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Monitoring sexual hormones in women going to high altitude—a pilot study

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Background: The susceptibility to acute mountain sickness (AMS) in relation to sexual hormones in women remains elusive, partly because hormones could not be conveniently measured. We evaluated a novel kit for self-monitoring sexual hormones in women and recorded AMS incidence during high-altitude sojourns.

Methods: Two groups of healthy, premenopausal women, mean \pm SD age 23.1 ± 2.3 years, residing $<1,000$ m underwent baseline evaluations at 760 m before travelling to and staying for 2 days and nights (48 h) at 3,100 m or 3,600 m, respectively. Participants self-monitored morning urine sexual hormone concentrations (estrone-1-glucuronide, E1G, pregnanediol-3-alpha-glucuronide, PdG, and luteinizing hormone, LH) daily for 30d including altitude sojourns using the simple "Proov" kit (MFB Fertility Inc). Follicular and luteal menstrual cycle phases detected by LH peak, altitude-related adverse health effects (ARAHE), AMS [Lake Louise score 2018 (LLS) ≥ 3 points including headache] and pulse oximetry (SpO₂) were assessed.

Results: 1,172 of 1,250 (93.8%) hormone measurements were successful, 78 of 1,250 (6.2%) failed due to nonadherence or technical failure. At 3,600 m, mean differences in urinary PdG concentration were 3.8 mcg/ml (95% CI, 0.6–7.1) between luteal and follicular cycle phases. At 3,100 m, corresponding difference was 8.5 mcg/ml (95% CI, 5.0–12.0). At 3,100 m, 9 of 21 (43%) women were diagnosed with AMS with SpO₂ of $93.0 \pm 1.6\%$ and LLS of 0.3 ± 1.4 in the morning after the first night. At 3,600 m, 12 of 21 (57%) women had AMS ($p = 0.355$ vs. 3,100 m) with SpO₂ of $86.8 \pm 1.8\%$ ($p < 0.05$ vs. 3,100 m) and LLS of 1.9 ± 1.4 ($p < 0.05$ vs. 3,100 m).

Conclusion: Self-monitoring female sexual hormones during high-altitude field studies with the employed kit is feasible and provides physiologically plausible trends of hormone levels over the menstrual cycle. Our data provide a valuable basis for designing further studies to evaluate AMS susceptibility in women.

KEYWORDS

high-altitude (HA), hormone/reproduction/sexual, AMS, self-monitoring, menstrual cycle phase

Introduction

To date, there is no reliable, validated, and simple tool for monitoring hormonal concentrations or reliably identifying menstrual cycle phases in women during altitude sojourns. The validation of a reliable tool is particularly important since the pathophysiology of altitude-related adverse health effects (ARAHE), particularly acute mountain sickness (AMS), and factors for individual susceptibility remain elusive (1). Importantly, it has not yet been quantitatively assessed whether women are more, equally or less prone to develop AMS than men (2). The unresolved issue might originate from underrepresentation of women in high altitude studies, lack of powered sex-specific analyses or the poor characterization of premenopausal women in regard of the menstrual cycle phase, sex hormone concentrations, in particular estrogen, luteinizing hormone and progesterone, and cycle day while staying at high altitude. Hormonal changes related to the menstrual cycle phases can alter breathing control, which may result in different altitude-related adaptations. Progesterone, which is up-regulated during the luteal phase and also during stress situations (3), is a well-known respiratory stimulant associated with elevated minute ventilation and decreased PaCO₂ during the luteal phase compared to the follicular phase (4, 5). Despite these observations at low altitude, previous studies found no relationship between menstrual cycle phase or sex hormones and AMS susceptibility, however, most studies did not quantify and assess sex hormones and cycle phase at high altitude. In contrast, a small study conducted in 1997 and 1998 assessed sex hormone levels at high altitude and found a significant difference of 15% in AMS incidence between menstrual cycle phases, though it concluded that the difference was not clinically relevant (6). Another study found sexual hormone changes in lowland women going to high altitudes but have not analyzed them in regard to AMS (7). Based on these previous reports and technological advancements, the primary purpose of this prospective pilot study was to evaluate the feasibility, functionality, and tolerability of using commercially available fertility self-monitoring kits to measure urinary sex hormone concentrations and to determine the menstrual cycle phases and cycle days when travelling to high altitude. Furthermore, to facilitate sample size estimations and provide preliminary insights into potential differences in clinical and physiological outcomes between the luteal and follicular menstrual cycle phases, additional measures—such as AMS, nocturnal pulse oximetry, subjective sleep quality and vital signs—were assessed.

Therefore, this pilot study examined the hypotheses that commercially available self-monitor fertility devices are suitable for urinary hormone assessments at high altitudes and that the

resulting hormone profiles allow an accurate determination of menstrual cycle phases and cycle days in females staying at high altitudes.

Methods

Study design and setting

This prospective, non-randomized pilot study was conducted at the National Center of Cardiology and Internal Medicine, Respiratory Medicine Department, Bishkek (760 m), Kyrgyzstan; at the Swiss-Kyrgyz High-Altitude Clinic in Tuja Ashu (3,100 m), Kyrgyzstan, which is a 4 h bus ride away from the first location and where participants spent 2 days and nights (48 h); and at the High Altitude Kumtor Gold Mine operation facility (3,600 m), Kumtor, Kyrgyzstan, 8 h by bus, where participants also spent 2 days and nights (48 h). The ascent to 3,100 m (Expedition 1, $n=21$) was performed in July 2022; the ascent to 3,600 m (Expedition 2, $n=21$) in September 2022 and both altitude ascents were scheduled independently of the menstrual cycle phases or cycle days of the participants. Sixteen participants from Expedition 1 participated also in Expedition 2 and 5 new participants had to be recruited (Figure 1).

Participants in this study were recruited through advertisements at different universities around Bishkek. Included were premenopausal, naturally cycling, eumenorrheic, non-smoking, healthy women with a BMI >18 kg/m² and <30 kg/m², aged 18–44 years, living at altitudes under 1,000 m. Exclusion criteria were any pre-existing disease, regular intake of medication (including oral contraception), other types of hormonal contraceptives (hormonal intrauterine device, vaginal ring, subcutaneous injections or implants), pregnancy or nursing, and any altitude trip <4 weeks prior to the study. The study was approved by the Ethic Committee of the National Center of Cardiology and Internal Medicine named after academician M. Mirrakhimov (Protocol No. 07 in the year of 2022) and participants provided written informed consent.

