



THE UNIVERSITY OF
CHICAGO
MEDICINE &
BIOLOGICAL
SCIENCES

“Primary hyperaldosteronism”

THE UNIVERSITY OF
CHICAGO
MEDICINE



THE UNIVERSITY OF
CHICAGO
MEDICINE &
BIOLOGICAL
SCIENCES

The objectives of the presentation:

- 1- Discuss the epidemiology/ pathophysiology of primary hyperaldosteronism
- 2- Clinical presentation of primary hyperaldosteronism
- 3- Diagnosis and management of primary hyperaldosteronism
- 4- Primary hyperaldosteronism during pregnancy

- H/P: 58 y/o male presented to our clinic for hypertension assessment.
- He was diagnosed with hypertension about 10 years ago and was managed with 2 BP meds with well controlled BP < 130/70s. However, 6-8 months prior to presentation, started having BP fluctuations with highest readings in the morning 160s/170s/90s-100.
- PCP tried him on different BP meds and ended up with 4 different medications including Losartan 100 mg, Clonidine 0.1 BID, Norvasc 10 mg, HCTZ 12.5/KCL 40 meq daily.. Yet BP remained poorly controlled.
- Reported being adherent to low salt diet. He avoids processed food. Cooks at home most of the time and reads labels when shopping to maintain sodium intake < 2500 mg a day.
- Denies sleeping issues and wakes up rested in the morning.
- Denies weight gain in the last one year.
- PMH is positive for hypertension with no other medical issues.
- FH of HTN in his Father who died of MI in his 70s.
- Denies smoking and drinks occasionally with no change in drinking habits.



Physical exam :

- Generally well- appearing male, BMI 55.
- ENT : Clear oropharynx
- Neck : Thyroid is normal and not palpable.
- Chest : Clear to auscultation bilaterally.
- Cardiovascular: Regular rate /Rhythm with no murmurs / LE edema.
- Abdomen : No organomegaly. No bruits.
- CNS : No focal deficits.
- Skin : No skin rash/ or striae
- Musculoskeletal : Normal gait and boney appearance



Workup

Glucose	Na	CL	K	CO	BUN	Cr	GFR	CA	Albumin
88	141	102	3.1	22	14	0.7	77	8.7	4.0

Aldosterone	Renin
25	< 0.6

24 h Urine aldosterone	Urine creatinine	Urine volume
19	---	2925

CT abdomen showed 1.5 cm right adrenal nodule and bilateral thickening

Vein	Aldosterone	Cortisol	A/C ratio	
Right adrenal	1510	634	2.38	
Left adrenal	297	222	1.38	1.72
Femoral vein	17	13		



Primary hyperaldosteronism (PH)

- PH represents subset of disorders collectively known as mineralocorticoid excess states.
- Aldosterone, Cortisol and deoxycorticosterone are the three major mineralocorticoid receptors ligands.
- Hypertension resulting from mineralocorticoid excess can be categorized based on levels of renin and aldosterone.



BOX 14.1

Mineralocorticoid Excess States

Low Renin and High Aldosterone

PRIMARY ALDOSTERONISM

- Aldosterone-producing adenoma (APA)—35% of cases
- Bilateral idiopathic hyperplasia (IHA)—60% of cases
- Primary (unilateral) adrenal hyperplasia—2% of cases
- Aldosterone-producing adrenocortical carcinoma—<1% of cases
- Familial hyperaldosteronism (FH)
 - Glucocorticoid-remediable aldosteronism (FH type I)—<1% of cases
 - FH type II (APA or IHA)—<2% of cases
 - FH type III (associated with the germline mutation in the *KCNJ5* potassium channel)—<1% of cases
- Ectopic aldosterone-producing adenoma or carcinoma—<0.1% of cases

Low Renin and Low Aldosterone

HYPERDEOXYCORTICOSTERONISM

- Congenital adrenal hyperplasia
 - 11 β -Hydroxylase deficiency
 - 17 α -Hydroxylase deficiency
- Deoxycorticosterone-producing tumor
- Primary cortisol resistance
- Apparent Mineralocorticoid Excess (AME)/11 β -Hydroxysteroid Dehydrogenase Deficiency
 - Genetic
 - Acquired
 - Licorice or carbenoxolone ingestion
 - Cushing syndrome

