Potential Venous Thromboembolism Risk in Female Astronauts

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BACKGROUND: Whether the unique environment of space affects astronaut risk of venous thromboembolism (VTE) is not known. On Earth, it is known that use of combined oral contraceptives (COCs) doubles the risk of VTE. Since some female astronauts choose to use COCs, this retrospective study examined known risk factors associated with VTE risk to determine whether the available data suggested elevated VTE risk in female astronauts.

METHODS: Longitudinal health data were requested for female astronauts who flew short and long duration missions between 2000 and 2014. Pre- and postflight hematological and biochemical blood markers were available and evaluated. Astronauts' postflight measurements were compared to clinically relevant terrestrial high risk levels to determine any trend toward increased risk for VTE following spaceflight. Secondarily, a comparison of pre- and postflight changes was made, as well as an assessment of COC impact.

RESULTS: A total of 38 astronaut-flights were included in this study and no VTE events were found. Analysis of potential VTE risk factors showed no evidence suggesting elevated VTE risk in female astronauts associated with spaceflight, regardless of contraceptive use.

DISCUSSION: Arguably, all astronauts encounter many physiological stressors during spaceflight missions, but women using the combined contraceptive pill add a known risk factor for VTE. The risk factors analyzed within this study showed no trend toward an increased risk of VTE for female astronauts. This study provides an evidence base supporting the safety of COC use by female astronauts and also reinforces the importance of healthy lifestyle on VTE risk reduction.

KEYWORDS: spaceflight, combined contraceptive pill, risk factors, microgravity, thrombosis, extreme environment.

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Venous thromboembolism (VTE) is a rare and potentially lethal blood clotting condition where risk is characterized by Virchow's Triad: hypercoagulability, unusual hemodynamics, and endothelial injury. One episode of VTE has recently been reported in an astronaut during a spaceflight mission,[1] but the relationship of spaceflight to VTE risk is unknown. If spaceflight does alter VTE risk, it would be prudent to understand the specific risks for astronauts before undertaking missions that travel farther away from Earth. A number of physiological adaptations have been described during and after spaceflights, including cephalic fluid shifts, spaceflight anemia, decreased fluid intake, and deconditioned muscles due to the reduction in gravitational forces during daily activities. Several of these known spaceflight-induced physiological changes could, in turn, alter coagulability, hemodynamics, or endothelial function, which characterize VTE risk.

Lifestyle and medical factors associated with increased VTE risk are known, and there are clinical VTE risk calculators that use them to help gauge a patient's individualized risk. These factors include age, inactivity, and use of combined oral contraceptives (COCs), but do not consider the unusual elements of the space environment.[9] Some terrestrial predictors for VTE (such as elevated body mass index or medical comorbidities) do not apply to astronauts who are fit and have undergone rigorous selection and training. Menstrual efflux is not impacted by

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spaceflight;[12] however, some female astronauts choose to use COCs in a continuous fashion for menstrual suppression during training and spaceflight missions.[11] COCs increase the risk for VTE significantly, dependent on the dose of ethinyl estradiol as well as the specific progestin,[14] thus the reason for this current analysis.

Women of reproductive age have a VTE risk of approximately 4–5 per 10,000 per year;[21] however, this increases by two- to sixfold[30] with COC use. Female astronauts typically use 30–35 μg ethinyl estradiol COC pills without placebo breaks,[13] which has VTE risk equal to low ethinyl estradiol pills[15] while also minimizing breakthrough bleeding.[30] As of 2014, the average age of a female astronaut at her first flight was 38 yr[23] and age for any long duration mission is increasing (mean age 44.6 yr) compared to earlier short duration Shuttle missions (mean age 40.4 yr). Women in the 40–50 yr age group have an almost doubled baseline VTE risk compared to women less than 30 yr of age.[30] The combination of age and contraceptive use increases the risk of VTE in an additive manner, with the highest risk in the initial months of COC use.[29] However, when adjusted for age, the rate of VTE decreases after year 1 for COCs containing second and third generation progestins, plateauing at 2 yr of use[29] until decreasing back to baseline within 3 mo of cessation. Taken together, female astronauts have factors that decrease VTE risk (fitness and healthy lifestyle) as well as factors that increase VTE risk (age and use of COCs). The spaceflight environment may also affect risk, but how and in which direction is not yet known.