Hormone monitoring

For 30 consecutive days, beginning on the day of baseline measurements at 760 m, all participants monitored their urine metabolite concentrations of estrogen, luteinizing hormone, and progesterone using their first urine sample of the day, collected before any food or fluid intake. The hormone assessments were performed using two different sex hormone monitoring devices, described in detail below.

Proov full cycle hormone insights kit (*Proov*, MFB Fertility Inc., CO, US)

This device was used during both Expedition 1 & 2. The procedure requires a hormone test strip into a fresh morning urine sample for 10–20 s, collected before any food or fluid intake. The *Proov* multi-hormone test strip lateral flow assay uses

Abbreviations

AMS, acute mountain sickness; E1G, estrone-1-glucuronide; PdG, pregnanediol-3-alpha-glucuronide; LH, luteinizing hormone; ARAHE, altitude-related adverse health effects; LLS, Lake Louise score; SpO₂, oxygen saturation; PaCO₂, partial pressure of carbon dioxide; BMI, body mass index; LLQ, Lake Louise questionnaires; UIAA, International Climbing and Mountaineering Federation.

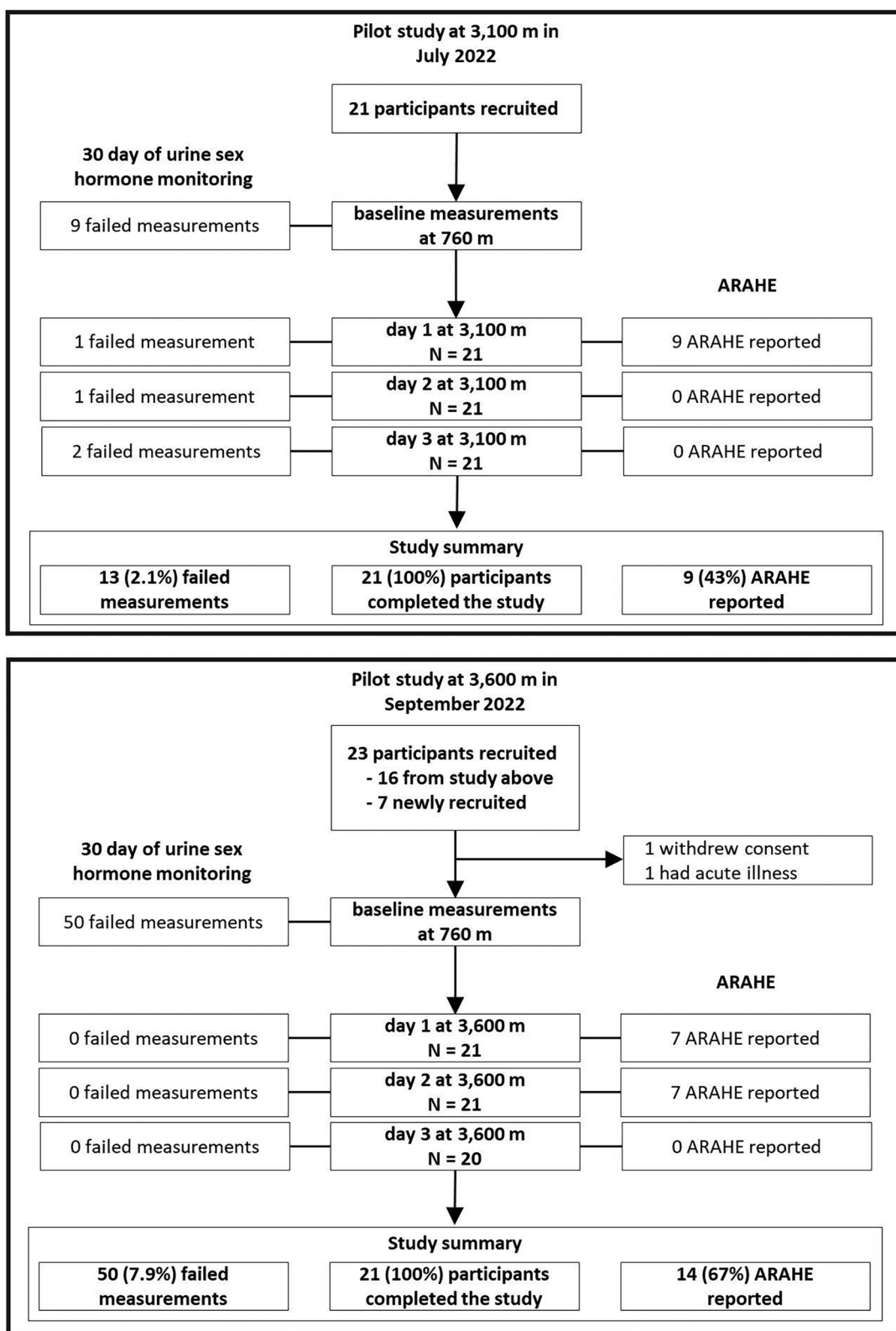


FIGURE 1 Study design of the pilot study. A pilot study validating the commercially available fertility monitor *Proov* to monitor hormones and menstrual cycle phases before, during and after an altitude sojourn. Women monitored their hormone for 30 consecutive days. During the hormone monitoring they ascended and stayed for 2-day and nights (48 h) at either 3,100 (Expedition 1) or 3,600 m (Expedition 2), respectively.

gold nanoparticles and buffered sample pads to adjust for pH and hydration levels, filter unwanted particulates and bind contaminants in urine that may interfere with test accuracy. The strip contains three test lines and one control line, corresponding to estrone-1-glucuronide (E1G), pregnanediol-3- α -glucuronide (PdG), and luteinizing hormone (LH) (beta subunit). These urinary metabolites can be used to determine the follicular phase, ovulation, and the luteal menstrual cycle phase in naturally cycling women (8). After 10 min, the participant takes a photo of the urine test strip with the smartphone and uploads it onto the company server using the *Proov* app. The application server employs machine learning algorithms specifically tailored to analyze photographed images of the test strip, accounting for variations in camera, lighting, and operating system, while also verifying input and output regularities and mathematically deriving the associated hormone levels (9). In the case of internet connection loss, the company can conduct offline analysis if the time, day and picture of the test strip of the participant are provided. In this study, daily concentrations of sex hormones E1G, PdG and LH were extracted from the *Proov* app.

