Impact of Menstrual Blood Loss and Oral Contraceptive Use on Oxygen-carrying Capacity

MELISSA F. KELLER, MICHELLE L. HARRISON, and SOPHIE LALANDE

Department of Kinesiology and Health Education, The University of Texas at Austin, Austin, TX

ABSTRACT

KELLER, M. F., M. L. HARRISON, and S. LALANDE. Impact of Menstrual Blood Loss and Oral Contraceptive Use on Oxygen-carrying Capacity. *Med. Sci. Sports Exerc.*, Vol. 52, No. 6, pp. 1414–1419, 2020. **Purpose:** The effect of menstrual blood loss on oxygen-carrying capacity remains equivocal. The purpose of this study was to determine the effect of menstrual blood loss on hemoglobin mass in young, healthy women. **Methods:** Twenty-one women (age, 23 ± 6 yr; height, 168 ± 7 cm; weight, 66.1 ± 12.6 kg) with regular menstrual cycles, either using ($n = 10$) or not using oral contraceptives, participated in the study. Hemoglobin mass was assessed using carbon monoxide rebreathing on three separate occasions over the course of one menstrual cycle. **Results:** Visits for women not using oral contraceptives were performed in the early follicular phase (3 ± 1 d after the onset of menses), late follicular phase (1 ± 1 d after the surge of luteinizing hormone in urine), and luteal phase (9 ± 1 d after the late follicular visit). Visits for women using oral contraceptives were performed in the early follicular phase (3 ± 1 d after the onset of menses), late follicular phase (15 ± 3 d after the onset of menses), and luteal phase (9 ± 2 d after the late follicular visit). Hemoglobin mass was not affected by menstrual cycle phase (early follicular, 618 ± 61; late follicular, 610 ± 65; luteal, 607 ± 68 g; $P = 0.52$). Interestingly, when normalized to weight, hemoglobin mass was 12% higher in women using oral contraceptives in comparison to nonusers (10.0 ± 1.2 vs 8.9 ± 1.2 $g \cdot kg^{-1}$, $P < 0.05$). **Conclusion:** Menstrual blood loss had no measurable effect on hemoglobin mass in eumenorrheic women. However, oral contraceptive use resulted in a greater oxygen-carrying capacity, potentially leading to a greater maximal oxygen uptake.

Key Words: HEMOGLOBIN MASS, MENSTRUAL CYCLE, EARLY FOLLICULAR, CARBON MONOXIDE REBREATHING

Regular menstrual blood loss, occurring during the early follicular phase of the menstrual cycle, ranges from 10 to 90 mL (1–3). Hemoglobin concentration, a common clinical marker of oxygen-carrying capacity, has been reported to either decrease (4–7) increase (8), or to not change (9–12) during the early follicular phase of the menstrual cycle. Variations in plasma volume, induced by changes in hydration status, posture during the blood draw, and fluid retention caused by oscillating progesterone and estradiol levels, contribute to these reports of varying hemoglobin concentration across the menstrual cycle (13,14). Moreover, hemoglobin concentration correlates only with a modest extent with red blood cell mass and therefore does not represent an optimal marker of oxygen-carrying capacity (15). Few studies have examined the effect of the menstrual cycle on red blood cell mass, and both reported that red blood cell mass remains unchanged throughout the menstrual cycle (16,17). However, red blood cell mass was calculated using hematocrit levels, which are also influenced by changes in plasma volume (16), or measurements were made during the early follicular phase of the menstrual cycle in only 2 women (17).