On entering the space environment, the lower extremities lose blood volume due to a cephalic fluid shift. Baroreceptors initiate the adaptation to this increase in thoracic volume by reducing the overall plasma volume and red cell mass within the body, thus creating a new euvolemic state. These changes are similar to a hypovolemic state on Earth, which would increase venous thromboembolism risk. The initial studies investigating spaceflight adaptation were conducted in male astronauts and it is unknown how these changes impact VTE risk in female astronauts who are concurrently taking the contraceptive pill. Taking this into consideration, this study investigated variables that impact VTE risk in order to gain an understanding into their potential effect for female astronauts using data previously collected for other purposes. These include hematological variables [hemoglobin, mean corpuscular volume (MCV), hematocrit, platelets, reticulocyte count] that reflect coagulability in a direct fashion and biochemical variables [vitamin B12, iron, ferritin, transferrin, total iron binding capacity (TIBC), and folate] that correlate with homocysteine level, which has a correlation with hypercoagulability. The aims of this study were twofold: 1) to compare dependent variables in postflight data from female astronauts to normative terrestrial data in order to understand the absolute risk of VTE after the astronauts have experienced the spaceflight environment; and 2) to compare preflight vs. postflight changes in these variables in order to determine any spaceflight associated differences seen in female astronauts after having experienced spaceflight. We hypothesized that female astronauts would not have a clinically relevant increase in postflight risk of VTE as compared to the terrestrial population.

METHODS

The National Aeronautics and Space Administration Johnson Space Center Institutional Review Board approved this study protocol. For this retrospective cohort study, the Johnson Space Center Lifetime Surveillance of Astronaut Health group supplied anonymized data for hemoglobin, hematocrit, MCV, platelet count, reticulocyte count, vitamin B12, iron, TIBC, transferrin, ferritin, and folate from all U.S. female astronauts who flew between 2000–2014.

Subjects

Subjects were classified by mission duration: short (≤30 d) or long (>30 d), and descriptive statistics (median and IQR) were provided for subject age at flight (**Table I**). However, these fields (mission length and age) could not be linked to subject lab data as it would have rendered the data identifiable. Therefore, statistical comparison between long and short duration flyers was not possible. No subjects included in this analysis used hormone replacement therapy. For protection of subjects' identities, certain variables relevant to VTE were not considered in this analysis; these include age and mission durations. The brand and formulation of the COC used by individual astronaut subjects was not included in this analysis. Subjects were grouped as COC users or non-COC users in order to delineate whether COC usage impacts the risk of VTE. Study size was determined by availability of data.

Data Collection

Data were derived from blood samples taken for medical monitoring or research studies at time points prior to and after spaceflight missions and were used for the purposes of this study. No in-flight data were available. The timings of pre- and postflight data supplied were not controlled by this study and are shown in **Table II**. The preflight data used for analysis were that nearest to the time of that individual's flight. Postflight data are the earliest data entries after return from space, but not later than 6 wk after flight, as this is the perceived at-risk period for full hematologic recovery following spaceflight.[25] We assumed that the change between the two data points would result primarily from any effects of exposure to the spaceflight mission, although a causal relationship cannot be confirmed because each subject was exposed to the launch environment, the environment on board the International Space Station (ISS) or space shuttle, and the landing environment, followed by some weeks of the Earth environment after landing. Some individual astronauts flew on multiple missions; in these cases, each mission was analyzed as an individual episode to ensure subject privacy, which required the assumption was that previous missions would not have long-lasting effects.

Statistical Analysis

All statistical analyses were conducted with Stata, IC (Version 14, 2015; StataCorp, College Station, TX, USA) and SAS (Version

Table I. Subject Demographic Information.

