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CONNed in Pregnancy

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CLINICAL–PATHOLOGICAL CONFERENCE

CONNed in Pregnancy

Spoorthy Kulkarni, Anna F. Dominiczak, Rhian M. Touyz, J. David Spence, Daniel Batlle, Mohammed Barigou, Morris Brown, Robert M. Carey, Fernando Elijovich, Sandra Taler, Ian B. Wilkinson

A 29-year-old patient, primigravida, at 15 weeks of gestation presenting with symptoms of sickness, palpitations, and shortness of breath, was referred from the maternity unit. She also had severe headache with photophobia, which was unrelieved by administration of paracetamol. Her shortness of breath had gradually worsened over the past few weeks, and she had episodes of orthopnea intermittently for 1 week. Initial assessment included blood pressure of 180/103 mm Hg and a normal pulse rate. She was dehydrated, and her urine tested negative for protein but positive for ketones. In the maternity unit, she had been treated with intravenous fluids, with a presumed diagnosis of hyperemesis gravidarum. The intravenous fluids aggravated her shortness of breath. On reviewing her medical history during prepregnancy and pregnancy, we noticed a normal blood pressure recording of 120/80 mm Hg at her first antenatal visit and a normal first trimester scan at 11 weeks. There were no records of blood pressure measurement before pregnancy, and she could not remember the time of last measurement.

She had symptoms of mild shortness of breath and intermittent palpitations since the beginning of this pregnancy. This had not affected her activities of daily living until 14 weeks, but she had discussed this with her general practitioner, who had in turn referred her to the cardiology team. At 14 weeks of gestation, which was a week before she presented to us, she had gone to a local hospital with symptoms of nausea and shortness of breath. Her blood pressure during that assessment was noted to be 150/90 mm Hg, and her potassium was slightly reduced (3.3 mmol/L). A diagnosis of pulmonary embolism was considered at that time, and in view of D-dimer she was discharged with further follow-up arranged and was prescribed oral potassium supplements. She was awaiting further tests and appointments with the cardiology team. She had no family history of congenital or other cardiac conditions, hypertension, preeclampsia, or any other cardiovascular complications. She had no history of hypertension or significant past medical history and was not on any regular medications.

On physical examination during current admission, she looked unwell. Her oral cavity looked dry on examination. Observations revealed normal temperature, high respiratory rate of 24 bpm, and high blood pressure of 220/113 mm Hg, equal in both arms. She had peripheral edema up to the knees and a jugular venous pressure of 6 cm above sternal angle along with bilateral crackles at both lung bases. Auscultation revealed a flow systolic murmur. Ophthalmoscopic examination showed bilateral papilledema. Her body mass index was in the overweight range, but there were no stigmata of Cushing disease, acromegaly, or any other secondary cause of hypertension.

A point of care investigation, including a renal blood profile revealed metabolic alkalosis, with profound hypokalemia at 1.7 to 2.3 mmol/L and the N-terminal pro–B-type natriuretic peptide elevated at 1493 pg/mL, consistent with the symptoms and signs of heart failure. Her complete blood count, clotting test, kidney function test, liver function test, thyroid function tests, plasma glucose, urine dipstick, and urine protein to creatinine ratio were all normal.

DISCUSSION

Prof. Spence: What were the plasma renin and aldosterone levels?

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Presented in part at the Clinical-Pathological Conference chaired by Anna F. Dominiczak and Rhian Touyz during the virtual event for Hypertension 2020 Scientific Sessions, September 11, 2020. Spoorthy Kulkarni and Ian Wilkinson presented the case and led the discussion.

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Prof. Dominiczak: Yes, well done.

Dr Kulkarni: We were considering this question; however, it takes around 4 to 6 weeks to get those test results in our hospital. We sent the sample after the initial blood test. During this time, she was moved to the intensive care unit for her correction of hypokalemia and management of heart failure and hypertension. ECG showed bifid P waves, right bundle branch block, and mildly elevated QTc (Figure 1).

INITIAL TEST RESULTS

We obtained the 24-hour ECG that her general practitioner had ordered. It showed a low ectopic burden of 1% and short periods of bigeminy and trigeminy. Her chest X-ray showed changes associated with pulmonary edema (Figure 2). She then had a bedside echocardiogram (ECG). The first ECG revealed bi-atrial dilatation with marked left atrial dilation and a low normal ejection fraction of 43%, which improved well with initial diuretic treatment. A repeat echocardiogram showed left ventricle was dilation with good systolic function; an ejection fraction of 60% with marked diastolic dysfunction and normal right ventricular function (Figure 3). We also examined the mitral valve inflow doppler scans, and this image showed a raised ratio of early diastolic filling and late diastolic, which is quite indicative of left ventricular diastolic dysfunction. Left ventricular diastolic dysfunction and atrial dilatation are found in a normal pregnancy, and there is a gray zone of abnormality in terms of ECG, which is usually interpreted in this context. She later had a bedside kidney and adrenal ultrasound, which were normal. The initial findings are summarized in Table.

DISCUSSION

Dr Bali: I would like to inquire about the timing of renin and aldosterone with regard to hypokalemia that was profound.