Measures of hemoglobin mass, assessed via the carbon monoxide rebreathing technique, remain unaffected by variations in plasma volume and consequently better represent oxygen-carrying capacity (18). Hemoglobin mass has previously been assessed in elite female athletes over prolonged periods of time to determine the variation in hemoglobin mass throughout a training season (19,20). However, these studies did not control for menstrual cycle phase, as it was estimated that menstrual blood loss would fall within the mean coefficient of variation of 2.2% reported for different carbon monoxide rebreathing techniques. It was therefore assumed that this minimal variation in hemoglobin mass would have no significant effect on oxygen-carrying capacity (21). Although there was no significant change in hemoglobin mass over these prolonged periods of time, the observed coefficient of variation for hemoglobin mass was repeatedly larger than the commonly reported error of the technique (19,20), suggesting that other factors contributed to the observed variation in hemoglobin mass. Indeed, hemoglobin mass assessed during a competitive season of road cycling lasting several months varied by 3.3%, with individual variation ranging from 2.0% to 4.4% (20). Similarly, the within-subject coefficient of variation

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Address for correspondence: Sophie Lalande, Ph.D., Department of Kinesiology and Heath Education, The University of Texas at Austin, 2109 San Jacinto, UT Mail Code D3700, Austin, TX 78712; E-mail: sophie.lalande@austin.utexas.edu.

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for hemoglobin mass measured several times over 1 yr was lower for men than for women (3.4% vs 4.0%, respectively) (19). Although the lower absolute hemoglobin mass observed in women partly explains the greater coefficient of variation, female athletes showed a greater SD of changes in hemoglobin mass over time in comparison to men athletes (19). Thus, the effect of menstrual blood loss on hemoglobin mass and consequently oxygen-carrying capacity remains equivocal. Therefore, the purpose of this study was to determine the effect of menstrual blood loss on hemoglobin mass in women with regular menstrual cycles. Women using and not using oral contraceptives were included in the study. We hypothesized that hemoglobin mass would not change across phases of the menstrual cycle.

METHODS

Study protocol. Healthy, eumenorrheic, nonsmoking women were recruited to participate in the study. All women provided informed written consent for participating in the study, which was approved by the institutional review board of the University of Texas at Austin. Hematological variables were assessed on three occasions throughout one menstrual cycle. Visits were scheduled in the early follicular phase (visit 1: 3–5 d after the onset of menses), late follicular phase (visit 2: 1–2 d after the surge of luteinizing hormone in urine), and luteal phase (9–10 d after visit 2) of the menstrual cycle. Eight days after the onset of menses, women started self-administering ovulation tests to detect luteinizing hormone in their urine. Tests were administered daily until positive for ovulation. Menstrual cycle phases were confirmed by measuring estradiol and progesterone levels from venous blood samples obtained on each visit. Visits for women using oral contraceptives were scheduled in the early follicular phase (visit 1: 3–5 d after the onset of menses), late follicular phase (visit 2: 14 d after the onset of menses), and luteal phase (visit 3: 9–10 d after visit 2) of the menstrual cycle. Average heart rate and blood pressure values were calculated from three measures obtained after 5 min of supine rest (Omron Healthcare, Inc., Lake Forest, IL).

Hematological variables. Hemoglobin mass, red blood cell volume, plasma volume, and total blood volume were determined using a modified version of the optimized carbon monoxide rebreathing technique (22,23). Participants laid in the supine position for 20 min before the start of the procedure to allow for stabilization of fluid movement between interstitial and intravascular spaces (24). A venous blood draw was first obtained to measure baseline levels for carboxyhemoglobin, hematocrit, and hemoglobin (ABL FLEX CO-OX, Radiometer, CA). The volume of carbon monoxide administered to each participant was then calculated based on body surface area and hemoglobin concentration (25). Carbon monoxide rebreathing was performed by introducing this bolus of carbon monoxide into a low-volume closed-circuit rebreathing system containing ambient air. The rebreathing system consisted of a 5-L anesthesia bag (Rusch Inc., Duluth, GA) connected to a four-way directional control valve (Hans Rudolph, Inc., Shawnee, KS). Participants were switched from breathing ambient air to the rebreathing system at end-exhalation. The bolus of carbon monoxide was immediately introduced into the rebreathing system through a small port in the four-way directional control valve. Participants rebreathed this mixture of carbon monoxide and ambient air for a period of 2 min while maintaining a normal breathing pattern. A second venous blood draw was obtained 10 min after the start of the rebreathing to assess carboxyhemoglobin levels. Hemoglobin mass, red blood cell volume, plasma volume, and total blood volume were calculated from the change in carboxyhemoglobin levels induced by the carbon monoxide rebreathing using equations developed by Burge and Skinner (25). The molar amount of carbon monoxide was corrected by 2.2% to account for the amount of carbon monoxide remaining in the system following rebreathing (22,25,26). The coefficient of variation for hemoglobin mass, based on duplicate measures performed on consecutive days in five individuals, is 2.6% in our laboratory, similar to the commonly reported mean coefficient of variation of 2.2% for different carbon monoxide rebreathing techniques (21), and to the coefficient of variation of 1.7% reported for the optimized carbon monoxide rebreathing technique (23).

