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Recurrent Herpes Labialis, Recurrent Aphthous Ulcers, and the Menstrual Cycle

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A prospective study of 104 student nurses determined the frequency of recurrent herpes labialis and recurrent aphthous ulcers within the menstrual cycle. Each nurse kept daily calendars recording inter alia menses and episodes of lesions. Episodes of aphthae were not associated with any specific intervals in the menstrual cycle. There was a greater than expected incidence of episodes of herpetic lesions in the eight days preceding the onset of menses.

Patients frequently report an association between the menstrual cycle and the onset of episodes of recurrent aphthous ulcers (RAU) and recurrent herpes labialis (RHL),¹ especially when they are severely affected, that is when they experience more than one episode per month. Although this association commonly is accepted as indicating an etiologic role for estrogens and progestogens in these two oral syndromes,²⁻⁵ attempts at documenting this relationship other than by anecdotal reports have not been convincing. Ship et al⁶ presented a graphic illustration of the incidence of RAU in each of four seven-day periods composing the menstrual cycle and demonstrated an apparent increase in RAU incidence during the seven-day period preceding onset of menses for all subjects; this increase was greater for those subjects with severe RAU. Analysis of data demonstrated that the association was not

statistically significant.⁷ Dolby⁵ showed that patients with RAU reported more episodes in the "post-ovulatory" period than in other periods of the cycle, but he did not test for statistical significance.

To avoid the problems inherent in these earlier reports, we examined data obtained prospectively from two groups of student nurses who recorded days of menstruation, onset of episodes of RAU and RHL, and a variety of other oral and general health data on a daily calendar.⁸ The study population included those who had experienced RAU, or RHL or both as well as those who had not. In this way statistical testing of an association between RAU and RHL onset and menstruation was possible. Also, the three-year period of study was considerably longer than that in earlier reports, this is important in studies of young adult women who frequently experience irregularities in their menstrual cycles.

Materials and Methods

Women were recruited from two successive classes of student nurses at the Philadelphia General Hospital.^a Details of data collection and method have been reported previously.⁸ In this study, the students recorded the presence of RAU and RHL on daily calendar forms that also asked informa-

^a Sixty-seven students in the first class were invited to participate and 61 (91%) gave both personal and parental consent for participation. Of these 61 students, 46 (75%) continued in the study for three years. Of the 15 (25%) students who did not continue in the study, 12 left school during the first semester. All 66 students in the second class agreed to participate, and 58 (88%) continued participation for the three years of school. Total participation rate for both classes combined was 78%.

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tion about menses, fever, medication, and other illnesses. Calendars were collected biweekly. The students were paid for keeping calendar forms, taking psychological tests, and bringing episodes of RAU and RHL to the attention of investigators for confirmation. Previous analysis had indicated that calendar reports of RAU and RHL had the same distribution as documented (investigator-examined) lesions and, hence, that data from calendar reports could be used for etiologic investigation.⁸ For each class, three years of data have been collected and stored on computer tape.

A program was written to list days of menses and days of RHL and RAU episode onset. An episode was defined to the computer as a day of symptoms preceded by five days with no symptoms. (RAU and RHL episodes were listed by nurse and by day for the first day of menses and each of 15 days preceding menses.^b) Length of the menstrual cycle is variable in the adolescent. Since ovulation usually precedes the onset of menses by two weeks, the 15-day period preceding the onset of menses was chosen for intensive study. It was felt that this interval represented the time in which the least variation might occur.

In a second analysis we tested for the effect of oral contraceptive medication. Fifty-one women (49%) reported taking oral contraceptives at some time during the study. We made no attempt to check accuracy or completeness of reporting and, hence, may be underestimating the frequency with which contraceptive medication was taken. There were, however, only 316 menstrual cycles in which oral contraceptives were taken (11.2% of a data base of 2,808 menstrual cycles).

Results

RHL.—Seventy-five RHL episodes occurred in the first class over the three-year period of study. Forty-one of these episodes began during the period including the first day of menses and the 15 days preceding menses. A bar graph of the number of RHL episodes starting on each day is shown in Figure 1. In the second class, 76 episodes occurred; 56 began during the period including the first day of menses and the 15 days preceding menses (Fig 2).

