. greater cardiac parasympathetic control) compared to non-users during posture change (Abidi et al., 2017), we hypothesized that a greater heart rate (HR) response to acute standing and a greater 30:15 HR ratio would be observed in women taking OCs. The 30:15 HR ratio is a standing response metric that reflects cardiac parasympathetic modulation by comparing the minimum to maximum HR during standing (around the 30th and 15th heartbeat, respectively)(Ewing et al., 1978); thus, the inclusion of this method could confirm the effects of OC on cardiac parasympathetic control.

2. Materials and methods

This is a secondary analysis of Abidi et al., 2017, which investigated the cardiovascular and cerebrovascular response to prolonged standing (10 min) compared to the current study investigating the acute response (within 30 s) in the same cohort of female participants. Ethics approval for the study was obtained via the Office of Research Ethics at York University and written informed consent was provided by participants prior to testing. Therefore, this research was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its amendments. The sample for the current study included young, healthy women with no history of cardiovascular or respiratory disease: 9 non-OC users (NOC; age 22 ± 2, height 157 ± 6 cm, body mass 59 ± 11 kg), and 12 OC users (age 22 ± 3, height 166 ± 5 cm, body mass 61 ± 6 kg). Additionally, OC users were only eligible if they had been on the same prescription of OC for the 3 months preceding their visit. Cerebrovascular measures were only available for 10 OC users due to signal quality concerns. Women were tested twice during the menstrual cycle, in the low hormone (LH) and high hormone (HH) phases. Trials were scheduled at the same time of day, and only women who completed both tests were included in this analysis. OC users were tested during the placebo pill week (LH) and during the third week of the active OC pill (HH); six were taking Tri-Cyclen [0.18, 0.215, and 0.250 mg of noregestimate and 0.035 mg of ethinyl estradiol (EE)], four were taking Alesse [100 μg of levonorgestrel and 0.020 mg of EE], one was taking Marvelon [0.15 mg of desogestrel and 0.03 mg of EE], and one was taking Novo-Cyprotenone/EE [2 mg of cyproterone acetate and 0.035 mg of EE]. The NOC group was tested from days 2–5 (LH) and days 18–24 (HH) of the natural menstrual cycle. The menstrual cycle was determined by self-report, after defining that day 0 of the menstrual cycle is the first day of menstrual bleeding. Only women reporting a regular 26–30 day cycle were tested. Twelve hours prior to testing, the consumption of fatty foods, caffeine, or alcohol, and any engagement in fatiguing physical exercise were avoided.

2.1. Experimental protocol

Participants made a single quick transition from a seated posture (maintained for 5 min) to a standing posture, with the assistance of a researcher if required. A Wii balance board was used to determine the exact time of standing as reported in the parent study (Abidi et al., 2017). Tests were terminated if systolic pressure fell below 70 mmHg or the participant experienced feelings of dizziness, nausea, or lightheadedness; however, this did not occur within the first minute of standing. Participants were equipped with a standard single-lead electrocardiogram (BioAmp, ADInstruments, CO, USA) to determine the R-R interval. Beat-to-beat BP and stroke volume were measured via volume clamp method, corrected for height at the heart level compared to the finger (Finometer Pro, Finapres Medical Systems, Amsterdam, The Netherlands) and calibrated to a standard manual BP measurement. Additionally, an arm sling was used to maintain the arm at the level of the heart during the postural transition. Cardiac output (Q) was determined from stroke volume and HR. End-tidal carbon dioxide ($ET\text{-}CO_2$) was continuously sampled via a fitted nasal cannula and was analyzed using infrared spectroscopy (VacuMed, Ventura, CA). To obtain blood velocity of the middle cerebral artery (MCA_V), a transcranial Doppler ultrasound probe (2 MHz; Multigon Industries, Yonkers, NY) was placed on the right temple and secured using a standard headband. A standardized search method was used to accurately identify MCA_V, which included probe placement, appropriate Doppler settings and expected velocity ranges of neighbouring arteries (Aaslid et al., 1982). All data was collected beat-to-beat and was acquired through a Powerlab acquisition device at a rate of 1000 Hz and recorded in Lab Chart Pro software (version 8.0, ADInstruments, CO, USA).