Dr Kulkarni: We knew that the results of renin and aldosterone at that point will be affected by multiple factors; therefore, we sent 2 sets of renin-aldosterone: the first value was sent on admission and the second value after correction of hypokalemia. It took 48 to 72 hours to stabilize her potassium levels, and this was achieved with a combination of intravenous and oral potassium replacement.

Prof. Spence: The serum potassium is not indicative of that in the whole body. The serum potassium can be rectified, and the whole-body potassium can still be low; therefore, we need to pay attention to whether renin is low and aldosterone is high, and not the potassium balance.

Dr Batlle: Considering the blood gas, for the international audience who are more familiar with reporting the pCO_2 in mm Hg rather than KPa, I did a quick calculation. The reported value of 4.7 kPa translates into 35.2 mm Hg (multiplying by 7.5).

Prof. Dominiczak: We are aware of this difference, but we live in an SI system country. The presenters and 2 chairs are from the United Kingdom, and we apologize profusely for any misrepresentation of data.

Dr Batlle: This is not a problem; with the calculations, we can obtain satisfactory results for all the participants. With the relatively low PCO_2 in venous blood, we can assume that it would be much lower in arterial blood by ≈5 mm Hg at least. Therefore, there is ongoing respiratory alkalosis, which is expected in pregnancy. Therefore,

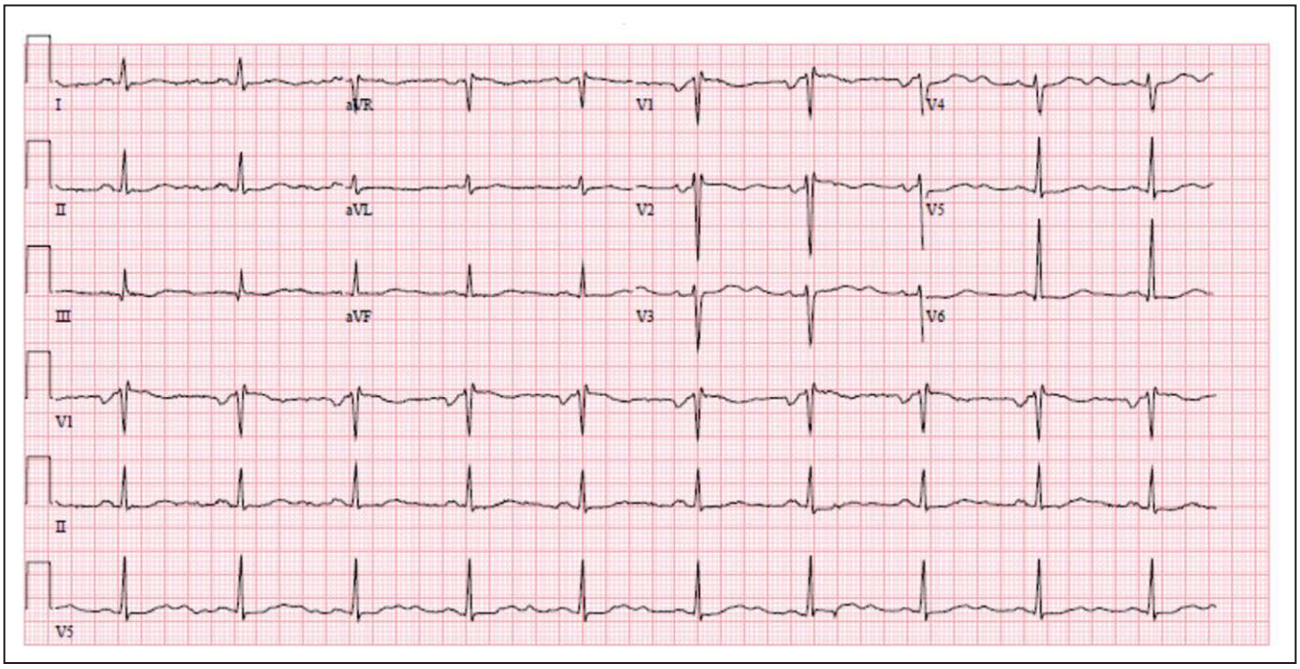

Figure 1. ECG sinus rhythm: Bifid P waves, right bundle branch block, and QTc: 475 ms, U waves.

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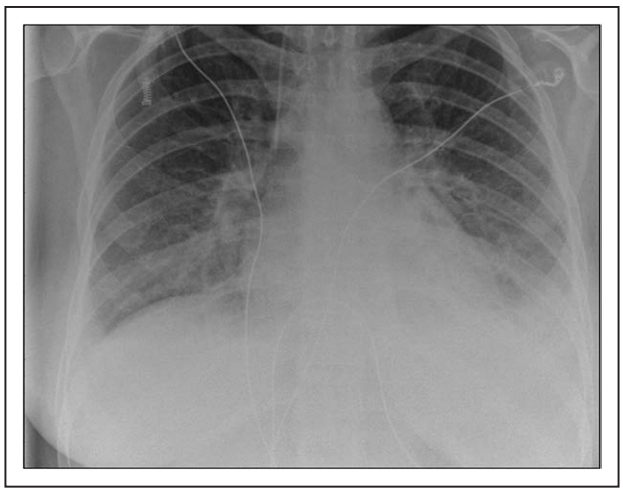

Figure 2. Chest x-ray showing evidence of pulmonary edema.

the appropriate diagnosis here is respiratory and metabolic alkalosis.