Mira fertility tracking kit (Mira—Crow Canyon PL, San Ramon, CA, USA)

This device was used during Expedition 2. Identical to the *Proov* testing procedure, *Mira* analysis requires to dip a hormone test strip for 10–20 s into a fresh urine sample collected in the morning before any fluid or food intake. Thereafter, the strip will be inserted into the *Mira* device to initiate the quantitative analysis of estrogen-3-glucuronide (E3G), LH and PdG. After approximately 21 min the results will be synchronized with the *Mira* smartphone app through Bluetooth. In case of an analysis error, the strip cannot be re-analyzed.

Together with the information regarding the first day of the participant's last menstrual bleeding, the measured sex hormones were visually plotted. Based on the visually confirmed LH peak and increment of PdG, the follicular (first day of menstrual bleeding to LH peak) and luteal menstrual cycle phases (LH peak to end of cycle) were identified. To ensure a high-quality hormone data collection, all participants attended a one-time instructional session on the proper use of the hormone monitoring kits and the accompanying app. The apps were installed and setup under the guidance of the investigators. The following morning, all participants performed their first hormone assessment in the hospital, allowing them to discuss questions related to the procedure. Thereafter, daily reminders regarding hormone monitoring were sent to the participants. Additionally, they were encouraged to submit their hormone values each day or, if no values were available, to provide a reason for the missing data.

Medical history, symptoms, and clinical examination

A medical history has been obtained, including information on menstrual cycle length and the starting and ending days of the

participants' last menstruation. Physical examination included measurements of weight, height, blood pressure, heart rate, and cardiac and pulmonary auscultation. At altitudes, adverse events and AMS incidences were assessed, using both the revised and original Lake Louise questionnaires (LLQ), as well as the Environmental Symptom Questionnaire cerebral score (AMSc) (10, 11). Primary definition of AMS incidence was a 2018 LLQ score of ≥ 3 points including headache, over the two-day period at high altitude; secondary AMS definitions included a 1993 LLQ score of ≥ 3 points and an AMSc of ≥ 0.7 . Since previous studies in both sick and healthy persons traveling to high altitudes reported the occurrence of non-AMS related ARAHE (12), this pilot study additionally assessed the incidence of ARAHE at high altitudes. ARAHE was defined as any medical health condition (including AMS) that occurred at high altitude and required medical intervention or premature descent.

Nocturnal pulse oximetry was performed at 760 m and at 3,600 m to assess nocturnal oxygenation. Sleepiness was assessed with the Karolinska Sleepiness Scale and subjective sleep quality with a 100-mm visual analogue scale ranging from 0 (extremely poor) to 100 (excellent) (13).

Outcomes

The main outcomes included the proportion and comparison of successful applications of the *Proov* and *Mira* hormone test kits, their failure rates, and reasons for failure. Additional outcomes included daily hormone concentrations throughout the menstrual cycle, differences in estrogen and progesterone concentrations between the follicular and luteal menstrual cycle phases, and the timing of the LH peak, defined as the day with the highest median value of 3 consecutive daily concentrations. The incidence of AMS and other ARAHE, nocturnal pulse oximetry, and subjective sleep quality as well as physiological variables in the different menstrual cycle phases were determined.

Statistics

No sample size estimation was performed for this pilot study. A convenience sample of 20 participants per expedition to 3,100 m and 3,600 m were recruited. The feasibility of hormone monitoring at low and high altitudes, as well as during experimental field expeditions, was quantified using descriptive statistics on successful instances of hormone monitoring, hormone concentrations, and failure rates associated with the use of the *Proov* or *Mira* devices, respectively. Based on the findings of the two devices, menstrual cycle phases, ovulation day, and failure rates were compared using Chi-square test statistics and Pearson correlation. AMS incidences and physiological variables were then compared between menstrual cycle phases and between altitudes using mixed linear regressions to compute mean differences and 95% confidence intervals. Continuous outcomes are presented as means \pm SE and binary outcomes as numbers and proportions. Two exploratory regression models

were used to evaluate (1) the associations between sex hormone concentrations and SpO₂ (mixed linear regression model); (2) the associations between menstrual cycle phases and the incidence of AMS (logistic regression model). Due to the small sample size, the parameters for the mixed models were predefined. Therefore, in the model for SpO₂, sex hormones (E1G, LH and PdG) and assessment altitudes (760 m, 3,100 m and 3,600 m) were used as predictors. A two-sided *p*-value of 0.05 was considered statistically significant. Statistical analyses were performed in STATA version 15 (StataCorp LLC, College Station, Texas, USA).

Results

The study flow chart is presented in Figure 1. Out of 26 participants with a mean ± SD age of 23.5 ± 2.5 years, a total of 21 (80.7%) went to 3,100 m; 21 (80.7%) went to 3,600 m and 16 (61.5%) participants completed both expeditions (Table 1). Based on the assessed hormone concentrations, 52.4% of participants were in their follicular, 40.5% in their luteal and 7.1% unknown menstrual cycle phase when staying at high altitudes. The menstrual cycle length assessed with the *Proov* app was 29 ± 2 days and almost identical with what participants reported during the screening visit (30 ± 2 days). The maximum deviation between the assessed and reported menstrual cycle length was 9 days.