2.2. Data and statistical analysis

Prior to standing, baseline seated one-minute averages were obtained from the beat-to-beat data for all variables using LabChart Pro software. Within the first 30 s of standing (Fig. 1), the single heartbeat containing the nadir blood pressure or nadir MCAv response was determined. The hemodynamic and cerebrovascular responses during standing were determined at these time points, respectively (diastolic, systolic, and mean). The changes presented were calculated as the value at nadir minus the baseline average. The maximum and minimum HR responses were also determined within 30 s post-transition to upright posture and divided (30:15 ratio) as an indicator of cardiovagal function (Ewing et al., 1978). In parallel with the parent study, Abidi et al. (2017), multiple indices of cerebrovascular resistance were calculated to fully elucidate the relationships between OC use, the menstrual cycle and the incidence of OI. Cerebrovascular resistance index (CVRi) was calculated as mean arterial pressure (MAP)/mean MCA_V. Resistance Index (RI) was calculated as (systolic MCA_V-diastolic MCA_V)/systolic MCA_V. Pulsatility Index (PI) was calculated as (systolic MCA_V-diastolic MCA_V)/mean MCA_V. Resistance area product (RAP) was calculated as (MAP-diastolic blood pressure)/(mean MCA_V-diastolic MCA_V). Critical closing pressure (CrCP) was calculated as MAP-(mean MCA_V x RAP). All resistance indices used the nadir MCA_V for calculations. Beat-to-beat cerebrovascular conductance index (CVCi) was calculated by dividing

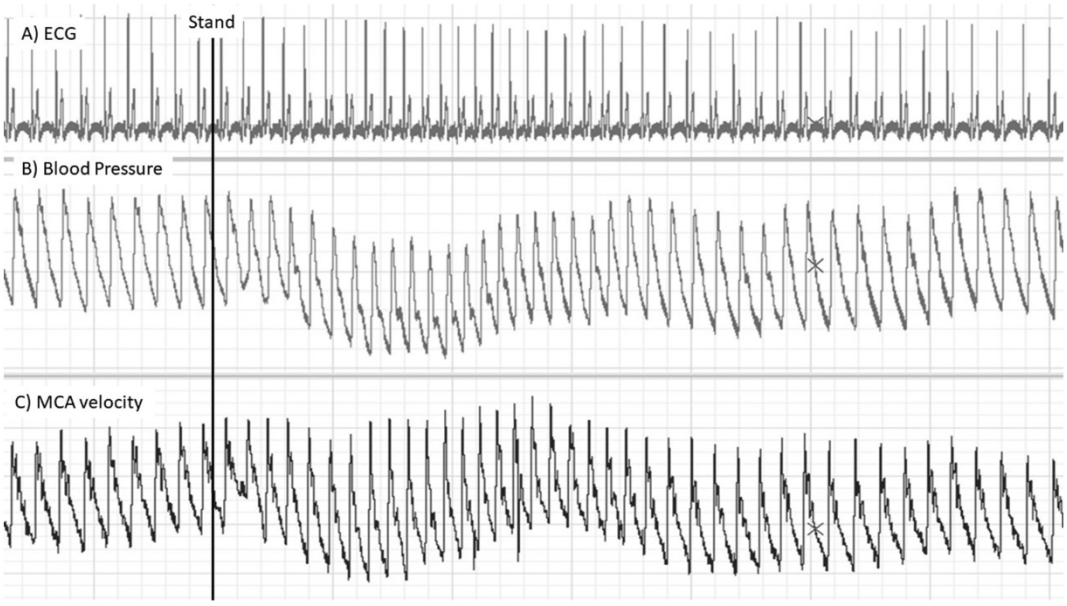

Fig. 1. Representative data illustrating the ECG (A), blood pressure (B) and middle cerebral artery (MCA) velocity (C) response for the first 30 s after postural transitions.

MCA_V by MAP to determine the rate of regulation (RoR) as an index of dynamic cerebral autoregulation. At the onset of the regulatory response (i.e. the time at which an increase in CVCi was observed immediately after standing (Labrecque et al., 2017; Lind-Holst et al., 2011)), the slope of the increase was calculated for 2.5 s. MAP was also calculated at this time. RoR was calculated as the (ΔCVCi/2.5 s)/[(Baseline MAP-MAP at time of RoR calculation)/Baseline MAP] (Aaslid et al., 1989; Ogoh et al., 2008).

