Renin, Aldosterone, and Cortisol in Pregnancy-Induced Hypertension

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Bibliography

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ABSTRACT

Introduction We aimed to assess renin, aldosterone, and cortisol in the early stages of pregnancy-induced hypertension (PIH), i. e., at the time of diagnosis.

Methods During the postural test, we measured aldosterone, renin [Liason DiaSorin Inc. (Italy)], as well as cortisol, sodium, potassium, and 24-h urinary sodium and potassium excretion in 62 women with newly diagnosed PIH, 70 healthy women during the 3rd trimester of pregnancy, and in 22 healthy non-pregnant women.

Results In all groups, there was a significant increase in aldosterone and renin in upright versus supine posture ($p < 0.01$). Both supine and upright aldosterone concentrations were higher in healthy pregnant women than in women with PIH and the lowest in healthy not-pregnant [supine (median ± intequartile range): 25.04 ± 18.4 ng/dL, 18.03 ± 12.58 ng/dL, and 7.48 ± 4.78 ng/dL, $p < 0.001$, upright: 31.60 ± 21.32 ng/dL, 25.11 ± 13.15 ng/dL, and 12.4 ± 12.4 ng/dL, $p < 0.001$, for healthy pregnant, pregnant with PIH, and non-pregnant, respectively]. Supine renin concentrations were higher only in healthy pregnant ($p < 0.001$), while in the upright position, there was a difference only between healthy pregnant and women with PIH ($p = 0.002$). Both in supine and upright positions, there was no difference in the aldosterone-to-renin ratio between healthy pregnant women and women with PIH, though, in both groups, the ratio was higher than in non-pregnant women ($p < 0.001$). Morning cortisol concentrations and 24-h urinary sodium excretion were lower in women with PIH than in healthy pregnant ($p < 0.001$, $p = 0.002$, respectively).

Conclusion Hyperaldosteronism is not involved in the etiology of PIH. In PIH, there is also a tendency towards lower sodium excretion and lower morning cortisol concentrations.

Introduction

Gestational hypertension (GH), also known as pregnancy-induced hypertension (PIH), is the most common hypertensive disorder during pregnancy, with a prevalence of about 10–15 % [1]. PIH is defined as systolic blood pressure (SBP) > 140 mm Hg and diastolic blood pressure (DBP) > 90 mm Hg. It is classified as mild (SBP 140–149 and DBP 90–99 mm Hg), moderate (SBP 150–159 and DBP 100–109 mm Hg), and severe (SBP ≥ 160 and DBP ≥ 110 mm Hg), while risk factors include maternal comorbidities, such as chronic kidney disease, hypertension and obesity, a family history of preeclampsia, nulliparity or multiple pregnancies, and previous preeclampsia or intrauterine fetal growth restriction [2]. Finally, preeclampsia (PE) is defined as a new onset of hypertension after 20 weeks of gestation and proteinuria (≥ 30 mg/mmol in the urine collection or albumin/creatinine ≥ 8 mg/mmol or dipstick reading ≥ 1) [3]. Women who develop PIH are at increased risk of developing PE; approximately 60 % who had GH before 28 weeks' gestation developed PE, 26 % between 28–33 weeks, 27 % between 34–36 weeks, and 12 % after 37 weeks of gestation [4].

The etiology of PIH is not fully elucidated at its early stages, though in more advanced diseases leading to PE, factors such as shallow placentation (leading to decreased perfusion/ischemia, increased oxidative stress, and defect in myometrial spiral artery remodeling), as well as increased circulating factors such as sFLT1 (soluble FMS-like tyrosine kinase-1, also known as soluble VEGF receptor 1) thus leading to decreased concentrations of available VEGF and placental growth factor (PlGF), or increased concentrations of an antiangiogenic soluble endoglin (sENG) and have been implicated [5].

Aldosterone concentrations are well recognized to be reduced in PE [6], the same being true for angiotensin II [7]. While factors such as increased endothelin-1 and atrial natriuretic peptide may contribute to decreased renin concentrations [8], it is not clear whether these alterations fully apply to the early stages of PIH.

