Aldosterone, maternal volume status and healthy pregnancies: a cycle of differing views

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In this month’s issue, Escher et al. [1] suggest that high aldosterone availability during pregnancy, measured as urinary tetra-aldosterone excretion, is associated with lower maternal blood pressure and larger, healthier neonates. The findings are preliminary with more studies required to confirm these authors’ suggestions, but of interest is that these data extend recent observations by this same group that recall past passionate debates concerning the volume status of normal gravidas and those developing preeclampsia. Also, the roles of the renin–angiotensin–aldosterone system (RAS), previously given short-shrift in discussions concerning preeclampsia’s pathogenesis and pathophysiology, have been resurrected by Escher et al.’s current observations and their previous publications, as well [1–4].

All agree that normal pregnancy is characterized by an absolute increment in both extracellular and intravascular volume (by some 6–7 L, at that), but investigators disagree on the meaning of these changes. For some (‘under-fill’ theory) it is an incomplete response to both the systemic vasodilation and markedly increased arterial global compliance characteristic of normal pregnancy, and indeed, the lower blood pressure and markedly stimulated RAS and aldosterone levels that persist during normal pregnancy are consistent with this paradigm. For others, this is an absolute hypervolaemia perhaps due to the higher levels of salt-retaining steroids that accompany gestation (‘overfill’ theory), and to still others, there is a constant resetting of the ‘volumestat’ as pregnancy progresses (‘normal-fill’ theory), the gravida always acting as if her current volume status were ‘normal’. There are data to support each view, detailed elsewhere [5,6], but the formulation popular with the authors of this commentary is that the observed physiologic changes characteristic of normal pregnancy, e.g. vasodilation, low normal blood pressure, increased cardiac output and activated RAS that responds normally to new volume challenges (e.g. salt loading or restrictions), appears consistent with the following formulation. There is an initial primary ‘under-filling’ very early in gestation, with rapid refilling, after which the gravida ‘senses’ her volume status as euvoalaemia or ‘normal-fill’ throughout the remainder of her pregnancy [5,6]. There is a need to prove which of these theories of how pregnant women ‘sense’ their volumes is correct, as this should have relevance to designing the appropriate therapeutic approaches. The article of Escher et al. [1] by linking aldosterone availability to larger neonates and better pregnancy outcomes also recalls an older literature whose authors stressed that the magnitude of the increased plasma volume in pregnancy correlated with better fetal outcomes (reviewed in [7,8]). The rest of this commentary focuses on the volume status of preeclamptics and the status of the RAS in this disease.

One of the most striking features of normal pregnancy, apparent both by physical examination and by haemodynamic and hormonal measurement, is early and marked vasodilation. The physiologic consequences—greater blood flow to the uteroplacental unit, increased renal blood flow and glomerular filtration rate, lower maternal blood pressure and increased cardiac output—are important accommodations to the growing fetus. Lower serum creatinine concentrations and increased plasma renin and aldosterone levels are some of the laboratory measures generally expected to accompany such physiological adaptations. In preeclampsia, characterized by hypertension and proteinuria after midgestation, the RAS is actually suppressed compared to women with uneventful gestations [5–7], although in most women, plasma renin activity and aldosterone levels are still considerably higher than in those with the non-pregnant state. The RAS is also suppressed in women with chronic hypertension who develop superimposed preeclampsia compared to hypertensive women who do not [9]. This suppression of the RAS occurs despite the fact that plasma volume, increased by ∼1.2 L in normal pregnancy, is lower in preeclampsia, the lowest values observed in women progressing to the convulsive phase of the disease eclampsia [6,10]. Again, and akin to differing interpretations given of the volume changes in normal pregnancy, the significance of lower plasma volume measurements in women with preeclampsia is debated—to classic thinkers applying their understanding of the endocrinology and physiology of volume homeostasis, these changes are not surprising. The RAS is suppressed by vasoconstriction and increased sodium retention, leading
to exaggeration of gestational hypervolaemia, hypertension and increased oedema formation. As for the seemingly paradoxical decrease in intravascular volume, this too is understandable by the classical approach as being a result of alterations in capillary Starling forces ultimately leading to fluid shifts from the intravascular to the extracellular compartment, the hypertension literally chasing fluid out of the circulation. Sounds reasonable, but not so fast!

There is a view that preeclampsia is actually a volume-contracted state representing a failure of the pregnant women to achieve and/or maintain the physiological volume expansion appropriate for normal gestation, although the sequence of how such events lead to hypertension remains to be elucidated. Supporting this view are data suggesting that plasma volume starts decreasing prior to presentation of the disease [11], and that preeclamptic women are in fact subtle ‘sodium leakers’. In this respect, data from Dr Mohaupt’s laboratory, including those in the current article, remind us of a perhaps forgotten older literature. In 1958, Robinson [12] published a study in Lancet suggesting that salt loading throughout gestation decreased the incidence of preeclampsia, and saline infusions temporarily improved blood pressure in hypertensive gravidas. Indeed, Dr Mohaupt’s group, who have hypothesized that inefficient aldosterone production during pregnancy may lead to preeclampsia (vida infra), have recently described a case where they believe salt loading throughout gestation avoided preeclampsia [4].