Hormone monitoring and comparisons between menstrual cycle phases

When using the *Proov* hormone test kit, the daily urinary hormone measurement error rates were 4.5% (95% CI of 3.0–6.5%) in the group travelling to 3,100 m, 7.9% (95% CI of 5.9–10.3%) in those travelling to 3,600 m, and 6.2% overall (95% CI of 5.0–7.7%) (Table 1). At 3,600 m, the corresponding error rate when using the *Mira* hormone test kit was 11.4% (95% CI of

9.8–15.0%, *P* < 0.001 between error rates of *Proov* vs. *Mira* at 3,600 m). The urinary hormone monitoring and the assignment of the participants to a specific menstrual cycle phase and cycle day while staying at altitude were successful and are illustrated in Figure 2, Upper Panel. Figure 2, Lower Panel shows the proportions of participants suffering from AMS during the follicular compared to the luteal phase, however, exploratory mixed logistic regression analysis showed no association between menstrual cycle phases and the incidence of AMS defined by the 2018 LLQ criteria (Odds ratio of 0.50, 95% CI 0.09–2.8, *p* = 0.430). Table 2 shows the comparison of the menstrual cycle phases and the mean differences (95% CI) in other physiological and clinical outcomes between the luteal and follicular phases. Both progesterone and estrogen were higher during the luteal compared to the follicular phase. During the nights at 3,600 m, participants in the luteal phase showed a trend toward faster SpO₂ acclimatization between nights 1 and 2, with a mean difference (95% CI) of 2.1% (−0.3 to 4.6, *p* = 0.085), compared to participants in the follicular phase (Table 3). These findings align with the results from mixed linear regression analysis on daytime SpO₂, showing a positive correlation with PdG concentration and a negative correlation with E1G and absolute altitude of measurement (Supplement Table S2).

AMS and other ARAHE

During the altitude sojourns, 9 of 21 (43%) participants at 3,100 m and 12 of 21 (57%) at 3,600 m developed AMS (Table 4, *p* = 0.355 between altitudes). At 3,600 m, 24% of participants experienced other ARAHEs not related to AMS, including fainting (*N* = 1) and fever (*N* = 1) on the day of arrival; panic attack (*N* = 1) during the first night and abdominal pain (*N* = 1) and diarrhea (*N* = 1) over the time course of the 2 days and nights (Table 4). As shown in Figure 3, a high proportion of participants who experienced an ARAHE or AMS at 3,100 m also experienced one at 3,600 m.

TABLE 1 Participant demographics.

Variable	All	Participants going to 3,100 m	Participants going to 3,600 m	Participants going to 3,100 and 3,600 m
<i>N</i>	26	21	21	16
Age, years	23.5 ± 2.5	23.1 ± 2.3	23.7 ± 2.7	23.1 ± 2.5
Height, m	1.63 ± 0.07	1.61 ± 0.07	1.63 ± 0.08	1.61 ± 0.07
Weight, kg	59.3 ± 8.2	59.0 ± 7.6	59.9 ± 7.5	60.3 ± 8.0
BMI, kg/m ²	22.4 ± 3.2	22.7 ± 3.3	22.7 ± 3.0	23.3 ± 3.5
Menstrual Cycle				
Self-reported Cycle length, days ^a	30 ± 3	29 ± 1	30 ± 5	29 ± 1
Measured Cycle length, days ^b	29 ± 2	29 ± 2	29 ± 2	29 ± 2
Length of menstruation, days ^a	5 ± 2	6 ± 1	5 ± 2	6 ± 1
<i>Proov</i> hormone monitoring measurement errors, <i>N</i>	78 of 1,250 (6.2%)	28 of 620 (4.5%)	50 of 630 (7.9%)	59 of 952 (6.2%)
<i>Mira</i> hormone monitoring measurement errors, <i>N</i>	71 of 624 (11.4%)	NA	71 of 624 (11.4%)	NA

Values presented in mean ± SD. BMI, body mass index.

^aProvided by asking each participant during the screening visit.

^bAssessed using the *proov* Fertility app.