	SHORT DURATION	LONG DURATION
Maximum number of subjects		
COC users	18	9
Non COC users	10	1
Age (years)		
Interquartile Range (25^{th} – 75^{th} percentile)	39–46	42–47
Median	43	44
Duration in space (days)		
Interquartile Range (25^{th} – 75^{th} percentile)	11–14	140–174
Median	13	165

9.4; SAS, IBM, Armonk, NY, USA) software using two-tailed alpha to reject the null hypotheses of 0.05. Three outcomes (ferritin, folate, and reticulocyte count) required natural log transformations to remove skew prior to hypothesis testing; however plots of all data are shown in their native scale. In this retrospective analysis, our aim was primarily descriptive, emphasizing graphic displays of data alongside estimated marginal means and 95% confidence intervals (CI). While unadjusted *P*-values are presented, our aim was to characterize the mean effects with 95% CI and evaluate the extent to which individual observations exceed clinically relevant thresholds. Means were plotted for each outcome, with 95% CI along with individual observations pre- and postflight. **Fig. 1** includes means (95% CI) for COC and non-COC users (indicated by filled symbols) for hematological variables, whereas in **Fig. 2**, there was insufficient data available to perform statistical analyses separated by COC use.

Astronauts' postflight primary outcomes were compared to clinically relevant terrestrial high-risk levels to determine whether a trend existed toward increased risk for VTE following short or long duration spaceflight. Secondarily, a characterization of pre/postflight changes was made. Primary hematological outcomes included: hemoglobin, hematocrit, MCV, platelet count and reticulocyte count, while biochemical outcomes included vitamin B12, iron, TIBC, transferrin, ferritin, and folate. The number of non-COC users was insufficient to permit statistical comparison to COC users.

We submitted pre- and postflight data to separate mixed-effects linear models for each primary outcome. The number of observations per outcome varied due to missing data and also because not all subjects underwent the same testing at the same time points. For this reason, mixed-modeling techniques were employed (rather than closed-form ANOVA modeling) in order to take advantage of all available data, without excluding subjects for whom both pre- and postflight data were unavailable. In the data set for this study, not all had both pre- and postflight measures, so random effects were used to link measures across the same subjects providing additional information to the model. Hematological outcomes were available pre- and postflight for most subjects, with data available from both COC and non-COC users sufficient for analysis. Each mixed-model included fixed main effect terms for comparing pre/postflight, COC use, and the interaction term evaluating whether the pre- and postflight changes were statistically

Table II. Total Number of Data Points Available for Each Variable with the Average Time Between Flight and Blood Draw.

			SHORT DURATION		LONG DURATION	
ANALYTE	FLIGHT TIMING	TIME TO/FROM FLIGHT MEAN (SD), DAYS	COC USER	NON-COC USER	COC USER	NON-COC USER
Vitamin B12	Pre	748.6 (1418.5)	2	2	7	1
	Post	0.57 (0.53)	0	0	6	1
Ln (Ferritin)	Pre	111.9 (97.4)	18	10	9	1
	Post	10.6 (16.0)	3	1	9	1
Iron	Pre	169.4 (276.2)	16	8	9	1
	Post	11.1 (16.2)	3	0	9	1
Ln (Reticulocyte Count)	Pre	124.1 (137.5)	18	10	9	1
	Post	5.7 (12.4)	6	5	9	1
Total Iron	Pre	170.8 (275.6)	16	8	9	1
Bind. Capacity	Post	11.3 (16.1)	3	0	9	1
Transferrin	Pre	126.5 (97.1)	16	7	9	1
	Post	11.3 (16.1)	3	0	9	1
Hematocrit	Pre	23.1 (18.9)	18	10	9	1
	Post	4.3 (11.4)	10	6	9	1
Hemoglobin	Pre	23.1 (18.9)	18	10	9	1
	Post	4.3 (11.4)	10	6	9	1
Mean Corp.	Pre	23.1 (18.9)	18	10	9	1
Volume	Post	4.3 (11.4)	10	6	9	1
Platelet	Pre	23.1 (18.9)	18	10	9	1
	Post	4.3 (11.4)	10	6	9	1
Ln (Folate)	Pre	726.3 (1458.0)	2	1	7	1
	Post	0.57 (0.49)	0	0	6	1

Measures (mean ± SEM) used in statistical analysis, showing subject numbers (in parentheses) for each measure and *P*-values. $P < 0.05$ is indicated by *. Blanks in the Non-COC Users column indicate insufficient subject numbers to complete analysis.