Two-way (OC x Phase) repeated measures ANOVA were used for all changes in hemodynamic and cerebrovascular variables (menstrual cycle as repeated measure, OC as non-repeated measure). A three-way (OC x Phase x Posture) repeated measures ANOVA was used to determine the effects of these variables on ET-CO_2. Finally, a student *t*-test was used to compare the differences in the pressor and cerebrovascular responses of the individuals who met the criteria for iOH compared to those who did not (groups and phases combined). Post-hoc tests were conducted using the Holm-Sidak method, with Sidak corrections for multiple comparisons. The Shapiro-Wilk test was used to assess normality, and most values were normally distributed, except for baseline mean MCA_V and change in RI ($p < 0.051$). Effect sizes are reported for significant comparisons using Eta squared (η^2), calculated as the sum of squares between groups divided by the total sum of squares. A Fisher exact test was conducted on the frequency of iOH per phase and pill use. Statistics were completed using Sigmaplot 13.2 (San Jose, California, USA), and a value of $p < 0.05$ was considered statistically significant. Data are presented as mean ± standard deviation.

3. Results

Resting HR was higher in women in the HH phase of the menstrual cycle (Table 1, $p = 0.033$, $\eta^2 = 0.049$). There were no other resting hemodynamic or cerebrovascular differences between menstrual phases or OC use (Table 1, all $p > 0.05$). Neither OC use nor menstrual cycle phase influenced the MAP, HR, or Q response to acute standing (all $p > 0.05$; Fig. 2A–C). The 30:15 ratios during standing were 1.61 ± 0.27 for NOC-LH, 1.51 ± 0.16 for NOC-HH, 1.57 ± 0.24 for OC-LH, and 1.60 ± 0.18 for OC-HH; there were no main effects of OCs ($p = 0.78$) or menstrual phase ($p = 0.39$) or their interaction ($p = 0.12$). The diastolic MCA_V and systolic MCA_V responses to standing were not significantly affected by OCs or menstrual phase (all $p > 0.05$; Fig. 3A and B). The

Table 1
Baseline hemodynamic and cerebrovascular values.

	NOC		OC		P value		
	LH	HH	LH	HH	OC	Phase	OCxPhase
MAP (mmHg)	91 ± 17	96 ± 15	96 ± 17	88 ± 18	0.6	0.6	0.1
DBP (mmHg)	74 ± 17	77 ± 12	76 ± 18	8 ± 18	0.5	0.5	0.1
SBP (mmHg)	116 ± 17	122 ± 23	124 ± 16	117 ± 21	0.8	1.0	0.2
Q (L/min)	3.7 ± 0.9	4.0 ± 1.0	4.4 ± 1.3	4.6 ± 0.8	0.1	0.3	0.7
HR (bpm)	70 ± 9	75 ± 10*	71 ± 10	75 ± 11*	0.9	0.03	0.6
Mean MCA V_V (cm/s)	63 ± 12	62 ± 9	67 ± 15	60 ± 11	0.8	0.2	0.3
Diastolic MCA V_V (cm/s)	41 ± 10	41 ± 9	47 ± 10	38 ± 12	0.7	0.1	0.1
Systolic MCA_V (cm/s)	98 ± 16	100 ± 13	99 ± 21	96 ± 18	0.8	0.9	0.6
CVRi (mmHg cm/s)	1.52 ± 0.45	1.57 ± 0.30	1.44 ± 0.45	1.48 ± 0.33	0.7	0.8	0.7
RI	0.98 ± 0.07	0.98 ± 0.07	0.96 ± 0.08	0.60 ± 0.14	0.5	0.2	0.2
PI	0.91 ± 0.18	0.95 ± 0.19	0.78 ± 0.35	0.98 ± 0.33	0.5	0.1	0.2
CrCP (mmHg)	42 ± 21	38 ± 16	28 ± 29	27 ± 25	0.2	0.7	0.8
RAP (mmHg/cm/s)	0.79 ± 0.12	0.96 ± 0.47	1.05 ± 0.67	1.03 ± 0.48	0.3	0.4	0.3

MAP is mean arterial pressure; DBP is diastolic blood pressure; SBP is systolic blood pressure; MCA_V is middle cerebral artery blood velocity; CVRi is cerebrovascular resistance index; RI is resistance index; PI is pulsatility index; CrCP is critical closing pressure; RAP is resistance area product; OC is oral contraceptive user; NOC is non-OC user; LH is low hormone phase; HH is high hormone phase; * indicates a significant effect of menstrual phase ($p < 0.05$). Data are Mean ± SD.

