Preeclampsia (PE) is a syndrome characterized by hypertension, proteinuria, and edema, occurring in the third trimester of pregnancy. The current approach to diseases is to prevent and not only to treat the patients with overt forms. This is very important in PE, because it is associated with liver, kidney, heart, coagulative, and neurological complications. Macdonald-Wallis et al1 have reported the measurement of blood pressure (BP) as a presumptive praecox characteristic of PE: at week 8 of pregnancy, BP was higher in patients who later developed PE than in normotensive healthy pregnant controls. The conclusion was that patients with early alteration of BP should be monitored during pregnancy for the risk of PE or treated before the full expression of the disease.

The finding of BP in the upper normal range at the beginning of pregnancy could be interpreted either as a similar situation of BP previous pregnancy or as an early onset of subclinical PE. It is important to note that PE can develop even in the absence of the fetus, as, for example, in cases of hydatidiform mole, and that the clinical picture of PE disappears after birth or abortion, when the placenta is no longer present. The study is consistent with PE being the final step of a process that starts early in pregnancy or before. In any case, prevention of a disease requires knowledge of its pathogenesis and not only the availability of tests to identify patients at risk. The question now is: what is the cause of the hypoperfusion of placenta in women who will develop PE, and why is there a defect of trophoblast invasion of the myometrium?

This disease seems to be characterized by the release into circulation of substances that later will lead to hypertension proteinuria and edema. PE implies complex endocrinologic and immunologic mechanisms, such as placental and endothelial dysfunction, oxidative stress, and inflammation. Several factors have been involved in the process, such as corticotrophin-releasing factor, neurokinin B, cortisol, type 2 11-hydroxysteroid dehydrogenase, aldosterone, mineralocorticoid receptors (MRs), angiotensin II, and antiangiotensin II type I receptor antibodies; but its pathogenesis remains unknown, and the disease is probably a complex syndrome involving a cascade of factors. An alternative explanation is that the placenta does not produce a substance that reduces BP and limits inflammatory status during physiological pregnancy.

The fall of BP during the first trimester of uncomplicated pregnancy is attributed to increased NO production and emergence of vascular resistance to angiotensin II. This situation should be followed by secondary hyperaldosteronism and increased inflammation, but we demonstrated previously that, in normal pregnancy, MRs are less sensitive also to aldosterone.2

In other clinical situations, BP is at the higher normal values, as, for example, in patients with polycystic ovary syndrome and in some women taking contraceptives. Both situations lead to a predisposition to PE and are characterized by a relative increase of aldosterone and/or of the aldosterone/renin ratio compared with normal controls.3 Excess of aldosterone can produce kidney and heart fibrosis and sometimes edema and other later complications of PE. In PE, aldosterone is increased to a lesser extent than in normal pregnancy, but the aldosterone/renin ratio is 2-fold greater.4 We previously studied the involvement of aldosterone2 in PE and demonstrated that, in normal pregnancy, MRs are less sensitive to aldosterone. The consequence is a decrease of BP and an increase of plasma aldosterone and renin without sodium depletion. In PE, as in polycystic ovary syndrome and during contraceptives, the relative increase of aldosterone and renin is associated with a slight increase of BP, and in PE it can later be involved in the onset of edema and proteinuria. This is probably because of the fact that patients with polycystic ovary syndrome are treated or contraceptives are withdrawn. We previously evaluated the biological function of aldosterone by measuring the rectal minus skin potential difference, which is an index of aldosterone activity on the classic target tissues. The value of skin potential difference in PE is equivalent to that reported in primary aldosteronism, whereas in normal pregnancy the skin potential difference is normal, notwithstanding the higher values of PRA and aldosterone. The conclusion of this study was that we should investigate normal pregnancy to identify this putative factor produced by the placenta that could impair the action of aldosterone at the level of MR.2

The dysregulation of the endocrine and immune system is very important not only in PE but also in other gynecological clinical situations, such as some cases of idiopathic sterility and of frequent abortivity. The endometrium is subject to cyclic morphological changes that imply the recruitment of mononuclear leukocytes (MNLS) from peripheral circulation,
leading to inflammation. All of the processes involved in ovulation and implantation are based on local inflammatory reaction. MNLs have receptors for estrogens, progesterone, cortisol, and aldosterone, and during the physiological menstrual cycle, normal amounts of MNLs arrive from the circulation to the uterine mucosa, and the menstruation is regulated by the interaction of these factors (invasion of lymphocytes, local inflammation, activity of estrogens, and progesterone). Aldosterone is usually higher in the pregestational phase, and frequently this is associated with the premenstrual syndrome.

During pregnancy, the amount and type of leukocytes detected in the decidua differ from those described during the menstrual cycle, and these leukocytes contribute to the formation of the placenta, producing angiogenic factors, such as epidermal growth factor, transforming growth factor, tumor necrosis factor-α, and other cytokines. At the moment of implantation, the maternal decidua is infiltrated by MNLs, and this is probably what allows for the process of implantation itself.5

Aldosterone can bind to MRs in MNLs.6 Excess of aldosterone or of its activity induces inflammation and fibrosis in several tissues, as, for example, in the kidney, heart, and vessels. All of these situations are characterized by an invasion of peripheral MNLs with their MRs, allowing aldosterone and/or cortisol to produce local inflammatory effects and to change the pH, exacerbating oxidative stress. The consequence is an endothelial dysfunction and progression of the situation. We found previously that incubation of MNL from normal subjects with 10 nmol/L of aldosterone increases the protein expression of plasminogen activator inhibitor 1 and p22phox, the main constituent of NADPH oxidase, and this effect is blocked by coincubation with canrenone.7 This theory is supported by the finding that MR blockers are active in preventing cardiovascular complications, even in normotensive and not sodium-loaded patients, as reported by Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study investigators.8

In PE, the interaction of higher amounts of estrogens, progesterone, and aldosterone at the level of MNLs could lead to higher inflammation, oxidative stress, altered placentation, increase of BP without proteinuria, and edema, which will develop later, because of the longer duration of this effect of aldosterone and the concomitant systemic action of many other factors, particularly cytokines. The early increase of BP is the first element in a possible prediction of PE. Therefore a strict monitoring of BP should be performed by all of the gynecologists who follow pregnancy, considering that BP is low in this period, and a value defined normal in nonpregnant women could be considered a risk factor for PE.

In conclusion, the interaction of several endocrine and immunologic factors is involved in both the genesis of the placental alterations of PE and the progression of the disease. The early finding of increased BP during the first trimester of pregnancy could be considered an initial marker of later PE. A dysfunction of the renin-angiotensin-aldosterone system could be involved both in the genesis of the placental alterations of PE and in the progression of the disease. Based on this assumption, treatment with aldosterone receptor blockers without antiandrogen or antiprogestinic effect may be recommended.

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Decio Armanini

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