EFFECT OF MENSTRUAL CYCLE ON INCIDENCE OF ACUTE MOUNTAIN SICKNESS IN WOMEN: PRELIMINARY RESULTS FOR TWO STUDIES

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RESUMEN: Efecto del Ciclo Menstrual en la Incidencia de Mal de Montaña Agudo en Mujeres: Resultados Preliminares de Dos Estudios

La mayor parte de estudios de mal de montaña en mujeres premenopáusicas que viajan a ambientes de altura no han tenido en cuenta la fase del ciclo menstrual en la que se encontraban las mujeres. Consecuentemente existe poca información acerca de los posibles efectos que tienen las fluctuaciones cíclicas que ocurren en las hormonas esteroideas en la ocurrencia de mal de montaña agudo (AMS). Nosotros hemos determinado la incidencia de AMS en 12 mujeres voluntarias durante una exposición de 36 h a 446 torr (aproximadamente 4300 m) en una cámara hipobárica durante la fase folicular temprana (EF) y la fase luteal (L) de su ciclo menstruall a través de un diseño de estudio transversal. Adicionalmente, hemos determinado la incidencia de AMS en otras 16 mujeres voluntarias durante una residencia de 12 d a 4300 m en la cima del Pikes Peak, Colorado, en la fase EF (8 sujetos) o en la fase L (8 sujetos), usando un diseño de estudio comparativo. Los resultados preliminares de estos estudios sugieren que la incidencia de AMS no difiere mucho entre las fases del ciclo menstrual.

Palabras claves: Mal de montaña agudo, Mujeres, Fases del ciclo menstrual

RÉSUMÉ: Effet du cycle menstruel sur l'apparition du mal aigu des montagnes chez les femmes : résultats préliminaires de deux études.

La plupart des études sur le mal des montagnes chez les femmes pré-ménopausiques se rendant dans des régions de haute montagne n'ont pas pris en compte la phase du cycle menstruel dans lequel elles se trouvaient. Il existe donc peu d'informations relatives aux effets possibles des fluctuations cycliques des hormones stéroïdes sur l'apparition du mal des montagnes aigu (AMS). Nous avons déterminé l'incidence de l'AMS chez 12 femmes volontaires soumises à une exposition de 36 heures à 446 torr (environ 4 300 m) dans une chambre hypobare, pendant la phase folliculaire précoce (EF) et la phase lutéale (L) de leurs cycles menstruels, en utilisant un plan d'étude transversale. Nous avons en outre déterminé l'incidence de l'AMS chez 16 autres volontaires au cours d'un séjour de 12 jours à 4 300 m, au sommet du Pikes Peak, Colorado, pendant la phase EF (8 sujets) ou la phase L (8 sujets), en utilisant un plan d'étude comparative. Les résultats préliminaires suggèrent que l'incidence de l'AMS ne diffère guère, quelle que soit la phase du cycle menstruel.

Mots-clés : Mal des montagnes aigus, Femmes, Phases du cycle menstruel.

SUMMARY: Most studies of altitude illness in premenopausal women traveling to high mountain environments have not controlled for phase of the menstrual cycle. Consequently, little information exists about the possible effects of cyclic fluctuations in ovarian steroid hormones on the occurrence of acute mountain sickness (AMS). We determined the incidence of AMS in 12 women volunteers during a 36 h exposure to 446 torr (~4300 m.) in a hypobaric chamber during the early follicular (EF) and luteal (L) phases of their menstrual cycle using a cross-over study design. Additionally, we determined the incidence of AMS in 16 additional women volunteers during a 12 d residence at 4300 m on the summit of Pikes Peak, Colorado in EF (8 individuals) or L (8 individuals) using a group comparison study design. Preliminary results of these studies suggest that the incidence of AMS in women does not differ greatly between menstrual cycle phases.

Key words: Acute mountain sickness, Women, Menstrual-cycle phase

Acute mountain sickness (AMS) is a syndrome which occurs in unacclimatized individuals from low altitude who travel to altitudes above approximately 2438 m and remain there for more than a few hours. The most common symptoms of AMS include headache, nausea, vomiting and lassitude. Altitude-associated sleep disturbances are often also considered to be a manifestation of AMS (1), although disrupted sleep can occur in well acclimatized individuals who lack other symptoms. The fundamental cause of AMS is prolonged hypobaric hypoxia. The pathophysiology is thought to involve hypoxia-induced subclinical cerebral edema that resolves with altitude acclimatization (1). Consequently, alterations in respiratory and fluid/volume responses to hypoxia could affect the occurrence of AMS.

The menstrual cycle of women during their reproductive years is characterized by regular fluctuations of ovarian steroid hormones (estrogens and progesterone) controlled by the hypothalamic-pituitary-ovarian axis. These fluctuations and their physiologic effects function to assure recurrent

physiologic opportunities for reproduction. Ovarian steroid hormones have discernable and well documented effects on respiratory function and body fluid/volume relationships. The different concentrations of ovarian hormones associated with different phases of the menstrual cycle could affect the degree of hypoxia and extent of fluid shifts experienced by women during high altitude exposure, which might alter the occurrence of AMS symptoms.

