Renin Activity in Human Uterus[1] (34501)

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Renin or an enzyme indistinguishable from renin has been found in the human uterus (1–3). With one exception, that of an autopsy specimen from an 8-month anephric patient (2), all reported measurements of uterine renin in humans have been for pregnant uteri (1, 3). The aim of the present study was to measure uterine activities in all reproductive phases of adult life.

Methods. Samples were obtained from uteri of nonpregnant women undergoing hysterectomy and of pregnant women during cesarean section. All samples were full-thickness wedge biopsies taken from the lower uterine segment. No attempt was made to separate serosa, endometrium, or myometrium. The locus of sampling excluded placental tissues from the samples. All samples were frozen immediately after removal.

At a later date, the frozen samples were thawed, blotted, and weighed. They were then finely minced by cutting strips along the muscle grain and then cross-cutting these strips into very small cubes. These were then homogenized for 30 min, using 3 ml of isotonic saline per gram of uterus. After centrifugation, the extract supernatent fluid was obtained, and 1 ml was added to 10 ml of pooled human plasma and 1 ml of 3.8% NH_4 EDTA. This extract–plasma mixture was then assayed for renin by a modification (4) of the method of Boucher *et al.* (5), originally developed for renin in plasma. The renin activity of a sample of the same pooled plasma (to which saline, rather than uterine extract) was added was simultaneously determined and subtracted from the extract-plasma values to obtain uterine renin activity. Uterine renin activities are expressed as nanograms of angiotensin generated during 3 hr of incubation per gram of uterus.

No pressor activity was detectable in the samples prior to incubation. The specificity of the method for renin was proved by the fact that the addition of antirenin[3] from rabbits immunized to human renin prevented the generation of the pressor substance during incubation. Uterine angiotensinases were completely inactivated since the recovery of exogenous angiotensin was not different in the extract-plasma samples from that in the saline-plasma samples.

Results. Figure 1 presents the uterine renin activities for most of the women in this study; for various reasons, certain of the women could not be included in any of the categories shown in Fig. 1, and their values will be described separately.

The women whose uterine values are shown in columns A and B of Fig. 1 appeared by history to be having normal menstrual cycles with no irregularities in timing or bleeding pattern. The phase of the cycle was confirmed by histological examination of the endometrium. There were no differences in renin values observed between early and late proliferative samples. There was no correlation with age of the women or number of pregnancies. Uterine samples were also obtained from three normally menstruating women who had undergone dilatation and curettage the day preceding hysterectomy. The renin values for these uterine samples which contained little or no endometrium are not shown in Fig. 1 and were as follows: proliferative (as evidenced by the previous day's curettings) = 16.5; secretory = 0 and 17.7.

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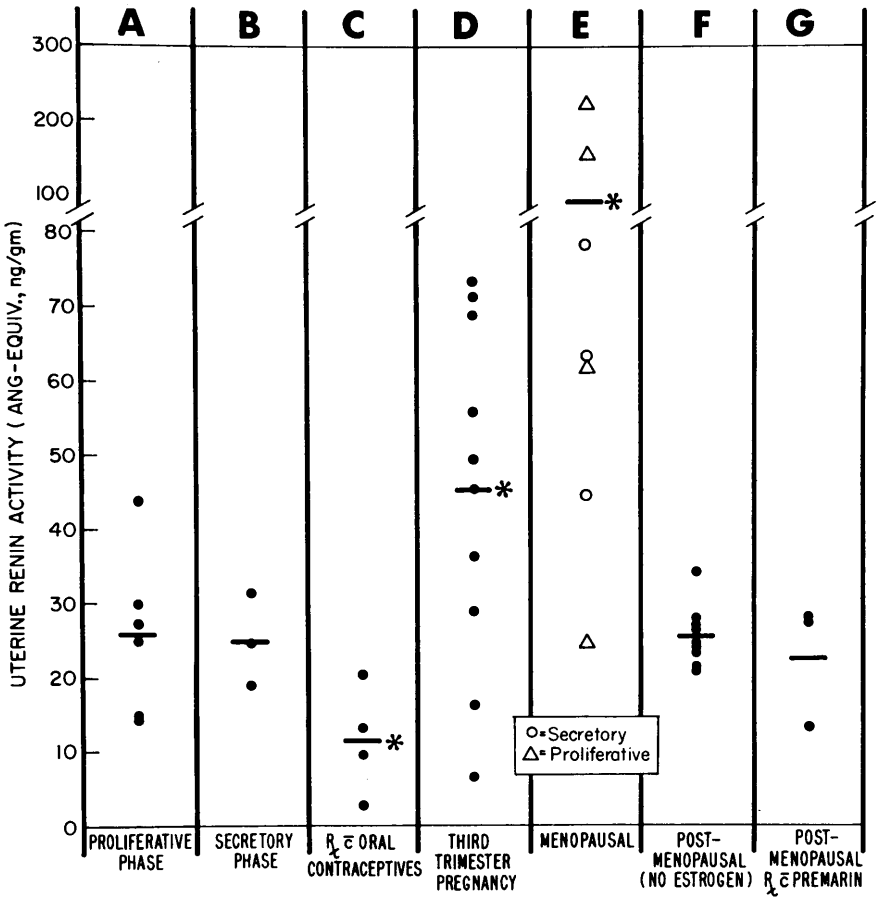

FIG. 1. Renin activity of uterine samples from women in various phases of reproductive life. See text for definitions of the different groups. *$P < .05$ as compared to the mean of the "proliferative phase" group.

