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The Relationship of the Renin-Angiotensin-Aldosterone System to Plasma Gonadotropin, Prolactin, and Ovarian Steroid Patterns during the Menstrual Cycle*

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Zusammenfassung. Bei 14 gesunden jungen Frauen erfolgten in 48stündigem Abstand über jeweils einen menstruellen Zyklus hinweg Blutentnahmen unter kontrollierten Bedingungen (nüchtern morgens vor dem Aufstehen); die Konzentrationen von Reninsubstrat, Aldosteron, LH, FSH, Östradiol-17β, Progesteron, 17α-Hydroxyprogesteron, 4-Androstendion und Prolaktin sowie die Reninaktivität im Plasma wurden bestimmt und ihr Verhalten verglichen.

Die Aktivität des Renin-Angiotensin-Aldosteronsystems steigt in der Lutealphase deutlich an, sehr wahrscheinlich als Folge der natriuretischen Wirkung von Progesteron. Bei niedrigen Progesteronwerten im Plasma fielen die Reninaktivität und die Aldosteronkonzentration schon frühzeitig wieder ab.

Bei einigen Versuchspersonen wurde ein Anstieg von Renin und Aldosteron auch in der späten Follikelphase oder zur Zeit des LH-Gipfels festgestellt. Obgleich der Mechanismus dieser Veränderungen noch unklar ist, so kann doch angenommen werden, daß die hier erstmals während des menstruellen Zyklus nachgewiesenen Schwankungen der Reninsubstratkonzentration dafür zumindest teilweise verantwortlich sind. Andererseits kann nicht ausgeschlossen werden, daß der präovulatorische Anstieg der Östradiolkonzentration über eine vorübergehende anfängliche Natriurese zu einer Steigerung der Reninfreisetzung aus der Niere führt.

Unerwarteterweise sind die Reninsubstratkonzentration und weniger deutlich auch die Reninaktivität in der Follikelphase von Frauen mit Corpus luteum-Insuffizienz höher als bei normaler Lutealphase. Weder Prolaktin noch Gonadotropine scheinen beim Menschen einen direkten Einfluß auf das Verhalten des Renin-Angiotensin-Aldosteronsystems während des menstruellen Zyklus auszuüben.

* Excerpts of this study were presented at the 41st Meeting of the Deutsche Gesellschaft für Gynäkologie und Geburtshilfe, Hamburg, September 1977 [1]

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Schlüsselwörter: Renin – Reninsubstrat – Aldosteron – Prolaktin – Menstrueller Zyklus.

Summary. Fasting supine renin activity, renin substrate concentration and aldosterone concentration in plasma were measured every other day during a complete menstrual cycle in 14 healthy young women; the patterns of LH, FSH, estradiol-17β, progesterone, 17α-hydroxyprogesterone, 4-androstendione, and prolactin in plasma were also determined radioimmunologically.

During the luteal phase, the activity of the renin-angiotensin-aldosterone system is increased, probably due to the natriuretic effect of progesterone; very low progesterone values are accompanied by an early decrease of renin activity and aldosterone concentration.

In some subjects, there were also peaks of renin and aldosterone in the late follicular phase or at the time of the LH surge. The mechanism of these changes is not yet clearly understood; however, it seems reasonable to assume that fluctuations of renin substrate concentration, which were demonstrated for the first time during the menstrual cycle, are related to this observation. Alternatively there may be a transient natriuresis induced by the estradiol secretion from the riping follicle. There is no temporal relationship between the periovulatory variations in 17α-hydroxyprogesterone concentration and in the renin-angiotensin-aldosterone system.

Unexpectedly, plasma renin substrate concentration and renin activity were higher in the follicular phase of women with luteal failure. Neither prolactin, which was slightly higher during the luteal phase and during menstruation, nor gonadotropins seem to be directly related to the behavior of plasma renin activity or aldosterone concentration during the menstrual cycle in man.

Key words: Renin – Renin substrate – Aldosterone – Prolactin – Menstrual Cycle.

The activity of the renin-angiotensin-system [2–9] and the plasma aldosterone concentration [9–12] are increased during the luteal phase of the menstrual cycle. On the other hand, no characteristic changes of renin substrate concentration were found [4, 7, 13]. There are different reports in the literature concerning a mid-cycle peak of plasma renin activity, which was described by us in 1972 using a rat pressor bioassay and in 1974 using an angiotensin I radioimmunoassay [14, 15]. The possibility of an inconsistent and insignificant increase of PRA in the preovulatory period was also mentioned by Sundsfjord and Aakvaag [10]. In some menstrual cycles examined by Skinner et al. [4] and Katz and Romfh [9] slight increases of PRA may be noticed, but were not described by the authors. In the meantime, preovulatory peaks of angiotensin II concentration [16] and of aldosterone concentration [10, 12, 16] were also demonstrated. However, in most of these investigations, no simultaneous estimations of ovarian steroids were carried out; therefore, the cause of the stimulation of the renin-angiotensin system and of aldosterone secretion in the luteal phase and – inconsistently – in the late follicular phase of the menstrual cycle remained unclear.

Previously, Sundsfjord had demonstrated a positive correlation between progesterone concentration, renin activity and urinary aldosterone excretion [25]; he concluded that the activation of the renin-angiotensin-aldosterone system in the luteal phase may be fully explained by the well known natriuretic effect of progesterone. However, this does not explain the preovulatory peak of plasma renin activity, since progesterone first begins to increase at the time of the LH peak. On the other hand, the rise of estradiol-17β secretion during the second half of the follicular phase would primarily promote renin substrate synthesis in the liver and thus lead to an increased substrate concentration in plasma; this has not yet been proved [4, 7, 13].

In the present paper, simultaneous measurements of renin activity, renin substrate, aldosterone, gonadotropins, prolactin and of ovarian steroids are reported. Moreover, the observation of cycles with corpus luteum insufficiency (luteal failure) may help to elucidate the question, which of the sex hormones is mainly responsible for the variations of the renin-angiotensin-aldosterone system during the different phases of the menstrual cycle.

Material and Methods

Subjects

Fourteen healthy women (students) between 20 and 27 years of age who had not taken hormonal contraceptives for at least 1 month before entering the study (except for C. W.) volunteered for this investigation. They had no history of cyclical or premenstrual edema and were nulliparous. Basal body temperature was measured daily. The subjects were asked to avoid salty meals; otherwise, their diet was unrestricted. Antecubital venous blood was drawn at home every second day throughout one cycle between 7.30 and 9.30 a.m. after at least 6 h of sleep (fasting and before arising from bed). The blood samples were immediately collected into prechilled polystryrol tubes containing disodium-EDTA (10 mg/10 ml blood) and kept at 4° C until centrifugation in the cold. The plasma was frozen at −25° C until analyzed.

Hormone Radioimmunoassays

Plasma renin activity was estimated by the method of Haber et al. [17], with the modification that plasma was incubated at pH 5.9 [18]. Plasma renin substrate (angiotensinogen) concentration was also determined (except in U. B., H. S., H. D. and A. W.) by radioimmunoassay of angiotensin I, as described earlier [18]; plasma samples were diluted 1 : 20 (v/v) instead of 1 : 50, the final multiplication factor thus being 16,000 instead of 40,000.

In most cases, plasma aldosterone was measured by a radioimmunoassay without previous chromatography [19]. The antiserum was received by immunization of rabbits against an aldosterone-oxim-protein conjugate; its immunological properties have been described in detail elsewhere [20]. The intra-assay variation was 11%; the recovery of ^{3}H-aldosterone added to the plasma varied between 85–95%. The plasma samples (2 ml) of five subjects (A. B., A. S., B. K., K. V., U. W.) were extracted with 12 ml dichloromethane, the extracts washed with 1 ml 0.1 N NaOH and 1 ml aqua dest. and then evaporated to dryness. The residues were dissolved in methanol and subjected to paper chromatography in the Bush B5 system. The aldosterone fraction was determined radioimmunologically; the procedural losses were corrected by addition of an internal standard to the original plasma.