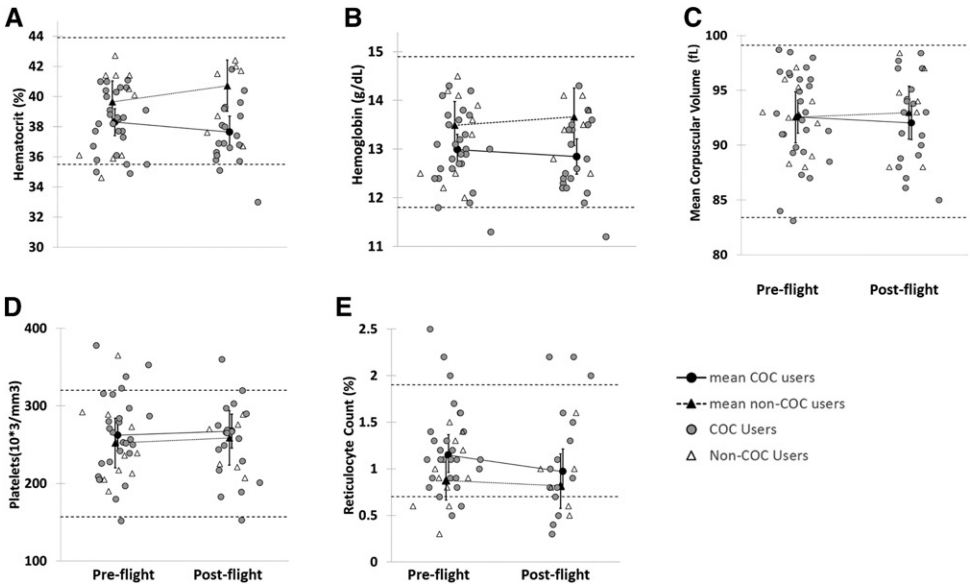

Fig. 1. The effect of spaceflight experience on hematological risk factors for venous thromboembolism. Hematological factors associated with VTE risk were compared before (left) and after (right) spaceflights for users (circles) and nonusers (triangles) of COCs. A) Hematocrit; B) hemoglobin; C) mean corpuscular volume; D) platelets; E) reticulocyte count. On each panel, clinical normal ranges are shown as dashed lines. COC users: individual data points are indicated by grey circles, means by black circles, and nonusers: individual data points are indicated by white triangles, means by black triangles. Numbers of data points available to analyze per variable are listed in Table II.

different for COC vs. non-COC users. We also included random y-intercepts for each mission to accommodate our longitudinal observational study design (repeated measures within individuals, e.g., both pre- and postflight measures). Unfortunately, there were insufficient pre- and postflight data from non-COC users for the biochemical outcomes for reasonable factorial analyses, so simpler mixed-effects models on COC users only were used to evaluate the effects of spaceflight only, with no group or interaction terms. These models also incorporated random intercepts to adjust for the repeated-measures variance structure.

RESULTS

Data were available from a total of 38 astronaut-flights: 28 short space shuttle missions and 10 longer ISS missions (Table I). Due to the relatively small cohort, data from different mission lengths were pooled for statistical analysis. COC use was documented during 18 short and 9 long duration missions. Among the COC users, median ethinyl estradiol dosage was 35 μg and the most frequently used progestin type was norethindrone. Only seven subjects had observations for all of the outcomes pre- and postflight; the majority had missing data for one or more outcomes (see Table II for numbers of observations per variable).

Elevations in any of the hematological measures would suggest more concentrated blood and, therefore, the potential for hypercoagulability, an important risk factor for VTE. When this cohort was analyzed as a whole (irrespective of COC use), statistical analysis of hematological outcomes showed no significant changes after spaceflights (Fig. 1, see **Table III** for *P*-values).

However, when COC users were analyzed separately from non-COC users, small but significant increases in hematocrit and hemoglobin were seen after spaceflight in the non-COC group, but not in the COC users (Fig. 1). It is important to note that this change is in the direction toward increased VTE risk. However, examination of data relative to terrestrial norms and known risk levels revealed no effect on VTE risk in this cohort for either spaceflight or COC use. Some data points were outside of the clinical normal ranges, but with only a single data point each pre- or postflight for this analysis, it was not possible to draw clinical conclusions. Additionally, values considered at-risk would be in the upper 20% of the normal range[3] (i.e., HCT = 42.22%) or as a 5% rise from any value[23] (as detailed in **Table IV**).