Column C of Fig. 1 shows the renin values for four women who were having regular cycles but who were receiving estrogen-progestin combinations, either Enovid (three women) or Orthonovum (one woman; renin = 9.3). The mean value for this group was significantly lower than that for the proliferative group of column A.

Table I and column D of Fig. 1 summarize uterine renin values for all the pregnant women (none of whom manifested signs of preeclampsia). The indications for the cesarean sections are shown in Table I. It is evident that there is a wide range of values for this group but that the mean is significantly higher than that of the proliferative group of column A. Only two of these women had either a present or past history of dysfunctional labor (*i.e.*, inadequate contractions), and these two women manifested the lowest renin values of this pregnant group. The presence or absence of labor at the time our sample was obtained did not seem to alter the renin value, as shown in Table I. A uterine sample was also obtained from a woman with a hydatidiform mole; the renin activity of this sample (not shown in Fig. 1) was 201.9.

Column E of Fig. 1 summarizes the uterine renin values for a group of women that we have called "menopausal." These women (aged 40–53) had all been having considerable menstrual irregularity for 2 months to 2 years. The most common manifestations

TABLE I. Renin Activity of Uterine Samples Collected at Cesarean Section.

Patient	Indications for cesarean section		In labor at time of cesarean section	Uterine renin (ang.-equiv. ng/g)
	Present	Past		
K.S.	Dysfunctional labor	—	Yes	6.4
J.R.	Repeat	Dysfunctional labor	No	16.2
D.Z.	Repeat	Cephalopelvic disproportion	Yes	29.1
M.G.	Repeat	Cephalopelvic disproportion	No	36.6
C.K.	Cephalopelvic disproportion	—	No	45.6
G.F.	Prolapsed cord	—	Yes	49.5
P.W.	Breech	—	Yes	55.8
R.M.	Repeat	Cephalopelvic disproportion	No	68.9
H.B.	Repeat	Transverse lie	No	72.0
M.W.	Repeat	Bleeding	No	73.5
Mean				45.4
SEM				± 7.4

were hyper or polymenorrhea. These uterine renins showed the greatest variability of all groups studied. The mean for the group was significantly higher than those for the normally menstruating women of columns A and B. As shown in the figure some of these women were clearly still having ovulatory periods (as evidenced by a secretory endometrium), and the phase of the period did not correlate with the renin value. A uterine sample was also obtained from a "menopausal" woman who had undergone dilatation and curettage the day prior to hysterectomy; this sample contained no endometrium and had a renin activity (not shown in the figure) of 45.0.

Columns F and G of Fig. 1 summarize the uterine renin data for women who were at least 2–6 years postmenopausal. It is evident that the mean of this group did not differ from that of the normally menstruating women. Moreover, the administration of premarin did not significantly alter uterine renin. Three of these samples (in women not receiving premarin) were carefully studied histologically and the endometrium was found to be extremely atrophic, being limited to a single-celled layer of epithelium. The values for three other postmenopausal women are not shown in the figure: two had undergone cobalt irradiation and their uterine renin activities were 2.1 and 1.5; the third had undergone bilateral oophorectomy 3 years earlier and her uterine renin value was 24.3.

Discussion. These data confirm previous reports of renin in pregnant human uterus (1, 3) and demonstrate that renin is present in this site not only during pregnancy but throughout adult life.

In what portion of the uterus is the renin located? Skinner *et al.* (3) demonstrated that myometrium contained renin in pregnant women; correcting for differences in incubation time and angiotensin recovery, the means for their myometrial values and our full-thickness values differ by only 12% (theirs being higher). In the nonpregnant uterus, myometrium also contains renin as evidenced by the postmenopausal samples (in which endometrium was extremely atrophic) and by the samples obtained 24 hours after dilatation and curettage. On the other hand, these latter three samples all had renins in the lower range of values for the other samples of their relevant groups. It seems likely, therefore, that both endometrium and myometrium contain renin, but quantitation of the relative amounts must await direct studies in which the layers are separated. Such studies in rabbits have demonstrated that endometrium and myometrium have approximately equal renin concentrations (1).

How does uterine renin concentration compare to that of plasma and kidney? A previous study (6) using identical methods gave a mean plasma renin of 11.3 ng/ml for women in the third trimester of pregnancy and of 2.9 ng/ml for nonpregnant women. It is evident,

therefore, that uterine renin concentration is considerably greater than that of plasma; a similar relationship was demonstrated by Skinner *et al.* (3). We did not measure renal renin in these experiments; however, the data of Skinner *et al.* clearly demonstrate that, even during pregnancy, uterine renin is quite low in comparison to renal renin (3). This is in contrast to the very great uterine renin content in rabbit. (1, 3, 7, 8).