As both aldosterone and renin increase in an upright posture, a single measurement, particularly in a supine position, may not be enough to provide adequate insight into the activity of the angiotensin-renin-aldosterone system. Indeed, some authors [9] suggest that taking samples following 2–4 h of an upright posture improves diagnostic sensitivity.

In our study, we have therefore endeavored to assess aldosterone, renin, and cortisol secretion during the postural test at the time of diagnosis of pregnancy-induced hypertension to address the question of whether alterations of aldosterone and/or cortisol secretion might be involved in the pathogenesis of PIH.

Materials and Methods

The study included 154 women categorized into three groups, i. e., 70 healthy pregnant euthyroid women aged 30.73 ± 4.51 (mean ± SD) years (range 22–42 years), at 32.38 ± 4.25 weeks of gestation (range 27–40 weeks), 62 women with PIH aged 30.4 ± 5.71 years (range 19–44), at 32.22 ± 3.96 weeks of gestation (range 26–40 weeks), and 22 healthy non-pregnant women aged 33.08 ± 8.72 years, ranging from 19 to 44 years. All subjects were admitted to the Polish Mother's Memorial Hospital – Research Institute for at least 24 h prior to testing and received an identical standard hospital diet. According to the current guidelines [1, 10], the acceptable upper limit of blood pressure was 140/90 mm Hg, though in practice mean blood pressure of our healthy pregnant women was about 110–120/60–80 mm Hg. In contrast, in women with PIH, average blood pressure (prior to the initiation of treatment) was within the range of 148–160/90–100 mm Hg.

Exclusion criteria were as follows: lack of informed consent, presence of proteinuria, race other than Caucasian, presence of more than two fetuses, ectopic pregnancy, age less than 18 years, any chronic diseases (such as asthma, hypothyroidism) that required continuous medication, and previously diagnosed essential hypertension or secondary hypertension other than PIH.

Investigations of all subjects with PIH were performed at the time of diagnosis, i. e., before starting any medication. The study has been approved by the Ethics Committee of the Polish Mother's Memorial Hospital Research Institute, decision no. 67/2017.

Aldosterone was measured by an automated chemiluminescence immunoassay (Liason DiaSorin Inc., Italy), where intraassay variation is 3.5 % at 6.8 ng/dL and 1.8 % at 28.8 ng/dL, respectively. The total coefficient of variation was 9.5 % at 6.8 ng/dL and 5.6 % at 28.8 ng/dL. Manufacturer reference for non-pregnant subjects is as follows: aldosterone supine 1.17–23.6 ng/mL, aldosterone upright 2.21–35.3 ng/mL.

Direct renin was measured by an immunoassay (Liason DiaSorin Inc., Italy), where intraassay variation was 12.4 % at 13.2 µIU/mL and 4.7 % at 260.3 µIU/mL, respectively. Total coefficient of variation was 0.6 % at 13.2 µIU/mL and 1.7 % at 260.3 µIU/mL. Manufacturer reference for renin for non-pregnant subjects is as follows: renin supine 2.8-39.9 µIU/mL, renin upright 4.4–46.1 µIU/mL.

The study protocol was as follows: fasting blood samples were taken at about 6–7 am in a supine position, and the patient was subsequently asked to remain out of bed and preferably go for a walk for about 120 min after they had been seated for about 5 min. The following parameters were assessed: sodium, potassium, creatinine, urinary sodium, and potassium concentrations, 24 h sodium and potassium excretion, thyroid stimulating hormone (TSH; once only), aldosterone, renin, and cortisol (supine and upright positions). Furthermore, in view of the data that SUSPPUP ratio calculated as serum sodium (mmol/L): urinary sodium (mmol/L)/[serum potassium (mmol/L)]^2: urinary potassium (mmol/L) as well as SUSPUP ratio, calculated as serum sodium (mmol/L): urinary sodium (mmol/L)/serum potassium (mmol/L): urinary potassium (mmol/L), are useful in the assessment of patients with primary hyperaldosteronism [11], we calculated the above parameters in healthy pregnant women and women with PIH.