MCV, platelets, and reticulocyte count all showed no differences associated with spaceflight or contraceptive use. The majority of these data fell within the normal ranges and those that were outside were too low to have an impact on VTE risk. Some platelet data (Fig. 1D) were somewhat above the clinically normal range of 157–320 $\times$ 10^3/mm^3. However, literature regarding reactive thrombocytosis[7] suggests these outliers would need to be greater than 1000 $\times$ 10^3/mm^3 in order to pose a risk of VTE, and there were no points in this cohort $>$ 400 $\times$ 10^3/mm^3. The at-risk terrestrial level for hemoglobin is $<$ 1st centile while for MCV the risk lies below 78 fL and above 101 fL (Table IV).[22] None of the data for these two variables falls beyond at-risk levels.

Homocysteine data were not routinely collected from astronauts, thus a set of biochemical measures previously shown to correlate with homocysteine were examined for this study. Postflight data showed significant decreases in levels of vitamin B12, folate, iron, and transferrin in the total cohort (Fig. 2, Table III).

In contrast to the iron and transferrin results, TIBC and ferritin (markers of low iron) showed no spaceflight-associated differences. However, insufficient data in all biochemical variables prevented the evaluation of changes in non-COC users; therefore, the effect of COC use could not be determined. As seen in the analysis of hematological data, only a small number of individual observations exceeded clinical reference ranges.

