INACTIVE AND ACTIVE RENINS, ALDOSTERONE AND CORTISOL IN PUERPERA AND NEWBORN

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SUMMARY

Eleven primiparae (aged from 20 to 31 years) have been sampled at the time of partum and throughout the puerperium for simultaneous determinations of plasma levels of inactive (prorenin) and active (PRA) renins, aldosterone (PA) and cortisol (PC). Biodata have been compared to time-qualified values obtained in non-pregnant adult women (aged from 17 to 37 years).

Pregnant women show peripartum levels of prorenin, PRA, PA and PC significantly higher than the time-qualified reference intervals. Gestational increment is meanly of 3-4 times for prorenin, of 5-8 times for PRA, of 17-19 times for PA, of 4-5 times for PC.

Puerperal levels of PRA, PA and PC show a progressive decline while those of prorenin suddenly fall and then remain quite stable.

Neonatal levels of prorenin, PRA, PA and PC are higher than normal. Neonates show levels of prorenin, PRA, PA and PC, respectively equal, increased equal and decreased when compared to mothers.

The different equipment of hormonal levels in mother and newborn leads to suggest a selective role of the placenta as a filter.

INTRODUCTION

Several studies have been designed to discern the behaviour of plasma renin and aldosterone in newborn and mother. Studies clarified that levels of plasma renin activity (PRA) are consistently higher in neonates than in infants, children and adolescents ([22, 23, 34, 48]). During the first week of life neonatal values of PRA show an increase along the 24-h span ([9, 23, 30, 39, 53]) and, subsequently, a progressive decrease ([9, 15, 30, 53]). As far as the mother is concerned, it has been well documented that pregnant women exhibit at the time of delivery levels of PRA consistently higher, above the range recorded in adult population ([2, 4, 7, 8, 17, 19, 20, 27, 31, 32 52, 58, 60]). Interestingly, maternal peripartum levels of PRA were seen to be lower than the neonatal renin assayed in cord blood ([9, 19, 24, 30, 33, 51]).

With respect to aldosterone, evidences have been accumulated that both plasma and urinary concentrations of the steroid show a behaviour in newborn ([30]) and mother ([24]) which is almost comparable.

This extensive research matter notwithstanding, several biological aspects are open to the discussion and require further investigations. In our opinion, a point of speculative interest could be the relationship between pregnancy and the behaviour of inactive renin, the inert precursor of active renin, already identified in maternal blood and amniotic fluid ([36, 52]). Particularly, the interest could be concentrated on studies investigating the simultaneous changes in inactive renin, PRA and plasma aldosterone at the time of vaginal delivery and throughout puerperium.

Accordingly, a research has been planned by our laboratory on this specific topic of biological inquiry by investigating the abovementioned biohumoral variables, plus plasma cortisol (PC), in a group of clinically healthy young women at the end of their first gestation, normal in its course,

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whose labour and delivery were spontaneous and uneventfull with a fetus at term, vital and normoponderal.

MATERIAL AND METHODS

Eleven clinically healthy primiparas (aged from 20 to 31 years) volunteered with informed consent for this investigation giving systemic venous blood at the time of delivery (phase A) and during the puerperium (phase B) for simultaneous measurements of inactive renin, PRA, PA and PC.

Blood samplings of phase A was undertaken twice, i.e., at the time of expulsive stage of labour (prepartum levels) and soon after the delivery in connection with the cut of the ombelical cord (postpartum levels). Blood collection of phase B was carried out over four consecutive days at a fixed time (8 a.m.). In order to avoid external interferences on biohumoral variables investigated, mothers were receiving a diet with a normal content of sodium (120 mEq/24-h) and potassium (50 mEq/24-h) for at least three weeks In addition they were sampled when supine position had been kept for at least three hours.

PRA, PA and PC were assayed by the methods of Haber *et al.* ([29]), McKenzie and Clements ([38]) and Murphy ([44]), respectively. PRA was measured at room temperature to avoid activation of inactive renin ([50]). This phenomenon was prevented by a previous storage of plasmas at −40 °C until the assay. Inactive renin, here assayed as prorenin the cryoactivable inert macromolecule, was determined by the method of Sealey *et al.* ([50]). Table 1 shows the characteristics of methods used. Statistical analysis of data was performed by the Student'st test.

Since the partum was a naturally-occurring event, the biohumoral variables assayed in maternal plasmas at the time of delivery have been indexed to time-qualified reference intervals knowing that prorenin ([12]), PRA ([11, 26, 32, 40, 55]), PA ([1, 11, 33, 40, 55]) and PC ([13, 35]), physiologically fluctuate over the 24-h span according to a circadian rhythm.