Taking into account the well-known effects of pregnancy on concentrations of cortisol-binding globulin, we concluded that comparison of cortisol concentrations to healthy non-pregnant subjects would not provide any novel data; therefore, cortisol concentrations were measured in pregnant subjects only. Total cortisol and TSH were measured by ECLIA immunoassay on Cobas e601 analyzer (Roche platform).

Statistical analysis

Statistical analysis was performed using MedCalc Software 12.6.1. The reference interval was calculated using the non-parametrical percentile method. Normal distribution was tested using the

D'Agostino-Pearson test. Comparison between the two groups was performed by the Mann-Whitney-U test, while the comparison of all three groups was performed by the Kruskall-Wallis H test. P-values of 0.05 were considered to indicate statistical significance.

Results

There were no significant differences in age (years) or the age of the pregnancy (in weeks) between healthy pregnant women and women with PIH.

Supine aldosterone concentrations (▶ **Table 1**) were the highest among healthy pregnant women (median ± intequartile range): 25.04 ± 18.4 ng/dL, 18.03 ± 12.58 ng/dL, and 7.48 ± 4.78 ng/dL for healthy pregnant, women with PIH, and healthy non-pregnant, respectively, and were significantly higher than in women with PIH ($p = 0.005$), and healthy non-pregnant ($p < 0.001$). Furthermore, women with PIH had higher aldosterone concentrations than healthy non-pregnant women ($p < 0.001$). A similar situation was observed in an upright posture (aldosterone upright: 31.60 ± 21.32 ng/dL, 25.11 ± 13.15 ng/dL, and 12.4 ± 12.4 ng/dL for healthy pregnant, women with PIH, and healthy non-pregnant women, respectively), where for healthy pregnant versus PIH: $p = 0.004$, healthy pregnant versus non-pregnant: $p < 0.001$, and PIH versus non-pregnant: $p = 0.002$. In all groups, there was a significant increase in aldosterone concentrations after a period of ambulation (supine versus upright, $p < 0.01$).

Supine renin concentrations (▶ **Table 1**) were the highest in the healthy pregnant group (20.23 ± 14.13 µIU/mL, 12.84 ± 8.50 µIU/mL, and 14.7 ± 12.23 µIU/mL, for healthy pregnant, women with PIH, and healthy non-pregnant, respectively), where significant differences were noted between healthy pregnant women and those with PIH ($p < 0.001$), and healthy pregnant and healthy non-pregnant women ($p = 0.024$), but there were no significant differences in supine renin concentrations between women with PIH and healthy non-pregnant women ($p = 0.99$). Upright renin concentrations (29.54 ± 22.02 µIU/mL, 19.65 ± 10.95 µIU/mL, and 30.76 ± 26.52 µIU/mL, for healthy pregnant, women with PIH, and healthy non-pregnant women, respectively) were significantly higher in healthy pregnant women in comparison to women with PIH ($p = 0.002$), but there were no significant differences between healthy pregnant and healthy not-pregnant ($p = 0.98$) and women with PIH versus healthy non-pregnant women ($p = 0.058$). Again, in all groups, there was a significant increase in aldosterone concentrations after a period of ambulation (supine versus upright, $p < 0.01$). In contrast, there was no significant change in cortisol (supine versus upright, $p = 0.46$); however, both in supine and in upright positions, cortisol concentrations were higher in healthy pregnant women than in women with PIH (supine cortisol: 28.38 ± 12.65 µg/dL versus 21.31 ± 8.14 µg/dL, upright cortisol: 32.29 ± 12.43 µg/dL versus 21.9 ± 8.61 µg/dL, $p < 0.001$, for healthy pregnant and women with PIH, respectively).