CUSHING SYNDROME

- Exogenous glucocorticoid administration—most common cause
- Endogenous
 - ACTH-dependent—85% of cases
 - Pituitary
 - Ectopic
 - ACTH-independent—15% of cases
 - Unilateral adrenal disease
 - Bilateral adrenal disease
 - Bilateral macronodular adrenal hyperplasia (rare)
 - Primary pigmented nodular adrenal disease (rare)

High Renin and High Aldosterone

- Renovascular hypertension
- Diuretic use
- Renin-secreting tumor
- Malignant-phase hypertension
- Coarctation of the aorta

ACTH, Adrenocorticotropin hormone, *AME*, apparent mineralocorticoid excess; *APA*, aldosterone-producing adenoma; *FH*, familial hyperaldosteronism; *IHA*, idiopathic hyperaldosteronism.

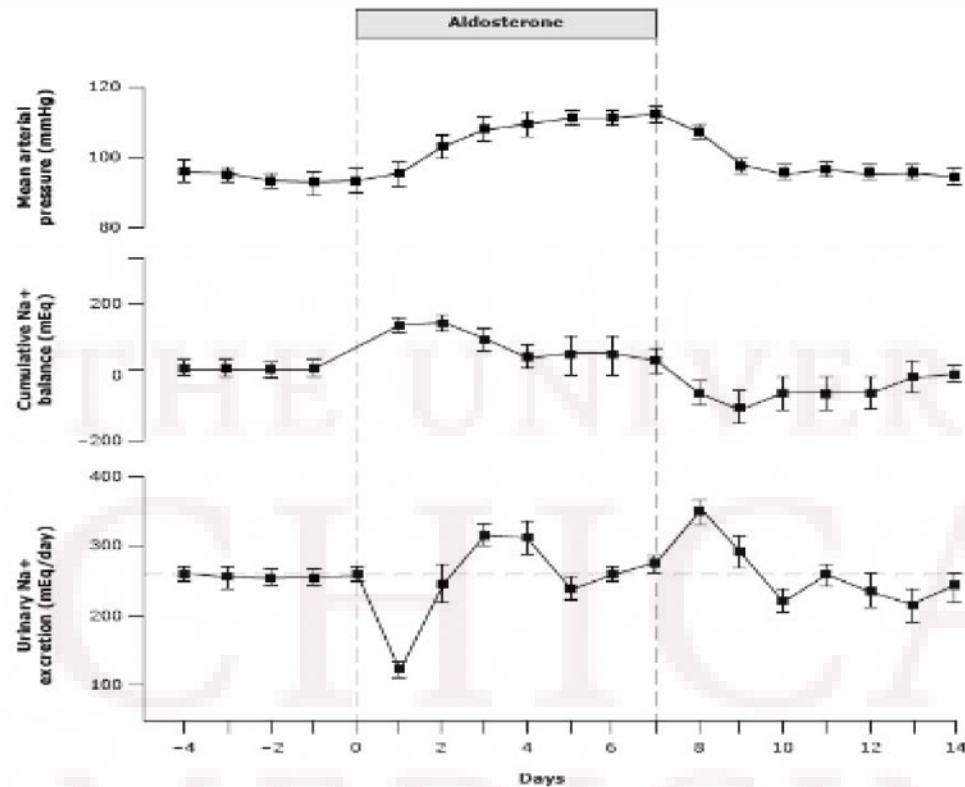


Pathophysiology/ Clinical presentation of PH :

- The diagnosis is usually made in patients who are in the third to sixth decade of life
- In the past, clinicians would not consider the diagnosis of PH unless patient presented with spontaneous hypokalemia. That diagnostic approach resulted in prevalence rate of $< 0.5\%$. However, it is now recognized that most patients with PH are not hypokalemic and screening tests can be completed while patients on anti-hypertensive medications. This approach increased the prevalence estimates for PH to 5-10 % of all patients with hypertension.
- Hypertension is the major clinical finding : Volume expansion / Increase in systemic vascular resistance that helps to preserve the hypertension
- Although, aldosterone induces water and sodium retention initially, this is followed by spontaneous diuresis (Aldo escape phenomenon) and new steady state of volume expansion driving up the blood pressure without evidence of LE edema on physical exam.