Time-qualified reference values for such rhythmic variables have been obtained in a concomitant study of ten non-pregnant adult women, clinically in health, ranging from 17 to 37 years of age, who consented to be sampled on sodium balance giving blood at 06.00, 08.00, 12.00, 18.00, 20.00 and 24.00 in a recumbent position. The reference data and values of pregnant women have been recorded in fall months.

Table 1. — *Radiochemical procedures and their analytical properties.*

Variable	Units	Sensitivity	Precision (CV in %)	
			Intra-assay	Inter-assay
Prorenin	ng/ml/h	0.001	2.9	4.2
PRA	ng/ml/h	0.008±0.003	5.5	16.6
PA	pg/ml	3.5±0.5	9.0	13.7
PC	ng/ml	2.5±0.7	4.1	14.4

CV = coefficient of variation.

RESULTS

Figure 1 displays pre- and post-partum values of prorenin, PRA, PA and PC in relation to clock-hours in which they have been sampled. Shaded areas represent the reference values of non pregnant women given as function of time.

Apart from one value, it is clear that all the other peripartum levels of prorenin, PRA, PA and PC are lying above the relative reference intervals. It must be noted that some values would have been considered within the normal limits (false negatives) by using morning fasting values as comparative range. Statistical analysis by Student's test reveals that the difference of pre- and post-partum levels from non-gestational concentrations is statistically significant with values of $p < 0.01$ and $p < 0.001$ for prorenin, of $p < 0.001$ and $p < 0.001$ for PRA, of $p < 0.001$ and $p < 0.001$ for PA, of $p < 0.001$ and $p < 0.001$ for PC.

As mean values (±SE) pregnant women exhibit at the time of delivery 2.15±0.52 ng/ml/h of prorenin, 4.47±0.77 ng/ml/h of PRA, 76.8±13.8 ng/dl of PA, and 41.5±2.7 μg/dl of PC. Early after the partum the values for each aforementioned variable are meanly 1.91±0.34 ng/ml/h, 7.42±1.34 ng/ml/h, 98.6±15.3 ng/dl and 49.5±4.4 μg/dl, respectively. The mean increment from normalcy of pre- and post-partum prorenin levels can be esti-

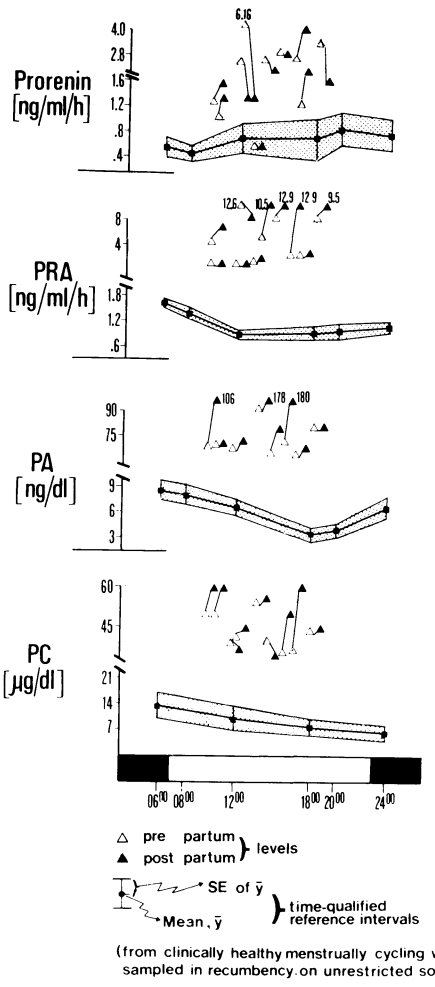

Fig. 1. — Plasma levels of inactive (prorenin) and active (PRA) renins, aldosterone (PA) and cortisol (PC) in pregnant women at the time of delivery.

mated as equal to 1.43±0.46 ng/ml/h and 1.24 ± 0.29 ng/ml/h, respectively. That of PRA is of 3.55±0.77 ng/ml/h and 6.49±1.33 ng/ml/h, respectively. Similarly, pre- and post-partum concentrations of PA meanly surpass the physiological reference values of 71.7±14.1 ng/dl and 93.4±15.4 ng/dl, respectively. Indeed, the gestational excess for PC is of 33.5 ± 2.7 µg/dl and 40.5 ± 4.4 µg/dl, respectively.