Analysis of the aldosterone-to-renin ratio is presented in ▶ **Table 2**. In all groups, there was no significant change in the aldosterone-to-renin ratio after the period of ambulation (supine versus upright). In both healthy pregnant and in women with PIH, the aldosterone-to-renin ratio was higher than in healthy non-pregnant women ($p < 0.001$), but there were no differences in the aldosterone-to-renin ratio between healthy pregnant women and women with PIH ($p = 0.57$).

Analysis of serum sodium, potassium, 24-h urinary excretion of sodium and potassium, as well as SUSPUP and SUSPPUP ratio are presented in ▶ **Table 3**. There were no significant differences in serum sodium and potassium between healthy pregnant women and women with PIH. There was also no significant difference in 24-h potassium excretion ($p = 0.083$). Women with PIH, however, demonstrated lower 24-h sodium excretion (115 ± 16 mmol/24 h versus 135 ± 50 mmol/24 h, $p = 0.002$, for medians, for women with PIH and healthy pregnant women, respectively). There was, however, no significant difference both in SUSPUP and in SUSPPUP ratios (▶ **Table 3**, $p = 0.36$ and $p = 0.35$, respectively). Given the lack of any difference in serum sodium and an identical diet during the hospital stay, thus ensuring a similar sodium intake, this may indicate that women with PIH demonstrate a tendency towards aldosterone-independent sodium retention.

▶ **Table 1** Comparison of supine and upright aldosterone, renin, and cortisol concentrations during postural test between three investigated groups. Aldosterone and renin concentrations were higher in upright vs. supine position in all groups ($p < 0.01$), and were significantly higher in healthy pregnant women than in other groups ($p < 0.001$).

	Healthy pregnant (n = 70)		Pregnant with PIH (n = 62)		Healthy non-pregnant (n = 22)		p-value
	Mdn	*IQR*	*Mdn*	*IQR*	*Mdn*	*IQR*	
Supine							
Aldosterone [ng/dL] #	25.04	18.40	18.03	12.58	7.48	4.78	< 0.001
Renin [µIU/mL] #	20.23	14.13	12.84	8.50	14.7	12.23	< 0.001*
Cortisol [µg/dL]#	28.38	12.65	21.31	8.13	–	–	< 0.001
Upright							
aldosterone [ng/dL] #	31.60	21.32	25.11	13.15	12.4	10.16	< 0.001
renin [µIU/mL] #	29.54	22.02	19.65	10.95	30.76	26.52	0.001**
cortisol [µg/dL] #	32.29	12.43	21.90	8.61	–	–	< 0.001

Mdn – median; *IQR* – intequartile range; p – test probability.; #comparative analysis between two groups performed by Mann-Whitney-U test; *p-values for supine renin: heathy pregnant vs. women with pregnancy-induced hypertension (PIH) ($p < 0.001$), and healthy pregnant vs. healthy non-pregnant ($p = 0.024$), women with PIH vs. healthy non-pregnant ($p = 0.99$) (Mann-Whitney-U test); **p-values for upright renin: healthy pregnant vs. healthy non-pregnant $p = 0.98$, pregnant with PIH vs. heathy non-pregnant $p = 0.058$, healthy pregnant vs. pregnant with PIH, $p = 0.002$ (Mann-Whitney-U test).; Conversion factor for aldosterone 1 ng/dL = 27.74 pmol/L, conversion factor for cortisol 1 µg/dL = 27.59 nmol/L.

▶ **Table 2** Comparison of the aldosterone-to-renin ratio during postural test (supine and upright positions) between healthy pregnant women, women with PIH, and healthy non-pregnant women.

Aldosterone/renin ratio [ng/dL/μIU/mL]	Healthy pregnant (n = 70)		Pregnant with PIH (n = 62)		Healthy non-pregnant (n = 22)		p-value
	Mdn	*IQR*	*Mdn*	*IQR*	*Mdn*	*IQR*	
Supine	1.36 [ns]	0.90	1.17 [ns]	0.82	0.66	0.34	< 0.001
Upright	1.31 [ns]	1.40	1.17 [ns]	0.87	0.52	0.26	< 0.001

Mdn – median; *IQR* – intequartile range; p – test probability.; [ns] – not significant in comparison to women with pregnancy-induced hypertension (PIH) (Mann-Whitney-U test); In both healthy pregnant and in women with PIH, aldosterone-to-renin ratio was higher than in healthy non-pregnant women ($p < 0.001$)

▶ **Table 3** Comparison of serum sodium and potassium, urinary 24-h urinary sodium and potassium excretion, and SUSPUP and SUSPPUP ratios in healthy pregnant women and in women with pregnancy-induced hypertension (PIH; Mann-Whitney-U test).