^b The first day of menses was listed as day zero and the days preceding menses were listed as days 1 to 15.

The 16 days analyzed comprised 57.1% of the average 28-day menstrual cycle. The percentages of RHL episodes occurring during this period could be expected to be much greater than 57.1% if this period of the menstrual cycle has a causal effect on the onset of the episodes. For the first class, 54.6% (41 of 75) of the RHL episodes started during this period. For the second class, 73.7% (56 of 76) of the RHL episodes started during this period. Analysis of the data by the chi-square test ($\chi^2 = 4.82$, $df = 1$, $P < 0.05$ level) suggests that there is a significantly greater frequency of RHL episodes during this 16-day period in the second class of nursing students. However, the combined data for the two classes showed that 64.2% (97 of 151) episodes of RHL started during this period. This yielded a χ^2 of 0.88, which is not significant at one degree of freedom.

Daily differences in frequency of RHL for the first day of menses and the 15 preceding days were tested with a one-way analysis of variance incorporating both RHL per day and RHL per nurse for each class. The first day of menses and the 15 days preceding menses made up the columns. In each instance the test showed that no one column is significantly different from any of the other columns. RHL episodes are no more frequent on any one specific day during this 16-day period, which includes ovulation and the onset of menses. When both classes were combined, a total of 151 RHL episodes occurred during the three-year study. Ninety-seven RHL episodes occurred in the period from the 15 days preceding menses to the onset of menses (Fig 3). A one-way analysis of variance of these combined data showed that RHL episodes are no more frequent on any one specific day during this 16-day period.

We then looked for differences in blocks of days other than 16-day periods. When the data for the two classes were combined, the period from the first day of menses to the eighth day preceding menses showed a slight but statistically significant increase in the frequency of RHL onset compared with the period from the ninth to the fifteenth day preceding the onset of menses. For this calculation an expected frequency of 6.06 RHL episodes per day was used (97 RHL episodes per 16 days). The chi-square test at one degree of freedom was significant at $P < 0.05$ level, suggesting that RHL epi-

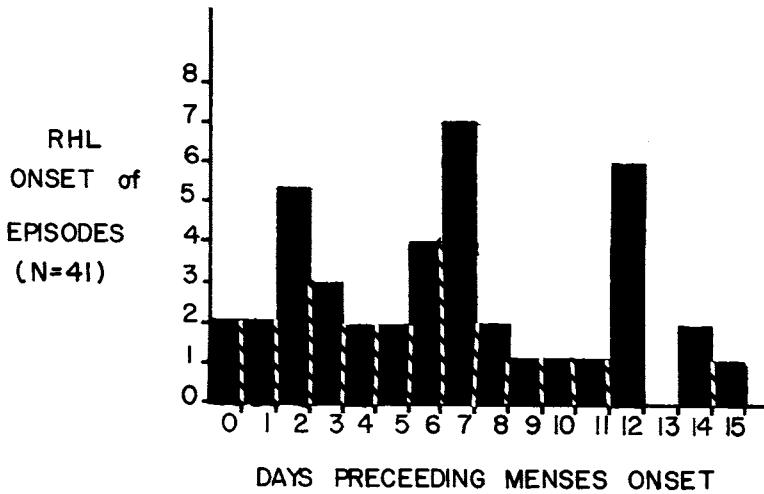


FIG 1.—Number of RHL episodes beginning on each individual day in 15-day period preceding onset of menses (day zero). First class of student nurses (N = 46).

sodes are more frequent during the eight days preceding menses. This phenomenon was not seen when the two classes were examined separately.

Since there were no students with severe RHL, no attempt was made to segregate them by severity of illness.

Oral contraceptive medication had no effect on incidence of RHL episodes. Incidence was the same (0.044 episodes per cycle) in cycles during which medication was taken as it was in "normal" cycles (0.055 episodes per cycle). Insofar as we could test with the small number of RHL episodes (18),

the distribution of these episodes within the cycle occurring while the students were taking oral contraceptive medication was not different from that reported for the larger group.

