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Menstrual Respiratory Changes and Symptoms

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SUMMARY The duration of standardised overbreathing required to produce slow wave activity in the EEG during different phases of the menstrual cycle has been studied, and changes in carbon dioxide sensitivity of the respiratory system. Normal subjects developed slow waves more quickly and had more sensitive CO_2 responses during the premenstrual/menstrual phases. This may be a factor contributing to premenstrual tension.

Menstruation is 'at best a physiological inconvenience; at worst it contributes to chronic ill health . . .' (British Medical Journal, 1979). Clusters of symptoms (Moos, 1969; Beaumont, Richards and Gelder, 1975), symptom profiles (Moos and Leideman, 1978) and timing of maximal occurrence (Rouse, 1977; Sampson and Jenner, 1977) have emerged from statistical treatment of data on the wide range of symptoms listed under the Premenstrual Tension Syndrome (Dalton, 1964). Nevertheless, understanding of the mechanisms underlying the syndrome remains far from complete.

Among the physiological correlates of the menstrual cycle, increase in alveolar ventilation has long been found in the luteal phase (see, for example, Hasselbalch, 1912; Plass and Oberst, 1938; Döring, 1955; Lyons, 1969). Progesterone is thought to be the main physiological agent responsible for the premenstrual fall of alveolar carbon dioxide because (1) the cyclic changes disappear with the menopause (Griffith *et al*, 1929) and (2) progestational agents increase ventilation (Lyons and Antonio, 1959; Tyler, 1960; Lyons and Huang, 1968) and respiratory chemosensitivity (Zwillich, Natalino, Sutton and Weill, 1978) in males.

Changes in sensitivity of the autonomic nervous system (Little and Zahn, 1974), EEG activity (Gautray, 1969; Creutzfeldt and associates, 1976) and reaction time (Metha, Mazumdar, Pathak and Skandhan, 1977) also suggest cyclic menstrual changes in CNS sensitivity to stimuli. This paper reports on the results from studies on end-tidal carbon dioxide concentration during the menstrual cycle and its relation to neurophysiological variables. The studies were designed to test the hypothesis that hyperventilation produced by the stress of life events is more likely to produce psychosomatic symptoms during the premenstrual and menstrual phases when the arterial PCO_2 is already reduced.

Subjects and methods

In a first phase, resting end-tidal carbon dioxide concentration ($PECO_2$) was measured every third day in a 40 year-old female patient, for three consecutive menstrual cycles, the estimations taking place between 09.00 and 10.00 h. The subject had suffered from a predictable bipolar manic-depressive illness, which was stopped by lithium carbonate therapy; she remained well when lithium was stopped. No medication was prescribed for six months before, nor during the investigation and no abnormal signs were observed; she took no oral contraceptives.

Resting $PECO_2$ was measured with a catheter placed 0.5 cm inside one nostril and connected to an infra-red medical gas analyser, Beckman LB2; it was monitored with the subject lying supine on a bed and after a resting period of 15 minutes. The analyser was calibrated using 2 per cent, 5 per cent or 7 per cent CO_2 mixtures in oxygen. The resting $PECO_2$ value was

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expressed as the mean of the CO_2 peaks for five consecutive minutes.

In a second phase, seven healthy subjects were selected with no history of premenstrual or menstrual distress requiring consultation. The subjects did not take oral contraceptives for at least one cycle before the beginning of the investigation nor during its period. The ages ranged from 19 to 37 years.

Resting $PECO_2$ and time of hyperventilation to produce a response of delta activity in the EEG and CO_2-response were measured. Time of hyperventilation necessary to produce delta activity response was estimated independently and blindly from the other data. Each subject was studied twice weekly (Monday and Thursday or Tuesday and Friday) for one menstrual cycle. The time in which the investigation started varied from subject to subject, so that the days of menstruation of different subjects were randomly distributed over the whole period of investigation.