	Healthy pregnant (n = 70)		Pregnant with PIH (n = 62)		*P*-value
	Mdn	*IQR*	*Mdn*	*IQR*	
SERUM					
K [mmol/L]	4.20	0.40	4.10	0.31	0.23
Na [mmol/L]	137.00	2.00	137.00	2.00	0.81
URINE					
K [mmol/24 h]	46.10	18.98	44.98	13.67	0.083
Na [mmol/24 h]	136.00	50.00	115.00	16.00	0.002
SUSPUP ratio	11.06	7.17	12.53	3.61	0.36
SUSPPUP ratio	2.63	1.76	2.99	0.94	0.35

Mdn – median; *IQR* – intequartile range; *P* – test probability; SUSPUP: serum sodium (mmol/L): urinary sodium (mmol/L)/serum potassium (mmol/L): urinary potassium (mmol/L); SUSPPUP: serum sodium (mmol/L): urinary sodium (mmol/L)/[serum potassium (mmol/L)]^2: urinary potassium (mmol/L).

Discussion

In our study, we have conclusively shown that hyperaldosteronism does not appear to be a driving force for the development of PIH, even at its early stages. Furthermore, we report that despite decreased aldosterone and renin concentrations in PIH, there is indeed no change in the aldosterone-to-renin ratio, though it remains higher than in healthy non-pregnant women. These data indicate that the renin-aldosterone system appears to be suppressed in PIH, possibly as an adaptive mechanism in the setting of a tendency for sodium retention and volume expansion.

The causes for the above-described phenomenon remain yet to be elucidated. It should be mentioned, however, that conditions associated with low renin hypertension, such as Liddle syndrome or apparent mineralocorticoid excess, have been excluded on clinical grounds as only healthy and previously normotensive women were recruited into the study, though non-classical forms of an apparent mineralocorticoid excess have been recently described [12].

Adlin et al. [13] described a bimodal aldosterone distribution in low-renin hypertension. They concluded that there are two pathophysiological variants of low renin hypertension, one that is aldosterone-dependent and one that is non-aldosterone-dependent. The latter notion clearly raises an issue of whether there might be a different (weak) mineralocorticoid other than aldosterone as a causative factor for some cases of low renin hypertension. Such a hypothesis had certainly been raised quite a while ago [14, 15], but, so far, it has not been conclusively confirmed. In the context of our study, we have to limit the interpretation of our findings to parameters that we have actually measured, though we suggest that assessment of a urinary steroid profile by the mass spectrometry method might provide more insight into the minutes of steroid metabolism in PIH. Indeed, the mass spectrometry method has already been employed to assess steroid metabolism in non-pregnant subjects [12].

Willenberg et al. [11] and Kanaan et al. [16] demonstrated increased SUSPUP and SUSPPUP ratios in patients with primary hyperaldosteronism. In such a setting, the lack of any significant differences in SUSPUP and SUSPPUP ratios ($p = 0.36$ and 0.35, respectively) also confirms, in our opinion, that hyperaldosteronism does not seem to play a significant role in the development of PIH.