LH and FSH plasma concentrations were measured by radioimmunoassay using dioxane for separation of antibody bound and free hormones [21]; immunochemicals were generously supplied by

the National Institutes of Health (Bethesda, Maryland) and the Medical Research Council (London).

Plasma concentrations of estradiol-17β, progesterone, 17α-hydroxyprogesterone (17-OHP) and 4-androstendione were also measured by radioimmunoassay [22]; separation of cross-reacting steroids was achieved by celite chromatography, using a system which allowed the simultaneous measurement of these steroids in one plasma sample.

Prolactin (PRL) was determined radioimmunologically using a commercial kit (Isotopen-Dienst West, D-6072 Dreieich).

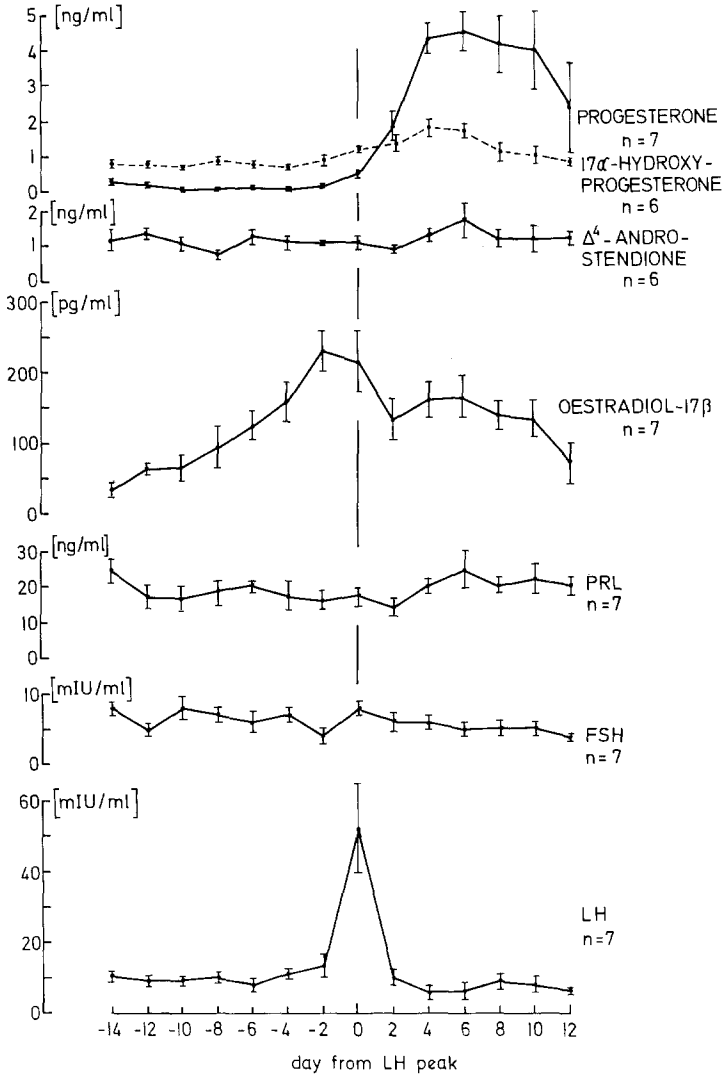

Fig. 1. Plasma concentrations of LH, FSH, prolactin, estradiol-17β, progesterone, 17α-hydroxyprogesterone, and 4-androstendione in seven women with presumably ovulatory cycles, synchronized on the day of maximal LH concentration. Means $\pm$ SEM

Results

Seven subjects had ovulatory cycles with a normal luteal function (luteal group) as indicated by basal body temperature, duration of the luteal phase (12–16 days between LH peak and beginning of the following menstruation) and plasma progesterone concentration (increase above 3–4 ng/ml 4–10 days after the LH surge). Four women (A. B., A. S., B. K., C. W.) showed ovulatory cycles with luteal failure (luteal phase of 6–9 days duration, and low progesterone values except for A. B.). Two subjects probably had also luteal failure: G. V. had been treated with 10 mg norethisterone acetate (NEAc) from the 20th to the 23rd day of the cycle (luteal supplementation). In subject H. D., there was no menstruation until the 35th day of her cycle; she reported later that her menstruation had started on the 38th day. The hormone assay showed an LH peak on the 32nd day of the cycle after a previous estradiol-17β surge; the very short luteal phase must be interpreted as luteal failure. – One subject (A. W.) had an anovulatory cycle; there was no LH peak, although

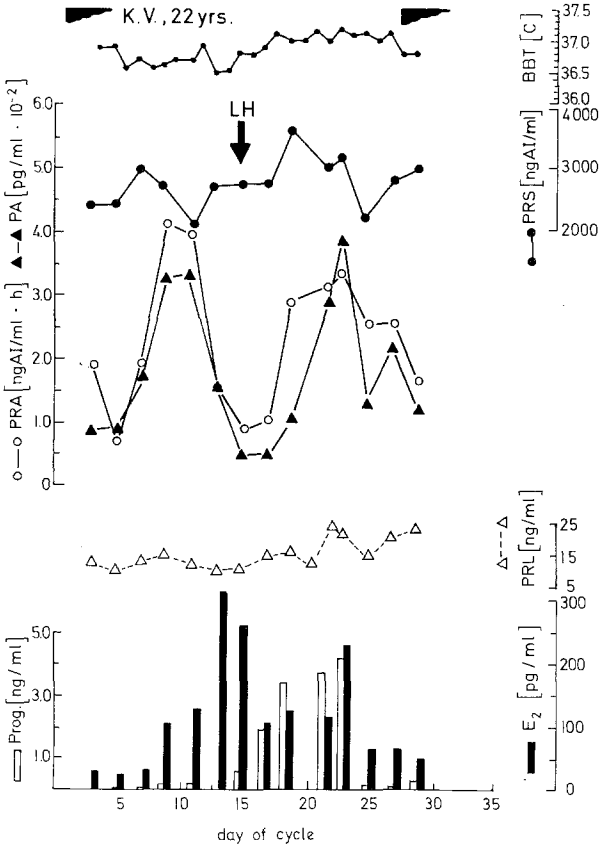

Fig. 2. Basal body temperature and plasma concentrations of renin substrate, aldosterone, prolactin, estradiol-17β, and progesterone, and plasma renin activity in K. V.

