

Case Report

Primary Aldosteronism Masquerading as Pregnancy-Induced Hypertension ; A Case-based Review

Ravindu K. A. N¹, Antonypillai C. N¹, Gajaweera G. M¹

¹ Diabetes and Endocrinology Unit, National Hospital, Kandy, Sri Lanka.

Abstract

Primary aldosteronism (PA) encompasses a heterogeneous group of disorders which is characterized by autonomous excessive aldosterone production resulting in low-renin hypertension. Rarely, PA might manifest as gestational hypertension for the first time because pregnancy related hormonal changes could unmask pre-existing subclinical PA. The data are sparse on prevalence, diagnosis and management of PA during pregnancy. We present a case of a 31-year-old previously normotensive woman who was diagnosed with gestational hypertension at 27th week of her second pregnancy with persistent hypokalaemia and metabolic alkalosis. She underwent emergency lower segment Caesarean section at 36th week of gestation due to inadequate control of blood pressure (BP). Her endocrine workup revealed an elevated plasma aldosterone concentration (PAC) and suppressed plasma renin concentration (PRC). The PAC to PRC ratio was markedly elevated, which is highly suggestive of primary aldosteronism and supports the diagnosis. Adrenal imaging with contrast enhanced computed tomography (CECT) revealed a right adrenal adenoma. So, at eighth week of postpartum, right side laparoscopic adrenalectomy was performed. Her potassium level normalised within a week and she became normotensive in three months. So, we suggest that PA must be considered even in gestational hypertension cases with atypical features.

Keywords: primary aldosteronism, hypertension, pregnancy, adrenalectomy

Correspondence email: nishanravindu@yahoo.com

ORCID ID: <https://orcid.org/0000-0003-1697-1285>

Copyright: This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited. (CC BY 4.0)

Introduction

Hypertensive disorders in pregnancy can be classified as either chronic nonpregnancy-related hypertension or pregnancy-induced hypertension (PIH)/Gestational hypertension which manifests after the 20th week of gestation in a previously normotensive woman. Rarely, primary aldosteronism (PA) - the leading endocrine cause of secondary hypertension, characterized by excessive aldosterone production leading to sodium retention and low-renin hypertension - might manifest for the first time as PIH. Data on the prevalence, diagnosis and management of PA during pregnancy are sparse. And diagnosing PA during pregnancy is particularly challenging due to pregnancy induced changes of renin-angiotensin-aldosterone system (RAAS) and overlapping clinical features with PIH.

Case Presentation

A 31-year-old previously normotensive woman with an uncomplicated first pregnancy was diagnosed with gestational hypertension at 27 weeks of her second pregnancy. She had stage 2 hypertension (Systolic blood pressure 160-179 mmHg / Diastolic blood pressure 100 - 109 mmHg) without evidence of hypertension mediated organ damage at the time of diagnosis.

Her hypertension responded and dropped to 130/90 mmHg after two weeks of treatment with oral labetalol 100mg three times a day (tds) and oral methyldopa 250mg mane. However, it did not remain controlled for long. At 33rd week of gestation, despite good treatment compliance, her blood pressure was 160/100 mmHg, prompting an increase in labetalol dose to 200mg tds. A week later, her blood pressure was still 190/130 mmHg. So, she was investigated for secondary causes of hypertension. Her serum creatinine was normal. The ultrasound scan of abdomen and pelvis plus bilateral renal arterial doppler were normal. Urine analysis revealed no proteinuria. However, the striking finding was persistent hypokalaemia (serum potassium level of 2.8 mmol/l) and metabolic alkalosis (serum bicarbonate level of 32 mEq/l). Hence, she was referred for the endocrinological evaluation. Meanwhile, as her blood pressure remained consistently elevated (160/100-180/110 mmHg) despite treatment with labetalol 400 mg tds and methyldopa 500 mg tds, an emergency lower segment Caesarean section was performed at 36 weeks of gestation, even in the absence of clinical or biochemical features of pre-eclampsia. The baby weighed 2.4 kg at birth and experienced an uncomplicated neonatal period. Nonetheless, there was no improvement in blood pressure even after the delivery. And, she complained of occasional episodes of muscle cramps.

Although she presented as PIH, her intermittent hypokalemic symptoms, the persistence of uncontrolled hypertension during postpartum and the presence of hypokalaemia & metabolic alkalosis raised concerns for an alternative diagnosis. Further investigations were carried out to explore the underlying cause. First, the antihypertensives were revised to the agents with negligible interference to plasma aldosterone, renin assay and urinary metanephrine assay. Then, her potassium was corrected and kept around 4 mmol/l prior to aldosterone/renin measurement.