Prof. Dominiczak: One more comment from Dr Barigou?

Dr Barigou: We are facing a situation of accelerated hypertension (premalignant hypertension), with a risk of progression to malignant hypertension. I think in this situation it would be suitable not to make an early assessment of the renin-angiotensin system, given the high renin would be associated with such complicated hypertension. We prefer waiting a few days to stabilize the blood pressure and to proceed making accurate measurements of the renin-angiotensin system.

Prof. Touyz: Could you please clarify the ethnic background of the patient?

Dr Kulkarni: She is White.

Prof. Brown: I would perhaps dispute the last comment about the timing of renin and aldosterone measurements.

Dr Kulkarni: I will discuss the renin and aldosterone measurements subsequently. Overall, we have this young woman presenting in her first pregnancy with malignant hypertension, with no history of hypertension. However, she did not have her blood pressure measured before pregnancy and could not remember. The concerns were the new onset heart failure and profound hypokalemia. She had no records of potassium values during prepregnancy or at the first visit in this pregnancy. At this point, I would like to ask the audience their opinions on differential diagnosis on etiological factors that may be responsible for the pathophysiology in this patient.

Prof. Brown: As has already been suggested, the different possibilities are due to a high renin, secondary aldosteronism causing the low potassium, or primary aldosteronism (PA). I would agree that clinically the findings might be in favor of secondary aldosteronism, because the papilledema of accelerated hypertension is unusual in PA. It is also unusual in PA to have sodium levels <140 mmol/L. However, if you are looking for something that is correctable, you should consider PA, and there are several reasons for its presentation in pregnancy. We have described pairs of somatic mutations which together lead to a pregnancy presentation. Therefore, she needs renin and aldosterone measurements immediately.

Prof. Dominiczak: Are there any other differential diagnoses such as malignant hypertension?

Prof. Spence: Besides PA, she could also have one of the Liddle phenotypes, for which there are at least 6 genes that cause low renin and low aldosterone hypertension. I think, most likely, this is PA, but another possibility would be low renin, low aldosterone, Liddle phenotype, for which the treatment would be administration of amiloride, whereas, the treatment for PA would be administration of spironolactone.

Prof. Dominiczak: Yes, but neither of these are indicated for use in pregnancy. Is there anything else that should be considered in this differential diagnosis of heart failure in a 29-year-old woman with no history of cardiovascular disease? How many weeks of pregnancy was she in when she first had high blood pressure?

Dr Kulkarni: She was 14 weeks pregnant when she presented to the local hospital and 15 weeks when she presented to us.

Prof. Dominiczak: This is early to be considered as preeclampsia.

Dr Carey: I want to add and follow-up with Morris Brown's comment. This could be secondary aldosteronism and may fall under the classification of a rapid onset of hypertension in a previously nonhypertensive individual. Renal vascular disease should be considered among the differential diagnoses.

Prof. Dominiczak: Yes, and the preeclampsia at 14 weeks gestation is to be assessed, although it does not abide by the definitions. Are there more differential diagnoses to be considered?

Dr Kulkarni: Yes, although preeclampsia can occur before 20 weeks, this was early, and there were no other associated features with no protein in urine or renal dysfunction of any degree. As suggested, secondary hypertension was highly likely. PA was the most probable among the differential diagnoses. Renal artery stenosis leading to secondary hyperaldosteronism was the second possibility. The other diagnoses included liquorice ingestion, which she denied and pheochromocytoma, since she had headache, palpitations, and raised blood pressure. Occasionally, phaeochromocytoma can present with hypokalemia and heart failure, secondary to crisis. We also considered that hypokalemia here might be a result of malignant hypertension along with hyperemesis. Malignant hypertension is usually associated with secondary activation of renin-angiotensin system leading to intravascular volume depletion. She had been vomiting and was administered fluids intravenously; therefore, we considered it as a contributing factor to the clinical picture. The other

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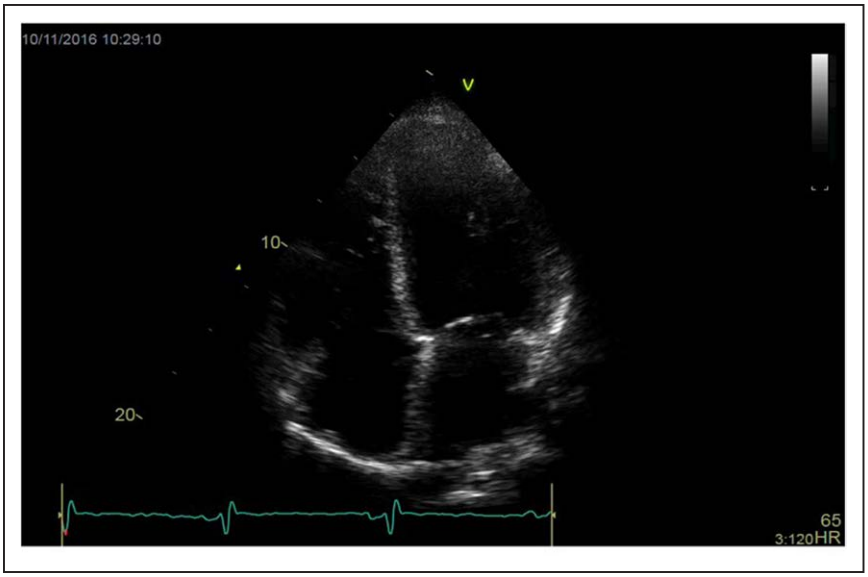