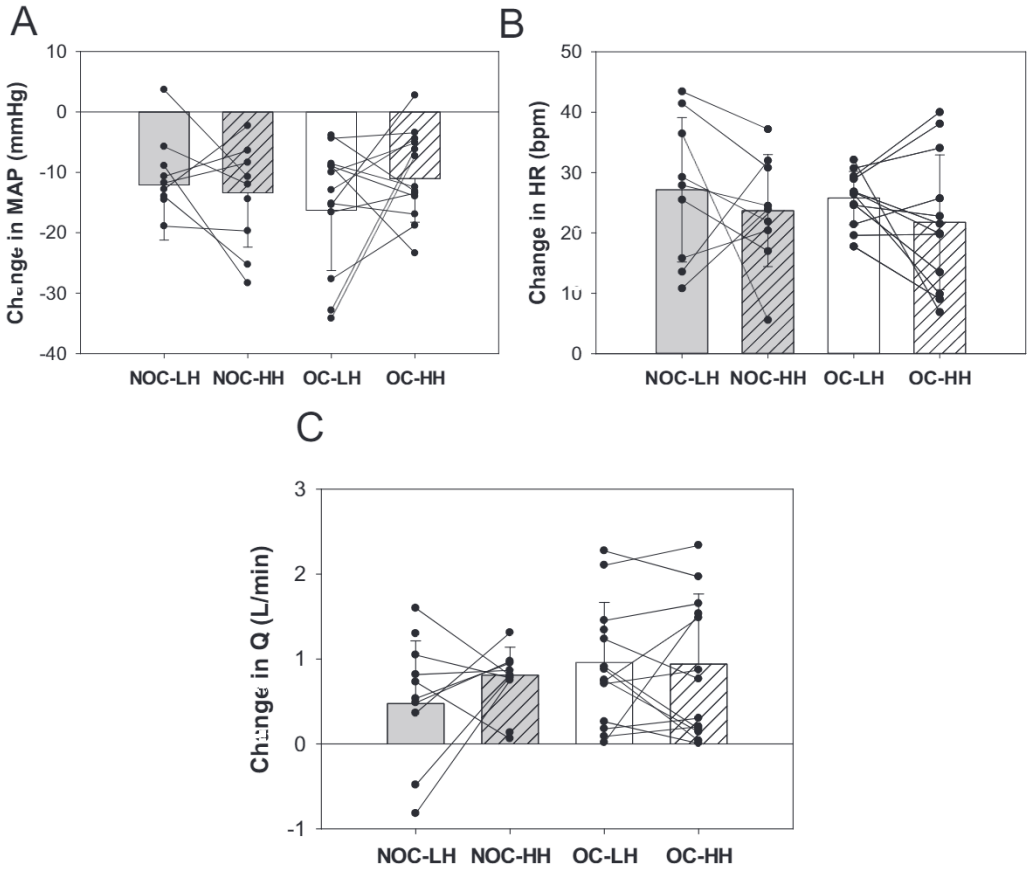

Fig. 2. Change in mean arterial pressure (MAP; A), heart rate (HR; B), and cardiac output (Q; C) from seated baseline to the nadir of MAP during acute standing. Oral contraceptives users are white bars, non-OC users (NOC) are grey bars. The low hormone (LH) menstrual phase is solid bars. The high hormone (HH) menstrual phase is hatched bars. Data are Mean ± SD.