Figure 2 displays the mean levels (±SE) of maternal variables investigated at the time of puerperium. It is evident that puerperal levels of PRA, PA and PC show a progressive decline, while those of prorenin exhibit a sudden fall the day after the partum, and then remain quite stable.

Figure 3 shows the values of prorenin, PRA, PA and PC assayed in maternal and cord blood. It is clear that neonatal levels of PRA are significantly higher than those recorded in mothers at the time of labour. No statistical difference has been found between maternal and neonatal values of PA. By contrast both the maternal PC levels appear to be significantly higher than those of cord blood. Interestingly, prorenin levels were found to be comparable in mother and progeny.

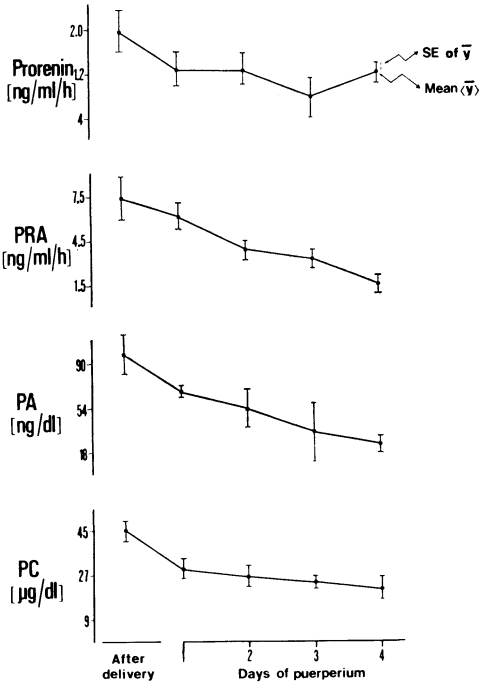

Fig. 2. — Maternal levels of inactive (prorenin) and active (PRA) renins, aldosterone (PA) and cortisol (PC) throughout the puerperium.

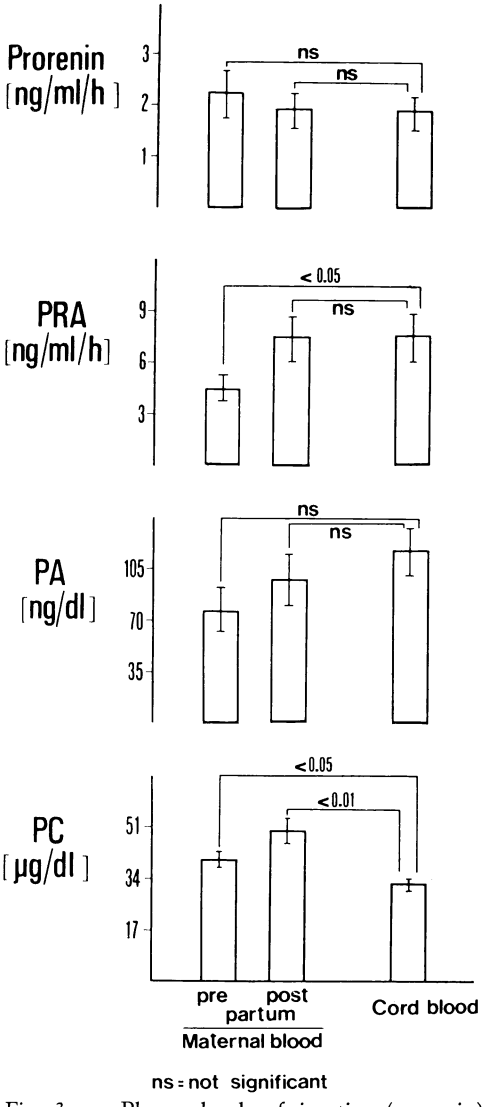

Fig. 3. — Plasma levels of inactive (prorenin) and active (PRA) renins, aldosterone (PA) and cortisol (PC) in maternal and cord blood.

DISCUSSION

One problem with biohumoral investigations at the time of spontaneous vaginal delivery is raised by the fact that the majority of biochemical components are not stable over the 24-h span but fluctuate in human fluids according to a circadian rhythm. Such a circadian periodicity characterizes the variables herein investigated. As a methodological consequence, any peripartum quantification of prorenin, PRA, PA, and PC may result inaccurate if unrespective of time, as already pointed out by Giovannelli *et al.* ([23]). Because of this basic consideration, the results of this investigation have been compared to time-qualified reference values. By indexing the values to time it has been possible a better approximation to the apparent increment of peripartum levels. Accordingly, the increase from normalcy of maternal levels at the time of delivery has been meanly of 3-4 times for prorenin, of 5-8 times for PRA, of 17-19 times for PA, of 4-5 times for PC.