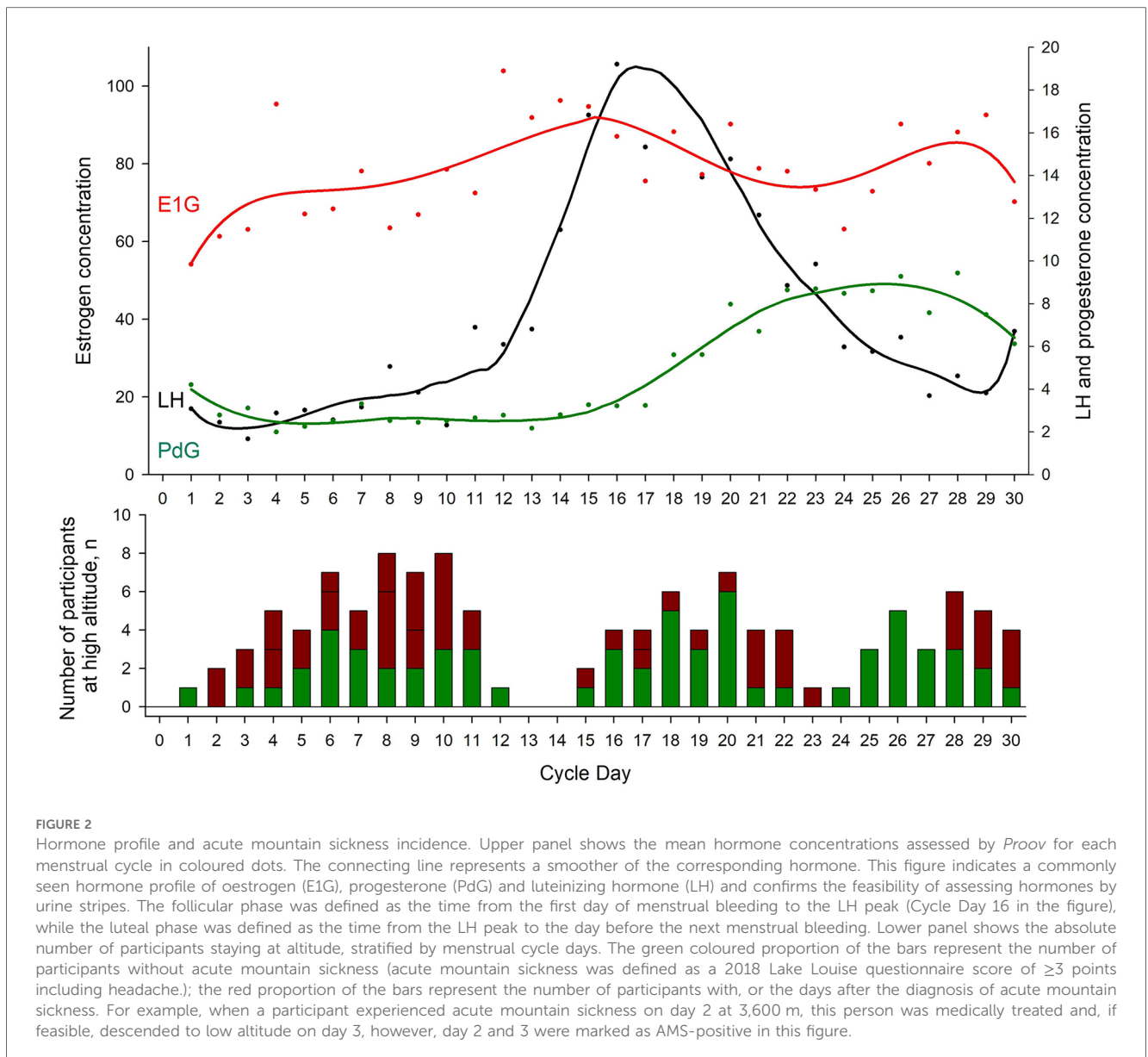


FIGURE 2

Hormone profile and acute mountain sickness incidence. Upper panel shows the mean hormone concentrations assessed by *Proov* for each menstrual cycle in coloured dots. The connecting line represents a smoother of the corresponding hormone. This figure indicates a commonly seen menstrual cycle profile of oestrogen (E1G), progesterone (PdG) and luteinizing hormone (LH) and confirms the feasibility of assessing hormones by urine stripes. The follicular phase was defined as the time from the first day of menstrual bleeding to the LH peak (Cycle Day 16 in the figure), while the luteal phase was defined as the time from the LH peak to the day before the next menstrual bleeding. Lower panel shows the absolute number of participants staying at altitude, stratified by menstrual cycle days. The green coloured portion of the bars represent the number of participants without acute mountain sickness (acute mountain sickness was defined as a 2018 Lake Louise questionnaire score of ≥ 3 points including headache.); the red proportion of the bars represent the number of participants with, or the days after the diagnosis of acute mountain sickness. For example, when a participant experienced acute mountain sickness on day 2 at 3,600 m, this person was medically treated and, if feasible, descended to low altitude on day 3, however, day 2 and 3 were marked as AMS-positive in this figure.

Secondary outcomes

On the morning of day 2 at 3,100 m, no significant differences were observed in vital parameters nor subjective sleep quality compared to 760 m, except for an expected decrease in SpO_2 (Table 5). In contrast, at 3,600 m, a significant decrease in SpO_2 and subjective sleep quality as well as a significant increase in diastolic blood pressure, heart rate and AMS severity were observed (Table 5). At 3,600 m, nocturnal SpO_2 dropped and oxygen desaturation index increased during the first night compared to 760 m, but significantly improved during the second night (Supplement Table S1).

Discussion

This pilot study confirms that daily urinary sex hormone concentration monitoring using the commercially available

fertility apps *Proov* and *Mira* is feasible for several consecutive days at high altitudes of up to 3,600 m, with the *Proov* device associated with lower error rates compared to *Mira*. Nevertheless, both hormone testing kits provide physiologically plausible urinary sex hormone concentrations to determine menstrual cycle phases and cycle days before, during, and after a high-altitude sojourn and can be considered as tools for future studies in premenopausal women evaluating susceptibility to AMS and its dependence on menstrual cycle phases. An important finding was that during the 2-day sojourns at high altitudes, the incidence of AMS was 43% at 3,100 m and 57% at 3,600 m. Moreover, other ARAHES in the absence of AMS were observed at 3,600 m, encompassing fainting, fever, panic attacks, abdominal pain and diarrhoea. This underscores the diverse array of hypoxia-related, clinically relevant conditions in women that have rarely been reported.

TABLE 2 Insights into menstrual cycle phase-related differences at high altitude.

Variable	Group 1 at 3,100 m				Group 2 at 3,600 m			
	Follicular phase	Luteal phase	Mean MCP difference (95% CI)	Mean effect size (95% CI)	Follicular phase	Luteal phase	Mean MCP difference (95% CI)	Mean effect size (95% CI)
<i>N</i>	12	7			11	10		
Hormones								
Estrogen, ng/ml	85 ± 20	92 ± 26	6 (−57 to 70)	0.07 (−0.63 to 0.78)	81 ± 22	145 ± 22	64 (5 to 123)	0.72 (0.06 to 1.38)
Progesterone, µg/ml	1.6 ± 1.1	10.1 ± 1.4	8.5 (5.0 to 12.0)	1.42 (0.84 to 2.01)	5.2 ± 1.2	9.0 ± 1.2	3.8 (0.6 to 7.1)	0.64 (0.09 to 1.19)
Luteinizing hormone, mIU/ml	4.6 ± 3.1	3.4 ± 4.1	−1.2 (−11.3 to 8.9)	0.10 (−0.89 to 0.70)	7.7 ± 3.4	10.2 ± 3.4	2.6 (−6.9 to 12.0)	0.20 (−0.55 to 0.95)
Clinical examination								
Systolic blood pressure, mmHg	106 ± 3	108 ± 3	2 (−4 to 8)	0.14 (−0.34 to 0.61)	104 ± 2	106 ± 2	2 (−4 to 8)	0.16 (−0.29 to 0.62)
Diastolic blood pressure, mmHg	75 ± 2	71 ± 2	−3 (−9 to 3)	−0.46 (−1.27 to 0.36)	77 ± 2	75 ± 2	−2 (−8 to 4)	−0.25 (−1.04 to 0.53)
Heart rate, bpm	88 ± 3	87 ± 4	0 (−10 to 9)	−0.04 (−0.76 to 0.69)	96 ± 3	95 ± 3	−1 (−9 to 8)	−0.05 (−0.74 to 0.65)
SpO ₂ , %	92.6 ± 0.5	93.9 ± 0.6	1.3 (−0.3 to 2.9)	0.30 (−0.07 to 0.66)	86.3 ± 0.6	86.6 ± 0.5	0.3 (−1.3 to 1.8)	0.06 (−0.29 to 0.42)
Acute mountain sickness								
2018 Lake Louise Score	0.4 ± 0.3	0.3 ± 0.5	−0.1 (−1.2 to 1.0)	−0.10 (−0.97 to 0.76)	2.2 ± 0.4	1.8 ± 0.4	−0.4 (−1.4 to 0.6)	−0.31 (−1.13 to 0.50)
1993 Lake Louise Score	0.5 ± 0.5	0.3 ± 0.6	−0.2 (−1.8 to 1.4)	−0.14 (−1.16 to 0.88)	3.0 ± 0.5	2.5 ± 0.5	−0.5 (−2.0 to 1.0)	−0.32 (−1.28 to 0.63)
AMSc score	0.06 ± 0.08	0.03 ± 0.11	−0.04 (−0.30 to 0.22)	−0.15 (−1.20 to 0.89)	0.48 ± 0.09	0.30 ± 0.09	−0.18 (−0.42 to 0.06)	−0.73 (−1.71 to 0.25)
Subjective sleep quality								
Karolinska Sleepiness Scale	4.1 ± 0.4	3.9 ± 0.5	−0.2 (−1.4 to 1.1)	−0.14 (−1.03 to 0.74)	4.4 ± 0.4	3.6 ± 0.4	−0.8 (−2.0 to 0.4)	−0.57 (−1.39 to 0.26)
Time until falling asleep, min	23 ± 12	21 ± 16	−2 (−42 to 38)	−0.05 (−0.92 to 0.82)	70 ± 14	45 ± 14	−25 (−62 to 13)	−0.54 (−1.36 to 0.28)
Number of nocturnal awakenings, n	1 ± 0	1 ± 0	0 (−2 to 1)	−0.33 (−1.18 to 0.51)	3 ± 0	1 ± 0	−2 (−3 to 0)	−1.17 (−1.96 to −0.38)
Waketime after sleep onset, min	5 ± 9	2 ± 12	−2 (−32 to 28)	−0.06 (−0.95 to 0.83)	11 ± 10	37 ± 10	26 (−3 to 54)	0.76 (−0.07 to 1.60)
Subjective sleep quality, %	71 ± 5	79 ± 6	8 (−7 to 22)	0.41 (−0.36 to 1.18)	61 ± 5	51 ± 5	−10 (−24 to 4)	−0.52 (−1.24 to 0.20)