Endocrine workup at third week of postpartum, revealed an elevated plasma aldosterone concentration (PAC) of 18.74 ng/dl (reference range: 3-16 ng/dl in supine position) with suppressed plasma renin concentration (PRC) of 1.0 mIU/l (reference range: 3.1-41 mIU/l in supine position). The PAC to PRC ratio was markedly elevated at 18.7 ngdl-1/ mIU/l (reference range: < 3.7), suggestive of PA. Her 24-hour urinary fractionated metanephrine level was 0.36 mg (<1mg/24 hrs) and she had suppressed cortisol level (<50 nmol/l) following 1 mg overnight dexamethasone suppression. Confirmatory testing for PA with saline infusion test was performed. PAC was 30.3 ng/dl (>10) after intravenous saline infusion. This confirmed the diagnosis of PA. Adrenal imaging with contrast enhanced computed tomography (CECT) revealed a 1.5 cm × 1.1 cm × 1.0 cm mass in the right adrenal gland with imaging characteristics consistent with a benign adrenal adenoma. Since she was less than 35 years old, we could confidently infer that the right sided aldosterone producing adenoma was the culprit for her hypertension and lateralisation study was not required.

At eighth week of postpartum she underwent right side laparoscopic adrenalectomy. On post operative day 2, PAC was measured to assess for cure. It was 2.1 ng/dl which was significantly lower than the preoperative value (18.7), favouring satisfactory long-term outcome. It further confirmed our preoperative subtyping of primary aldosteronism; right side aldosterone producing adenoma. The histology revealed benign adrenocortical adenoma arising from zona fasciculata, positive for melan A and inhibin, and negative for chromogranin. Postoperatively, serum potassium normalized within a week, and blood pressure gradually returned to normal over three months. She remains normotensive at one-year follow-up.

Discussion

Despite a high prevalence documented in research studies, primary aldosteronism is still an underdiagnosed secondary cause for hypertension in adults^[1]. Considering the prevalence data of PA in general hypertensive population, Riester et al. speculated that 0.6–0.8% of all pregnant women would suffer from PA^[2]. Nevertheless, since the first report described by Crane et al. in 1964^[3], excluding familial forms, less than 80 cases of pregnant women with PA have been reported so far, probably due to the low case detection rate^[2,4,5].

In pregnancy, there is a physiological upregulation of the RAAS^[6,7]. It is demonstrated that plasma aldosterone levels are tenfold higher than baseline by the end of pregnancy, resulting in sodium retention and fluid overload, essential to obtain adequate placental perfusion^[8]. Despite this marked rise, normal pregnant women do not show features of hyperaldosteronism because of the antagonistic action of progesterone^[9,10]. There are several hypotheses which describe mechanisms of PA development or unmasking during

pregnancy. Several studies have proven that there could be a potential relationship between gonadotropin stimulation and aldosterone overproduction. It has been shown that in pregnant women with aldosterone producing adenomas, there is an overexpression of aberrant luteinizing hormone (LH) and/or gonadotropin releasing hormone (GnRH) receptors that might lead to aldosterone overproduction in the presence of high levels of human chorionic gonadotropin (hCG), disclosing or triggering symptomatic PA during pregnancy in previously asymptomatic normotensive women^[11-14]. In addition to that aldosterone producing adenomas express higher levels of prolactin receptors, suggesting a stimulatory role of elevated prolactin on adenoma during gestation and postpartum^[15]. Peripartum drop of progesterone and rise in prolactin explain why some patients develop severe hypertension immediately postpartum^[16,17]. However, we were unable to assess for aberrant receptor expression in histological specimen due to limited facilities.

The course of PA in pregnancy is heterogeneous. Pregnancy can either worsen primary aldosteronism induced hypertension and hypokalaemia or settle it^[18-20]. This variable effect is due to the cumulative effect of progesterone and aldosterone actions. If progesterone is high enough to mitigate the effects of aldosterone, which is the case in most milder cases of PA, the hypertension control gets better^[20]. Nezu et al reported 2 women who had virtually uneventful gestational period, developing progressive postpartum hypertension due to PA^[21]. Both might have had primary aldosteronism concealed by pregnancy, that eventually caused unexpected severe hypertension in the postpartum period.