Estradiol, progesterone, and ferritin levels. To confirm menstrual phase in women not using oral contraceptives, a blood sample was obtained before the carbon monoxide rebreathing protocol. Venous blood was collected into a serum separator tube, and the serum was aliquoted and stored at −80°C for subsequent analyses. Once all samples were collected, concentrations of serum estradiol and progesterone were determined using MILLIPLEX MAP Multi-Species hormone magnetic bead panel (MilliporeSigma, Burlington, MA) and an enzyme-linked immunosorbent assay (BioVendor, Asheville, NC), respectively. Serum ferritin levels were determined using an enzyme-linked immunosorbent assay (BioVendor).

Statistical analysis. A repeated-measures analysis of variance was used to evaluate the effect of different phases of the menstrual cycle (early follicular, late follicular, and luteal) on all variables. A two-way repeated-measures analysis of variance was used to evaluate the effect of group (women using oral contraceptives vs women not using oral contraceptives) and phases of the menstrual cycle (early follicular, late follicular, and luteal). When appropriate, *post hoc* analyses were performed using Tukey's test. Significance was set at $P \leq 0.05$. All values are reported as mean ± SD.

RESULTS

Twenty-one women (age, 23 ± 6 yr; height, 168 ± 7 cm) participated in the study. Serum ferritin levels were 19.5 ± 19.4 ng·mL^{-1} for the group and were not correlated with hemoglobin concentration or hemoglobin mass. For women not using oral contraceptives, visit 1 took place 3 ± 1 d after the onset of menses, visit 2 took place 1 ± 1 d after a positive ovulation test result, and visit 3 took place 9 ± 1 d after visit 2. Estradiol and progesterone levels changed as expected across phases of the

menstrual cycle (estradiol: 43 ± 52 pg·mL^{-1} for visit 1, 192 ± 213 pg·mL^{-1} for visit 2, 92 ± 124 pg·mL^{-1} for visit 3; progesterone: 0.3 ± 0.1 ng·mL^{-1} for visit 1, 0.5 ± 0.2 ng·mL^{-1} for visit 2, and 2.7 ± 2.8 ng·mL^{-1} for visit 3; $P < 0.05$). For women using oral contraceptives, visit 1 took place 3 ± 1 d after the onset of menses, visit 2 took place 15 ± 3 d after menses, and visit 3 took place 9 ± 2 d after visit 2.

Effect of menstrual cycle phase. There was no effect of menstrual cycle phase on weight, systolic and diastolic blood pressure, hemoglobin level, or hematocrit level (Table 1). The menstrual cycle had a significant effect on heart rate, with a lower heart rate being observed in the early follicular phase in comparison to the luteal phase. Absolute hemoglobin mass and hemoglobin mass normalized to weight did not differ between menstrual cycle phases. Similarly, there was no difference in red blood cell volume, plasma volume, or total blood volume across phases of the menstrual cycle (Table 1).