Values presented as means ± SE or mean differences (95% CI). MCP, menstrual cycle phase; SpO₂, arterial oxygenation assessed by finger pulse oximetry; AMSc, Environmental Symptom Questionnaire cerebral score. No statistical analyses were performed due to the nature of a pilot study.

TABLE 3 Nocturnal pulse oximetry stratified by menstrual cycle phases.

Variable	Follicular phase			Luteal phase			Mean difference in the acclimatization effect between luteal vs. follicular phase (95% CI)
	3,600 m, 1st night	3,600 m, 2nd night	Mean acclimatization effect (95% CI)	3,600 m, 1st night	3,600 m, 2nd night	Mean acclimatization effect (95% CI)	
Mean nocturnal SpO ₂ , %	79.6 ± 0.8	81.2 ± 0.8	1.7 (−0.1 to 3.4)	78.9 ± 0.8	82.7 ± 0.8	3.8 (2.1 to 5.5)	2.1 (−0.3 to 4.6)
Heart rate, bpm	84 ± 2	77 ± 2	−7 (−11 to −3)	85 ± 2	80 ± 2	−5 (−9 to −1)	2 (−4 to 8)
Oxygen desaturation index, events/hour	7.8 ± 0.8	7.3 ± 0.9	−0.5 (−2.5 to 1.6)	9.5 ± 0.8	6.2 ± 0.8	−3.3 (−5.2 to −1.4)	−2.8 (−5.6 to 0.0)
SpO ₂ < 95%, % TIB	100 ± 3	100 ± 4	0 (−10 to 10)	100 ± 3	100 ± 3	0 (−9 to 9)	0 (−14 to 14)
SpO ₂ < 90%, % TIB	99 ± 1	99 ± 1	0 (−3 to 3)	100 ± 1	99 ± 1	−1 (−3 to 2)	−1 (−5 to 3)
SpO ₂ < 85%, % TIB	92 ± 5	77 ± 5	−15 (−28 to −3)	96 ± 5	70 ± 5	−26 (−38 to −14)	−11 (−28 to 6)
SpO ₂ < 80%, % TIB	48 ± 8	28 ± 9	−20 (−38 to −2)	48 ± 8	17 ± 8	−31 (−48 to −14)	−11 (−37 to 14)
SpO ₂ < 75%, % TIB	11 ± 5	12 ± 6	1 (−13 to 14)	15 ± 5	1 ± 5	−14 (−27 to −1)	−15 (−33 to 4)
SpO ₂ < 70%, % TIB	2 ± 2	1 ± 2	0 (−5 to 5)	4 ± 2	0 ± 2	−4 (−9 to 0)	−4 (−11 to 3)

Values presented as means ± SE or mean differences (95% CI). SpO₂, arterial oxygenation assessed by finger pulse oximetry; TIB, time in bed.

TABLE 4 AMS and other ARAHE incidence rates.

Variable	3,100 m (n = 21)	3,600 m (n = 21)	p-value
AMS, 2018 LLS ≥3	9 (43%)	12 (57%)	0.355
AMS, 1993 LLS ≥3	9 (43%)	12 (57%)	0.355
AMS, AMSc ≥0.7	1 (5%)	6 (29%)	0.093
Composite endpoint			
ARAHE incidence, total ^a	9 (43%)	14 (67%)	0.121
Components of ARAHE			
AMS, LLS 2018 ≥3 or AMSc ≥0.7	9 (43%)	13 (62%)	0.217
Fainting	0 (0%)	1 (5%)	1.000
Fever	0 (0%)	1 (5%)	1.000
Panic attack	0 (0%)	1 (5%)	1.000
Abdominal pain	0 (0%)	1 (5%)	1.000
Diarrhea	0 (0%)	1 (5%)	1.000
Vomiting	0 (0%)	3 (14%)	0.232

ARAHE, altitude-related adverse health effect; AMS, acute mountain sickness; LLS, Lake Louise Questionnaire score; AMSc, Environmental Symptom Questionnaire cerebral score. The observed incidence provides important insights for future sample size estimations in randomized clinical trials. For example, in a randomized, placebo-controlled parallel trial at 3,600 m, investigating whether acetazolamide can reduce the incidence of AMS from 57% by 50% to 28.5%, with 80% power and a two-sided alpha level of 5%, a total of 94 women (47 women per group), would be required for the final analysis.

