Are Aldosterone Levels Inappropriately Low in Preeclampsia?

To the Editor:

With great interest, we read the elegant study by Gennari-Moser et al1 in the May issue of Hypertension. In this report, the authors demonstrate that vascular endothelial growth factor (VEGF) directly stimulates aldosterone production of human adrenocortical cells. Furthermore, in rats overexpressing the VEGF-inactivating soluble fms-like tyrosine kinase-1 (sFlt-1), capillary rarefaction of the adrenal glands was observed and plasma aldosterone and sFlt-1 levels were inversely correlated. This suggests that VEGF can stimulate aldosterone production also indirectly, that is, by enhancing adrenal capillary density. Because sFlt-1 levels are much higher in preeclampsia than in normal pregnancy, the authors conclude that these findings may explain why the aldosterone concentration is inappropriately (relative to the diminished plasma volume) low in preeclampsia.1

In the accompanying Editorial, Delles and Free1 simultaneously provide a link to the relative aldosterone excess in normal pregnancy: here, the aldosterone levels are higher than expected on the basis of the renin levels. An attractive explanation would then be that in normal pregnancy, VEGF, in addition to renin, becomes an important contributor to the increased aldosterone production. In other words, in normal pregnancy, the aldosterone/renin ratio is elevated2 compared with that in nonpregnant controls because VEGF comes into play, and in preeclampsia, the ratio is lowered again because sFlt-1 now inactivates VEGF. However, in reality, the aldosterone/renin ratio is further elevated in preeclampsia,3 and thus the aldosterone levels are inappropriately high in this disorder. This is particularly related to the reduction in renin, which may indeed be described as inappropriate, given the reduced plasma volume in women with preeclampsia compared with women with normal pregnancy.4

Clearly, the suppression of renin–angiotensin–aldosterone system is counterintuitive in preeclampsia, and why aldosterone is less suppressed than renin in patients with preeclampsia is unknown. To explain the latter, one does not need the removal of a system that stimulates aldosterone production (ie, VEGF) but rather the addition of 2 systems that stimulate aldosterone independently of the renin–angiotensin axis. Indeed, various candidates have been proposed: for instance, the elevated levels of autoantibodies directed at the angiotensin II type 1 receptor,5 a greater sensitivity to angiotensin II,6 and thus the aldosterone levels are inappropriately high in this disorder. This is particularly related to the reduction in renin, which may indeed be described as inappropriate, given the reduced plasma volume in women with preeclampsia compared with women with normal pregnancy.5

Future clinical studies should now evaluate the interplay between renin–angiotensin–aldosterone system, autoantibiotic antibodies directed at the angiotensin II type 1 receptor, VEGF, sFlt-1, and endothelin-1 in normal pregnancy and preeclampsia to obtain a full understanding of the inappropriate renin–angiotensin–aldosterone system levels in these conditions. Furthermore, a precise definition of the inappropriateness of the aldosterone levels in preeclampsia (versus renin or versus volume status?) is warranted.

Disclosures

None.

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