Figure 3. Severely dilated left atrium (LA size 30 cm², LA volume 52 mL/m²; normal value: <34 mL/m²).
Left ventricular dilatation with diastolic dysfunction with normal systolic function.

less likely causes included Cushing syndrome, but she had no signs or symptoms suggesting it. She had gained weight, however, was not obese, had no diabetes mellitus or striae or any other features. We had no other reasons to suggest rare monogenic causes of hypertension, as primarily they are rare, and she had no family history. We were confident that it was not cardiomyopathy based on ECG, but coarctation of aorta presenting in pregnancy was still a possibility.

Dr Luther: If it is low aldosteronism, low renin is also considered, as well as liquorice ingestion or other substances such as some of the antifungals, which she is apparently not on. Also, thyroid disease, I didn't see that excluded yet.

Dr Kulkarni: Her thyroid stimulating hormone levels were normal, and we did not follow it up subsequently.

Dr Elijovich: In a situation with low renin with low aldosterone and hypokalemia, one may assume that something other than aldosterone is stimulating the mineralocorticoid receptor. Because this lady is pregnant, we must remember that progesterone can be the culprit if the patient has the appropriate mutation in the mineralocorticoid receptor. This is a rare cause of hypertension but could be possible in this patient if those were the biochemical findings.

Prof. Dominiczak: Yes and I think, so far, there are only one or 2 families with such mutations reported in the whole world, but yes, it is a differential diagnosis.

Prof. Brown: Yes. Gain of mineralocorticoid receptor function was due to a mutation, which enabled stimulation of the receptor by progesterone elevation during pregnancy, which effectively unmasks the mutation. Geller' syndrome is the name of the condition.

Prof. Dominiczak: Would you expect any family history then, or not necessarily?

Prof. Brown: Yes, but I cannot remember for certain if it is autosomal dominant or recessive.

Prof. Dominiczak: I think it is dominant but rare. I think family history was taken, and there was nothing suggestive of it.

Dr Luther: To comment on the Geller syndrome, the mineralocorticoid receptor activating mutation, the proband was a male. Even though it is called hypertension in pregnancy, family history extends to male members as well.

Prof. Dominiczak: I think we had the richest differential diagnosis discussion in any of our CPS's. I appreciate the effort and contribution.

EVALUATION OF ALDOSTERONE-RENIN RATIO IN PREGNANCY

The provisional diagnosis at this stage was malignant hypertension with hypertensive heart failure in pregnancy, probably secondary to PA. The findings are suggestive of PA because of the profound hypokalemia. The foremost test results based on our differential diagnosis included renin 7 mU/L (normal nonpregnancy range: 5.4–60 mU/L) and aldosterone 2000 pmol/L (normal nonpregnancy range: 90–720 pmol/L). The 24-hour urine-free cortisol, 24-hour urine metanephrines, and plasma metanephrines were normal. In normal pregnancies, a rise in renin and subsequent rise in aldosterone resulting in a secondary hyperaldosteronism state is expected. Another point to consider was a higher value of renin in the context of malignant hypertension. Although renin is in the normal range here, those reference values are not for pregnancy, and although aldosterone was noted to be higher than the upper limit of normal, it can rise to 2 to 4× in pregnancy, reaching sometimes to 10× in normal pregnancy towards the term.

Therefore, overall we had more information, and we could say we were more convinced with our provisional diagnosis, although it was still questionable.

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Table. Summary of Case Presentation

Initial BP, mm Hg	220/113 mm Hg
Presenting symptoms	Palpitations since start of pregnancy, shortness of breath progressed from NYHA class 2 to 4 in a span of 2–3 wk, orthopnea, vomiting
Past medical history	None
Family history	None
Social history	Nonsmoker
Investigations and results	
Examination	Papilledema B/L, raised JVP, bilateral pedal edema, bilateral crepitations at bases, flow systolic murmur at cardiac apex.
Urine dipstick/urine protein creatinine ratio	1+ protein/11 mg/mmol (0–30)
FBC and clotting	WBC–9.5×10⁹/L; RBC–6.20×10⁹/L; Hct–0.337 L/L
	PLT–284×10⁹/L
	Neutrophil count–12.10×10⁹/L
	PT. APTT- normal
Venous blood gas	PH: 7.49 (7.35–7.45)
	K: 1.74 (3.5–5.1 mmol/L)
	Na: 139 (136–145 mmol/L)
	HCO3: 26.6 (22–26 mmol/L)
	pCO2 4.7 kPa
	pO2: 5.5 kPa
	Lactate: 1.7 mmol/L (0.6–1.4 mmol/L)
	Random glucose–7.5 mmol/L
Adjusted calcium	2.20 mmol/L (2.20–2.60 mmol/L)
Magnesium	0.73 (0.7–0.9 mmol/L)
Creatinine	43 (44–97 µmol/L)
Liver function tests	Normal except albumin 25 (35–50 g/L)

APTT indicates activated partial thromboplastin time; B/L, bilateral; BP, blood pressure; FBC, full blood count; HCT, haematocrit; JVP, jugular venous pressure; PLT, platelet count; PT, prothrombin time; NYHA, New York Heart Association; RBC, red blood; and WBC, white cell blood cell.