Resumption of the steady state in primary aldosteronism



The combination of aldosterone administration and the ingestion of a high Na⁺ diet leads initially to Na⁺ retention, volume expansion, and a rise in systemic blood pressure. After several days, however, there is a spontaneous diuresis, resulting in the return of Na⁺ balance toward normal but persistent hypertension.

Na: sodium.

From: Hall JE, Granger JP, Smith MJ Jr, Premen AJ. Role of renal hemodynamics and arterial pressure in aldosterone "escape". *Hypertension* 1983; 6:1183. Copyright © 1983 American Heart Association. Reproduced with permission from Wolters Kluwer Health. Unauthorized reproduction of this material is prohibited.

Graphic 62044 Version 5.0



- Hypokalemia : historically has been considered to be one of the major clinical findings, however, it is now estimated that only up to 1/3 of patients with PH are hypokalemic.
- In a retrospective international report combining data from five centers including Italy, USA, Singapore, Chile and Australia, < 50 % of patients with PH were hypokalemic at presentation.
- Aldosterone mainly stimulates Na reabsorption through ENaC, which makes the collecting duct lumen relatively electronegative and thereby promotes K loss through specialized K channels in the luminal membranes.
- Hypokalemia itself results in reduction of the activity of these K channels (Aldosterone channels), potentially mediated by angiotensin II, and this may explain why hypokalemia is inconsistent finding in PH.
- In some patients like in our patient, the hypokalemia becomes evident only with the addition of K- wasting diuretics.



- **Diagnostic evaluation:**
- The diagnostic approach can be considered in three phases : Case-detection tests, confirmatory tests and subtype evaluation tests.
- **A- Case detection test :**
- It is paired measurement of PAC and PRA in a random morning ambulatory blood sample to avoid postural stimulation.
- Hypokalemia should be corrected before the test because low K tends to suppress aldosterone.
- BP medications can be continued except ACE/ARBs, and mineralocorticoid receptors antagonists.

Consider Testing for Primary Aldosteronism:

- Hypertension and hypokalemia
- Resistant hypertension (3 drugs and poor BP control)
- Adrenal incidentaloma and hypertension
- Onset of hypertension at a young age (<30 yr)
- Severe hypertension (≥ 160 mm Hg systolic or ≥ 100 mm Hg diastolic)
- Whenever considering secondary hypertension



Case Detection Testing:

Morning blood sample in seated ambulant patient

- Plasma aldosterone concentration (PAC)
- Plasma renin activity (PRA) or plasma renin concentration (PRC)



↑ PAC (≥ 15 ng/dL; ≥ 416 pmol/L)

↓ PRA (< 1.0 ng/mL/hr) or ↓ PRC ($<$ lower limit of detection for the assay)

and

PAC/PRA ratio ≥ 20 ng/dL per ng/mL/hr (≥ 555 pmol/L per ng/mL/hr)



Confirmatory Testing:

- 24-hr urine aldosterone on a high Na⁺ diet

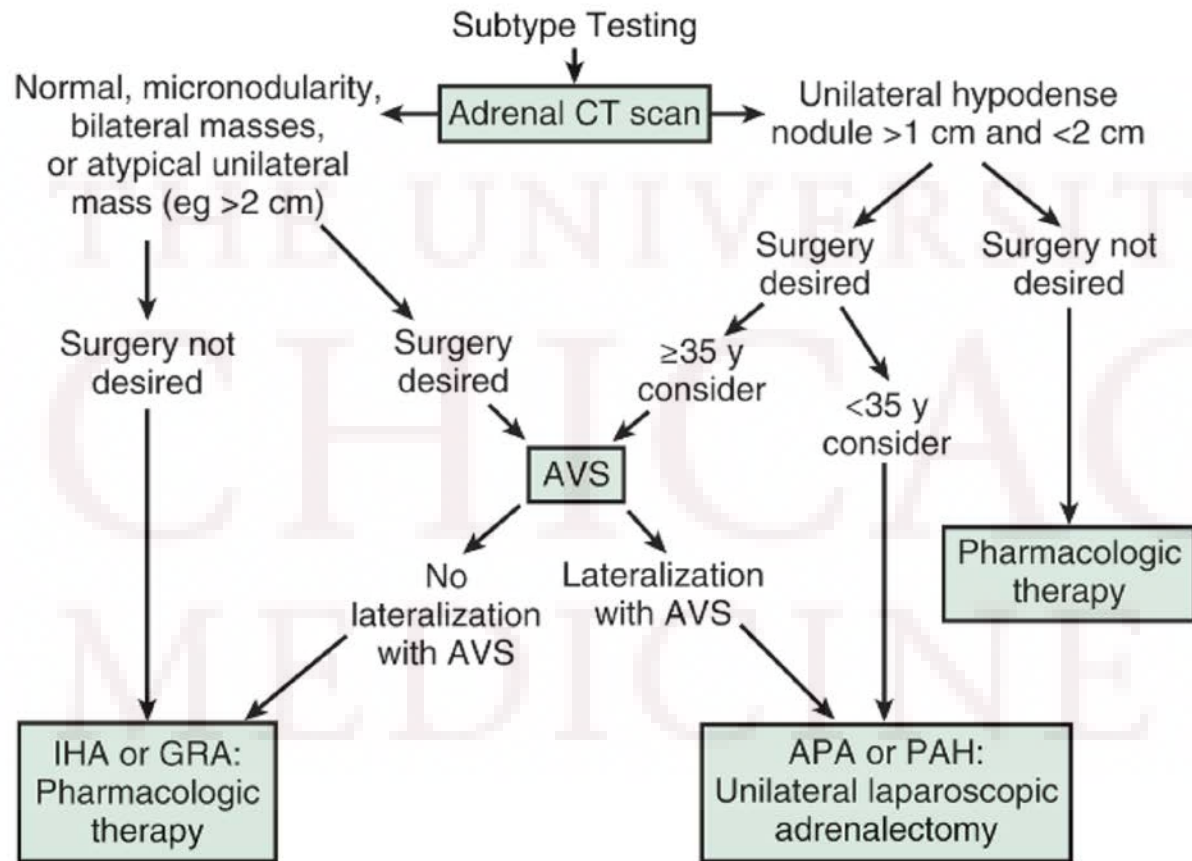


Confirmatory test:

- The case detection test is not diagnostic by itself, and inappropriate aldosterone secretion must be confirmed.
- Aldosterone suppression test can be performed with either orally administered sodium chloride or IV sodium chloride.
- with oral sodium loading test, the patient is instructed to have a high sodium diet supplemented with sodium tablets if needed for 3 days. The goal is 5000 mg of sodium a day. Hypokalemia is expected and close monitoring of K level is recommended. On the third day, 24-hour urine is collected for aldosterone, creatinine and sodium. To document adequate sodium repletion, the 24-hour urinary sodium excretion should > 200 meq. Urinary Aldosterone excretion > 12 mcg/24h in this setting is diagnostic of PH. The sensitivity and specificity of the test is 96%, and 93% respectively.
- With saline infusion test, 2 liters of NS 0.9% infused over 4 hours. PAC levels decrease to < 5 ng/dl in normal subjects while PH don't suppress to < 10 ng/dl. Preliminary data suggest that seated position is more accurate.



- After the syndrome is confirmed, subtype study is needed to guide the therapeutic approach and distinguish Aldosterone-producing adenoma and unilateral adrenal hyperplasia (Surgery is an option) from bilateral adrenal hyperplasia (Only tx medically).



- Adrenal venous sampling is the gold standard test to distinguish between unilateral and bilateral disease.
- The procedure requires an experienced radiologist because cannulation of the right adrenal vein can pose a challenge.
- At some centers like Mayo clinic, continuous cosyntropin infusion during AVS is used to a)- maximize cortisol gradient from adrenal vein to IVC and thus confirm successful sampling of the adrenal vein and b) - maximize secretion of aldosterone.
- Adrenal vein/IVC cortisol ratio is typically > 10 :1 in successful catheterization.
- Then calculate cortisol-corrected ratio to correct the dilutional effect of the inferior phrenic vein flow into the left adrenal vein

Vein	Aldosterone ng/dl	Cortisol mq/dl	A/C	
R adrenal vein	250	647	0.4	
L adrenal vein	4267	495	8.6	21.5 : 1
IVC	98	22	4.5	



Back to our patient :

- Is it successful cannulation ?
- is it unilateral or bilateral disease ?
- What should we offer him ?