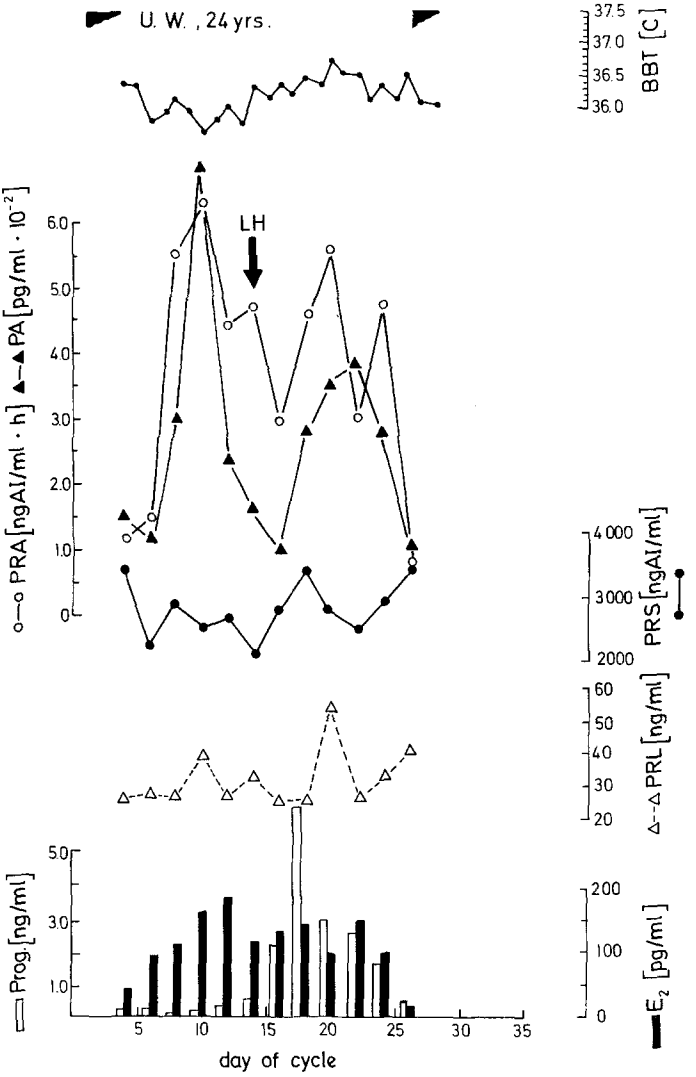

Fig. 3. Plasma renin activity and concentrations of renin substrate, aldosterone, prolactin, estradiol-17β, and progesterone in U. W.

estradiol-17β increased between day 15 and 19 of her cycle, and no elevation of plasma progesterone.

Figure 1 shows the mean concentration and the standard error of the mean (SEM) of LH, FSH, prolactin and gonadal steroids in the seven subjects of the luteal group, synchronized on the day of maximal LH concentration in plasma (day 0). The concentrations of these hormones show the typical pattern. Prolactin is slightly elevated during the late luteal phase and at the time of menstruation. Estradiol-17β begins to increase already on day −8 and reaches a peak shortly before the LH surge. 4-androstendione shows no characteristic variations in the cycles examined.

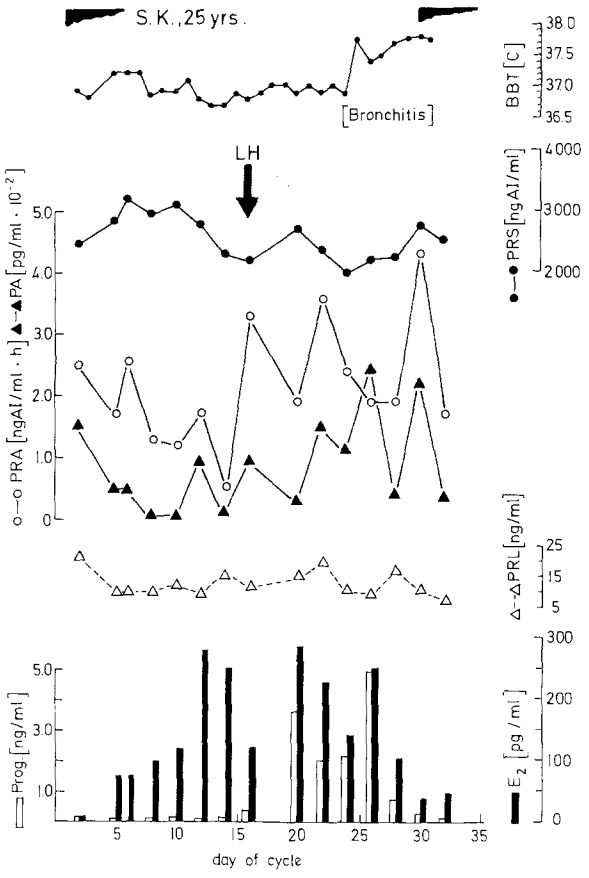

Fig. 4. Plasma renin activity and concentrations of renin substrate, aldosterone, prolactin, estradiol-17β, and progesterone in S. K.

In the luteal failure group, the most characteristic features, besides low progesterone concentrations during the second half of the cycle, are a late (day −4) and smaller elevation of estradiol-17β in the follicular phase and lower values during the luteal phase, decreasing to the baseline already on day +6. There are no significant differences in the plasma concentrations of gonadotropins and of prolactin in the luteal failure group.

Figure 2 shows a characteristic behavior of the renin-angiotensin-aldosterone system in a 22-year-old student (K. V.). There is a close parallelism between plasma renin activity (PRA) and plasma aldosterone (PA) concentration with peaks 4–6 days before the LH surge and during the luteal phase. Maxima of these parameters are followed by two minima of plasma renin substrate concentration (PRS). The more pronounced elevations of estradiol-17β (E_2) are followed by an increase of PRS 2–4 days later. Parallel to the sharp fall in progesterone concentration between day 23 and 25 of this cycle, there is also a decrease of aldosterone, which is more distinct than that of PRA.

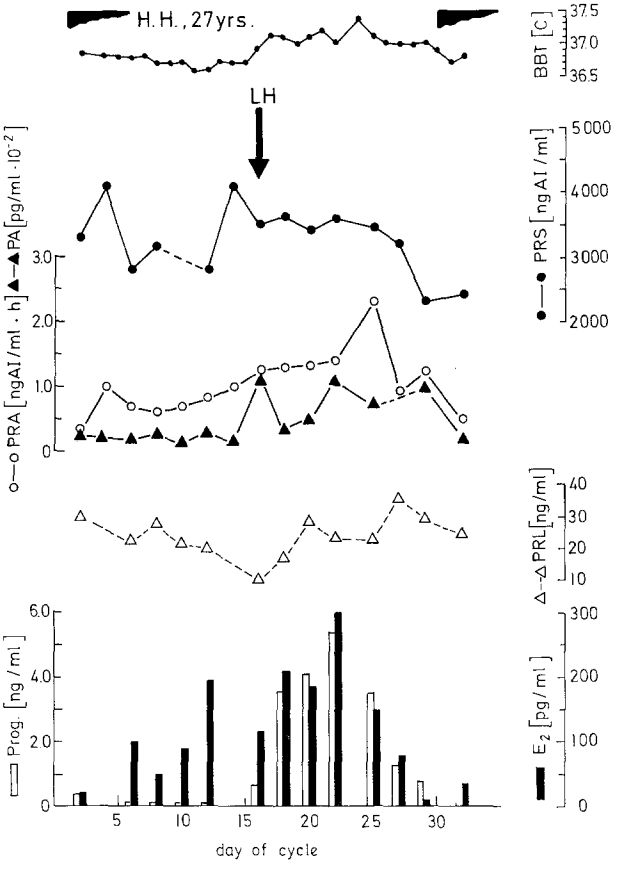

Fig. 5. Plasma renin activity and concentrations of renin substrate, aldosterone, prolactin, estradiol-17β, and progesterone in H. H.

Figure 3 shows a similiar pattern in subject U. W. The preovulatory peaks of PRA and PA occur on day −4. The beginning of their luteal phase elevation coincides with the rising PRS and progesterone concentrations. PRS is also relatively high at the time of menstruation. Prolactin concentration is rather high in this cycle; two peaks coincide with those of renin and aldosterone. In S. K. (Fig. 4), there is a first clear-cut peak of PRA at midcycle, not preceded by an increase of PRS or progesterone. Although PRS is lower in the second half of this cycle, the values of PRA and PA are higher at the same time as compared to the follicular phase. The variations of PRS are poorly correlated to estradiol-17β concentration. Prolactin is rather constant throughout this menstrual cycle.

Figure 5 shows a cycle with minor changes of PRA and PA, but a tendency to higher values during the second half of the cycle. This is also true for prolactin which has a minimum at the time of the LH peak. The increase of PRS on day −2 is possibly correlated to the preovulatory estradiol-17β surge.