^aParticipants experienced one or more ARAHE.

AMS and ARAHE

The comparably high incidence of AMS observed in our study is confirmed by generally accepted data. In a study by Li et al., during a two-day stay at an altitude of 3,270 m, women had a higher incidence of AMS than men (50% vs. 10%, *p* < 0.05).

Furthermore, multivariable regression analysis showed that not only the incidence, but also the severity of AMS, was significantly higher in women than in men (14). In contrast, the 2023 UIAA statement on AMS in women suggests that there is no sex difference in AMS susceptibility; however, this statement has not been quantitatively confirmed by any meta-analysis examining the influence of sex on AMS. This situation, together with the revised LLS definition of AMS in 2018 and the lack of any recent prospective studies on AMS in women and men, does not allow evidence-based conclusions on sex-differences in AMS susceptibility.

Underlying sex-differences potentially contributing to the higher AMS susceptibility in women could be related to the lower hypoxic ventilatory response compared to men. In a study by Camacho-Cardenosa et al. (15), it was shown that, during the first hours of hypoxia, SpO₂ decreased more markedly in women than in men, probably due to an initially lower and/or less efficient respiratory response to moderate hypoxia. In addition, there is evidence that women experience headaches more frequently at low altitudes (16), indicating a potential susceptibility to AMS-like symptoms even before climbing to high altitude. This and other pre-existing conditions may contribute to the development of AMS (17, 18).

Adding even further variability, studies have reported differences in ventilation rates throughout the menstrual cycle (19–21). In particular, PdG, acting on both peripheral and central chemoreceptors, is thought to be a potent respiratory stimulant (22) enhancing minute ventilation during the mid-luteal phase compared to the follicular menstrual cycle phase

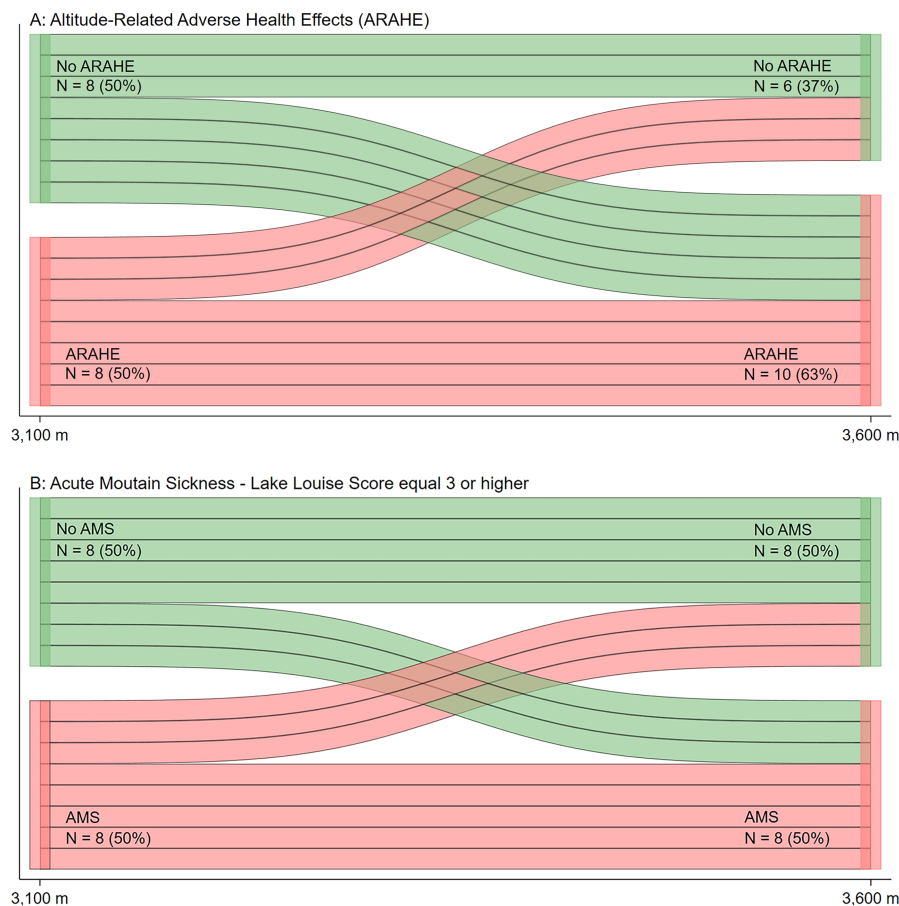


FIGURE 3

Incidences of acute mountain sickness (AMS) and altitude-related adverse health effects (ARAHE) in participants travelling to 3,100 and 3,600 m ($N = 16$). The data from 16 participants who completed both expeditions were analyzed. Green bars indicate participants free of AMS (B) or ARAHE (A) while red bars indicate participants suffering from AMS or ARAHE at the respective altitude. Acute mountain sickness was defined as a 2018 Lake Louise questionnaire score of ≥ 3 points including headache.

(23, 24). Our exploratory analysis showed the same correlation, indicating that higher PdG concentrations are associated with higher daytime SpO_2 values (Supplement Table S2), independent of location. In contrast, a recent study by Gardner et al. has not confirmed this relationship between PdG and AMS (25).

Nevertheless, several previous studies and recommendations concluded that there are no sex-related differences in AMS susceptibility (2). The controversies will remain until we obtain robust findings from prospective studies specifically designed and powered to investigate and detect sex-related differences in AMS (defined by the revised LLS). With the emergence of wearables and modern technologies, this challenge became solvable, as demonstrated in our study that monitored hormones and determined menstrual cycle phases and cycle days of women staying at high altitudes. Our findings in premenopausal women are promising and important since they highlight the high adherence of participants monitoring urine hormones with *Proov*.