DISCUSSION

Dr Barigou: Given the physiological stimulation of both renin and aldosterone during pregnancy, is there any specified cutoff values to diagnose PA in pregnant women?

Dr Kulkarni: I could not find any internationally approved predefined cutoff values; however, based on published evidence, there is a suggestion of the ranges that we could use. And these values change with every trimester. The major shifts happen typically towards the third trimester. In normal pregnancies, high renin and high aldosterone is seen, however, the aldosterone-renin ratio is expected to be near normal or low. And here, it seems like aldosterone is still probably in normal range. The renin was probably suppressed given the compelling scenario, and this probably leads to an overall high aldosterone-renin ratio here. Most published literature on these values indicate a relative rise in aldosterone, and unless we knew her prepregnancy renin and aldosterone levels, which is not known, it is difficult to be sure of the diagnosis at this point.

Dr Taler: Therefore, did you measure aldosterone and sodium?

Dr Kulkarni: We cannot undertake 24-hour urine aldosterone test because the assay was not available in our hospitals.

Dr Taler: Ok.

Prof. Dominiczak: Ok.

Dr Cushman: I thought the plasma metanephrine or 24-hour urine metanephrine would be the usual tests for pheochromocytoma; can you enlist the other tests that were performed?

Prof. Dominiczak: Yes and we will examine that further in a minute but a typical set of tests for pheo are presented here.

Dr Elijovich: Although we are not certain about the implication of these levels at this stage of pregnancy, I agree with your assumption that renin is relatively suppressed. This is because even if the elevation of aldosterone was due to pregnancy, renin, which should be driving such an elevation, is not concomitantly increased. Therefore, I think of this situation as a possible autonomous production of aldosterone. The question remains of the method of investigating this possibility.

Dr Kulkarni: We totally agree with that. We need further tests to investigate this.

Prof. Brown: Was the patient on any drug treatment at the time the blood was drawn for measuring renin aldosterone?

Dr Kulkarni: Yes. She was 24 hours into hospitalization and was being administered labetalol.

Prof. Brown: This is highly relevant, because labetalol causes mixed alpha and beta blockade, and beta blockade will markedly suppress renin. You should note the renin to get an idea of what it would have been in the absence of beta blockade. The patients I have seen who definitely have PA in pregnancy have suppressed renin and often a potassium in the 1's or 2's and an aldosterone of 2000 to 4000. So, there is no relevant data here for the diagnosis of PA, especially since now we know of the beta blockade.

Dr Kulkarni: Yes. We agree with that.

FURTHER INVESTIGATIONS: IMAGING

Dr Kulkarni: At this point, she already had cardiac magnetic resonance imaging arranged by her cardiologist. This did not reveal much in terms of cardiac findings. The radiologists also decided to look further down at the adrenal gland in view of possible diagnosis. They highlighted that there was a possible nodule around 12 mm on the superior limb of left adrenal gland. However, the radiologist commented that though on the matched in/out phase imaging of this region, a decrease in the intensity of the signal was seen suggesting some lipid content which is a hallmark of adrenal adenoma, the decrease was not as expected on T2 weighted signal.

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And hence, they could not confirm if it was an adrenal adenoma. Overall impression was indeterminate adrenal lesion, probably adenoma, and no biochemical evidence for pheochromocytoma.

Dr Kulkarni: At that point, this was all the information that we had, and I would like to ask the audience to choose next best management plan for us.

1. Do we confirm the diagnosis with confirmatory test of computed tomography of the adrenal glands with further subtyping?
2. Do we stabilize with medical treatment, monitored closely throughout the pregnancy?
3. Shall we stabilize medically and then proceed to surgery of the adrenal gland?
4. We got the diagnosis wrong, and we should keep looking for causes.

DISCUSSION

Dr Barigou: Currently, I would stabilize the medical treatment and monitor closely throughout the pregnancy. A surgical approach will be high-risk for this patient.

Prof. Spence: Most PA is due to bilateral hyperplasia; hence, excising this nodule is not indicated unless the adrenal vein aldosterone levels clearly lateralize. The treatment is usually administration of spironolactone (or eplerenone for men). Amiloride would be an alternative, but as it does not block the direct effects of aldosterone on the myocardium and the arteries, it would be inferior to aldosterone antagonism in the long-term.