Figure 6 demonstrates a menstrual cycle with a prolonged follicular phase followed by a normal luteal phase. At the time of the LH and estradiol-17β surge, there

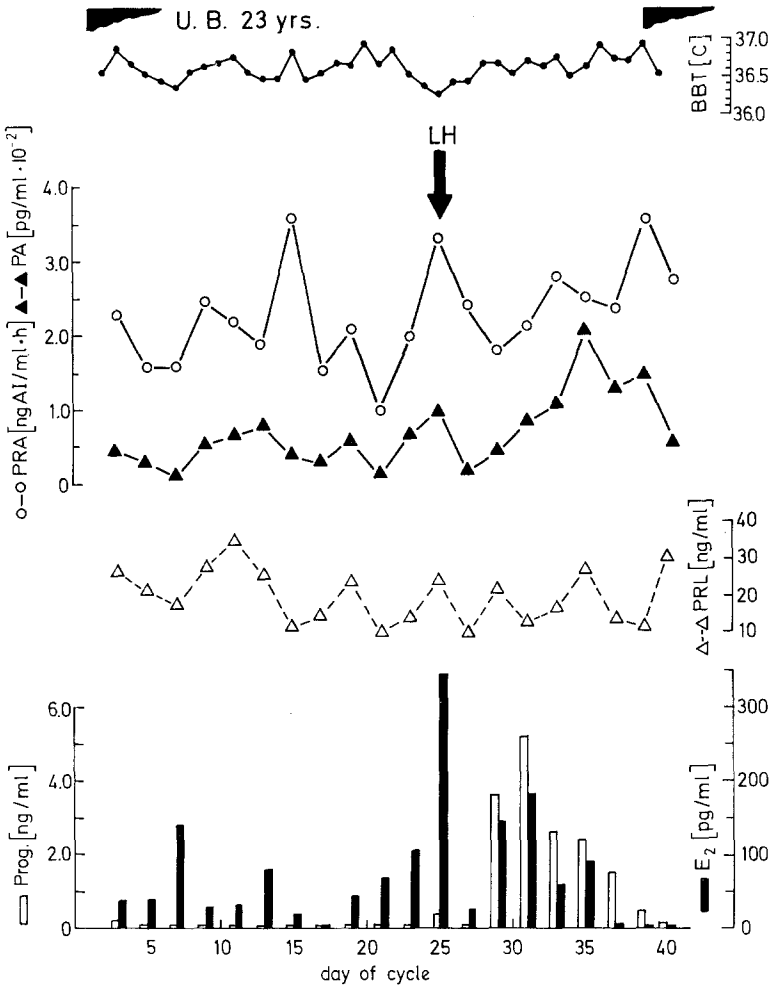

Fig. 6. Plasma renin activity and concentrations of aldosterone, prolactin, estradiol-17β, and progesterone in U. B.

are also peaks of PRA and – to a lesser degree – of PA. During the premenstrual period of this cycle, renin and aldosterone are also increased compared to the follicular phase. Prolactin shows an uncharacteristic profile. In the subject D. H. (Fig. 7), ovulation occurred on the 21st day of the menstrual cycle, followed by a normal luteal phase of 12 days. PRS and PRA show a short peak on day 11 and a minimum of PRS 2 days later. There is a second surge of PRS in the mid-luteal phase. Aldosterone has a peak on the 15th day of the cycle and – simultaneous to the increased progesterone levels – a broad elevation from day 25–31 (exact values are not given because of poor duplicates in this aldosterone assay).

Figure 8 shows a very long cycle with a follicular phase of 43 days and a normal luteal phase of 15 days. PRA and PA reveal uncharacteristic changes during this menstrual cycle with a tendency to higher PA values in the luteal phase, parallel to a

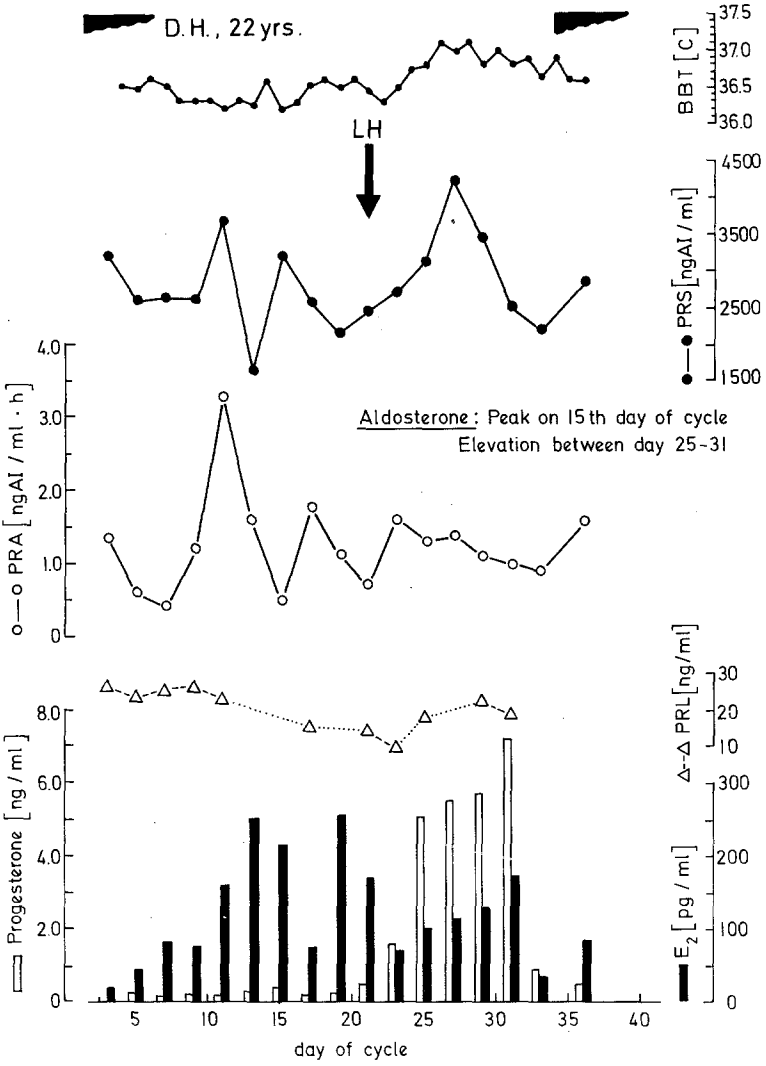

Fig. 7. Basal body temperature, plasma renin activity and plasma concentrations of renin substrate, prolactin, estradiol-17β, and progesterone in D. H.

transient PRA peak and to a typical elevation of progesterone concentration. Prolactin is increased around menstruation.

The following figures demonstrate the behavior of the renin-angiotensin-aldosterone system in six menstrual cycles with luteal failure (H. D. and G. V. included). In the 22-year-old subject A. B. (Fig. 9), there was a short luteal phase (8 days) with normal progesterone concentrations at that time. The changes of PRS are much higher than possible methodological variations; particularly, PRS increases during the week before ovulation and decreases definitely in the early luteal phase. PRA and PA are both higher during the second half of the cycle with a short peak of PRA in the preovulatory and in the premenstrual phase. The periovulatory increase and