Use of oral contraceptives. Ten of 21 women were using oral contraceptives. There was no difference in weight, body mass index, systolic and diastolic blood pressure, heart rate, and hemoglobin, hematocrit, and serum ferritin levels between women using oral contraceptives and women not using oral contraceptives (Table 2). Similarly, absolute hemoglobin mass, red blood cell volume along with plasma, and blood volume were not different between groups across phases of the menstrual cycle (Table 3). However, when normalized to weight, hemoglobin mass was greater in women using oral contraceptives in comparison to women not using oral contraceptives across phases of the menstrual cycle (10.0 ± 1.2 vs 8.9 ± 1.2 g·kg^{-1}, $P < 0.05$; Fig. 1).

DISCUSSION

The purpose of this study was to determine the effect of menstrual blood loss on hemoglobin mass in women with regular menstrual cycles. As hypothesized, there was no significant change in hemoglobin mass across phases of the menstrual cycle, indicating that regular menstrual blood loss does not affect oxygen-carrying capacity. The coefficient of variation for hemoglobin mass over the course of one menstrual cycle was 4.1%, which is above the coefficient of variation of 2.2% commonly reported for the carbon monoxide rebreathing technique but similar to the variability reported in elite female athletes over training seasons (19,20). Heart rate was the only physiological variable affected by the menstrual cycle. Heart rate was lower in the early follicular phase in comparison to the luteal phase. Although most studies report no change in resting heart rate over the menstrual cycle, several others have reported a similarly increased heart rate during the midluteal phase (27), possibly due to increased body temperature (28).

TABLE 1. Participant characteristics across phases of the menstrual cycle.

	Early Follicular	Late Follicular	Luteal
Weight (kg)	66.1 ± 12.6	66.3 ± 12.4	66.4 ± 12.6
Systolic blood pressure (mm Hg)	113 ± 9	110 ± 10	111 ± 9
Diastolic blood pressure (mm Hg)	71 ± 8	68 ± 7	70 ± 9
Heart rate (bpm)	62 ± 8	67 ± 10	68 ± 7[a]
Hemoglobin (g·dL^{-1})	13.0 ± 1.2	12.8 ± 0.9	12.9 ± 0.9
Hematocrit (%)	40.1 ± 3.5	39.4 ± 2.6	39.5 ± 2.6
Hemoglobin mass (g)	618 ± 61	610 ± 65	607 ± 68
Hemoglobin mass (g·kg^{-1})	9.5 ± 1.3	9.4 ± 1.2	9.3 ± 1.4
Red blood cell volume (mL)	1896 ± 188	1874 ± 200	1865 ± 208
Plasma volume (mL)	3345 ± 565	3375 ± 466	3328 ± 425
Blood volume (mL)	5241 ± 702	5249 ± 621	5194 ± 582

[a]Different between early follicular and luteal phase.

TABLE 2. Characteristics of women not using oral contraceptives and women using oral contraceptives.

	No Oral Contraceptives (n = 11)	Oral Contraceptives (n = 10)
Weight (kg)	68.3 ± 15.0	64.1 ± 8.2
Body mass index (kg·m^{-2})	24.5 ± 5.0	22.6 ± 2.4
Systolic blood pressure (mm Hg)	109 ± 10	113 ± 8
Diastolic blood pressure (mm Hg)	67 ± 8	72 ± 7
Heart rate (bpm)	64 ± 8	68 ± 9
Hemoglobin (g·dL^{-1})	12.8 ± 1.0	13.0 ± 1.0
Hematocrit (%)	39.3 ± 3.0	40.0 ± 2.9
Serum ferritin (ng·mL^{-1})	21.6 ± 24.5	18.9 ± 11.7

A strong relation exists between hemoglobin mass and maximal oxygen uptake (18). Therefore, the observed lack of change in hemoglobin mass in this study supports previous literature demonstrating that maximal oxygen uptake does not change across phases of the menstrual cycle. Indeed, similar maximal oxygen uptakes were reported across phases of the menstrual cycle in sedentary and moderately active women, runners, cyclists, and triathletes (8,29–33). In contrast, Lebrun et al. (11) reported that maximal oxygen uptake was 1.9% lower in the midluteal compared with the follicular phase in 16 women with maximal oxygen uptake greater than 50 mL·kg^{-1}·min^{-1}. Although the mechanism behind this reduction remains unclear, the authors reported no difference in hemoglobin concentration between phases of the menstrual cycle.