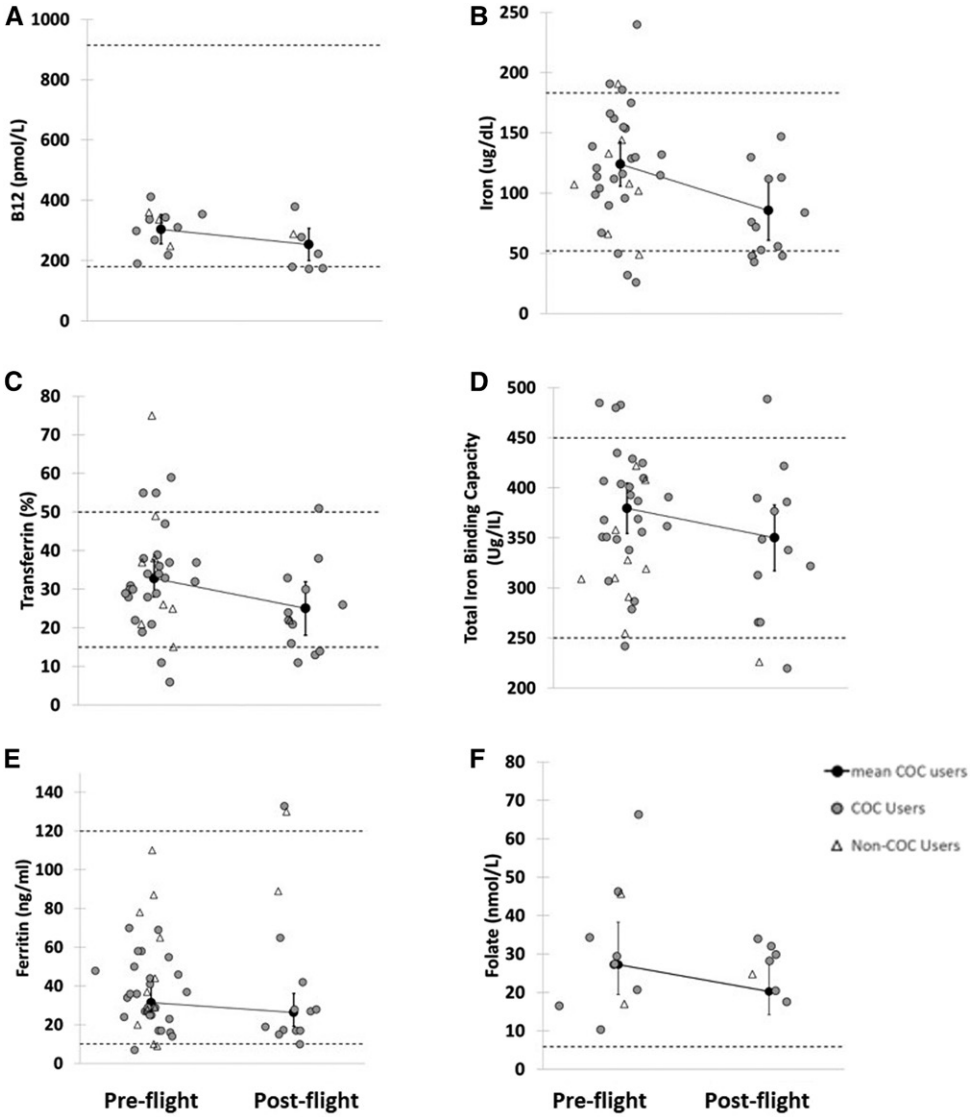

Fig. 2. The effect of spaceflight experience on biochemical risk factors for venous thromboembolism. Nutritional factors associated with VTE risk were compared before and after spaceflights for users (circles) and nonusers (triangles) of COCs. A) Vitamin B12; B) iron; C) transferrin; D) total iron binding capacity; E) ferritin; F) folate. On each panel, clinical normal ranges are shown as dashed lines; preflight values are on the left and postflight values are on the right. COC users: individual data points are indicated by grey circles, means by black circles, and nonusers: individual data points are indicated by white triangles. Numbers of data points available to analyze per variable are listed in Table II.

DISCUSSION

Analysis of available data showed no large changes in VTE risk factors after spaceflight regardless of contraceptive use. None of the variables investigated fall into the absolute at-risk thresholds postflight, despite some individual data points lying outside of the normal clinical ranges. Pre- to postflight comparisons do not suggest a change in any of the outcomes toward a potential increase in VTE risk. Only four variables differed postflight (folate, iron, transferrin, and vitamin B12) and these were based on a small number of observations, and furthermore, each of these is linked to other factors that displayed no change in VTE risk, such as hemoglobin or homocysteine.

The limited data available at this point support the hypothesis that female astronauts are not likely to be at an increased risk of VTE with respect to the intervention of spaceflight. However, many factors unique to spaceflight need to be considered before finalizing such a conclusion.

Astronauts generally lead active lifestyles with average to above average physical fitness levels. Spending hours in a cramped seated position increases the risk of VTE due to pressure points providing initiation sites for thrombi.[28] Astronauts' training includes periods of immobility during Soyuz training, long-haul travel, or other confined operations prior to launch which may temporarily increase risk prior to a spaceflight mission. This may be of limited clinical significance on otherwise active healthy individuals considering the literature derives data from the general population with variable fitness; the extrapolation to such a fit cohort is unknown.

During microgravity in spaceflight, pressure points do not develop. However, for several hours during prelaunch astronauts are temporarily confined to a seated position, allowing pressure points to become the potential foci for thrombus formation. Cephalic fluid shift as a physiological adaptation to microgravity is thought to result in a 12–15% decrease in circulating plasma volume. This triggers a splenic removal of nucleated red blood cells to attain a normal hematocrit. Combined with secondary red cell lysis as the body becomes euvolemic in the initial 2 wk in space, the potential arises whereby VTE could develop.

The red cell lysis effect could potentially affect commercial spaceflight protocols of the future. The population of commercial spaceflight participants (CSP) who would engage in such programs are likely to not be as fit and healthy as the astronaut population, and therefore it is unknown if these early time periods in space would cause CSPs to have an increased risk for VTE, requiring consideration of thromboprophylaxis.

Table III. Detailed Statistical Analysis.