Dr Elijovich: We all seem to agree that the biochemical data suggests autonomous secretion of aldosterone. However, spironolactone treatment in pregnancy is a problem because of the other hormonal effects of the drug. One could consider blocking aldosterone-induced epithelial sodium channel hyperactivity with amiloride instead. Even if it is not primary hyperaldosteronism, amiloride would be an antihypertensive that addresses the likely underlying mechanism of hypertension in this patient. I am not aware of a contraindication for the use of amiloride in pregnancy.

Prof. Brown: Thank you. I agree with amiloride the sodium blocker of choice in pregnancy and spironolactone contraindication because of its effect on the fetus. And in terms of diagnosis, a 12 mm adenoma in the adrenal gland could certainly be causing aldosteronism to result in this condition. And I probably would not agree that most PA presenting at this age is due to bilateral disease. We have not addressed the reason for pregnancy unmasking a cause of severe hypertension and papilledema, and not everything is justified because the renin was not suppressed despite blockade. However, we now have a 12 mm adenoma in the left adrenal gland. Therefore, I would suggest further imaging, probably by magnetic resonance imaging during pregnancy, to try and be certain of the condition in the left adrenal gland and also to investigate Bob Carey's suggestion that it could be a renin artery lesion causing secondary aldosteronism.

Dr Taler: I do not agree because PA is usually masked in pregnancy, and this is in contradiction. The numbers do not agree. I certainly would not recommend any surgery on the adrenal glands during pregnancy, as it does not seem to be severe. Hence, I agree with Dr Brown that we need to evaluate this further.

Dr Carey: Could it be a nonfunctioning adrenal incidentaloma, the prevalence of which is about 7%? I agree with Morris that more investigation is needed.

Dr Serawant: Can we undertake selective aldosterone-renin blood sampling of the adrenal glands?

Prof. Dominiczak: Yes, but this is a pregnant patient. It requires X-ray activity and is contraindicated.

Dr Batlle: I find this case atypical for a PA presentation, and if you want more functional evidence estimating the renin and aldosterone levels, a few times together with the serum potassium levels would help. I say so because we have a case of elevated aldosterone with a mildly suppressed renin, but there are several cases reported where renin is not fully suppressed in primary hyperaldosteronism.

Dr Bali: Amiloride is not a good choice.

Dr Batlle: This case shows the importance of distal sodium delivery in the development of massive hypokalemia. With the modest increase in aldosterone, there is no possibility of this massive hypokalemia, had it not been because sodium was excreted in the urine perhaps as part of the pregnancy. Otherwise, I could not explain such a massive hypokalemia. You need both high distal delivery and high aldosterone for the potassium wastage to be so severe.

Dr Kulkarni: We examined the magnetic resonance imaging for renal artery stenosis the renal arteries and the kidney size were normal. We did not undertake a comprehensive CT scan given the pregnancy. We went with option 2, wherein we stabilized her on medical treatment and monitored her blood pressure and potassium levels.

I will go through her course in pregnancy now (outlined in Figure 4). She was hospitalized until 15 to 16 weeks of gestation; she was in the intensive care unit/high dependency unit for a week, and this was her list of medications at the time of discharge:

1. Furosemide 40 mg OD
2. Labetalol 200 mg TDS
3. Nifedipine 60 mg 24-hour MR OD
4. Amiloride 5 mg OD
5. Oral potassium supplements as needed.

Over the next 2 months (up to 30 weeks gestation), amiloride was increased to 20 mg, and other medications were added, namely, hydralazine 25 mg TDS and isosorbide mononitrate at 29 weeks.

At 30 weeks, she developed breathlessness at rest and reduced fetal movements (despite being on 5