In severe cases of PA where aldosterone levels are well above the normal pregnancy related limits, progesterone cannot counterbalance the effects of hyperaldosteronism. So, we believe that the above mechanism has unmasked our patient's pre-existing subclinical PA during the pregnancy. Our case study corroborates the findings of the previously reviewed literature which have shown that the majority of the cases has associated with progressive hypertension during pregnancy, some warranting urgent surgical intervention. As opposed to nonpregnant adult PA patients whose usual subtype is bilateral idiopathic adrenal hyperplasia, pregnant patients with PA had unilateral aldosterone producing adenoma in most cases^[22,23].

In literature, higher incidence of pregnancy-associated maternal complications is reported in PA than general obstetric population. Preeclampsia, in particular was observed in one third of pregnancies with PA. We were able to deliver the baby before our patient develops such detrimental complications. In 2022, Foresteiro et al. reviewed nearly 80 case reports with PA in pregnancy and they found that almost half of pregnancies developed pre-term birth, with a mean period of gestation at delivery of 33 weeks, while caesarean section for either uncontrolled hypertension, severe intra-uterine growth restriction (IUGR) or maternal complications was performed in half of the cases^[24]. Likewise, in our patient, delivery was expedited due to uncontrolled hypertension. But she tolerated the pregnancy until 36th week of gestation.

Screening protocol for PA in pregnancy is not different to nonpregnant adults. But the pregnancy specific cut-offs for plasma aldosterone and renin concentrations are lacking. Confirmatory testing and subtype evaluation can be postponed to postpartum in cases where screening detects PA. Currently no recognized guideline recommendations exist for the management of

PA during pregnancy. Spironolactone is contraindicated in pregnancy unless its blood pressure lowering benefit outweighs its anti-androgenic teratogenicity. Eplerenone has satisfactory safety data to use as a valid option for blood pressure control in pregnant PA patients. In young individuals (<35 years) with marked PA and unilateral >1.0 cm adrenal adenoma, unilateral laparoscopic adrenalectomy is the treatment standard for those who wish to pursue this option. In such pregnant patients, performing surgery in the second trimester is recommended because of the lowest risk for foetal and maternal complications^[24,25].

After adrenalectomy, almost all reported cases showed partial clinical response with improvement of BP control and reduction of number of anti-hypertensive drugs, while complete response was achieved in one case (25). So, our case adds to the limited literature on PA in pregnancy, with the notable distinction of achieving complete remission after unilateral adrenalectomy performed postpartum. Unlike previously reported cases where adrenalectomy was conducted during pregnancy, our case highlights the effectiveness of surgical intervention in the postpartum period.

Conclusion

Primary aldosteronism is a rare cause of secondary hypertension during pregnancy. Its clinical presentation can overlap with PIH. In cases where atypical features or persistence of hypokalaemia are present, further investigations should be pursued to exclude alternative diagnoses and to optimise patient's outcome.