Each session started at the same time of day in each subject, usually in the morning. It had the following schedule: the subject rested supine on a bed for 15 minutes before $PECO_2$ and EEG activity were recorded simultaneously for five minutes. The subject was then asked to hyperventilate for five minutes; she had received instructions to keep the degree of hyperventilation constant, not only in each session but also from session to session. The recording of resting $PECO_2$ was continued until the level returned to the resting value. When this was added to the study, the session was completed with the determination of the CO_2-response.

Resting $PECO_2$ was monitored as described above. EEG activity was recorded from four longitudinal bipolar derivations with the Elema-Schönander Mingograph EEG. CO_2-response was determined with a modification of the rebreathing technique described by Read (1967). The subject rebreathed for three or four minutes into a closed system consisting of a six-litre bag which was initially filled with oxygen. Ventilation was calculated for 20-second segments and plotted against the mean $PECO_2$ value of the segment; CO_2-response was expressed as the slope of the regression line $\triangle VE/\triangle PECO_2$. The values for the first minute were disregarded because of the erratic initial ventilatory response.

Each subject was asked to complete one copy of the Menstrual Distress Questionnaire (form T) every evening (Moos, 1969).

Results

The first subject studied showed marked periodic changes in resting $PECO_2$, the lower values always occurring during the luteal phase. The menstrual cycles were superimposed and the observed values are shown (Fig 1). A sine wave was fitted by a least square method and the goodness of fit (Bliss, 1970) showed statistical significance at the 1 per cent level.

The inspection of the data from the group of subjects studied in the second phase also showed clear variations in all the physiological variables. The menstrual cycles varied from 27 to 36 days; the data are presented on circular charts, with each whole cycle as 360° for phase comparison (Fig 2). The highest and lowest values which were observed (Table I) were considered to

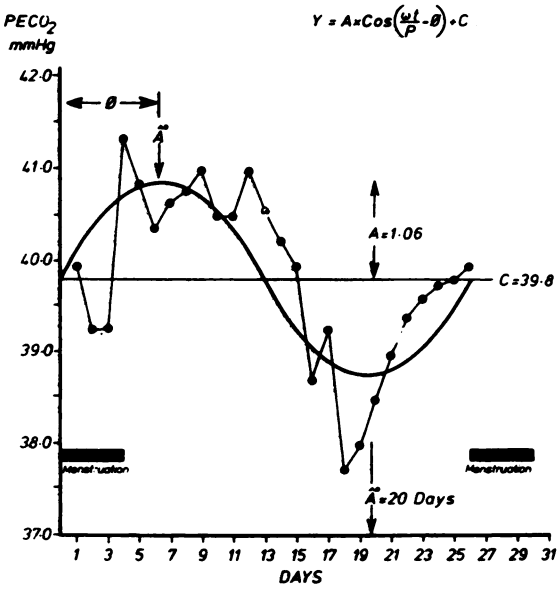


FIG 1.—Composite for resting end-tidal PCO_2 values (black dots) observed in 3 consecutive menstrual cycles in manic-depressive woman. The least mean square fitted sine wave is also shown; this is the one for which the sum of the squares of the deviations of the sine wave from the crude data is minimal.

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calculate the mean angle for the group and angular dispersion for each variable (Zar, 1974).

In six of these subjects, the lowest resting $PECO_2$ values occurred premenstrually, i.e. between the seventh premenstrual day and the first day of menstruation. The mean phase angle for these six subjects is highly statistically significant ($P < 0.005$). When all the subjects of the group are treated together, it is still statistically significant at the 2 per cent level. In the subject who deviated from the general trend, the premenstrual values were lower than the post-menstrual, but the lowest value was observed at the theoretical point of rising progesterone levels. It is interesting that the lowest resting $PECO_2$ value was in this case followed two days later by a peak in the total scores of the menstrual distress questionnaire.

The day of the lowest value for the time of hyperventilation necessary to produce delta activity response—indicative of higher CNS sensitivity to hyperventilation—was significantly related with the day of the lowest $PECO_2$ value ($p < 0.001$). The latter occurred usually before the former.

The highest CO_2-response values—indicative of higher sensitivity of the respiratory centres to CO_2—were always observed premenstrually or menstrually. Fig 2 summarises the results and shows that the mean angle for the group on which the highest CO_2-response was observed almost coincides with that on which the least time of hyperventilation was required to produce delta activity.