Relative suppression of aldosterone was observed in PIH [17, 18], and there was also no significant increase in renin compared to non-pregnant subjects [19]. However, in contrast to our findings, Brown et al. [17] reported an increase in aldosterone-to-renin ratio (PIH 411 (range 277 to 598) versus normal pregnancy 195 (range 158–337), $p < 0.001$), while the study of Elsheikh et al. [19], involved measurements of plasma renin activity, rather than direct renin, and comparative analyses in the above study included relatively small subgroups (e. g., only 16 normotensive versus 6 hypertensive women in the 1st trimester, 14 versus 10 in the 2nd and 15 and 12 in the 3rd trimester, as well as 12 normotensive and 12 hypertensive non-pregnant women). Furthermore, the authors' conclusion that *"aldosterone biology seems to be directly or indirectly involved in the etiology of gestational hypertension"* was based primarily on a comparison of 12 women with PIH versus 12 non-pregnant hypertensive women (i. e., non-pregnant women with essential hypertension), that is not comparable to groups analyzed in our study (i. e., healthy pregnant versus pregnant with PIH and healthy non-pregnant women). It is also worth noting that, in contrast to

studies listed above, we assessed renin and aldosterone at the early stages of PIH, i. e., before any medication was started, and we used a postural test to improve the validity of our findings. It should be mentioned that the postural test was not considered necessary in the diagnosis of primary hyperaldosteronism in the setting of the availability of an adrenal vein sampling, but recently it has turned out to be the opposite, as the test not only provides more insight into the renin aldosterone system but also appears to increase diagnostic sensitivity [20, 21]. Hence, in our opinion, we provide more valid data on what actually takes place in pregnancy as we demonstrate what happens to aldosterone and renin in women with PIH both in the supine and upright positions, thus mimicking the real physiology (day – predominantly upright versus night – predominantly supine). Indeed, very few studies in PIH involved a formal assessment of aldosterone and renin response to postural stimuli in patients with PIH. Fagundes et al. [22], failed to notice any postural response in the renin-angiotensin-aldosterone system, but their study was based on data from only ten women with PIH, in contrast to a much larger cohort (n = 62) in our study.

Though assessment of aldosterone and renin secretion might be potentially better assessed by mass spectrometry method, we need to mention that our study was performed by a modern and validated chemiluminescence assay (Liason DiaSorin Inc., Italy) that was used in several important recent studies on the renin-aldosterone system [23–25].

Interestingly, lower aldosterone concentrations in women with PIH compared to that in healthy pregnant women might not necessarily represent a satisfactory phenomenon. Birukov et al. [26] demonstrated that urinary aldosterone excretion at gestational week 29 independently contributed to placental and birth weights (adjusted β-coefficients [95 % CI], 24.50 [9.66–39.35] and 9.59 [4.57–14.61], respectively), and suggested that suppression of aldosterone in pregnancy may have adverse trophic effects.

A healthy pregnancy is a state of hyperactivity of the hypothalamic-pituitary-adrenal axis and of hypercortisolism, while the placenta remains an important source of corticotropin-releasing hormone [27]. Our study demonstrated lower cortisol concentrations in women with PIH compared to healthy pregnant women at the time of peak cortisol secretion (i. e., in the morning hours). This might indicate that hypercortisolemia does not seem to significantly contribute to the pathogenesis of PIH. This is interesting given that in pre-eclampsia, the activity of placental 11β-hydroxysteroid dehydrogenase type 2 (that converts cortisol to inactive cortisone) is decreased [28], but despite this, an overall increased metabolism of cortisol in PIH has been described [29]. As a result, reduced cortisol concentrations were described both in pre-eclampsia and PIH [30]. It should be noted, however, that our study was not primarily designed to study cortisol metabolism in PIH, while a full assessment of cortisol secretion should also involve assessment of 24-h urinary free cortisol, so our data on partial suppression of morning cortisol concentrations of women with PIH cannot be automatically extrapolated to 24-h cortisol excretion. Hence, without a formal assessment of 24-h urinary cortisol excretion, it is not possible to conclude whether overall cortisol secretion is indeed altered in women with PIH.

Brown et al. [17] also reported lower 24-h urinary sodium excretion in women with PIH. The cause of this phenomenon remains to be elucidated, but in the setting of an identical hospital diet, we can raise a hypothesis, that it might be caused by a form of aldosterone-independent sodium retention. This hypothesis, however, requires further study.