mean MCA_V response to standing was influenced by both OC use and phase ($p < 0.05$; $\eta^2 = 0.18$). OC users in the LH phase had a greater reduction than NOC-LH ($p = 0.042$) and OC-HH ($p = 0.015$), while OC users in the HH phase had a smaller reduction than NOC-HH ($p = 0.046$; Fig. 3C). None of the cerebrovascular resistance indices were influenced by OC use or menstrual phase (all $p > 0.05$; Table 2). Similarly, the RoR was not influenced by either menstrual cycle or OC use (NOC-LH: 0.34 ± 0.25 s^{-1}, NOC-HH: 0.24 ± 0.15 s^{-1}, OC-LH: 0.49 ± 0.29 s^{-1}, OC-HH: 0.34 ± 0.16 s^{-1}; $p = 0.30$ for menstrual phase, $p = 0.14$ for OC use, $p = 0.25$ for interactions). The time to the nadir MCAv response was 5.8 ± 1.9 s in OC-LH, 5.2 ± 1.5 s in OC-HH, 5.4 ± 2.0 s NOC-LH, and 5.8 ± 1.3 s NOC-HH. There were no effects of OC use or menstrual cycle (OC and menstrual cycle: $p > 0.4$). The time to the regulatory response was 6.0 ± 1.9 s in OC-LH, 5.0 ± 1.6 s in OC-HH, 5.2 ± 1.4 s in NOC-LH, and 5.8 ± 1.3 s in NOC-HH. There were no effects of OC use or menstrual cycle (OC and menstrual cycle: all $p > 0.6$). The rate of MCAv decline to the time of onset of regulatory response was −1.5 ± 1.2 cm/s/s in OC-LH, −0.5 ± 1.0 cm/s/s in OC-HH, −0.7 ± 0.7 cm/s/s in NOC-LH and −1.5 ± 1.0 cm/s/s in NOC-HH (OC and menstrual cycle: all $p > 0.9$). End-tidal CO_2 did not change in the first 15 s of upright posture, and there were no effects of menstrual cycle (Position and menstrual cycle: all $p > 0.19$; Baseline – NOC LH: 42 ± 3 mmHg, NOC HH: 42 ± 4 mmHg, OC LH: 39 ± 3 mmHg, OC HH: 38 ± 4 mmHg vs. Standing – NOC LH: 41 ± 4 mmHg, NOC HH: 40 ± 2 mmHg, OC LH: 38 ± 2 mmHg, OC HH: 38 ± 2 mmHg). OC users had lower ET-CO_2, regardless of phase or posture ($p < 0.001$, $\eta^2 = 0.19$).

By using the clinical cut-off points for clinical iOH (a drop in systolic blood pressure of >40 mmHg or a drop in diastolic blood pressure of >20mmH), NOC-LH met these criteria 1 time, NOC-HH met the criteria 3 times, OC-LH met the criteria 3 times, and OC-HH met the criteria 2 times (Fisher exact test between groups, $p = 0.52$). While no significant pattern was discernable, it may be of potential interest to clinicians that of the 8 women who displayed drops in blood pressure equivalent to iOH, 7 out of these 8 women displayed this drop at only one phase in their menstrual cycle. A single OC user displayed iOH equivalent drops in blood pressure in the LH and HH phases. Combined, the individuals with iOH experienced a greater drop in pressor response (systolic BP, −27 ± 9 vs. −9 ± 6 mmHg, $p < 0.001$; diastolic BP, −26 ± 4 vs. −9 ± 6 mmHg, $p < 0.001$; MAP, −27 ± 6 vs. −10 ± 5 mmHg, $p < 0.001$), and a greater drop in cerebrovascular resistance (CVRi, −0.24 ± 0.21 vs. −0.004 ± 0.17, $p < 0.001$) compared to those who did not meet the criteria for iOH. The decrease in diastolic MCA_V tended to be greater in those with iOH (diastolic MCA_V, −11 ± 6 vs −6 ± 8 cm/s, $p = 0.052$; systolic MCA_V, 3 ± 10 vs. 4 ± 9 cm/s, $p = 0.4$; mean MCA_V, −8 ± 7 vs. −6 ± 6 cm/s, $p = 0.2$).

4. Discussion

This study aimed to determine the effects of OC and the menstrual cycle on the cardiovascular and cerebrovascular response within the initial 30 s of standing. While the systemic hemodynamic response to acute standing was not affected by OC use or menstrual cycle, compared to NOC, there was a greater decrease in MCA_V in the LH phase of OC users, which was reversed in the HH phase. Interestingly, in our cohort of 21 young, healthy women, 8 displayed drops in BP during standing that met the diagnostic criteria of iOH. Furthermore, while there was not a consistent phase of the menstrual cycle where most women experienced iOH, most of the women (7/8) only displayed this drop in BP in a