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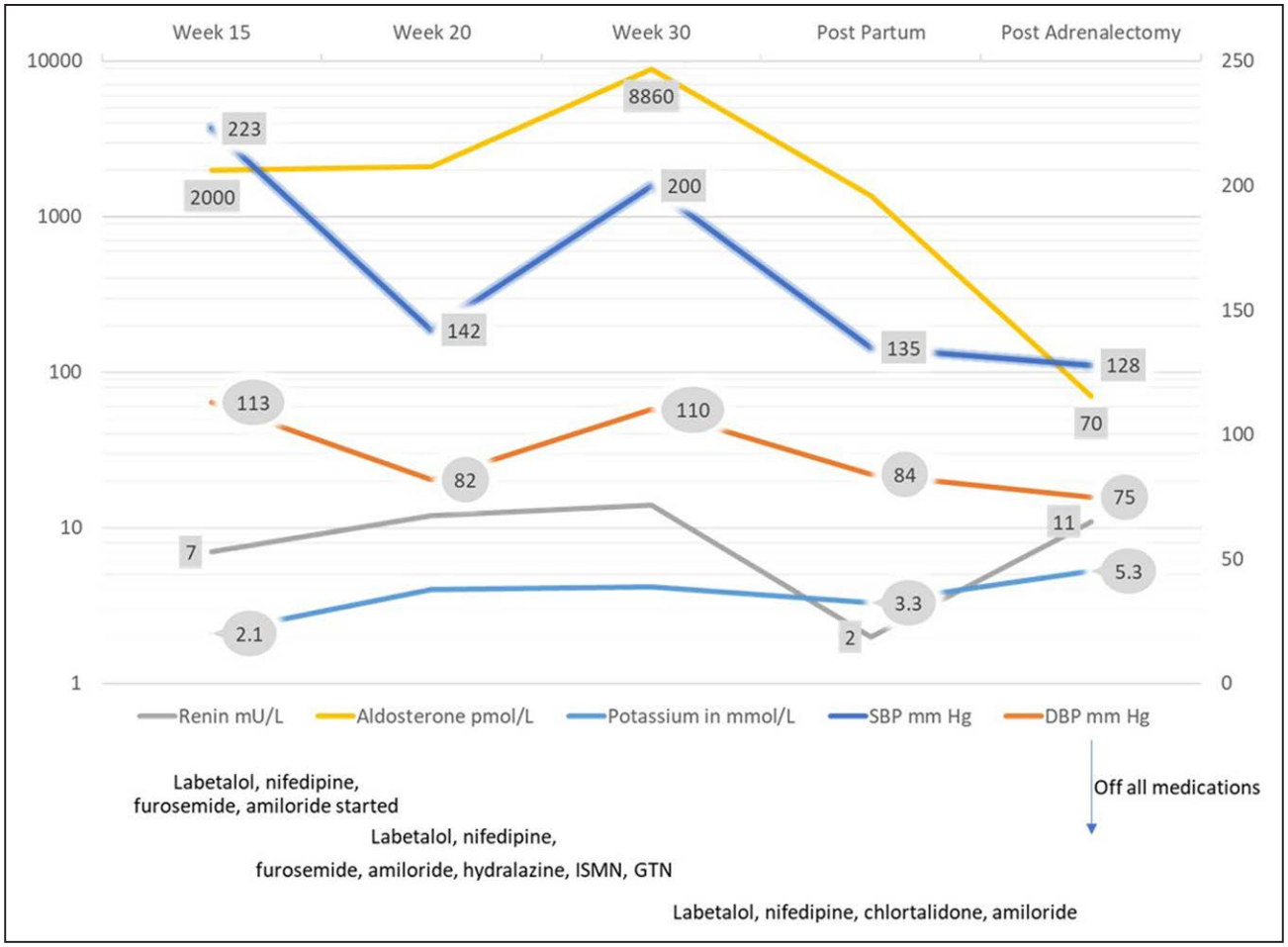

Figure 4. Course in pregnancy.
Trends in blood pressure (BP), renin, aldosterone, and potassium. DBP indicates diastolic blood pressure; GTN, glyceryl tri-nitrate; ISMN, isosorbide mononitrate; and SBP, systolic blood pressure.

antihypertensive agents). She was admitted for heart failure and administered glyceryl-tri-nitrate intravenously.

She was re-evaluated with ECG, which continued to show left ventricular diastolic dysfunction. Her fetal growth scan showed slowing of fetal growth to fifth percentile.

While considering the patient's expectations on a multidisciplinary team discussion involving the obstetrician, cardiologist, anesthetist, and clinical pharmacologist, a decision of semi-urgent C-section was undertaken. She subsequently delivered a premature baby girl weighing 1.2 kg, who recovered well after a period of neonatal intensive care unit admission.

Postpartum: She continued to have hypokalemia, hence was prescribed spironolactone briefly. This was stopped once she started breast-feeding. Her blood pressure and heart failure symptoms remained stable on 5 agents, namely, labetalol, lisinopril, nifedipine long acting, chlorthalidone, and amiloride.

She then had a dedicated adrenal magnetic resonance imaging which showed 1.8 cm diameter adenoma arising from the lateral limb of the left adrenal gland with marked signal decrease on out of phase imaging confirming adenoma (Figure 5). She also underwent adrenal venous sampling, which showed lateralization to the left with a ratio of 74:1.

Approximately at 3 months postpartum, she underwent laparoscopic left adrenalectomy with uneventful postoperative course. Histopathology confirmed presence of an adrenocortical nodule composed predominantly of nests and trabeculae of lipid-rich cells in keeping with an adrenocortical adenoma (Figure 5). Immunohistochemistry and mutation panel of the adenoma were as follows:

CYP11B1: negative CYP11B2: strong positivity

KCNJ5: strong positivity with same distribution as CYP11B2

Mutation panel:

KCNJ5: negative

LH-CGR (luteinizing hormone–chorionic gonadotropin receptor) and

GNRHR (gonadotropin-releasing hormone receptor) expression: negative

CTNNB1: negative

Postoperative: 2 months postadrenalectomy, her BP was normal with stable potassium levels and normalized aldosterone-renin ratio.