Although AMS has been investigated frequently in males, it has not been studied adequately in women to discern whether there is an effect of ovarian steroid-hormone fluctuations. Two types of studies exist within the English literature that report AMS in women. First, there are studies in which an explicit or implicit assumption was made that no difference in response to altitude exists between men and women. Those studies examined both genders together without differentiating between them (2-6). The second type of study reported is that in which women were compared directly to men within the same investigation (7-10) or were compared to male historical controls (11,12). No consistent conclusions can be drawn from the studies. Grollman (7) reported "mild" AMS symptoms in his wife, but not in himself, during the first 36 h on the summit of Pikes Peak in Colorado, USA. Harris et al. (11) found that the pattern of AMS symptoms in women was different than that in men. Hannon (13) suggested that women acclimatized to high altitude "more readily" than men based upon several studies his group performed on the summit of Pikes Peak. The other studies did not demonstrate a discernable difference between men and women in AMS symptoms (8- 10, 12), but none of the reported studies controlled for menstrual cycle phase.

We hypothesized that the different levels of estrogens and progesterone present during different phases of the menstrual cycle would alter the physiologic response to altitude exposure and cause differences in the occurrence of AMS symptoms. We tested that hypothesis by assessing AMS symptoms in women volunteers during a 36 h exposure to 446 torr in a hypobaric chamber and in other women volunteers during a 12 day exposure to 4300 m on a mountain during two different phases of their menstrual cycle. The preliminary results from these recently completed studies are presented.

Hypobaric Chamber Exposure

The purpose of the hypobaric chamber study was to determine if there were differences in occurrence of AMS symptoms between the early follicular (EF) and luteal (L) phases of the menstrual cycle during early altitude acclimatization. The chamber was used to facilitate precise control of ambient environmental conditions (barometric pressure, temperature, humidity).

The subjects for this study were 12 women volunteers with normal menstrual cycles. They had a mean (±S.E.M.) age of 26.3±1.2 years, a height of 60.1±2.4 cm and a weight of 55.6±7.9 kg. All were low-altitude residents and had not been exposed to altitudes greater than 1500 m for at least six months prior to their participation in the study. All were nonsmokers.

A within-subjects factorial design was used in which each volunteer was evaluated at sea level and at simulated high altitude (446 torr; ~4300 m) during both EF and L of their menstrual cycle. The follicular phase was defined as beginning with the first day of menses and lasting until detection of"ovulation" using a commercial assay for LH in the urine (First Response, Tambrands Inc.). The luteal phase was defined as beginning the day of detection of "ovulation" until the onset of menses.

During each menstrual cycle phase, the volunteer was first evaluated in the hypobaric chamber for 24 hours at sea level. The chamber was then decompressed at a rate of 15 torr/minute to a pressure of 446 torr, and the volunteer remained at that pressure 32 hours. The ambient temperature and relative humidity were maintained at 23±1 °C and 55±5% throughout all exposures. Volunteers had unrestricted access to a balanced diet and fluid for consumption throughout the study, but were not allowed to ingest caffeine.

Symptoms were assessed in the volunteers at sea level and at 4 and, 24 hours after decompression ("ascent") using the Environmental Symptoms Questionnaire (ESQ). The ESQ is a self-administered 68-question inventory of symptoms that occur in stressful environments (14). It is well validated and has been often used for detection of AMS. Weighted averages of cerebral symptoms designated "AMS-C" and respiratory symptoms designated "AMS-R" were calculated (14) for each subject at each assessment.

The symptom score data was evaluated for statistical significance using a two-way ANOVA (altitude/time, menstrual cycle phase) with repeated measures in both factors. Significant differences were localized by *post hoc* analysis using Student-Newman-Keuls method. All tests were two-tailed and the level of significance was designated as $p=0.05$.

The overall pattern of symptoms in the volunteers conformed to the pattern seen in previous chamber studies with males at similar altitudes, i.e., there was onset of symptoms by 3-_ hours after ascent with maximal symptom intensity during the first 24 hours followed by a progressive decrease in symptoms. Mean AMS-C scores at 4 and 24 hours of altitude exposure and mean AMS-R scores and 24 hours of altitude exposure were significantly increased over the mean scores at sea level.

There were no statistically significant differences in ESQ scores between menstrual cycle phases.

Pikes Peak Study

The second study was designed to determine whether menstrual cycle phase affected AMS symptoms by altering the normal course of altitude acclimatization. The study was performed in the research facility on the summit of Pikes Peak in Colorado, USA (4301 m) to allow prolonged altitude exposure without restricting volunteers to the confined space of the hypobaric chamber. Ambient barometric pressure was uncontrolled in this setting and fluctuated from 458 to 464 torr during the study.

Sixteen women volunteers with normal menstrual cycles performed as subjects for this study. They had a mean age of 21.7±0.5 years, height of 167.4±1.1 cm and weight of 62.2±1.0 kg. All were low altitude residents, and all but one had not been exposed to altitudes greater than 1500 m for at least six months prior to their participation in the study. All were nonsmokers.