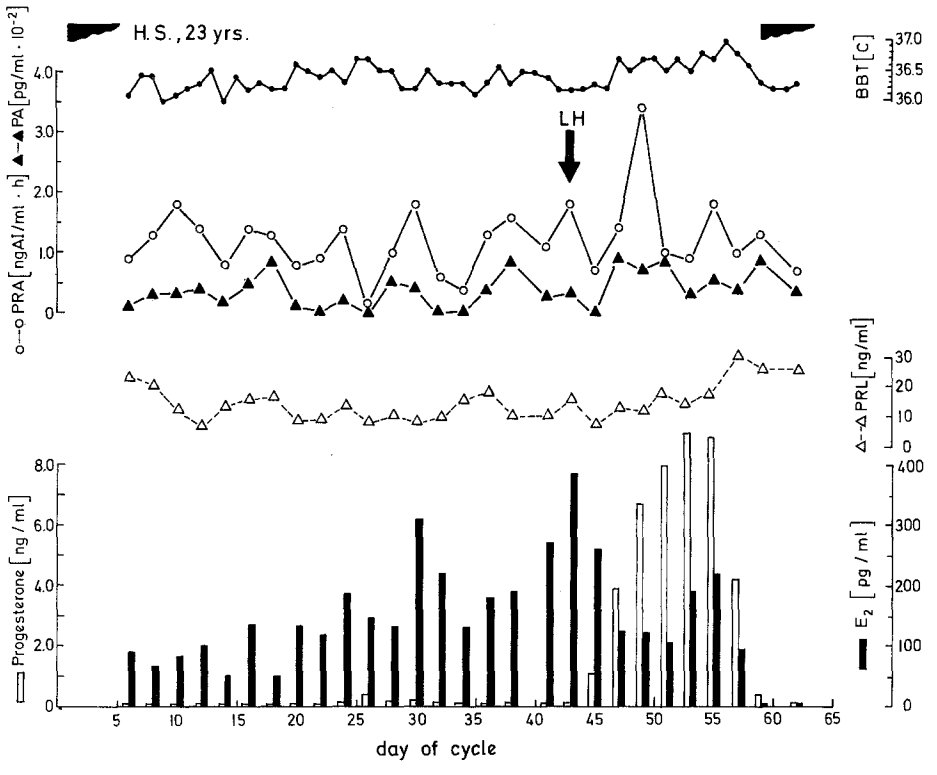

Fig. 8. Plasma renin activity and concentrations of aldosterone, prolactin, estradiol-17β, and progesterone in the abnormally long menstrual cycle of H. S.

decrease of PRS seem to be time-correlated to the slowly rising estrogen secretion and to the activation of the renin-angiotensin system, respectively. The otherwise constant prolactin concentration shows a premenstrual surge.

In A. S. (Fig. 10), the LH peak occurs on the 17th day of a cycle of 25 days. There is a good relationship between the changes of PRS, PRA and PA throughout the whole cycle with a first peak on the 8th day, another surge around ovulation and a parallel decrease during the short luteal phase. Estradiol-17β and progesterone values are low, prolactin behaves uncharacteristically.

Figure 11 (C. W.) demonstrates luteal failure after hormonal contraception in the previous cycle. PRS values fall continuously over 2—3 weeks after discontinuation of the hormonal contraception. They increase again simultaneously to LH, together with surges of PRA and PA. PRA is clearly higher during the second half of this menstrual cycle, while aldosterone is much less elevated compared to the early follicular phase. Prolactin is transiently increased 1 day before the onset of menstruation.

In the cycle demonstrated in Figure 12 (B. K.), there is also a close parallelism in the pattern of PRS, PRA and PA; moreover, the changes of PRS precede those of the other parameters, or coincide with them. Small peaks of prolactin are observed during the preovulatory and during the premenstrual period.

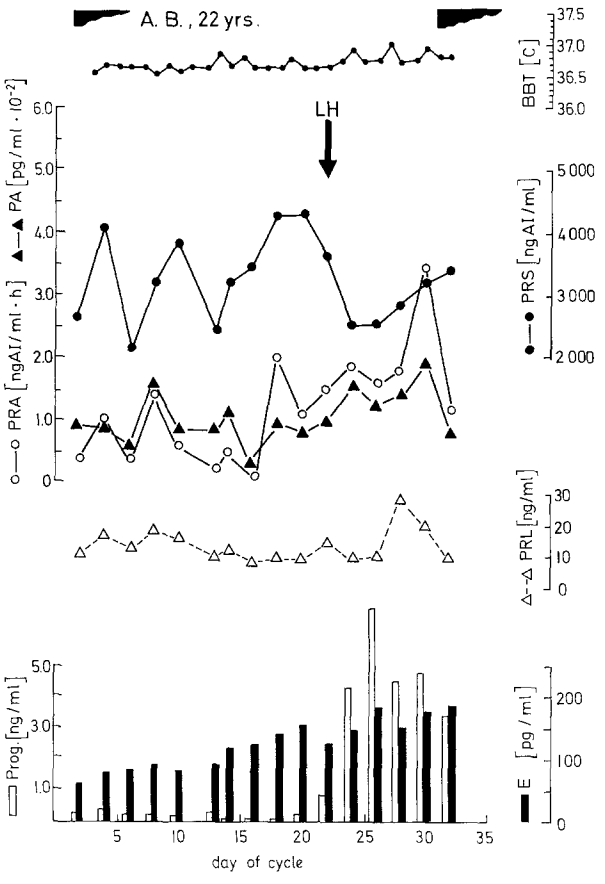

Fig. 9. Plasma renin activity and concentrations of renin substrate, aldosterone, prolactin, estradiol-17β, and progesterone in A. B.

The cycle of the subject H. D. (Fig. 13) primarily was thought to be anovulatory (see BBT), but the hormone determinations showed an increase of estradiol-17β with a subsequent LH surge to 47 mIU/ml on the 32nd day. As already mentioned, blood samples could not be obtained during the last week of this cycle, and progesterone concentration is therefore unknown at this time. Even if there was no ovulation but only luteinization of the follicle, there is a distinct peak of PRA before the LH surge; in the test protocol, however, physical (sexual) activity has been mentioned before venipuncture which may perhaps explain the high PRA (and PRL?) value on the 25th day of this cycle. PA is low throughout the whole cycle.

In G. V. (Fig. 14), the hormone analysis revealed an LH peak on the 18th day, when there was a small prolactin surge. 1 week earlier, a PRA peak was observed. Few days after the assumed ovulation, PRA and PA increased again. At this time, however, a treatment with norethisterone acetate (NEAc) had started for 4 days, which was not planned at the beginning of this study. PRS shows a tendency to higher values in the preovulatory and during the short luteal phase.

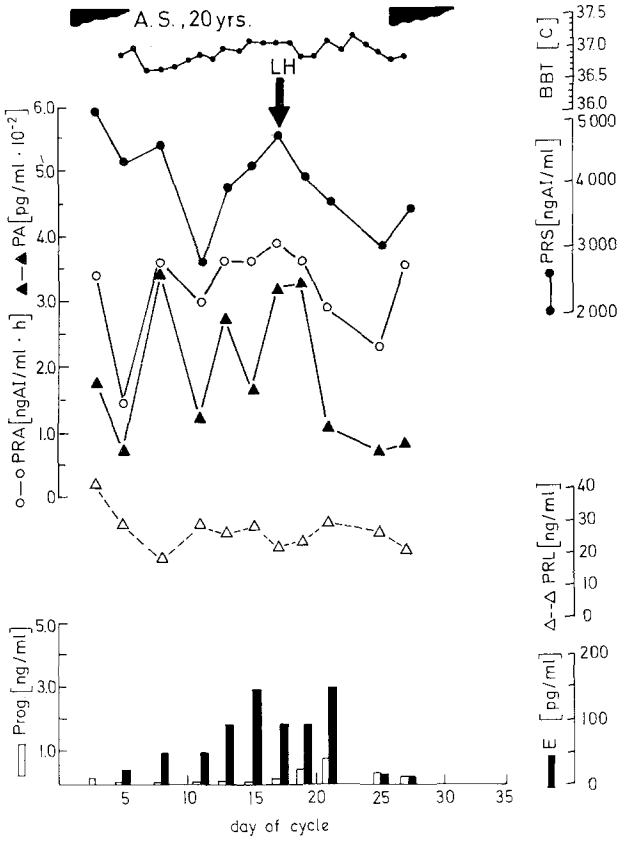

Fig. 10. Plasma renin activity and concentrations of renin substrate, aldosterone, prolactin, estradiol-17β, and progesterone in A. S.