Vein	Aldo	Cortisol	A/C ratio	
R adrenal	1510	634	2.38	
L adrenal	297	222	1.38	1.72
Femoral	17	13		

Treatment:

- Mineralocorticoid receptors are present in the kidneys, colon, brain, and CV system.
- Therefore, the goal of treatment should not be only controlling BP, but protecting these organs from aldosterone deleterious effects.
- Unilateral adrenalectomy is the preferred treatment option for patients with adrenal adenoma or unilateral hyperplasia.
- However, average long-term cure rate for HTN ranges 30-60%. Swaka et al.
- Laparoscopic approach is preferred over open approach with shorter hospital stay and less total long-term morbidity.
- After surgery, K should be monitored weekly for 4 weeks with generous sodium intake to avoid hypokalemia.
- Usually hypertension resolves in 1-3 months after surgery in patients with more favorable predictors.



Primary Aldosteronism: Factors Associated with Normalization of Blood Pressure after Surgery

Anna M. Sawka, MD; William F. Young Jr., MD; Geoffrey B. Thompson, MD; Clive S. Grant, MD; David R. Farley, MD; Cynthia Leibson, PhD; and Jon A. van Heerden, MD

Background: Hypertension often persists after adrenalectomy for primary aldosteronism.

Objective: To determine factors associated with resolution of hypertension after adrenalectomy for primary aldosteronism.

Design: Retrospective cohort study.

Setting: Tertiary care referral center in Rochester, Minnesota.

Patients: All patients who underwent adrenalectomy for primary aldosteronism between 1 January 1993 and 31 December 1999.

Measurements: Preoperative plasma renin activity, plasma and urinary aldosterone concentrations, and adrenal imaging. Follow-up blood pressure, measured at a clinic visit or at home, was reviewed.

Results: 97 adrenalectomies were performed, and follow-up was available in 93 patients. Hypertension was resolved at follow-up (blood pressure < 140/90 mm Hg) without use of antihyperten-

sive agents in 31 of 93 patients (33%). According to a stepwise multivariable logistic regression analysis adjusted for duration of follow-up, resolution of hypertension was independently associated with family history of hypertension in no more than 1 first-degree relative (odds ratio [OR], 10.9; $P < 0.001$) and preoperative use of two or fewer antihypertensive agents (OR, 4.7; $P = 0.005$). Additional factors associated with resolution of hypertension based on univariate analysis included younger age, shorter duration of hypertension, higher preoperative ratio of plasma aldosterone concentration to plasma renin activity, and higher urine aldosterone level ($P < 0.05$).

Conclusions: Resolution of hypertension after adrenalectomy for primary aldosteronism is independently associated with a lack of family history of hypertension and preoperative use of two or fewer antihypertensive agents.

Ann Intern Med. 2001;135:258-261.

www.annals.org

For author affiliations, current addresses, and contributions, see end of text.



- Medical therapy is the treatment of choice for bilateral adrenal hyperplasia, and patients not fit/unwilling for surgical intervention.
- No placebo-controlled randomized trials have evaluated the efficacy of drugs in the treatment of PH.
- Spironolactone has been the drug of choice to treat PH
- The goal is (a)- achieve high normal K concentration without the aid of K supplements and (b) to antagonize the aldosterone receptors and protect patients from target organ damage.
- spironolactone is not selective for the mineralocorticoid receptor and may antagonize testosterone and progesterone receptors as well.
- Eplerenone is a selective mineralocorticoid receptor antagonist with 0.1 % binding affinity to androgen and < 1% affinity to progesterone receptors.