Low CNS and respiratory sensitivity—as expressed by high values of time of hyperventilation necessary to produce delta activity and low values of CO_2-response—were always observed in the post-menstrual period.

Discussion

Increased ventilation has consistently been found in the luteal phase of the menstrual cycle in normal women. Our results, similar to many

TABLE I

Maximal and minimal values for end-tidal carbon dioxide concentration ($PECO_2$), time of hyperventilation necessary to produce delta activity response (Time) and CO_2-response, and maximal total scores on the Menstrual Distress Questionnaire (MDQ). In brackets is given the angle corresponding to the day of the menstrual cycle on which the value was observed. Angular concentration (r) is given below the corresponding mean angle and angular dispersion.

(*Angular concentration varies inversely with angular dispersion*)

		$PECO_2$ (mm Hg)		Time (seconds)		CO_2-response		MDQ
Subject	Age	Peak	Nadir	Peak	Nadir	Peak	Nadir	Peak
1	29	35.4 (195°)	29.3 (278°)	100 (103°)	40 (298°)			78 (349°)
2	31	39.9 (50°)	36.4 (360°)	340 (223°)	100 (50°)			95 (0°)
3	24	37.8 (150°)	34.2 (320°)	320 (150°)	120 (40°)			55 (330°)
4	19	39.9 (360°)	36.2 (160°)	160 (67°)	20 (160°)	1.07 (360°)	0.42 (160°)	94 (13°)
5	19	41.0 (124°)	32.9 (298°)	220 (124°)	70 (335°)	1.07 (87°)	0.40 (211°)	108 (12°)
6	28	35.9 (140°)	32.3 (320°)	180 (210°)	60 (300°)	0.25 (320°)	0.11 (180°)	95 (340°)
7	37	37.0 (99°)	32.9 (298°)	320 (99°)	180 (347°)	0.40 (298°)	0.22 (37°)	93 (12°)
Mean	26.7	38.1	33.5	234	84	0.70	0.29	88
Stand. Dev.	±6.6	±2.17	±2.45	±93.6	±5.4	±0.43	±0.15	±17.1
Mean Angle		(65°)	(302°)	(135°)	(350°)	(347°)	(168°)	(359°)
Angular Dispersion		(±63°) r = 0.55	(±45°) r = 0.73*	(±56°) r = 0.61	(±70°) r = 0.47	(±58°) r = 0.59	(±66°) r = 0.51	(±15°) r = 0.96**

* $p < 0.02$

** $p < 0.001$

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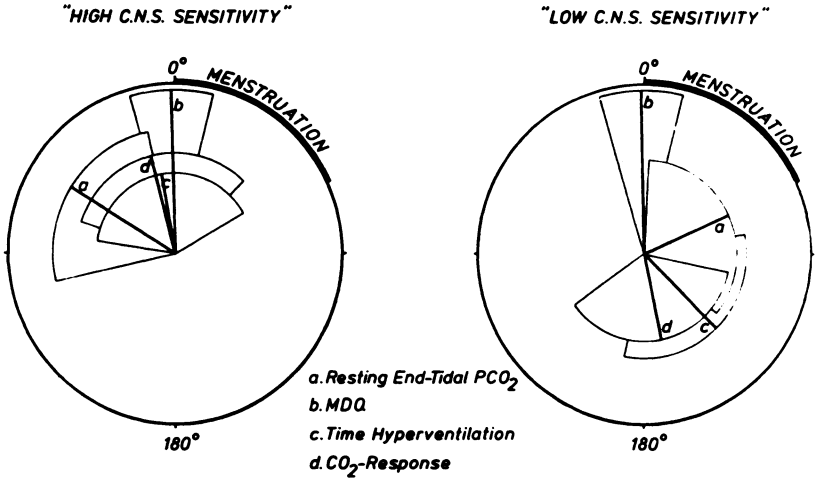