In summary, we demonstrated retained postural responses for aldosterone and renin in healthy pregnant women and women with pregnancy-induced hypertension. Though aldosterone concentrations increase both in healthy pregnant women and women with PIH, a significant increase in renin is observed only in healthy pregnant women and in the supine position only. Furthermore, both the renin-aldosterone system and morning cortisol appear to be suppressed in PIH in comparison to healthy pregnant women. Hence, in our opinion, both hyperaldosteronism and hypercortisolemia seem unlikely to contribute to the pathophysiology of PIH.

Data Availability Statement

The data presented in this study are available on request from the corresponding author.

Ethics Statement

The study was approved by the Bioethical Committee at the Polish Mother's Memorial Hospital -Research Institute (PMMH-RI) in Lodz, Poland, decision no. 67/2017. Informed consent was obtained from all subjects involved in the study.

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Conflict of Interest

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

References

[1] Braunthal S, Brateanu A. Hypertension in pregnancy: Pathophysiology and treatment. SAGE Open Med 2019; 7: 2050312119843700. doi:10.1177/2050312119843700

[2] Kintiraki E, Papkatsika S, Kotronis G et al. Pregnancy-induced hypertension. Hormones 2015; 14: 211–223. doi:10.14310/horm.2002.1582

[3] (NICE) NIfHaCE. Hypertension in pregnancy: Diagnosis and management (NG133). 2019

[4] Romero-Arauz JF, Ortiz-Díaz CB, Leaños-Miranda A et al. Progression of gestational 362 hypertension to preeclampsia. Ginecol Obstet Mex 2014; 82: 229–235

[5] Phipps EA, Thadhani R, Benzing T et al. Pre-eclampsia: Pathogenesis, novel diagnostics and therapies. Nat Rev Nephrol 2019; 15: 275–289. doi:10.1038/s41581-019-0119-6

[6] Brown MA, Wang J, Whitworth JA. The renin-angiotensin system in preeclapsia. Clin Exp Hypertens 1997; 19: 713–726. doi:10.3109/10641969709083181

[7] Brosnihan KB, Merrill DC, Yamaleyeva LM et al. Longitudinal study of angiotensin peptides in normal and pre-eclamptic pregnancy. Endocrine 2020; 69: 410–419. doi:10.1007/s12020-020-02296-3

[8] Zafirovska KG, Maleska VT, Bogdanovska SV et al. Plasma human atrial natriuretic peptide, endothelin-1, aldosterone and plasma-renin activity in pregnancy-induced hypertension. J Hypertens 1999; 17: 1317–1322. doi:10.1097/00004872-199917090-00012

[9] Stowasser M, Ahmed AH, Pimenta E et al. Factors affecting the aldosterone/renin ratio. Horm Metab Res 2012; 44: 170–176. doi:10.1055/s-0031-1295460

[10] Prejbisz A, Dobrowolski P, Kosiński P et al. Management of hypertension in pregnancy – prevention, diagnosis, treatment and long-term prognosis. A position statement based on expert consensus of the Polish Society of Hypertension, Polish Cardiac Society and Polish Society of Gynecologists and Obstetricians. Arterial Hypertens 2019; 23: 117–182. doi:10.5603/AH.a2019.0011

[11] Willenberg HS, Kolentini C, Quinker M et al. The serum sodium to urinary sodium to (serum potassium)^2 to urinary potassium ratio in patients with primary aldosteronism. Eur J Clin Invest 2009; 39: 43–50. doi:10.1111/j.1365-2362.2008.02060.x

[12] Tapia-Castillo A, Carvajal CA, Lopez-Cortez X et al. Novel metabolomic profile of subjects with non-classic apparent mineralocorticoid excess. Sci Rep 2021; 11: 17156. doi:10.1038/s41598-021-96628-6

[13] Adlin EV, Braitman LE, Vasan RS. Bimodal aldosterone distribution in low-renin hypertension. Am J Hypertens 2013; 26: 1076–1085. doi:10.1093/ajh/hpt091