RAU.—There were 145 RAU episodes for the first class during the three-year study. Sixty-five of these began during the period from the first day of menses to the 15th preceding day (Fig 4). Comparable figures for the second class were 147 episodes; 76 began from the first day of menses to the 15th preceding day (Fig 5). Combined, there were 292 RAU episodes in the two

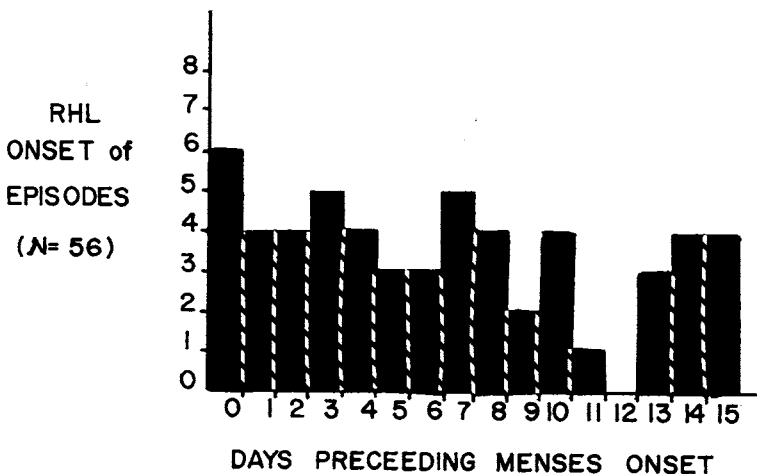


FIG 2.—Number of RHL episodes beginning on each individual day in 15-day period preceding onset of menses (day zero). Second class of student nurses (N = 58).

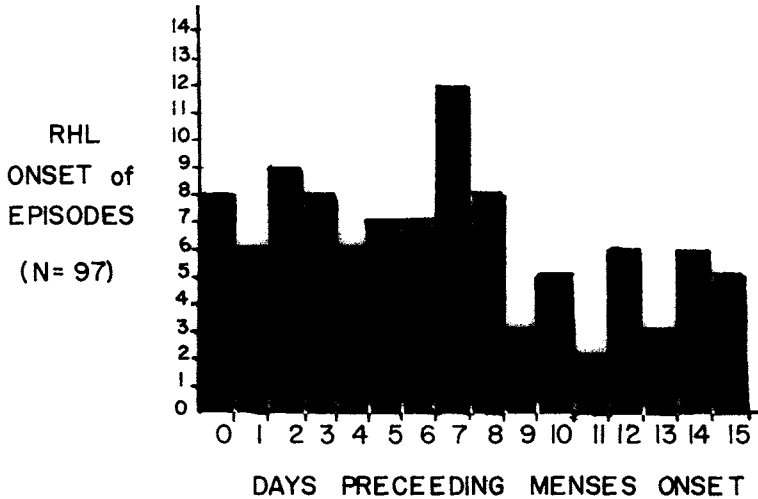


FIG 3.—Number of RHL episodes beginning on each individual day in 15-day period preceding onset of menses (day zero). Combined classes of student nurses ($N = 104$).

classes and 141 episodes began during the 16-day period studied (Fig 6). All tests described previously for RHL frequency were applied to the RAU data and revealed no significant differences in RAU frequency with the menstrual cycle.

Three students had severe RAU (12 or more episodes per year). Even in these women, no relationship between the timing of episode onset and the day or phase of menstrual cycle was found.

Incidence of RAU episodes (0.108 epi-

sodes per cycle) when students were taking oral contraceptives was no different than it was during cycles when no such medication was taken (0.103 episodes per cycle). There was no discernible effect of oral contraceptives on the distribution of episodes within the cycle.

Discussion

The results of this study showed no consistent relationship between the menstrual cycle and either RAU or RHL episodes.