The short cycle of A. W. (Fig. 15) probably was an anovulatory cycle (no LH or typical progesterone surge observed). On day 17, maxima of PRA and PA occurred at the time of increased secretion of estradiol-17β. PRS was not determined. The pattern of PRL concentration is uncharacteristic. The values of 4-androstendione are strikingly high, expecially during the first half of this menstrual cycle.

The patterns of PRS, PRA and PA in four cycles with luteal failure (A. B., A. S., B. K., C. W.) as well as of some cycles with a normal luteal phase are summarized in Figure 16. It is evident from this figure that both PRS and – to a lesser degree – PRA are higher in menstrual cycles with luteal failure; this is also true for PRS during the follicular phase, although estradiol-17β secretion is decreased in this condition. In the normal cycles ($n = 5$) there are slightly elevated values of PRS found during the luteal phase. In seven cycles of the luteal group, slight elevations of PRA are seen on day –6 to –4, at the time of the LH surge and again around day +6. The changes of aldosterone concentration are parallel to those of PRA in both groups of subjects; they also tend to be higher in the luteal failure group.

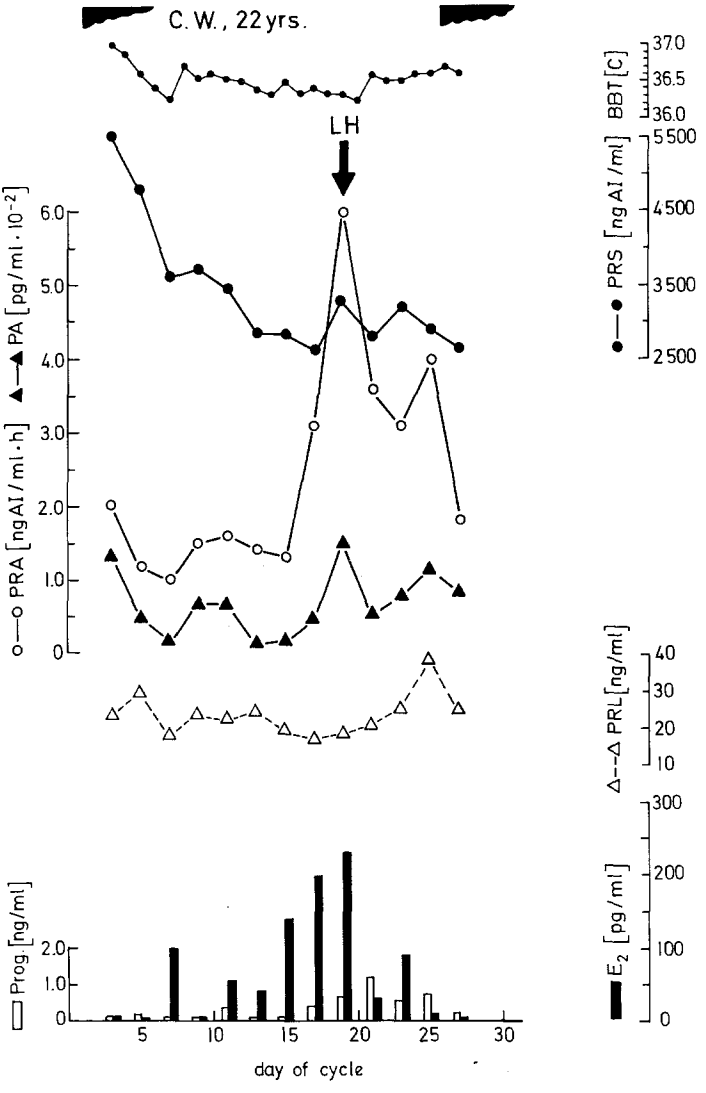

Fig. 11. Plasma renin activity and concentrations of renin substrate, aldosterone, prolactin, estradiol-17β, and progesterone in C. W.

Discussion

Subjects with ovulatory cycles had an increased fasting supine PRA and PA not only during the luteal phase of the menstrual cycle, but, in some cases, also showed marked preovulatory maxima (above all K. V. and U. W.) or peaks at the time of ovulation (U. B., S. K.). This may explain the previous observation of Thorn et al. [23] that many women gain more than 1 kg of body weight during the periovulatory period. In some subjects (K. V., U. W., D. H.), a parallelism between the changes of PRA and PRS was found. PRS did not reveal a typical biphasic pattern, but higher

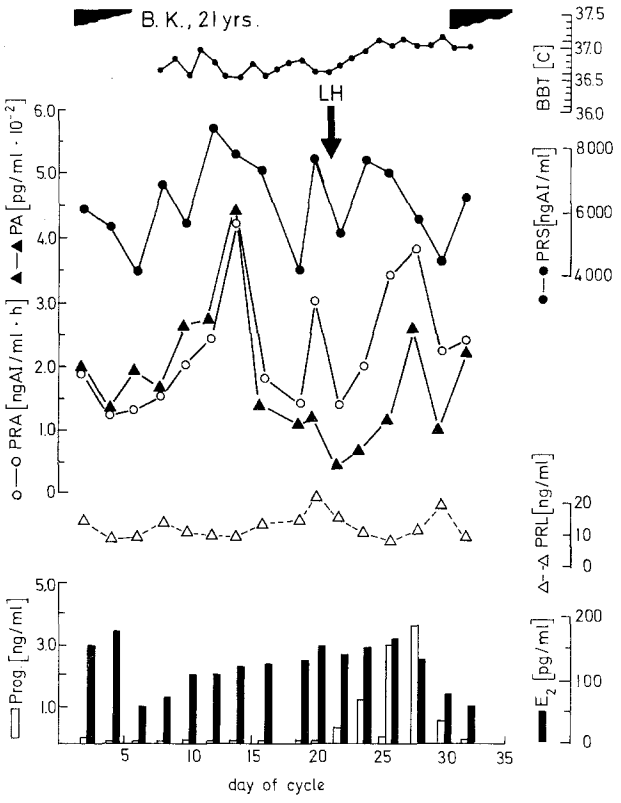

Fig. 12. Plasma renin activity and concentrations of renin substrate, aldosterone, prolactin, estradiol-17β, and progesterone in B. K.

mean values in the early follicular phase (days −10/−12), relatively low values in the preovulatory period (day −4/day 0), and a broad elevation in the luteal phase.

In the luteal failure group, PRS was elevated throughout the cycle, especially during the first half of the follicular phase, compared to those women with luteal phases of 12–16 days duration. A similar observation was published by Sundsfjord and Aakvaag [7]. An explanation for this finding is still lacking; differences in the estrogen secretion rate cannot be related to this phenomenon, because estradiol-17β concentration is known to be lower in women with luteal failure. This is clearly demonstrated also in our subjects. Increases of PRS are frequently paralleled by variations of PRA (e.g., in A. S. and B. K.). In most cases, there are preovulatory or ovulatory peaks of PRA and PA. A further increase of both parameters may be seen during the luteal phase of some subjects (e.g., A. B. and C. W.). Renin and aldosterone also tend to be higher in the luteal failure group, probably due to the higher PRS described above.