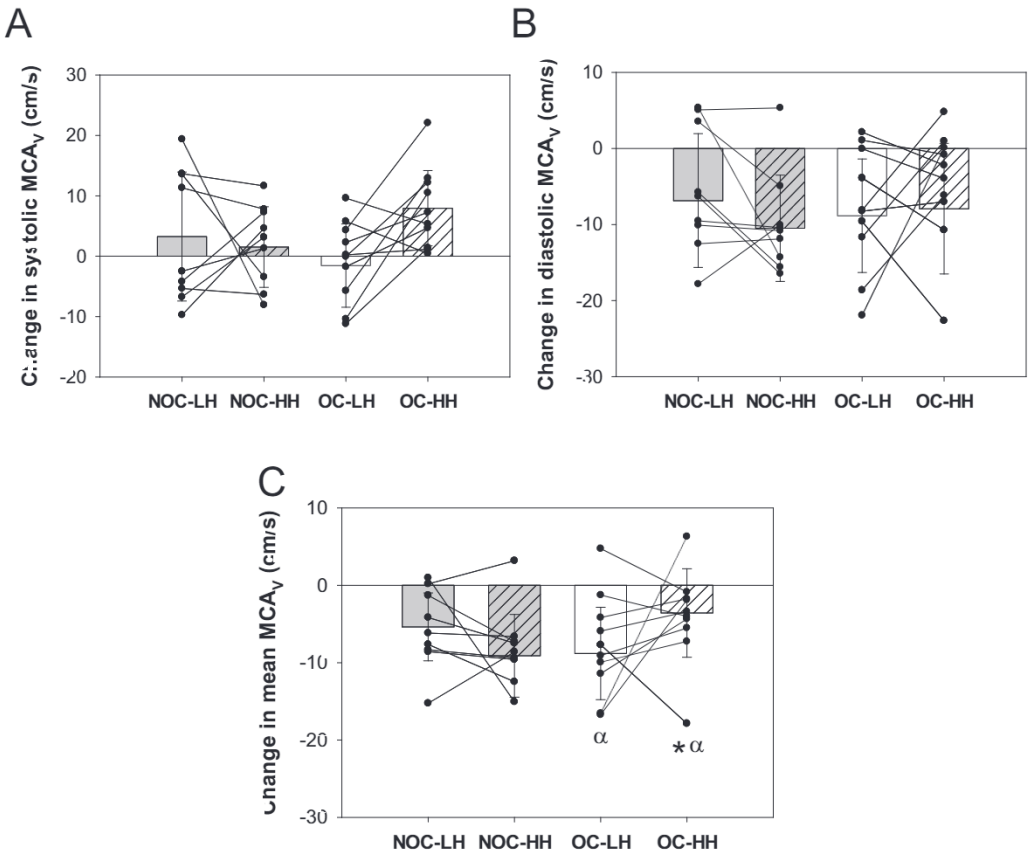

Fig. 3. Change in mean middle cerebral artery velocity (MCA_V; A), systolic MCA_V (B), and diastolic MCA_V (C) from seated baseline to the nadir of MAP during acute standing. Oral contraceptives users are white bars, non-OC users (NOC) are grey bars. The low hormone (LH) menstrual phase is solid bars. The high hormone (HH) menstrual phase is hatched bars. *indicates a significant difference from OC-LH ($p < 0.05$); α indicates a significant difference from NOC within the same phase ($p < 0.05$). Data are Mean ± SD.

Table 2
Change in cerebrovascular resistance indices from seated baseline to the nadir MCAv during acute standing.

	NOC		OC		P values		
	LH	HH	LH	HH	OC	Phase	OCxPhase
CVRi (mmHg/cm/s)	−0.12 ± 0.14	−0.01 ± 0.17	+0.013 ± 0.28	−0.08 ± 0.18	0.6	0.7	0.2
RI	+0.08 ± 0.06	+0.11 ± 0.07	+0.08 ± 0.08	+0.10 ± 0.07	0.6	0.3	0.4
PI	+0.26 ± 0.16	+0.40 ± 0.20	+0.26 ± 0.22	+0.37 ± 0.32	0.7	0.1	0.7
CrCP (mmHg)	+0.78 ± 12.7	+3.5 ± 11.5	−2.5 ± 12.2	−2.8 ± 14.6	0.3	0.9	0.6
RAP (mmHg/cm/s)	−0.17 ± 0.14	−0.20 ± 0.31	−0.05 ± 0.17	−0.07 ± 0.36	0.2	0.9	0.8

CVRi is cerebrovascular resistance index; RI is resistance index; PI is pulsatility index; CrCP is critical closing pressure; RAP is resistance area product; OC is oral contraceptive user; NOC is non-OC user; LH is low hormone phase; HH is high hormone phase. Data are Mean ± SD.

single phase of their menstrual cycle.