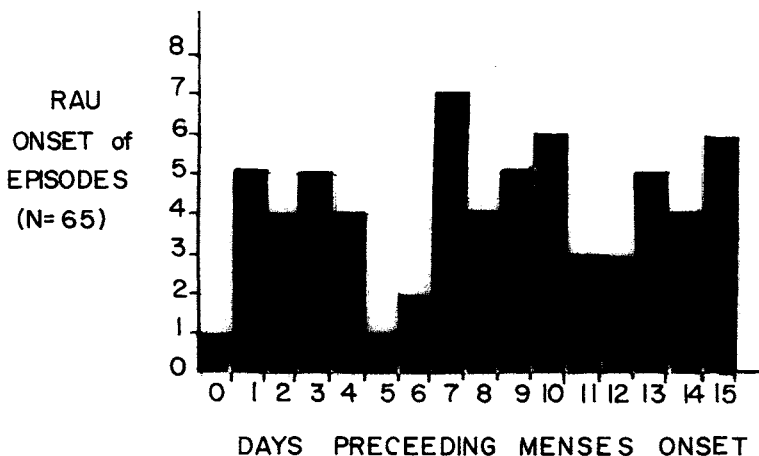


FIG 4.—Number of RAU episodes beginning on each individual day in 15-day period preceding onset of menses (day zero). First class of student nurses ($N = 46$).

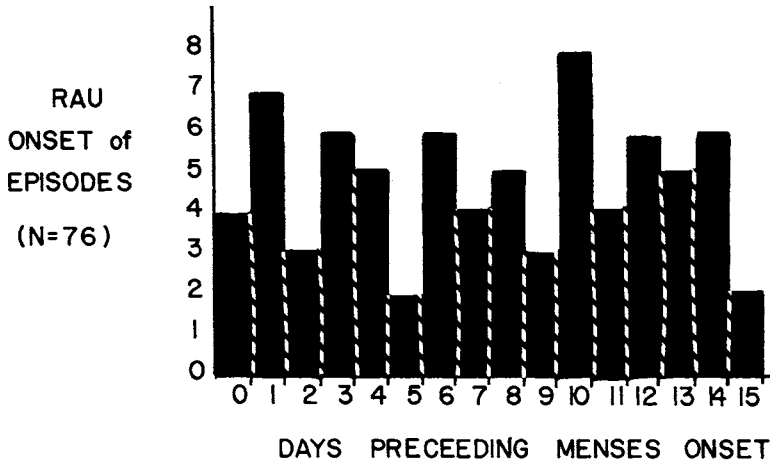


FIG 5.—Number of RAU episodes beginning on each individual day in 15-day period preceding onset of menses (day zero). Second class of student nurses (N = 58).

These findings differ from those of both Ship et al⁶ and Dolby⁵ who claim a relationship between RAU incidence and phases of the menstrual cycle. Ship et al used a prospective study design in which subjects made entries in a monthly diary only when an event of menses or RAU occurred. These "diary cards" were collected on a month-to-month basis for a fifteen month period from 110 women. On the basis of questionnaire data submitted by medical history information, those of the 110 women with a

history of RAU episodes were classified as mildly or severely affected. Those with no history of RAU were not included. Ship et al recorded that students with severe RAU onset (12 or more episodes per year) "demonstrated a distinct pattern characterized by exacerbation during the premenstrual week." They also state that "in the milder group in which less than one new lesion appeared monthly, the menstrual and premenstrual weeks were similar and relatively high." Their data were presented in a bar

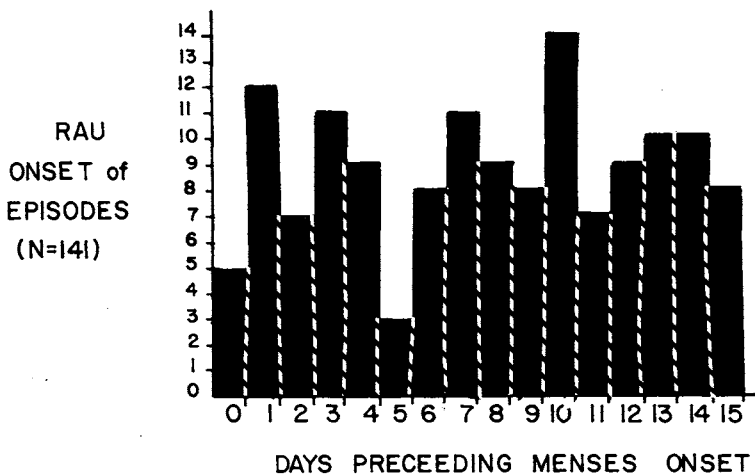


FIG 6.—Number of RAU episodes beginning on each individual day in 15-day period preceding onset of menses (day zero). Combined classes of student nurses (N = 104).