References

1. Mulatero P, Monticone S, Deinum J, et al. Genetics, prevalence, screening and confirmation of primary aldosteronism: a position statement and consensus of the Working Group on Endocrine Hypertension of the European Society of Hypertension. *J Hypertens*. 2020;38(10):1919-1928. doi:10.1097/HJT.0000000000002510
2. Rießer A, Reincke M. Progress in primary aldosteronism: mineralocorticoid receptor antagonists and management of primary aldosteronism in pregnancy. *Eur J Endocrinol*. 2015;172(1):R23-R30. doi:10.1530/EJE-14-0444
3. CRANE MG, ANDES JP, HARRIS JJ, SLAIE WG. PRIMARY ALDOSTERONISM IN PREGNANCY. *Obstet Gynecol*. 1964;23:700-708.
4. Zelinka T, Petrák O, Rosa J, Holaj R, Štrauch B, Widimský J Jr. Primary Aldosteronism and Pregnancy. *Kidney Blood Press Res*. 2020;45(2):275-285. doi:10.1159/000506287
5. Vidyasagar S, Kumar S, Morton A. Screening for primary aldosteronism in pregnancy. *Pregnancy Hypertens*. 2021;25:171-171. doi:10.1016/j.preghy.2021.06.005
6. Landau E, Amar L. Primary aldosteronism and pregnancy. *Ann Endocrinol (Paris)*. 2016;77(2):148-160. doi:10.1016/j.ando.2016.04.009
7. Monticone S, Auchus RJ, Rainey WE. Adrenal disorders in pregnancy. *Nat Rev Endocrinol*. 2012;8(11):668-678. doi:10.1038/nrendo.2012.155
8. Wilson M, Morganti AA, Zervoudakis I, et al. Blood pressure, the renin-aldosterone system and sex steroids throughout normal pregnancy. *Am J Med*. 1980;68(1):97-101. doi:10.1016/0002-9343(80)90178-3
9. Pirani BB, Campbell DM, MacGillivray I. Plasma volume in normal first pregnancy. *J Obstet Gynaecol Br Commw*. 1973;80(10):884-887. doi:10.1111/j.1471-0528.1973.tb02146.x
10. Ronconi V, Turehi F, Zennaro MC, Boscaro M, Giacchetti G. Progesterone increase counteracts aldosterone action in a pregnant woman with primary aldosteronism. *Clin Endocrinol (Oxf)*. 2011;74(2):278-279. doi:10.1111/j.1365-2265.2010.03901.x
11. Sauer-Amigh K, Mayhew BA, Mantero F, et al. Elevated expression of luteinizing hormone receptor in aldosterone producing adenomas. *J Clin Endocrinol Metab*. 2006;91(3):1136-1142. doi:10.1210/jc.2005-1298
12. Zwermann O, Sittmann Y, Bidlingmaier M, Beuschlein F, Reincke M. Screening for membrane hormone receptor expression in primary aldosteronism. *Eur J Endocrinol*. 2009;160(3):143-151. doi:10.1530/EJE-08-0711
13. Albiger NM, Sartorato P, Mariniello R, et al. A case of primary aldosteronism in pregnancy: do LH and GnRH receptors have a potential role in regulating aldosterone secretion? *Eur J Endocrinol*. 2011;164(3):405-412. doi:10.1530/EJE-10-0879
14. Teo AE, Garg S, Shaikh LH, et al. Pregnancy, Primary Aldosteronism, and Adrenal CYP11B1 Mutations. *N Engl J Med*. 2015;373(15):1429-1436. doi:10.1056/NEJMoa1504869
15. Williams TA, Dietz AS, Theodoropoulou M, et al. Coexisting Prolactinoma and Primary Aldosteronism: Is There a Pathophysiological Link? *J Clin Endocrinol Metab*. 2015;100(9):11263-11269. doi:10.1210/jc.2015-2422
16. Ohara N, Kobayashi M, Yoneoka Y, et al. Primary Aldosteronism Presenting with Hypertension Five Days after Delivery: A Case Report and Literature Review. *Intern Med*. 2022;61(4):507-512. doi:10.2169/internalmedicine.1178-21
17. Hu Y, Ding Y, Yang M, Xiang Z. Serum prolactin levels across pregnancy and the establishment of reference intervals. *Clin Chem Lab Med*. 2018;56(5):838-842. doi:10.1515/clin-2017-0641
18. Biglieri LG, Slaton PE Jr. Pregnancy and primary aldosteronism. *J Clin Endocrinol Metab*. 1967;27(11):1628-1632. doi:10.1210/jcem-27-11-1628
19. Aoi W, Doi Y, Tasaki S, Mitsuoka T, Suzuki S, Hashiba K. Primary aldosteronism aggravated during peripartum period. *Jpn Heart J*. 1978;19(6):946-953. doi:10.1536/jhj.19.946
20. Murakami T, Watanabe Ogura E, Tanaka Y, Yamamoto M. High blood pressure lowered by pregnancy. *Lancet*. 2000;356(9246):1980. doi:10.1016/s0140-6736(00)03311-0
21. Nezu M, Mura Y, Noshiro T, Inoue M. Primary aldosteronism as a cause of severe postpartum hypertension in two women. *Am J Obstet Gynecol*. 2000;182(3):745-746. doi:10.1067/jmob.2000.104229
22. Matsumoto J, Miyake H, Iozaki T, Koshino T, Araki T. Primary aldosteronism in pregnancy. *J Nippon Med Sch*. 2000;67(4):275-279. doi:10.1272/jnms.67.275
23. Bretherton I, Pattison D, Pattison S, Varadarajan S. An Endocrine Cause of Acute Post-partum Hypertension. *Obstet Med*. 2013;6(1):30-32. doi:10.1258/OM.2012.120012
24. Foresiero V, Sconfienza L, Mulatero P, Monticone S. Primary aldosteronism in pregnancy. *Rev Endocr Metab Disord*. 2023;24(1):39-48. doi:10.1007/s11154-022-09720-6
25. Shukhar S, Haykal R, Kamilaris C, Stratakis CA, Hannah Shmouni E. Curative resection of an aldosteronoma causing primary aldosteronism in the second trimester of pregnancy [published online ahead of print, 2020 Aug 4]. *Endocrinol Diabetes Metab Case Rep*. 2020;2020:20-0043. doi:10.1530/EDM-20-0043