A point of interest in this investigation is that concerning the relationship between prorenin and PRA as a matter for discussing the causes underlying the activation of the RAAS* in mother and newborn. Theoretically, the PRA elevation in pregnancy could be generated by extrarenal sources of renin such as uterus and placenta ([18, 25, 28, 43, 54]). Some evidences, however, tend to reinforce the thesis that the gestational enhancement of renin is, at least in part, of peripheral origin since estrogen-mediated increases in plasma renin substrate have been reported during pregnancy ([31, 32, 59, 60]). However, Wilson and coworkers ([61]) evaluated that only 50% of renin increase may be attributed to the substrate. Therefore, the augmentation in hepatic synthesis of angiotensinogen alone is not sufficient to fully explain the increase of PRA circulating in maternal blood.

Little is known of a possible delay in metabolism as a cause of renin increase in pregnant women. We are not aware of investigations on the renal vein renin contribution in normal pregnancy. There is a lack of reports on gestational PRA in binephrectomized pregnant women. This gap notwithstanding, the renal origin of

* Renin-angiotensin-aldosterone system.

hyperreninemia in pregnancy cannot be neglected. In this respect, it must be cited that the results of studies designed to explore the effects of posture and sodium intake on PRA ([4, 59]) were consistent with a renal matrix of hyperreninism in normal pregnancy.

Data of the present investigation can enter this discussion emphasizing the role of the placenta as a discriminatory barrier. In women herein investigated, the inactive and active renins were found to change not in parallel at the time of puerperium. While puerperal levels of PRA were seen to decline in a gradual fashion, those of prorenin showed an abrupt decrease. Because of this dissociation, one is reinforced in the concept that the behaviour of the renin-angiotensin system in normal pregnancy must be discussed keeping in mind the placenta. Circumstantial data suggest that both PRA and angiotensin II (AII) are increased in pregnant women ([46]) but less than in newborn. The maternal-neonatal ratio is lower than I for PRA and AII levels, and vice-versa for plasma renin substrate. Converting enzyme activity was found to be normal in pregnant women and augmented in their neonates ([46]). These findings are compatible with the thesis of a certain autonomy of the renin-angiotensin system in mothers and fetuses. The opinion that high renin levels of full-term or preterm babies are not of maternal origin seems to be supported by the evidence that placental barrier is not permeable for maternal renin and angiotensinogen and that estrogen-induced synthesis of maternal renin substrate is not registered at the site of fetus ([24]). On the other hand, further studies are consistent with the autocthonous activation of the fetal renin-angiotensin system. Animal studies stressed that fetal renin decreases when kidneys are bilaterally removed in fetus but not in mother ([5, 6]). Human studies documented the presence of renin in fetal kidneys beyond to 20th week of intrauterine life ([42]).

Interestingly, no difference has been detected in the present study between maternal and neonatal levels of prorenin. Such a similarity is convincing for a key role of placenta as a selective barrier for the renin-angiotensin system. The placenta appears to be capable in contrasting the maternal-fetal diffusion of active renin but not that of inactive renin.

The present study and other investigations ([24]) revealed that the maternal-neonatal difference is negligible for PA levels. Accordingly, one can argue that the placenta is a structure permeable for the circulating aldosterone.

Plasma cortisol dynamics in pregnant women requires some specific comments. Plasma cortisol levels are increased in pregnancy as stated by several studies ([10, 21, 37]). Effects of hypercortisolism are, however, not visible since the amounts of free plasma cortisol are less modified because of a proportional increase in transcortin levels ([16]). Interestingly, in the present investigation plasma cortisol concentrations in blood cord were seen to be less elevated than those circulating in mother. The placenta seems to be a barrier for maternal-fetal by-pass of cortisol. But other explanations may be invoked for this disequality i.e., a disparity in secretion of the hormone, an inequality in cortisol metabolism. Each or both these mechanisms could be active since no sign of glucocorticoid excess characterizes the baby at the birth. Some evidences are available. Transcortin concentrations are lower in fetal plasma when compared to those of maternal blood ([47]) even though the binding affinity of fetal transcortin is unchanged ([14]). Fetal adrenal cortex is able in synthetizing all the glucocorticoids ([3, 56, 57]), but fetal cortisol normally is of maternal origin ([45]). The placenta seems to be unable to synthetize cortisol ([41]). Cortisol metabolites, such as glucuronide derivatives, are higher in blood cord than in maternal blood indicating that glucocorticoids are actively catabolized by fetus.

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