Oxygen-carrying capacity and oral contraceptive use. Women with regular menstrual blood loss using or not using oral contraceptives were included in this study; thus, 10 of our 21 participants were using oral contraceptives. Interestingly, hemoglobin mass normalized to weight was higher in women using oral contraceptives compared with women not using oral contraceptives. This finding is important because the 1.1 g·kg^{-1} difference in hemoglobin mass observed between groups theoretically corresponds to a difference in maximal oxygen uptake of approximately 4 mL·kg^{-1}·min^{-1}, and therefore implies a 12% greater maximal oxygen uptake in women using oral contraceptives vs women not using oral contraceptives (18). Oral contraceptive use decreases menstrual blood loss and increases serum iron levels, which may contribute to the greater oxygen-carrying capacity observed in women using oral contraceptives. A regular menstrual cycle represents a loss of 5–40 mg of iron, a mineral essential to erythropoiesis (34), with each menstruation (35). Menstrual blood loss decreases by half after 6 months of oral contraceptive use (36), representing a consistently smaller loss of iron each month. Consequently, increased serum iron levels are reported for oral contraceptive users when compared with nonoral contraceptive users (37). Serum ferritin levels, an indicator of iron status, were reported to increase with oral contraceptive use (38) or to not change after 6 months of oral

TABLE 3. Hematological variables in women using and not using oral contraceptives across phases of the menstrual cycle.

	No Oral Contraceptives (n = 11)			Oral Contraceptives (n = 10)		
	Early Follicular	Late Follicular	Luteal	Early Follicular	Late Follicular	Luteal
Hemoglobin mass (g)	604 ± 69	588 ± 68	590 ± 74	632 ± 51	635 ± 55	626 ± 57
Red blood cell volume (mL)	1855 ± 212	1805 ± 208	1813 ± 227	1941 ± 156	1950 ± 169	1923 ± 178
Plasma volume (mL)	3322 ± 552	3270 ± 457	3276 ± 396	3371 ± 608	3491 ± 472	3386 ± 470
Blood volume (mL)	5176 ± 713	5075 ± 609	5089 ± 557	5312 ± 721	5440 ± 605	5308 ± 617

contraceptive use, despite the reduced menstrual blood loss (36). In the present study, there was no difference in average serum ferritin levels between oral contraceptive users and nonusers. However, depleted iron stores (serum ferritin levels <15 $ng \cdot mL^{-1}$) were observed in seven women not using oral contraceptives, whereas only two women using oral contraceptives had depleted iron stores. Thus, a chronically reduced menstrual blood loss in conjunction with adequate iron availability potentially contributed to the observed greater hemoglobin mass normalized to weight in women using oral contraceptives.