graph correlating mean RAU episodes per student with the four seven-day periods of the 28-day menstrual cycle. A chi-square test of these data showed that no one week in the cycle for both mildly and severely affected women had any increase in frequency of onset of RAU and, hence, the apparent variations do not have statistical significance. The data of Ship et al thus support our conclusions.

Dolby's⁵ study was conducted with 20 patients who complained of RAU. They kept diaries of menses and RAU episodes for a period of two to ten months. Dolby concluded that the frequency of RAU was higher during the two weeks after ovulation, but he shows only a bar graph with no reference to statistical tests.

Our study used daily, prospective data from a large population of nursing students at a big city hospital. Unlike Ship et al and Dolby we saw no changes in the frequency of RAU episodes, but we did note a small increase in the frequency of RHL episodes for the time period from the first day of menses to the eighth day preceding menses for the combined classes and also during the 16-day study period for the second class.

We know of no prospective study of RHL frequency and menses, a significant admission considering the surety with which a relationship between this disease and menses is asserted. Larato², as stated previously, reports that RHL and RAU "may appear at the time of menstruation" but did not document this conclusion. On the basis of our study, hormonal influences alone could explain only a very small fraction of the variance in RHL incidence. This observation has the necessary implication that many other causal variables may interact with hormone changes to produce the disease episode. The variation reported in the literature may result from the influence of a selected subset of women whose episodes are triggered by the endocrine changes of the menstrual cycle. Alternatively, there may be interaction between changes in the menstrual cycle and other events like fever, trauma, and sunburn which appear to affect RHL onset.⁹ At present, combinations of multi-variant events are being studied in relation to RAU and RHL onset and will be reported in a subsequent publication.

It seems to be the rule rather than the

exception that in articles dealing with disease onset and the menstrual cycle, conclusions are made and based on data collected retrospectively or from small patient populations, if not single case studies.¹⁰ Patients with RAU severe enough to motivate consultation may be quite different from many in the general population who experience milder disease. The limited number of students with severe RAU and the absence of any with severe RHL indicates that our sample is more representative of a general population than a patient sample. Retrospective associations are probably not always accurate assessments of past events. Menses may be a convenient reference point by which to remember disease onset, and subjects may forget onsets of other episodes that occur at other times. The tendency to associate disease with menses may reflect cultural as well as individual psychological bias. Menstrual blood is traditionally thought of as a pollutant, and dirty substances have long been thought to yield illness.¹⁰ The negative results of this study emphasize the importance of collecting data prospectively from a large sample population over long time periods.

Conclusions

A study of two successive classes of 104 student nurses was conducted over a period of three years to determine the incidence of RHL and RAU in relation to the menstrual cycle. No greater incidence of RHL or RAU was found when the postmenstrual half of the cycle was compared with the premenstrual period. Testing by analysis of variance showed no one specific day in the fifteen days preceding menses had a higher frequency of RHL onset than any other day in this period of the menstrual cycle. However, a test showed an increase in frequency of RHL episodes in the eight-day period preceding menses for the combined classes, but this increase was not seen when the classes were studied as separate populations. A chi-square test also showed a small increase in the frequency of RHL episodes in the second class during the 15 days preceding menses, but this was not seen in the first class or when the classes were combined.

We would like to acknowledge the assistance provided by I. Ship in the organization of this prospective study and for discussion of the data used in his 1961 publication. The cooperation of the students and administration of the School of Nursing of the Philadelphia General Hospital also is gratefully acknowledged.

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