What about the suggestion that genetically determined variations in aldosterone production might explain the pathophysiology of preeclampsia? In 2004, Shojaati et al. [2] suggested that some women who develop preeclampsia carry genetic mutations that primarily lead to the decreased activity of aldosterone synthase (CYP11B2), resulting in inefficient aldosterone production. They further suggested that this results in inefficient volume expansion and poor placental perfusion in early pregnancy, the latter believed by many to be the initiating event of the preeclampsia syndrome. In a stimulating review, Escher and Mohaupt [3] go further, extending their theory that perturbations in steroid pathways result in poorer pregnancy outcomes including preeclampsia. Cortisol has an affinity for the mineralocorticoid receptor similar to aldosterone, availability controlled by 11β-hydroxysteroid dehydrogenase (11β-HSD-2). This enzyme inactivates cortisol into cortisone; the latter unable to bind to the mineralocorticoid receptor. Interestingly, data suggest that 11β-HSD-2 is a major placental enzyme that plays a role in regulation of the feto-placental circulation. There is preliminary evidence for reduced 11β-HSD-2 expression and activity in preeclampsia, as well as correlations with Ang II receptor subtype 1 expression (thus, it would have been illuminating to measure renin as well as Ang II activity in all their studies, and fetal growth). The work presented in this issue stresses aldosterone availability in terms of larger and healthier babies, and fewer pregnancy complications.

The focus on adrenal mineralocorticoid production and a healthy robust volume expansion is indeed of interest, but a bit surprising. In pregnancy, a vast part of the increased mineralocorticoid activity relates to the greatly increased production of deoxycorticosterone (DOC) whose circulating levels, like those of aldosterone, are markedly high in pregnancy [5,13–15]. However, most of this DOC is produced from progesterone and at an extra-adrenal site. Progesterone, a natriuretic hormone, also increases markedly and would normally counter volume expansion, but activity of renal steroid 21-hydroxylase, an enzyme that enhances conversion of progesterone to DOC, may be particularly high during gestation, a considerable portion of the DOC then being produced in the vicinity of the renal receptors whose stimulation enhances sodium reabsorption, and thus we might not have to worry about a genetically tricked adrenal gland [13–16]!

It would be of interest to know the status of renin activity and Ang II levels in the women with genetic variations that lead to decreases in aldosterone synthase and or activity. Though the RAS is stimulated in pregnancy, it reacts normally to volume maneuvers (e.g. salt restriction and loading, posture and diuretics), but apparently around a new and substantially higher set point [8,17]. Thus, decreased aldosterone production and lower plasma volume should be accompanied by renin and Ang II levels that are actually higher than those measured in normal gestation. Also, the plasma aldosterone to renin ratios rise as gestation progresses, and the highest values are observed in women with overt preeclampsia, such a scenario in patients whose disorder stems from a salt-losing scenario would be surprising [18].

As indicated, the role of the RAS took a back seat to preeclampsia research when investigators proclaimed its suppression in preeclampsia. It has now been resurrected not only by the work of Mohaupt and colleagues, but by findings in other areas. Angiotensin 1–7, contrary to Ang II, is a vasodilating peptide, whose levels increase in normal pregnancy but are decreased in preeclampsia [19–21]. Then there is that fascinating and growing literature that agonistic autoantibodies to the AngII AT1 receptor are detected in the blood of women with preeclampsia [22,23]. All these areas though need considerably more investigation.

Where are we in 2009? Women with preeclampsia may develop severe hypertension, modestly reduced glomerular filtration rate and significant oedema—at times resembling patients with acute glomerulonephritis—however, we no longer restrict sodium intake or prescribe prophylactic diuretics in preeclampsia. Now some are saying pour on the salt again! We once used diuretics to treat preeclampsia, but now, except for special circumstance, that is taboo. What should we do now? The answer is simple; go back to clinical settings and/or the laboratory and do more and well-designed research. The gravidas who keep the world in business are counting on us.

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References

End-stage kidney disease patients in the intensive care unit

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Introduction

Chronic kidney disease (CKD) is an important public health issue. In the US adult population, the prevalence of CKD is estimated at >13% (representing ~40 million), and has increased appreciably in recent years [1]. This increasing trend has been attributable to an ageing population, along with increasing rates of diabetes mellitus, hypertension and obesity [1–3]. This mounting burden of CKD is also projected to contribute to greater numbers of patients progressing to end-stage kidney disease (ESKD) and requiring maintenance renal replacement therapy (RRT). Data provided by the United States Renal Database System (USRDS) show that both the prevalence and incidence of ESKD have increased

Reference


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