Limitations

This study was designed as a pilot study to test the feasibility of monitoring female sex hormones at high altitudes. Therefore, no sample size estimation related to AMS incidence differences between menstrual cycle phases and altitudes were performed. Moreover, the lack of a male control group limits the interpretability of AMS found in this pilot study. We applied a 30-day hormone-monitoring regimen; however fewer consecutive days of urine hormone monitoring might be sufficient to determine the menstrual cycle phases in participants staying at altitude. Despite the long duration of hormone monitoring, the observed error rate remained minimal, and adherence of the participants high, suggesting that this approach is feasible in future studies. Absence of internet access may hamper immediate analysis of urinary hormone levels with the *Proov* kit. However, by being aware of such conditions, taking a photograph of the test strip noting the date and time allows for offline analysis at a convenient later time, which significantly reduces the risk of data loss.

TABLE 5 Secondary findings assessed in the morning on day 2.

Variable	Group 1			Group 2			Mean difference in altitude effect (95% CI)
	760 m	3,100 m	Mean altitude effect (95% CI)	760 m	3,600 m	Mean altitude effect (95% CI)	
Clinical examination							
Systolic blood pressure, mmHg	106 ± 2	106 ± 2	0 (−3 to 3)	105 ± 2	105 ± 2	1 (−2 to 4)	1 (−4 to 5)
Diastolic blood pressure, mmHg	73 ± 2	74 ± 2	1 (−3 to 5)	70 ± 1	76 ± 2	6 (2 to 9)*	5 (0 to 10)
Heart rate, bpm	85 ± 2	87 ± 2	2 (−3 to 7)	78 ± 2	95 ± 2†	17 (12 to 22)*	15 (8 to 22)*
SpO ₂ , %	96.1 ± 0.4	93.0 ± 0.4	−3.1 (−4.2 to −2.1)*	97.2 ± 0.4	86.8 ± 0.4†	−10.4 (−11.5 to −9.4)*	−7.3 (−8.8 to −5.8)*
Acute mountain sickness							
2018 Lake Louise Score	0.0 ± 0.3	0.3 ± 0.3	0.3 (−0.4 to 1.0)	0.0 ± 0.3	1.9 ± 0.3†	1.9 (1.2 to 2.6)*	1.6 (0.6 to 2.6)*
1993 Lake Louise Score	0.0 ± 0.4	0.4 ± 0.4	0.4 (−0.6 to 1.4)	0.0 ± 0.4	2.6 ± 0.4†	2.6 (1.6 to 3.6)*	2.2 (0.8 to 3.7)*
AMSc score	0.00 ± 0.06	0.04 ± 0.06	0.04 (−0.12 to 0.21)	0.00 ± 0.06	0.37 ± 0.06†	0.36 (0.20 to 0.53)*	0.32 (0.09 to 0.56)*
Subjective sleep quality							
Karolinska Sleepiness Scale	3.4 ± 0.3	4.0 ± 0.3	0.6 (−0.2 to 1.4)	3.5 ± 0.3	3.8 ± 0.3	0.3 (−0.5 to 1.1)	−0.3 (−1.4 to 0.8)
Time until falling asleep, min	17 ± 10	30 ± 10	13 (−13 to 38)	14 ± 10	55 ± 10	41 (15 to 67)*	27 (−9 to 65)
Number of nocturnal awakenings, <i>n</i>	0.3 ± 0.3	0.8 ± 0.3	0.5 (−0.3 to 1.2)	0.8 ± 0.3	1.7 ± 0.3	0.9 (0.2 to 1.6)*	0.4 (−0.6 to 1.5)
Waketime after sleep onset, min	2 ± 7	3 ± 7	2 (−18 to 21)	3 ± 7	23 ± 7	20 (0 to 39)	18 (−9 to 45)
Subjective sleep quality, %	79 ± 4	75 ± 4	−4 (−13 to 5)	82 ± 4	58 ± 4†	−24 (−34 to −16)*	−20 (−33 to −8)*

SpO₂, arterial oxygenation assessed by finger pulse oximetry; AMSc, Environmental Symptom Questionnaire cerebral score. Values presented as means ± SE or mean differences (95% CI). **P* < 0.05 vs. 760 m. †*p* < 0.05 vs. 3,100 m.

Conclusion

This pilot study in healthy, premenopausal women demonstrated good adherence and feasibility in monitoring female sexual hormones using the commercially available fertility monitoring kits and apps *Proov* and *Mira* during a sojourn at high altitudes. Therefore, future studies can apply this sexual hormone monitoring technique to enable in-depth analyses of the influence of sex, menstrual cycle phase, and hormone-related differences on AMS susceptibility. These insights allow better interpretability and comparability of AMS-related findings across studies and regions worldwide. In this pilot study, premenopausal women showed a high AMS incidence at both 3,100 m and 3,600 m, and these AMS incidences allow for evidence-based sample size estimations for future studies investigating sex-related differences in AMS incidence and the efficacy of preventive AMS measures, while monitoring and controlling for potential confounders, such as sex hormones and menstrual cycle phases. For example, in a randomized, placebo-controlled parallel trial at 3,600 m investigating whether acetazolamide can reduce the incidence of AMS from 57% by 50% to 28.5%, a total of 94 women (48 per group), taking either acetazolamide or placebo, would be required for the final analysis, with 80% power and a two-sided alpha level of 5%.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethic Committee of the National Center of Cardiology and Internal Medicine named after academician M. Mirrakhimov (Protocol No. 07 in the year of 2022). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

AT: Conceptualization, Data curation, Investigation, Methodology, Resources, Visualization, Writing – original draft, Writing – review & editing. MM: Conceptualization, Data curation, Formal analysis, Resources, Visualization, Writing – original draft, Writing – review & editing. SU: Conceptualization, Data curation, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. GM: Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. MM: Data curation, Investigation, Writing – original draft, Writing – review & editing. ML: Conceptualization, Validation, Writing – original draft, Writing – review & editing. CB: Conceptualization, Data curation, Methodology, Validation, Writing – original draft, Writing – review & editing. TS: Conceptualization, Investigation, Methodology, Supervision, Writing – original draft, Writing –

review & editing. SU: Writing – review & editing, Conceptualization, Data curation, Methodology, Supervision, Validation, Writing – original draft. KB: Funding acquisition, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing. MF: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The evaluation of the *Proov* Full Cycle Hormone Insights Kit and the *Mira* Fertility Tracking Kit was conducted solely for

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research purposes to assess a potential method for monitoring sex hormones at altitude.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fgwh.2025.1544832/full#supplementary-material>

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