FIG 2.—Data from seven healthy women. Mean angle and angular dispersion for resting end-tidal PCO_2 (a); time of hyperventilation required to produce delta activity (c); CO_2-response (d); and maximal total scores on the Menstrual Distress Questionnaire, MDQ (b). On the left circle are represented the values corresponding to increased CNS sensitivity (lowest $PECO_2$, least time of hyperventilation necessary to produce delta activity, and highest CO_2-response); the mean angles are premenstrual. On the right circle are represented the values corresponding to decreased CNS sensitivity; the mean angles are post-menstrual. For each variable, angular concentration (r value—Table I) is represented by a radius of appropriate length.

others, show that carbon dioxide concentration starts to decrease early in the luteal phase and the lowest values are premenstrual. These values are not outside the quoted normal range for adults' arterial PCO_2 (33.0–42.0 mm Hg for 95 per cent range) or women's capillary PCO_2 at 37°C (31.0–41.7 mm Hg also for 95 per cent range) (Documenta Geigy, 1973). The findings suggest that women are more vulnerable to psychosomatic symptoms during the premenstrual phase, when stress would increase ventilation at a time when carbon dioxide levels are already low.

The differences in the temporal distribution in the curves for end-tidal carbon dioxide and progesterone levels suggest that factors other than progesterone play a part in inducing the menstrual changes in the respiratory centres. The role of psychological factors in the causation of hyperventilation is well established (see, for example, Lewis, 1953, 1957). Traits of personality (Terman and Miles, 1936) and attitudes to menstruation and the female's social role (Rand, 1968; Goldberg, 1974; Slade and Jenner, 1978) are most likely to play an additional and significant role in the causation of the periodic increase in ventilation and distress of the menstrual cycle.

The sensitivity of the CNS to hyperventilation always increased during the premenstrual and menstrual phases. There are, however, complicating factors that should be considered in the evaluation of the EEG data: (1) the degree of voluntary hyperventilation was usually greater than that one would expect to occur in response to most life events. The decrease in end-tidal PCO_2 at the time of delta activity response varied from 25 per cent to 56 per cent ($\bar{x} = 42.9 \pm 8.9$ per cent, $n = 51$) of the initial resting value; (2) the degree of voluntary hyperventilation varied from subject to subject and slight fluctuations were also observed between recordings from the same subject; (3) end-tidal PCO_2 can be accepted as an indicator of arterial PCO_2 at rest, but not during hyperventilation; and (4) in some subjects, the end-tidal PCO_2 peaks in the crude tracings became irregular during hyperventilation, making it difficult to assess the end-tidal carbon dioxide

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level at the point of delta activity response. Thus, it is not possible to relate the results to arterial carbon dioxide concentration and to exclude the possibility that, at least in some sessions, delta activity response occurred sooner because of a more marked degree of hyperventilation. Nevertheless, (1) most of the decrease of end-tidal carbon dioxide concentration was accomplished within 20–30 seconds of hyperventilation; (2) delta response always occurred sooner in the premenstrual and menstrual phases, despite the fact that the investigation started at different phases of the menstrual cycle for different individuals; and (3) symptoms were experienced before the onset of delta activity. The symptoms included dizziness, restlessness, slight clouding of consciousness, headache, backache, sickness, sensation of coldness in the extremities and sensory disturbance in the limbs or only in the fingers and toes.

The symptoms of hyperventilation are only some among those mentioned in premenstrual studies, but they are listed (Moos, 1969) and it is suggested here that overbreathing, which must itself be induced, is more likely to add to the woman's difficulties at this time by adding these symptoms. The higher responsiveness of the respiratory centres to CO_2 was also observed in the premenstrual and menstrual phases. This indicates higher sensitivity of the CNS before and during menstruation.

The method used to analyse the data took into account only the days on which maximal and minimal values were observed. Studies are now in progress to determine profiles of neurophysiological, hormonal and psychological variables in order to study their temporal correlations. Nevertheless, evidence does seem to have been presented for the hypothesis that hyperventilation in vulnerable periods of the menstrual cycle is more likely to cause symptoms than at other times. Hence, this may be one factor contributing to the so-called premenstrual tension syndrome.

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