	TOTAL COHORT MEAN ± SEM (*N*)			COC USERS MEAN ± SEM (*N*)		NON COC-USERS MEAN ± SEM (N)		*P*, COC USERS vs. NONUSERS		*P*, COC USERS ONLY
	PREFLIGHT	POSTFLIGHT	*P*	PREFLIGHT	POSTFLIGHT	PREFLIGHT	POSTFLIGHT	PREFLIGHT	POSTFLIGHT	PRE TO POST
Hct (%)	38.7 ± 0.4 (38)	38.5 ± 0.5 (26)	0.665	38.3 ± 0.4 (27)	37.6 ± 0.4 (19)	39.6 ± 1.0 (11)	40.7 ± 0.8 (7)	0.223	0.004*	0.469
Hgb (g/dL)	13.1 ± 0.1 (38)	13.1 ± 0.1 (26)	0.712	13.0 ± 0.1 (27)	12.8 ± 0.2 (19)	13.5 ± 0.3 (11)	13.7 ± 0.2 (7)	0.164	0.007*	0.651
MCV (fL)	92.6 ± 0.6 (38)	92.3 ± 0.6 (26)	0.286	92.6 ± 0.8 (27)	92.0 ± 0.8 (19)	92.5 ± 0.9 (11)	93.0 ± 1.1 (7)	0.980	0.490	0.411
Platelet (103/mm^3)	259.3 ± 8.4 (38)	264.99 ± 9.5 (26)	0.377	262.3 ± 10.2 (27)	267.5 ± 10.6 (19)	252.0 ± 14.5 (11)	267.5 ± 10.6 (7)	0.567	0.702	0.477
Retic (%)	1.15 ± 0.07 (38)	1.07 ± 0.11 (21)	0.497	1.23 ± 0.09 (27)	1.14 ± 0.15 (15)	0.95 ± 0.11 (11)	0.90 ± 0.14 (6)	0.066	0.270	0.455
B12 (pmol/L)	367.9 ± 61.1 (12)	321.3 ± 61.9 (7)	0.033*	383.9 ± 78.3 (9)	337.3 ± 79.0 (6)					
Iron (μg/L)	121.4 ± 8.0 (34)	79.3 ± 9.3 (13)	0.003*	124.0 ± 9.8 (25)	85.8 ± 9.9 (12)					
TIBC (μg /dL)	367.3 ± 10.5 (34)	339.2 ± 16.5 (13)	0.080	379.6 ± 12.1 (25)	350.1 ± 17.4 (12)					
Transferrin (%)	33.5 ± 2.4 (33)	24.7 ± 3.0 (13)	0.043*	32.8 ± 2.4 (25)	25.0 ± 3.2 (12)					
Ferritin (ng/ml)	38.9 ± 3.7 (38)	45.3 ± 9.9 (14)	0.480	35.6 ± 3.2 (27)	35.7 ± 9.1 (12)					
Folate (nmol/L)	31.1 ± 4.7 (11)	20.9 ± 2.8 (7)	0.026*	31.0 ± 5.3 (9)	22.0 ± 3.0 (6)					

Measures (mean ± SEM) used in statistical analysis, showing subject numbers (in parentheses) for each measure and *P*-values. $P < 0.05$ is indicated by *. Blanks in the Non-COC Users column indicate insufficient subject numbers to complete analysis.

Research on decompression sickness (DCS) risk in sports divers reveals that DCS risk in women is greater in the first week of the menstrual cycle.[14] However, the overall risk of DCS in female sports divers is less than in male sports divers,[27] and the use of COCs does not appear to alter risk of DCS.[5] Astronauts experience decompressions from different exposures (extravehicular activity, hypobaric chamber use, neutral buoyancy laboratory training) compared to sports divers and are protected by safety protocols to minimize the risk of DCS. However, the possibility of DCS due to exposure to these environments exists. Intravascular bubble formation is a known occurrence during decompression either for diving training preflight or extravehicular activity during spaceflight. Their presence is thought to affect blood viscosity, activate complement, and cause mechanical damage to the endothelium. Proteins may adhere to the bubble surface, making interaction with the endothelium possible. This leads to an inflammatory prothrombotic state;[16] however, it is unknown how this is affected by COC use or whether the risk of VTE is temporarily or locally increased. Other features of the spaceflight environment might have an impact on the overall VTE risk. It is known that endothelial cells are highly sensitive to microgravity, leading to structural and functional changes; for example, an increase in cell membrane permeability and cytoskeletal damage, with some of these changes persisting in readapted cells.[17] Further research is required in order to delineate the impact of COC use during spaceflight on endothelial damage to better understand the relationship with VTE risk. Radiation can cause oxidative stress and damage at a cellular level, yet it is unknown whether the exposures encountered during spaceflight would lead to an increase in VTE risk. Immunological stress (for example, an acute infection) is known to increase the risk of VTE on Earth; however, this has not been studied in flight. Furthermore, this study was conducted as a retrospective analysis of de-identified data; therefore use of medications, vitamins, or supplements was not considered. Precise age, blood type, exercise regimes or long duration travel logs were not available. These may be potential confounders.