The increase in plasma renin activity and aldosterone concentration during the second half of the cycle is well known and is very pronounced if values from the first week of the menstrual cycle are compared to those from the mid-luteal phase (Fig. 16). This is supposed to be due to the natriuretic effect of progesterone [24], whose

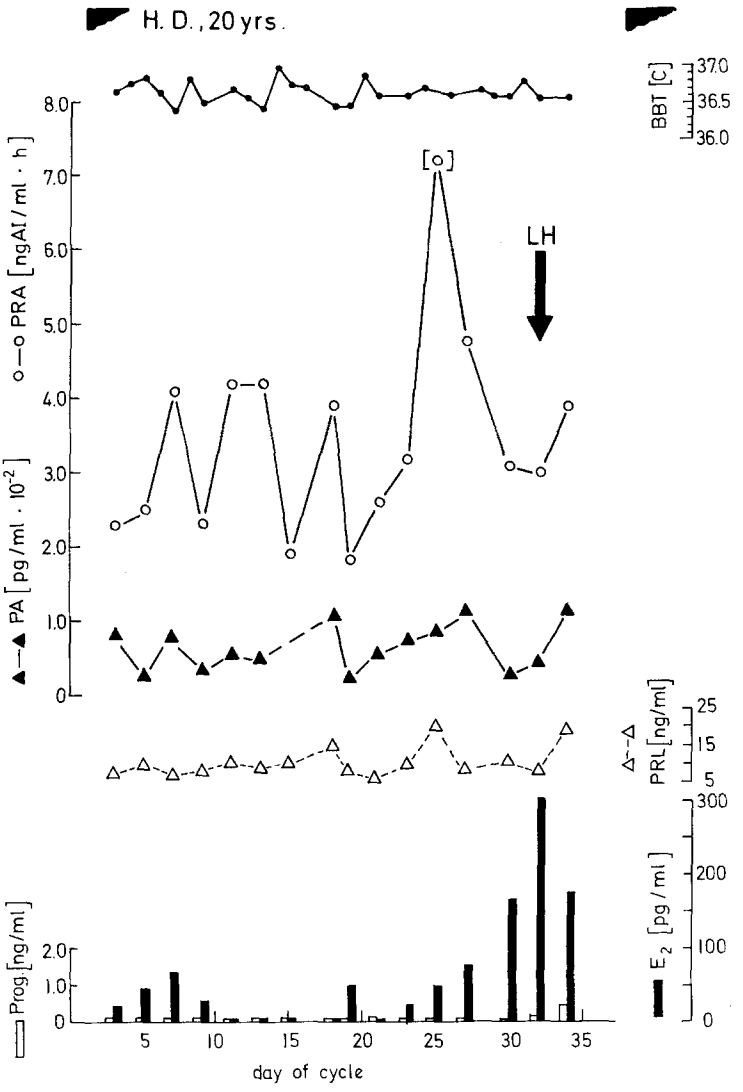

Fig. 13. Plasma renin activity and concentrations of aldosterone, prolactin, estradiol-17β, and progesterone during the follicular and periovulatory phase in H. D.

secretion is increased during the luteal phase. The pattern of renin activity and aldosterone secretion during the second half of the menstrual cycle in our subjects may indeed be explained by preceding or simultaneous changes in plasma progesterone concentration; very low progesterone values are accompanied by an early decrease of PRA and PA (e.g., in A. S. and A. W.). The quantitatively different behavior of renin and aldosterone in the various subjects is possibly explained by the fact that high salt intake abolishes the progesterone-induced rise of PRA [25]. Although it has been shown that the concentration of corticosterone (compound B) is

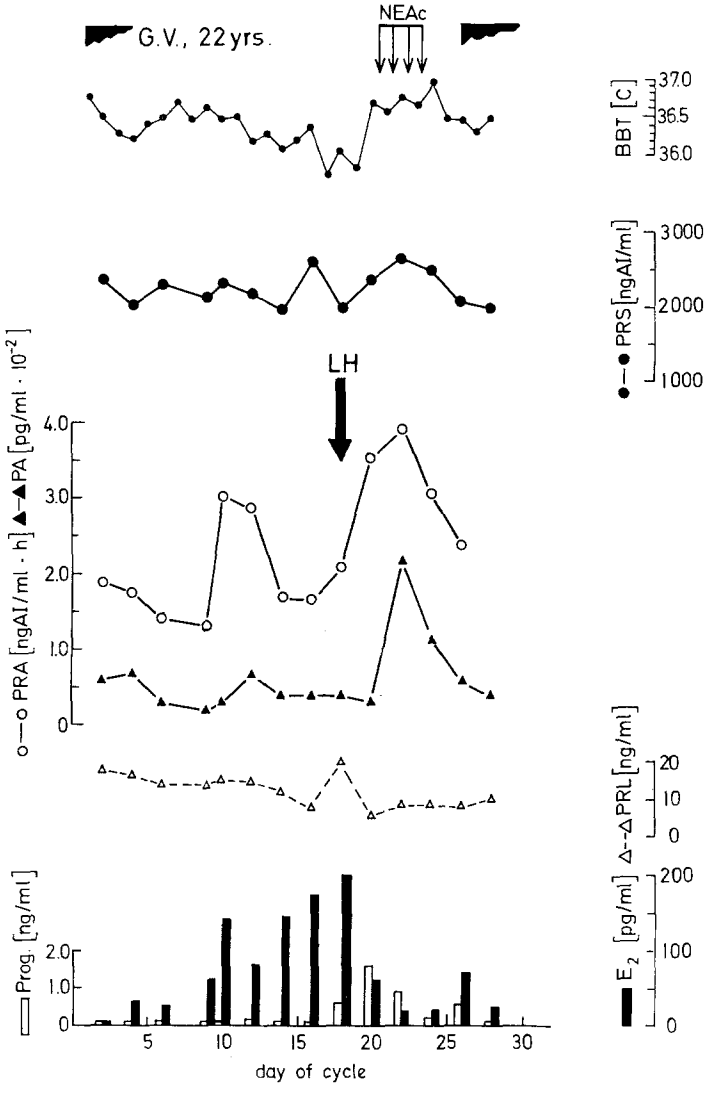

Fig. 14. Plasma renin activity and concentrations of renin substrate, aldosterone, prolactin, estradiol-17β, and progesterone in G. V., who was treated with 10 mg norethisterone acetate (NEAc) daily from the 20th to the 23rd day of the menstrual cycle

also higher during the luteal phase [26], the mechanism of this increase has not yet been elucidated; radioimmunological determinations of cortisol concentration in our subjects revealed no significant changes; no correlation between aldosterone and cortisol was observed (unpublished data).

The periovulatory peaks of PRA and PA are less consistent and more difficult to correlate to changes in renin substrate concentration or in the secretion of the ovarian hormones. It would be most interesting to know if and how endogenous estrogens may stimulate PRA. In some cases (e.g., A. S. and B. K.), increases of PRA

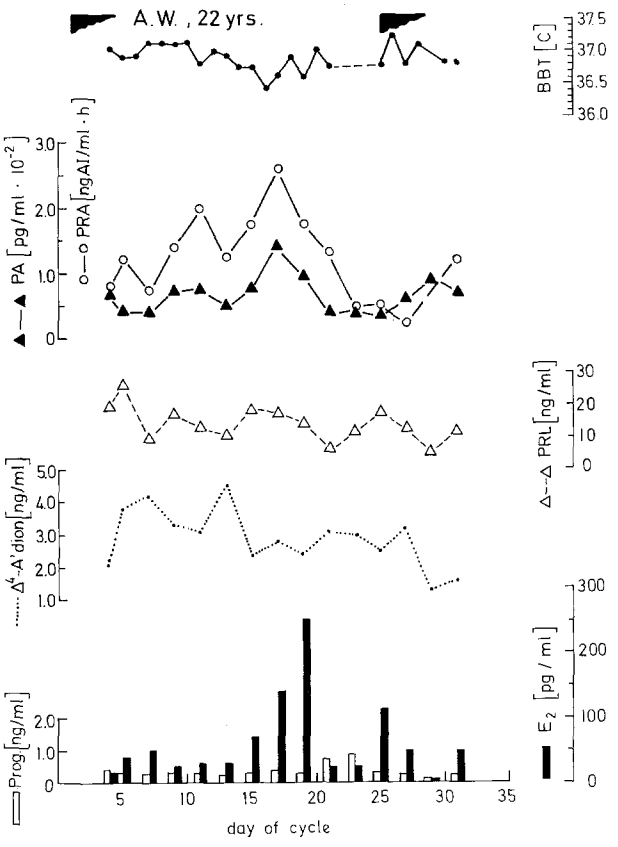

Fig. 15. Plasma renin activity and concentrations of aldosterone, prolactin, estradiol-17β, and progesterone during the presumably anovulatory cycle of A. W. The relatively high values of 4-androstendione in this subject are also demonstrated

during the follicular phase correlate to changes in plasma renin substrate concentration (PRS). In other subjects (e.g., K. V. and C. W.), there are marked changes of PRA and PA, but only small rises in PRS at the same time. The following mechanisms may play a role in the regulation of PRA and PA during the follicular phase:

1. A stimulation of renin substrate synthesis in the liver, due to the rising estrogen secretion, could lead to an elevated PRA if renin substrate is considered to be a rate-limiting factor in the reaction of renin with its substrate in vivo. Reports in the literature are very contradictory and have recently been reviewed by Pallas et al. [27]; at present, most authors support the view that an increase of renin substrate concentration may elevate plasma renin activity in vivo.

2. It cannot be exluded that estradiol-17β may lead to a transitory natriuresis and a subsequent sodium retention by a direct effect on the kidney, as has been suggested by Katz and Kappas [28]. Our observation that PRA may increase before PRS after application of 17α-ethinyl estradiol-17β (0.4 mg daily) and estradiol benzoate (single i.m. injection of 5—10 mg) in women after hysterectomy and bilateral

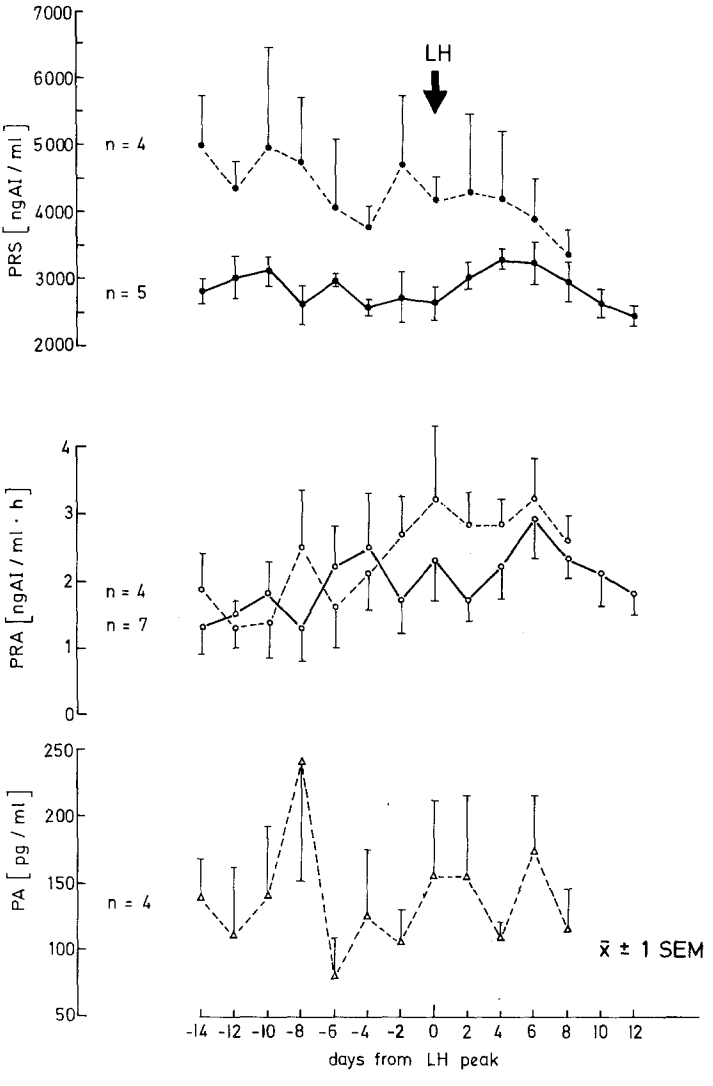

Fig. 16. Plasma renin activity (PRA) and plasma concentrations of renin substrate (PRS) and aldosterone (PA) in four subjects with luteal failure (A. B., A. S., B. K., C. W.); for comparison, mean PRA and PRS of subjects with a presumably normal luteal function are shown. Means ± SEM

ovariectomy (unpublished data) clearly supports the hypothesis that estrogens may stimulate renin release from the kidney.

3. On the basis of the observations, that basal levels of plasma ACTH show an increase 1 day before and on the day of the LH peak [29] and that after sodium restriction, PRA is increased by ACTH infusion [30], a possible contribution of ACTH to the ovulatory surge of PRA and PA should be kept in mind.

4. Furthermore, there exists a possibility that other factors such as hemodynamic changes (e.g., renal blood flow), changes of sodium concentration in the

macula densa or alterations in the local sympathetic activity could influence preovulatory renin secretion.

5. On the other hand, the results described here do not support the suggestion [10] that 17α-hydroxyprogesterone, by its possible natriuretic effect, may cause the preovulatory activation of the renin-angiotensin-aldosterone system, since the secretion of this gestagen, as well as that of progesterone, begins to rise only shortly before the LH peak (see Fig. 1).

In some subjects (e.g., K. V.), PRS seems to decrease at the time, or after periods, of high renin activity. An inverse relation between plasma levels of renin activity and renin substrate has been described in animals and also in man [31] after changes in sodium balance. The decrease of PRS is explained by substrate consumption; the interval between the elevation of PRA and the decrease of PRS depends probably on the dynamic equilibrium between renin substrate production and consumption [31]. Another explanation for these cyclical variations in PRS, which have, to our knowledge, not yet been described, would be the presence of a direct or indirect negative feedback between angiotensin or aldosterone and sodium retention on the one side and hepatic renin substrate synthesis on the other. Our results are in contrast to those of Katz et al. [13], who found lower (around 1000 ng/ml) and very constant PRS values in three of four nontreated normal subjects throughout the menstrual cycle.

The increased plasma renin activity and aldosterone concentration before and during the short period of treatment with norethisterone acetate in G. V. (Fig. 14) may have been due to the previous surge of estradiol secretion with a consequent activation of renin substrate synthesis; an additional stimulating effect of norethisterone acetate, which, due to its slight estrogenic properties [32], is known to increase renin substrate concentration, cannot be excluded.

Conflicting results have been reported on prolactin levels during the menstrual cycle. In contrast to McNeilly and Chard [33] who described irregular and inconsistent fluctuations, Vekemans et al. [34] recently found a significant increase in serum prolactin during the late follicular phase, with a maximum concomitant to the LH peak, and higher values during the luteal phase than during the early follicular phase. In the subjects reported here, plasma prolactin was higher during the luteal phase and at the time of menstruation (maxima on day +6 and day −14) both in the luteal group (Fig. 1) and in the luteal failure group; only in two women (Figs. 12 and 14) there was a periovulatory peak. No temporal relationship was found between the pattern of estradiol-17β, progesterone and aldosterone levels on one hand and that of circulating prolactin during the menstrual cycle on the other. Thus, on the basis of the observations reported here, it is reasonable to assume that neither gonadotropin nor prolactin secretion may directly influence the renin-angiotensin-aldosterone system in man.

It was the aim of the present study to obtain more information on the endocrine regulation of renin and aldosterone during the menstrual cycle. From the results obtained it may be concluded that both progesterone and estradiol-17β are capable of influencing the activity of the renin-angiotensin-aldosterone system during the menstrual cycle.

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