[14] Adlin EV, Channick BJ, Marks AD. Salivary sodium-potassium ratio and plasma renin activity in hypertension. Circulation 1969; 39: 685–692

[15] Crane MG, Harris JJ, Johns VJ Jr. Hyporeninemic hypertension. Am J Med 1972; 52: 457–466

[16] Kanaan E, Hasse M, Vonend O et al. Diagnostics 2020; 10: 545. doi:10.3390/diagnostics10080545

[17] Brown MA, Zammit VC, Mitar DA et al. Renin-aldosterone relationships in pregnancy-induced hypertension. Am J Hypertens 1992; 5: 366–371. doi:10.1093/ajh/5.6.366

[18] Israel A, Peceño A. Renin-angiotensin-aldosterone system in pregnancy-induced hypertension. J Hum Hypertens 2000; 14: S36–S39. doi:10.1038/sj.jhh.1000985

[19] Elsheikh A, Creatsas G, Mastorakos G et al. The renin-aldosterone system during normal and hypertensive pregnancy. Arch Gynecol Obstet 2001; 264: 182–185. doi:10.1007/s004040000104

[20] Luo P-Y, Chen S-H, Yu Y-R. The value of postural stimulation test combined with adrenal CT in the diagnosis of aldosterone-producing adenoma. J Sichuan Univ (Med Sci Edition) 2020; 51: 87–91. doi:10.12182/20200160604

[21] Fuss CT, Brohm K, Fassnacht M et al. Reassessment of postural stimulation testing as a simple tool to identify a subgroup of patients with unilateral primary aldosteronism. J Clin Endocrinol Metab 2022; 107: e865–e873. doi:10.1210/clinem/dgab611

[22] Fagundes VG, Lamas CC, Francischetti EA. Renin-angiotensin-aldosterone system in normal and hypertensive pregnancy. Response to postural stimuli. Hypertension 1992; 19: II74–II78. doi:10.1161/01.hyp.19.2_suppl.ii74

[23] Solanki P, Gwini SM, Doery JSG et al. Age- and sex-specific reference ranges are needed for the aldosterone/renin ratio. Clin Endocrinol (Oxf) 2020; 93: 221–228. doi:10.1111/cen.14199

[24] Wang K, Hu J, Yang J et al. Development and validation criteria for sparing confirmatory tests in diagnosing primary aldosteronism. J Clin Endocrinol Metab 2020; 105: 1–8. doi:10.1210/clinem/dgaa282

[25] Ma L, Song Y, Mei M et al. Age-related cut-offs of plasma aldosterone/renin concentrations for primary aldosteronism screening. Int J Endocrinol 2018; 2018: 8647026. doi:10.1155/2018/8647026

[26] Birukov A, Bjørkholt-Andersen L, Herse F et al. Aldosterone, salt, and potassium intakes as predictors of pregnancy outcome, including preeclampsia. Hypertension 2019; 74: 391–398. doi:10.1161/HYPERTENSIONAHA.119.12924

[27] Mastorakos G, Ilias I. Maternal and fetal hypothalamic-pituitary adrenal axes during pregnancy and postpartum. Ann NY Acad Sci 2003; 997: 136–149

[28] Kosicka K, Siemiątkowska A, Główka F. 11β-Hydroxysteroid dehydrogenase 2 in preeclampsia. Int J Endocrinol 2016; 2016: 5279462. doi:10.1155/2016/5279462

[29] Kosicka K, Siemiątkowska A, Szpera-Goździewicz A et al. Increased cortisol metabolism in women with pregnancy-related hypertension. Endocrine 2018; 61: 125–133. doi:10.1007/s12020-018-1586-4

[30] Ho JT, Lewis JG, O'Loughlin P et al. Reduced maternal corticosteroid-binding globulin and cortisol levels in pre-eclampsia and gamete recipient pregnancies. Clin Endocrinol (Oxf) 2007; 66: 869–877. doi:10.1111/j.1365-2265.2007.02826.x