In order to monitor risk for VTE in the pre- and postflight period, thrombophilia screening could be offered prior to initiating COC use[8] and coagulation screening could be added to regular health checks if astronauts continue to use COCs. This would include degradation of cross-linked fibrin (d-dimer), fragmin f1.2, thrombin generation, coagulation cascade variables,[26] and research biomarkers for endothelial activation, including V-CAM-1 and E-selectin. Correlation with blood group may also be considered as non-O group blood types have higher levels of factor VIII and therefore a higher risk of VTE.[4] It is feasible, however, to use ultrasound imaging during missions if VTE is suspected. A progestin-only contraceptive could be considered[31] as the risk of VTE is not increased with the levonorgestrel intrauterine device when compared with estrogen-levonorgestrel COCs.[15] High VTE risk products are not advised in women over the age of 35 yr, therefore COCs with 30 μg estrogen should be considered to replace the 50-μg estrogen containing pills currently stored onboard the ISS to treat breakthrough bleeding.[11,19,29] As the average age of first childbirth in

Table IV. Possible Risk Factors for Venous Thromboembolism (VTE) in Spaceflight.

RISK FACTOR	ACCEPTABLE CLINICAL REFERENCE RANGE	RISK THRESHOLDS	VTE ODDS RATIO
Hemoglobin (Hb)	11.8–14.9 ($g \cdot dL^{-1}$)	<1st centile [Rezende S. Written communication; July 2015]	3.4 (95% CI 1.7–6.7)[22]
		Polycythemia	No conclusive evidence of increased risk[1]
Mean Corpuscular Volume (MCV)	83.4–99.1 (fL)	<1st centile (< 78.09)—linked with iron deficiency	1.95 (95% CI of 1.15–3.31)[22]
		>99th Centile (>101.48)—linked with B12 deficiency	2.65 (95% CI of 1.61–4.35)
Hematocrit (Hct)	35.5–43.9 (%)	5% increase in Hct	1.25 (95% CI: 1.08–1.44)[24]
		Hct in the upper 20% of normal range	1.5[2]
Reticulocyte count	0.7–1.9 (%)	Theoretical Risk – unknown if increased reticulocyte count due to neocytolysis during early stages of spaceflight missions increase the risk of VTE	Theoretical – potentially increased viscosity, however no evidence found (last search October 2019). Abnormal cell shape (e.g., sickle cells) increase risk of VTE more so than absolute reticulocyte count.
Platelet count	157–320 ($10^3/mm^3$)	$>250 \times 10^9/L$	1.67 (95% CI 1.23–2.26)[18]
		$500 \times 10^9/L$[10]	Hazard Ratio 5.3 (95% CI 1.7–16.4)
Homocysteine		>95th percentile—linked with decreases in B12 and folate	2.5 (95% CI 1.8–3.5)[20] to 2.95 (95% CI 2.08–4.17)[6]

The effect on VTE listed above is based on terrestrial studies and is not impacted by combined oral contraceptive pill (COC) use.

the United States is increasing, women may desire reversible contraception for longer durations. Occupational considerations may drive female astronauts to use COCs beyond the age of 35 yr; however, these women may not be the only ones faced with this decision as a result of their career.

This study supports the hypothesis that the intervention of spaceflight does not appear to increase a female astronauts' overall risk of VTE. It also reinforces the importance of healthy lifestyle on VTE risk reduction as well as highlighting how occupational requirements may impact VTE risk beyond that which is measurable by traditional VTE risk assessment models, emphasizing the need for a holistic approach to contraceptive prescribing.

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