A double-blind, randomized study comparing the antihypertensive effect of eplerenone and spironolactone in patients with hypertension and evidence of primary aldosteronism

Hari K. Parthasarathy^a, Joel Ménard^b, William B. White^c, William F. Young Jr^d, Gordon H. Williams^e, Bryan Williams^f, Luis Miguel Ruilope^g, Gordon T. McInnes^h, John M. Connellⁱ and Thomas M. MacDonaldⁱ

Background Eplerenone is claimed to be a more selective blocker of the mineralocorticoid receptor than spironolactone being associated with fewer antiandrogenic side-effects. We compared the efficacy, safety and tolerability of eplerenone versus spironolactone in patients with hypertension associated with primary aldosteronism.

Methods The study was multicentre, randomized, double-blind, active-controlled, and parallel group design. Following a single-blind, placebo run-in period, patients were randomized 1:1 to a 16-week double-blind, treatment period of spironolactone (75–225 mg once daily) or eplerenone (100–300 mg once daily) using a titration-to-effect design. To be randomized, patients had to meet biochemical criteria for primary aldosteronism and have a seated DBP at least 90 mmHg and less than 120 mmHg and SBP less than 200 mmHg. The primary efficacy endpoint was the antihypertensive effect of eplerenone versus spironolactone to establish noninferiority of eplerenone in the mean change from baseline in seated DBP.

Results Changes from baseline in DBP were less on eplerenone (-5.6 ± 1.3 SE mmHg) than spironolactone (-12.5 ± 1.3 SE mmHg) [difference, -6.9 mmHg (-10.6 , -3.3); $P < 0.001$]. Although there were no significant differences between eplerenone and spironolactone in the overall incidence of adverse events, more patients randomized to spironolactone developed male gynaecomastia (21.2 versus 4.5%; $P = 0.033$) and female mastodynia (21.1 versus 0.0%; $P = 0.026$).

Conclusion The antihypertensive effect of spironolactone was significantly greater than that of eplerenone in hypertension associated with primary aldosteronism. *J Hypertens* 29:980–990 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Journal of Hypertension 2011, 29:980–990

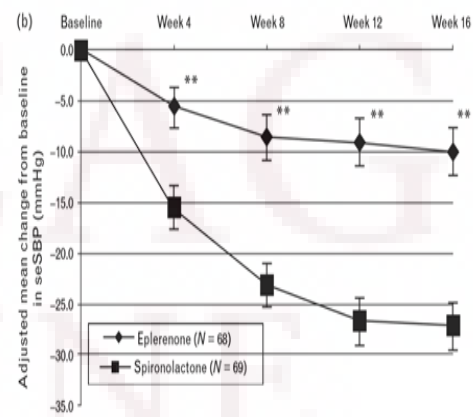
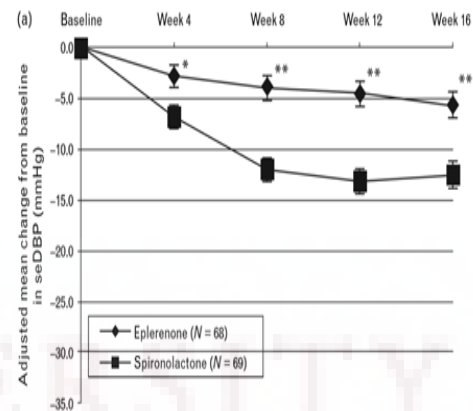
Keywords: aldosteronism, eplerenone, hypertension, spironolactone, treatment

Abbreviations: ANCOVA, analysis of covariance; BP, blood pressure; EPHEUS, Eplerenone Post-Acute Myocardial Infarction Heart failure Efficacy and Survival Study; IEC, independent ethics committee; IRB, institutional review board; PRA, plasma renin activity; PRO, patient-reported outcomes; QoL, quality of life; RAAS, renin-angiotensin-aldosterone system; RALES, randomised aldactone evaluation study

^aDepartment of Cardiology, Papworth Hospital, Cambridge, UK, ^bCentre d'Investigation Clinique AP-HP/INSERM, Hôpital Européen George Pompidou, Paris-Descartes University, Paris, France, ^cDivision of Hypertension and Clinical Pharmacology, Calhoun Cardiology Center, University of Connecticut School of Medicine, Farmington, Connecticut, ^dMayo Clinic, Rochester, Minnesota, ^eBrigham and Women's Hospital, Boston, Massachusetts, USA, ^fDepartment of Cardiovascular Sciences and NIHR Cardiovascular Biomedical Research Unit, University of Leicester, Leicester, UK, ^gHosp Doce De Octubre, Cta De Andalucía, Madrid, Spain, ^hWestern Infirmary, Glasgow and ⁱNinewells Hospital and Medical School, University of Dundee, Dundee, UK