Our observation of a greater oxygen-carrying capacity, and a possibly greater maximal oxygen uptake, with oral contraceptive use contradicts reports of either a lack of effect or a negative effect of oral contraceptives on maximal oxygen uptake. Indeed, several studies have reported either no change (31,39) or decreases (32,40–42) in maximal oxygen uptake with the use of oral contraceptives. Four months of oral contraceptive use decreased peak aerobic capacity by 11% in six moderately active, eumenorrheic women (32). The authors concluded that a reduced oxygen-carrying capacity was not responsible for the reduced peak aerobic capacity because hemoglobin concentration remained unchanged with oral contraceptive use. However, oral contraceptive use increases the activity of the renin–angiotensin–aldosterone system (43), which leads to an increase in plasma volume, which could have masked an increase in hemoglobin mass in these women. Moreover, without a compensatory increase in hemoglobin mass, a decreased hemoglobin concentration would have instead been observed after an increase in plasma volume. Accordingly, Lebrun et al. (41) reported a 4.7% decreased maximal oxygen uptake in the second month of oral contraceptive use in seven highly active women. The observed reduction in maximal oxygen uptake was not linked to alterations in oxygen-carrying capacity of the blood because hemoglobin concentration, mean red cell volume, and hematocrit levels did not differ significantly over 6 wk of oral contraceptive use. In contrast, our findings suggest an increase in maximal oxygen uptake owing to an increased oxygen-carrying capacity with oral contraceptive use. Oral contraceptive use may therefore have deleterious effects on maximal oxygen uptake despite an increased oxygen-carrying capacity. In summary, conclusions on the effect of oral contraceptive use on maximal oxygen uptake are currently limited by studies with small sample sizes, a wide range of testing protocols, and varying types and durations of oral contraceptive use.

Because the main objective of the present study was to determine the effect of menstrual blood loss on hemoglobin mass in women with regular menstrual cycles, no distinction was made between women using and not using oral contraceptives, or regarding the type and duration of oral contraceptive use. Participants had an average hemoglobin concentration of 12.9 $g \cdot dL^{-1}$. Thus, the 10- to 90-mL blood loss associated with a regular menstrual cycle (1–3) would correspond to a 1- to 12-g reduction in hemoglobin mass in our participants. The group average hemoglobin mass of 612 g in combination with our established coefficient of variation of 2.6% resulted in a typical error of approximately 16 g in the measure of hemoglobin mass. Therefore, the potentially larger variation in hemoglobin mass associated with the carbon monoxide rebreathing technique than with menstrual blood loss limited our ability to detect a significant change in hemoglobin mass across phases of one menstrual cycle. Nevertheless, a difference in hemoglobin mass normalized to weight was detected between women using and women not using oral contraceptives. Physical activity levels were not specifically assessed, but all our participants were recreationally active women. Although there was no difference in weight or body mass index between women using and women not using oral contraceptives, assessment of lean body mass would have resulted in a more precise normalization of hemoglobin mass. In conclusion, menstrual blood loss did not affect hemoglobin mass in a physiologically relevant manner over the course of one menstrual cycle in eumenorrheic women. Hemoglobin mass, when normalized to weight, was 12% greater in women using oral contraceptives, possibly due to the reduced menstrual blood loss in conjunction

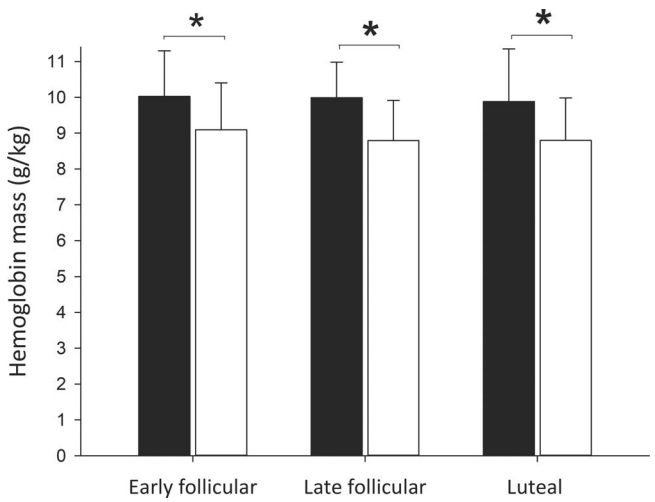

FIGURE 1—Hemoglobin mass normalized to weight across phases of the menstrual cycle in women using oral contraceptives (*black bars*) and women not using oral contraceptives (*white bars*). *Different between women using and not using oral contraceptives.

with adequate iron availability. Therefore, the use of oral contraceptives resulted in a greater oxygen-carrying capacity, which could potentially lead to a greater maximal oxygen uptake.

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