In the same cohort of participants, Abidi et al. found minimal effects of the menstrual cycle or OC use on the cardiovascular and cerebrovascular resistance responses to 10 min of standing. However, while the changes in the resistance indices at the level of the MCA were not influenced by OC use or menstrual cycle in the current study, there was a greater fall in mean MCA_V in OC-LH, potentially indicating a greater drop in brain blood flow during acute standing. Since the RoR (i.e., autoregulation) was not affected by menstrual cycle or OC use, the reduced mean MCA_V during standing in OC-LH may be due to chronic impairment of the myogenic tone of resistance vessels in OC users, which is improved in the presence of exogenous estrogen/progesterone (i.e., OC-HH). Since we did not observe this improvement due to the presence of sex hormones in the naturally cycling women, these effects appear purely pharmaceutical in nature. Cerebral autoregulation reflects pressure-induced changes in vasomotor tone; thus, if the regulation of this relationship is maintained, then properties such as smooth muscle or endothelial cell-related responses of the cerebrovasculature may be altered by synthetic hormones. For example, OC users have enhanced β2-adrenergic receptor-mediated vasodilation during the placebo phase of OC use compared to NOC (Limberg et al., 2016). This enhanced peripheral vasodilation could contribute to reduced brain blood flow during upright posture. There is limited research on the role of β2 receptor-mediated cerebrovascular vasodilation in humans; however, animal models demonstrate that β2 receptor antagonists reduce cerebral blood flow during hemodilution and cerebral oxygenation during nitric oxide-mediated cerebral vasodilation, respectively (Hare et al., 2006; Uchida et al., 2002). This suggests that β2 receptors may influence cerebral blood flow. It should also be noted that our current measure of RoR as an index of autoregulation during acute standing may not be robust enough to adequately inform due to the use of only a single stand rather than multiple posture changes. The use of a single time point increases the likelihood of error. Future studies should investigate the cerebrovascular response to postural transitions (i.e., multiple sit to stands) with alternative non-invasive measures of cerebral autoregulation, such as transfer function analysis (Claassen et al., 2016).

It is possible that perhaps the lower ET-CO_2 observed at all-time points in OC users (Abidi et al., 2017; Assadpour et al., 2020) is

enough to negate a compensatory increase in cerebral blood flow during standing. Lower ET-CO_2 suggests hyperventilation in OC users, which has been shown to reduce cerebral blood flow velocity and exacerbate symptoms of OI during head-up tilt (Novak et al., 1998). OC users also experience enhanced sympathetic and cardiovagal baroreflex sensitivity during the LH phase, which could interact with the chemoreflex to modify respiratory drive and thus brain blood flow (Biscoe et al., 1967a, Biscoe et al., 1967b). Since the greatest reduction of mean MCAv was observed in the LH phase of OC users and not in the HH phase, the presence of pharmaceutical female sex hormones could be protecting against this impairment. This phenomenon is not observed in the non-OC users in the presence of cyclic natural hormones indicating a specific influence of the pharmaceutical hormones. Our results suggest that women who take OCs may exhibit a reduced ability to regulate brain blood flow in their placebo pill phase.

Our observation that the 7/8 women who displayed drops in blood pressure equivalent to iOH (i.e., >40 mmHg drop in systolic and/or >20 mmHg drop in diastolic) only had this occur during a single phase of the menstrual cycle is important to note. While there was no discernable pattern regarding OC use or menstrual phase, our results indicate that to obtain an accurate diagnosis of iOH, women should have diagnostic testing multiple times throughout their menstrual cycle to increase the accuracy of diagnosis and/or determine novel menstrual cycle-dependent conditions. Many factors can influence the experience of OI. For example, hydration status could decrease plasma volume, which is already decreased in the early follicular phase (Spaanderman et al., 2000). Further, endothelial vasodilation peaks in the late follicular to luteal phases of the menstrual cycle (Hashimoto et al., 1995). Varying levels of OI may depend on the individual sensitivity to the factors mentioned above. Furthermore, although not significant, OC users with iOH were more frequently observed to have this occur in the LH phase corresponding to the observed decrements in mean MCA_V during standing - potentially pointing to cerebral dysregulation in the LH phase of OC users. This again suggests that the chronic adaptation to OC use, rather than the presence of increased levels of circulating hormones, might alter cerebrovascular function in OC users. Clinicians should account for the natural menstrual cycle and hormonal contraceptive use when assessing women for autonomic dysfunction or OI.