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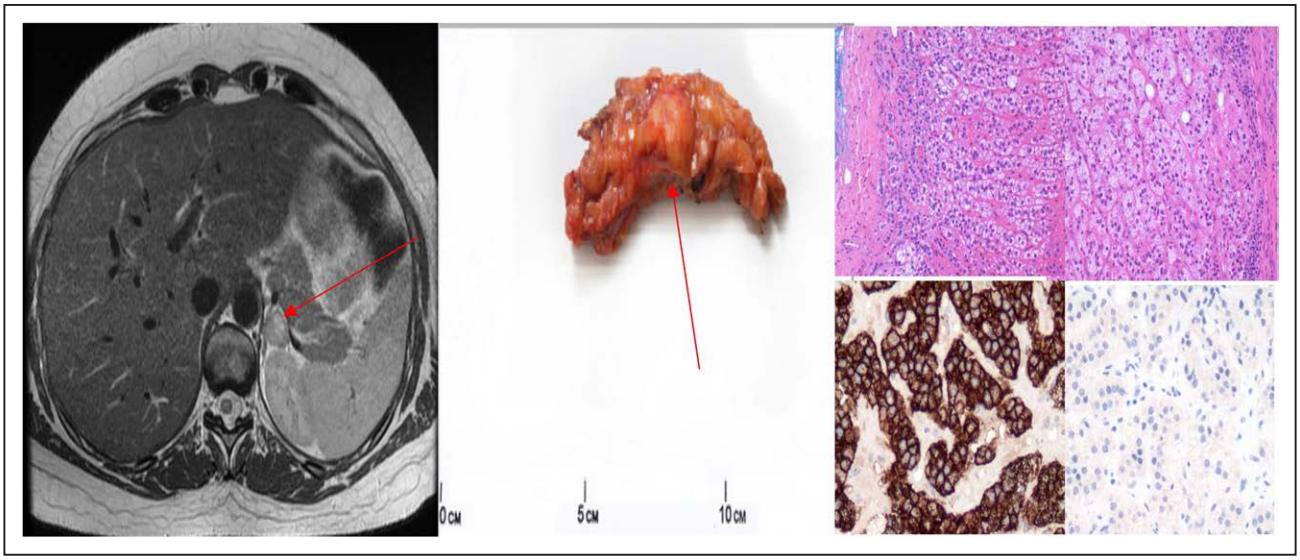

Figure 5. Magnetic resonance imaging adrenal glands showed adrenal adenoma.
Histopathology confirmed adrenal adenoma with typical microscopic and immunohistochemistry features.

The final diagnosis was Conn syndrome, leading to malignant hypertension and heart failure in pregnancy.

CASE REFLECTION

PA affects 5% to 10% of all patients with hypertension. This approximately increases to 20% in treatment-resistant hypertensive patients. It can be extrapolated that ≈0.6% to 0.8% of chronic hypertension associated with pregnancies may be related to PA. More than 50 cases of PA in pregnancy have been published in English literature.[1] Though less common, PA remains a significant factor in maternal and fetal mortality and morbidity. Among the cases described, 3 reports mention pulmonary edema along with PA, with identifiable factors leading to pulmonary edema. Our case is probably one of the atypical cases with presentation in pregnancy, malignant hypertension complicated by heart failure with preserved ejection fraction. The first and foremost challenge as highlighted in the discussion above was the interpretation of renin and aldosterone in pregnancy. There is a lack of reference ranges in pregnancy, specifically at various stages of pregnancy, and more research into alternatives for this test is needed.[2] The second intriguing point, which was brought up in the discussion above was that many published case reports describe worsening of hypertension postpartum rather than during pregnancy.[3] This leads us to believe that there may be 2 distinct phenotypes of PA in pregnancy. The balance between progesterone and aldosterone and the sensitivity of the mineralocorticoid receptors to pregnancy hormones may be some of the contributory factors that determine this.[4] The histological subtype of PA and underlying somatic mutation may also have a role.[5] The third point is about management. Few case histories describe surgical intervention (adrenalectomy) being successfully undertaken during pregnancy, which may be appropriate in some cases[6]; however, this has to be decided on a case-to-case basis. In some of these patients, surgery rendered hypertension more manageable; however, it did not necessarily change the outcome of pregnancy in all patients.[7]

The challenging aspect of managing these patients includes sound prescribing during pregnancy. There is less evidence to define the best strategy for managing hypertensive crisis in pregnancy (outside the context of eclampsia and preeclampsia) associated with PA. There is lack of safety data on the use of mineralocorticoid receptor antagonists in pregnancy. We chose amiloride which blocks the epithelial sodium channel on the bases of the observational safety evidence and experience especially when used for Bartter syndrome/PA in pregnancy.[8,9] Similarly, there are case reports showing that eplerenone can be considered safe in pregnancy[10]; however, the doses needed for efficacious use generally exceeds the licensed dose (≈100 mg), hence we did not choose it. Spironolactone is categorized as FDA category C drug. A single abstract has been published so far reporting spironolactone use in early trimester leading to ambiguous genitalia in the male infant.[11] Multiple other reports show safe use of spironolactone in pregnancy. However, this conflicting evidence and the biological plausibility of the adverse effect make spironolactone less suitable for use in pregnancy. Ultimately, it is the benefit versus risk assessment that determines rational prescribing of drugs during pregnancy.

TAKE HOME MESSAGE

It is important to have a high index of suspicion for diagnosis of PA in patients with hypertension presenting in

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pregnancy. Early diagnosis, personalized management with aggressive blood pressure monitoring, adequate therapy, and an multidisciplinary team approach can ensure good outcomes in the mother and the baby. Further research to understand various phenotypes of PA in pregnancy and improved research/reporting of safety of medications in pregnancy is needed.

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