What is the source of uterine renin? The only data of ours which may relate to this question are the extremely low renin activities in the two women who had undergone cobalt irradiation. This suggests that the uterus synthesizes renin; however, one cannot rule out the possibility that the irradiation had destroyed the protein-synthesizing apparatus for renin-binding proteins rather than for renin itself. The only other data in the literature relevant to humans is the finding by Symonds *et al.* (9) that cells in human uterine muscle are capable of producing renin during *in vitro* culture; however, these cells (unlike those of chorion) did not begin to produce renin until 10–15 days after culturing was begun. In the rabbit, the evidence for uterine synthesis of renin is more solid (1, 10, 11), but the extrapolation of these data to humans is not warranted at present. A related question is whether the uterus, were it actually to synthesize renin, contributes to circulating renin. The data of Capelli *et al.* (2) for anephric females strongly supports the possibility that renin can be synthesized in a nonrenal site, but do not establish that this site is the uterus. This question is of particular interest in pregnancy, a situation in which plasma renin is elevated (6, 12–15). Moreover, a patient with hydatidiform mole was reported by Brown *et al.* (16) to have an extremely high plasma renin value just as the patient in our series had markedly elevated uterine renin. Measurements of uterine arteriovenous renin differences will be helpful in answering these questions, and such studies are now in progress.

What is the function of uterine renin? The present study was not designed to deal with this important question, but there is at least one aspect of the data which is intriguing in this regard; namely, the fact that the two lowest renin values of the pregnant group were in the only two women with a present or past history of poor uterine contractions during labor. Angiotensin is a powerful oxytocic agent ((17), and it is possible that the renin—angiotensin system plays a role in parturition. Perhaps relevant to this is the previous demonstration that plasma renin during labor is significantly elevated when compared to prelabor third-trimester samples for the same women (6).

Finally, what factors determine the uterine concentration of renin and the differences observed between the various groups of this study? Brown *et al.* (18) and Skinner *et al.* (19) have reported that plasma renin is higher in the second half than in the first half of the menstrual cycle. Bing and Eskildsen (20) have demonstrated that, in mature rabbits, uterine renin was decreased by castration and restored by estradiol administration. It was somewhat surprising, therefore, that uterine renin activities were similar in the proliferative and secretory phases of the menstrual cycle as well as in postmenopausal women (including a patient who had undergone bilateral oophorectomy) regardless of whether the latter were receiving estrogen or not. Moreover, the administration of oral contraceptives was associated with reduced uterine renin content. Previous studies (19, 21–23) had demonstrated that, in humans, plasma renin activity was increased by the administration of estrogen or estrogen–progestin combinations; however, it seems that this increased activity was due to increased plasma angiotensinogen, and that renin concentration (as opposed to activity) was actually reduced (19, 23). Taken all together, the data indicate that neither estrogen nor progesterone is an important factor in maintaining uterine renin in the nonpregnant human. On the other hand, it is possible that the very high levels of estrogen or progesterone which occur during pregnancy may play a role in enhancing uterine renin.

In contrast, the data are somewhat more consistent with the possibility that uterine renin is responsive to changes in gonadotro-

pins, particularly luteinizing hormone (LH) and the closely related chorionic gonadotropin (CG). This is suggested by the reduction of uterine renin induced by oral contraceptives and the increase seen in menopausal women since the levels of gonadotropins would be changing in the same direction as uterine renin under these conditions. The high levels of uterine renin seen during pregnancy would also be consistent with this possibility as would the extremely high uterine renin manifested by the patient with the hydatidiform mole. Nor is the similarity between values in the proliferative and secretory phases inconsistent with this concept, since the average values of pituitary gonadotropins during the first and second portions of the menstrual cycles are quite similar, the mid-cycle LH and FSH peaks being only transient (24). On the other hand, the similarity of uterine renin concentrations in women during active reproductive life and after the menopause is clearly not consistent with the gonadotropin hypothesis unless the uterus, after menopause, manifests a reduced "sensitivity" to the high levels of circulating gonadotropins.

In any case it should be emphasized that data such as ours cannot solve these questions involving the dynamics of protein synthesis, binding, release or inactivation, but are suggestive of future studies needed in this potentially important area.

Summary. Renin activity was determined in uterine samples obtained from nonpregnant women undergoing hysterectomy and from pregnant women during cesarean section. All samples were full-thickness biopsy specimens from the lower uterine segment. In women having normal menstrual cycles, there was no significant difference between the mean renin activities of uteri in the proliferative and secretory phases. Uterine renin was significantly reduced in women receiving oral contraceptives. Pregnancy was associated with a significant increase in uterine renin. The lowest values of this group were for two women with a present or past history of dysfunctional labor. Uterine renin was extremely elevated in a woman with a hydatidiform mole. In women undergoing menopause renin was significantly elevated. However, in women at least 2 years postmenopausal the mean renin value was not different from that of normally menstruating women, regardless of whether or not estrogen was being administered. Renin was extremely low after cobalt irradiation. The locus, function, and control of uterine renin are discussed.

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