4.1. Limitations

A limitation of the present study was that participants were not specifically screened for a history of dizziness, fainting, autonomic dysfunction, or other symptoms/ conditions that may predispose them to iOH. A validated questionnaire, such as The Orthostatic Hypotension Questionnaire (Kaufmann et al., 2012), should be included in the exclusion process of future studies, which will ensure that participants are not more likely to experience presyncope. Additionally, the current investigation did not quantify or inquire about menstrual blood loss or iron levels, which can influence iOH. Previous research has demonstrated that neurally-mediated syncope is associated with anemia or low iron stores (Jarjour and Jarjour, 2008). However, there is limited evidence on the relationship between anemia or low iron stores and iOH. Women with excessive menstrual blood loss lose 5–6 times more iron than healthy women (Napolitano et al., 2014); thus, individuals who experience greater menstrual blood loss may be predisposed to iOH. Additionally, OC users lose about half the amount of menstrual blood as non-users (Nilsson and Solvell, 1967). Since OC users did not differ in their experience of iOH from non-users in the present study, many factors may be at play for the experience of iOH or OI.

The physical activity levels of participants were not assessed. Since cardiorespiratory fitness levels have been shown to influence autonomic function (Grässler et al., 2021), and fit women are less able to buffer large or rapid blood pressure oscillations (Labrecque et al., 2019), the varying cardiorespiratory fitness levels of the current cohort may have confounded the relationships between female sex hormones and orthostatic stress on these variables. Further, the menstrual cycle phase of the women in this study was determined by self-report. It is unclear if women in the NOC-HH group had ovulated as we did not measure or confirm plasma concentrations of sex hormones. Moreover, the data from OC users was obtained cross-sectionally rather than through a longitudinal study investigating participants before and during OC use. Due to the nature of obtaining instantaneous data points, a further limitation in the present study is stationarity. Even in the strictest methodologies, non-stationarities (i.e., external factors, such as environment changes, respiration or blood flow) may influence markers of autonomic function and bias results towards sympathetic control; therefore, stationarity should be assessed in short-term recordings of autonomic function (e.g., <300 beats for heart rate variability) (Magagnin et al., 2011). The present study also had a small sample size and power calculations were not calculated a priori due to the secondary nature of this analysis; hence each comparison is accompanied with an effect size to further clarify the findings.

Only young, healthy women were assessed in the primary investigation; thus, these findings cannot be extended to older women in the post- or perimenopausal period with or without hormone replacement therapy. Indeed, in a previous investigation assessing sex differences in the responses to acute orthostatic stress, it was reported that postmenopausal women had a smaller acute drop in MAP with an attenuated HR response during standing compared to younger women (Edgell et al., 2012), suggesting age-related differences in the cardiovascular responses to orthostatic stress. It should also be noted that different types of OC pill generations were used among the OC cohort. For example, Alesse is a 2nd generation progestin, whereas Tri-Cyclen and Marvelon contain a 3rd generation progestin. It has previously been reported that 2nd generation OCs have been associated with a reduced risk of thrombosis compared to 3rd generation OCs (Kemmeren et al., 2004), yet the duration of use of 2nd generation OCs is associated with impaired vascular function (Shenouda et al., 2018). Further investigations are needed to identify whether different OC pill generations may affect the hemodynamic and cerebrovascular variables measured. Lastly, the results of the current study cannot be extended to other cerebral arteries, such as the posterior cerebral arteries; however, a recent study suggests that there is no difference between middle or posterior cerebral artery reactivity to CO_2 nor in cerebral autoregulation in young endurance-trained women (Labrecque et al., 2021).

5. Conclusions

In response to the first 30 s of standing, there was no influence of menstrual phase or OC use on the hemodynamic or autoregulatory responses. However, OC users experienced a smaller decrease of mean MCA_V during standing in the HH phase compared to the LH phase and non-OC users in the HH phase, perhaps suggesting that the presence of pharmaceutical estrogen and progesterone could be protective against falls in cerebral blood flow due to upright posture. During the placebo pill week, the OC users displayed a greater fall in brain blood flow compared to non-users indicating a negative influence of chronic pill use. As this was a secondary analysis, greater statistical power is required, as are more robust measures of cerebral autoregulation, such as the squat-stand maneuver.

Of note, women displayed iOH-like drops in BP during a single phase of their menstrual cycle – demonstrating the need for multiple assessments throughout the menstrual cycle. Clinicians should consider that a patient's symptomology may change throughout the menstrual cycle and/or be influenced by hormonal contraceptives, and therefore, should consider testing women multiple times throughout their menstrual cycle to determine OI.

Declaration of competing interest

On behalf of all authors, the corresponding author states that there is

no conflict of interest.

Data availability

Data will be made available on request.

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