Correspondence to Professor Thomas M. MacDonald, Professor of Clinical Pharmacology, Division of Medical Sciences, Ninewells Hospital and Medical School, University of Dundee, Dundee DD1 9SY, UK
Tel: +44 1382 632575; fax: +44 1382 642637;
e-mail: tom@memo.dundee.ac.uk

Received 25 October 2010 Revised 5 January 2011
Accepted 3 February 2011



(a) Mean change from baseline in DBP at each time point. *Statistically significant difference versus spironolactone at $P = 0.011$, ** $P < 0.001$.
(b) Mean change from baseline in SBP at each time point. **Statistically significant difference versus spironolactone ($P \leq 0.001$).

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.



- PH is uncommon during pregnancy with few cases reported in the literature.
- PH can lead to intrauterine growth retardation, preterm delivery and intrauterine fetal demise.
- The diagnostic approach is similar to non-pregnant women, however, MRI without gadolinium is the test of choice. CT and AVS should be avoided during pregnancy.
- The degree of the disease may get improved or aggravated during pregnancy because of the balance of other hormones i.e. progesterone and HCG.
- Spironolactone crosses the placenta and is an FDA category C, because of feminization of newborn male rats, while eplerenone is category B. Nonetheless, it should be cautiously considered.



Take home points :

- PH is not uncommon disease and physicians should always have high suspicion.
- Hypokalemia is NOT a primary criterion to consider work ups.
- The goal of medical therapy and the possibility of persistent hypertension after surgery should be discussed in details with patients.



- References :

- 1 **J.W. Conn:** Presidential address. I. Painting background. II. Primary aldosteronism, a new clinical syndrome. *J Lab Clin Med.* 45:3-17 1955 [PMID: 13233623](#)
- 2 **J.W. Funder:** Genetics of primary aldosteronism. *Front Horm Res.* 43:70-78 2014 [PMID: 24943299](#)
- 3 **L.M. Fishman, O. Kuchel, G.W. Liddle, A.M. Michelakis, R.D. Gordon, W.T. Chick:** Incidence of primary aldosteronism uncomplicated “essential” hypertension. A prospective study with elevated aldosterone secretion and suppressed plasma renin activity used as diagnostic criteria. *JAMA.* 205:497-502 1968 [PMID: 5695306](#)
- 4 **N.M. Kaplan:** Hypokalemia in the hypertensive patient, with observations on the incidence of primary aldosteronism. *Ann Intern Med.* 66:1079-1090 1967 [PMID: 6027943](#)
- 5 **G.S. Andersen, D.B. Toftdahl, J.O. Lund, S. Strandgaard, P.E. Nielsen:** The incidence rate of pheochromocytoma and Conn’s syndrome in Denmark, 1977-1981. *J Hum Hypertens.* 2:187-189 1988 [PMID: 3236322](#)
- 6 **G. Berglund, O. Andersson, L. Wilhelmsen:** Prevalence of primary and secondary hypertension: studies in a random population sample. *Br Med J.* 2:554-556 1976 [PMID: 963430](#)
- 7 **D.H. Streeten, N. Tomycz, G.H. Anderson:** Reliability of screening methods for the diagnosis of primary aldosteronism. *Am J Med.* 67:403-413 1979 [PMID: 474586](#)
- 8 **R.M. Tucker, D.R. Labarthe:** Frequency of surgical treatment for hypertension in adults at the Mayo Clinic from 1973 through 1975. *Mayo Clin Proc.* 52 1977 549-545
- 9 **A.M. Sinclair, C.G. Isles, I. Brown, H. Cameron, G.D. Murray, J.W. Robertson:** Secondary hypertension in a blood pressure clinic. *Arch Intern Med.* 147:1289-1293 1987 [PMID: 3606286](#)