The study used a mixed factorial design in which one group of volunteers (n=8) was assessed for AMS symptoms at sea level and high altitude during the early follicular phase of their menstrual cycle and were compared to another group (n=8) assessed under the same conditions during the luteal phase of their cycle. The menstrual cycle phases were defined as in the previous chamber study (see above).

Assessment of symptoms at sea level was accomplished on multiple occasions in each phase of the menstrual cycle during a five month period prior to beginning the altitude exposure. Following sea-level exposure, the volunteers were assigned to either EF or L groups. They were then transported by commercial airplane and automobile to the laboratory facility on the summit of Pikes Peak over a period of approximately six hours on the second day of the cycle phase corresponding to their assigned group. The volunteers remained on the summit for 10-12 days. During the entire study period they consumed a controlled, vegetarian diet which was designed to minimize weight change. They were restricted from consuming caffeine.

As in the previous chamber study, symptoms were assessed at 4 and 24 hours after ascent using the ESQ. Weighted symptom averages (AMS-C and AMS-R, see above) were calculated for each volunteer from the ESQ data.

Symptom score data were evaluated for statistical significance using a two-way ANOVA (altitude/time, menstrual cycle phase) with repeated measures within the altitude/time factor. Significant differences were localized by post hoc analysis using the Student-Newman-Keuls method. All tests were two-tailed and the level of significance was designated as p=0.05.

The overall pattern of symptoms in these women volunteers generally conformed to the pattern seen previously in men and women at the Pikes Peak facility. Mean AMS-C and AMS-R scores were significantly increased over sea-level scores 24 hours after ascent. There were no statistically significant differences between menstrual cycle phases in ESQ or LLS scores.

Figure 1 presents the mean ESQ scores during follicular and luteal menstrual cycle phases from both studies combined. Each cycle phase group represents a total of 20 women.

DISCUSSION

Although we postulated that fluctuations in ovarian steroid levels associated with different phases of the menstrual cycle might alter the occurrence of AMS symptoms by altering the physiologic response to high altitude exposure, the preliminary analysis of the data from the two studies suggests that menstrual cycle phases have little effect. The explanation for these results is not clear from the limited information available at this time. At least three possible explanations should be considered: l) altitude exposure suppressed ovarian steroid hormone levels, 2) the magnitude of ovarian steroid hormone effects is insufficient to affect AMS, or 3) the inherent variability of hormone levels between and within individuals is sufficiently great to preclude detection of statistical significance with the sample sizes used for these studies. Some observations from previous studies (11, 12) suggest that altitude exposure might alter the menstrual cycle, but we are not aware of any definitive data in the English literature concerning this subject. Likewise, we are not aware of previous literature concerning the magnitude of physiologic effects of ovarian steroids relative to

altitude acclimatization and AMS symptoms. The occurrence of individual variability in ovarian steroid levels is well known, but the extent of individual variability in these two studies has not been evaluated yet. Hopefully, planned analysis of additional data from these studies will help to clarify the relationship of menstrual cycle phase to AMS in women exposed to high altitude;

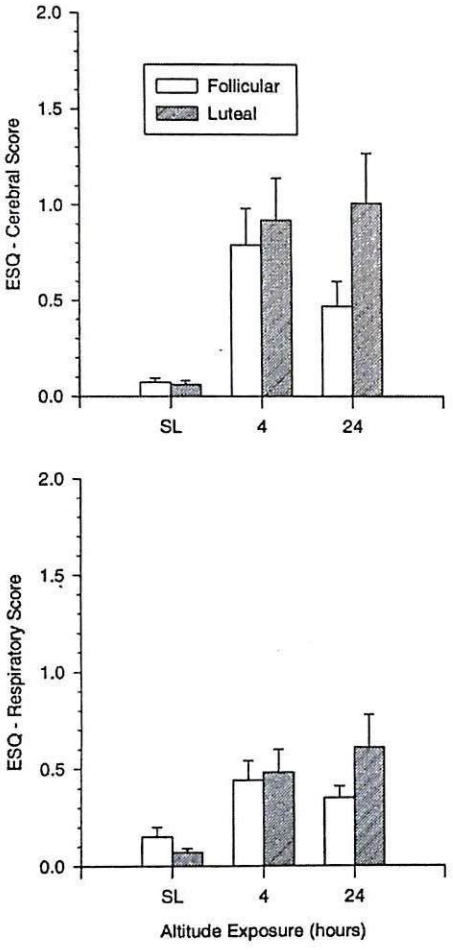

Figure 1. Environmental Symptom Questionnaire (ESQ) scores at sea level and at 4 and 24 hours decompression to 446 torr in a hypobaric chamber or ascent to 4300 m at Pikes Peak. Volunteers were exposed in the follicular (n=20) and luteal (n=20) phases of their menstrual cycle. Bars indicate standard error of the mean (SEM).

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