Research Article

Primary Aldosteronism and Pregnancy

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Keywords

Primary aldosteronism · Hypertension · Pregnancy · Aldosterone · Adrenalectomy

Abstract

Objective: Primary aldosteronism (PA) may present at younger age and may thus complicate pregnancy. Our aim was to identify female patients in whom PA was diagnosed after pregnancy complicated with hypertension and to analyze possible hypertension-related complications during pregnancy. **Methods:** We performed retrospective analysis of female patients with PA diagnosed and treated at our Department who were pregnant before the diagnosis of PA. **Results:** We found 14 patients with PA (age at diagnosis 32.2 ± 4.2 years, hypertension duration 5.4 ± 3.6 years) suffering from hypertension 3 (IQR 0, 4) years before pregnancy (6 patients had hypertension diagnosed during pregnancy). Three subjects were pregnant twice, and 1 patient had been pregnant three times before the final diagnosis of PA was made. Ten subjects delivered by Caesarean section (in 3 cases due to early-onset preeclampsia and 2 subjects due to significantly increased blood pressure), and 9 cases spontaneously (1 subject complicated twice due to late-onset preeclampsia). Preterm delivery occurred in 5 cases – the earliest one in the sixth month of gestation. Subsequent diagnosis of PA (sometimes with a long delay up to a maximum of 12 years) was made on the basis of significantly low potassium values (2.7 ± 0.4 mmol/L; 2 subjects even suffered from muscle cramps) and hypertension (mostly moderate), elevated plasma/serum aldosterone (54.1 ± 20.2 ng/dL) and suppressed plasma renin activity (0.4 ± 0.2 ng/mL/h) or plasma renin (1.9 ± 1.6 ng/L). Thirteen subjects underwent laparoscopic adrenalectomy (in all but 2 cases, diagnosis of a large cortical adenoma [16 ± 5.9 mm] was made), and 1 subject was classified with bilateral hyperplasia accord-

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ing to adrenal venous sampling. Operation normalized BP in 10 subjects and improved BP control in the remaining 3 subjects. Two patients became pregnant after adrenalectomy, and their pregnancies were uneventful. **Conclusion:** PA is associated with a high rate of pregnancy-related complications. The most frequent complication is preeclampsia, in some cases leading to preterm delivery. The optimal prevention of these complications is early diagnosis of PA, and in these particular hypertensive cases, the awareness of hypokalemia.

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Introduction

Primary aldosteronism (PA) was first described by Litynsky [1] in 1953, and 2 years later by Conn. It is currently considered as one of the most common causes of secondary hypertension, with an estimated prevalence of approximately 3–6% in unselected hypertensives [2, 3] and about 20% in subjects with severe hypertension [4]. It is characterized by autonomous aldosterone production with suppressed renin, either from one adrenal (mostly aldosterone-producing adenoma, APA) or from both adrenal glands (mostly bilateral hyperplasia; idiopathic hyperaldosteronism, IHA). It is treated by surgery (unilateral disease) or conservatively with antagonists of mineralocorticoid receptor with subsequent blood pressure (BP) normalization or improvement of hypertension control, depending mostly on patient age, hypertension duration, and severity.

Recent discoveries show that in up to 88% of adenomas, somatic mutations of genes involved in the regulation of aldosterone synthesis may be found: *KCNJ5*, *CACNA1D*, *ATP1A1*, *ATP2B3*, and *CTNNB1* [5]. Mutations of the *KCNJ5* gene are found in approximately 35–50% of APAs and are characterized by excessive hypokalemia, large tumors, and occur more frequently in Asian females and younger subjects [6].

Hypertension may complicate about 10% of pregnancies. We can therefore speculate that PA may occur in pregnancy more frequently than previously anticipated. In pregnancy, not only all components of the renin angiotensin aldosterone system (RAAS) increase, but also other hormones, such as estrogen or progesterone, which counteract aldosterone action on the mineralocorticoid receptor [7]. All these facts may lead to an unpredictable course of PA during pregnancy, with subsequent BP deterioration.

As case reports or review papers to date have only been focused on PA during pregnancy, our aim was to search for the pregnancy course in female subjects who had diagnosed hypertension either before or during pregnancy and who had subsequently diagnosed PA either as APA or IHA at our institution.

Methods

For the purpose of this study, we retrospectively reviewed the electronic database of subjects with diagnosed PA in our Hypertension Center, with the following criteria: female gender and diagnosis of hypertension before or during pregnancy. The main reasons for suspected PA were hypokalemia and hypertension.

Diagnosis of PA

Diagnosis of PA was made based on an elevated aldosterone to renin ratio, with elevated plasma (serum) aldosterone level and suppressed plasma renin activity values or plasma renin levels. For the diagnosis of PA, plasma renin activity was used until 2012, when it was substituted by direct renin measurement [8]. All subjects were switched for at least 2 weeks

(in the case of spironolactone, 6 weeks) to antihypertensive treatment with verapamil or doxazosin before hormonal testing (serum aldosterone was measured either by commercial RIA or chemiluminescence immunoassay, plasma renin activity by RIA assay, and plasma renin either by RIA or later by chemiluminescence immunoassay). Computed tomography was used for morphological examination of the adrenal glands. In 5 cases, adrenal venous sampling was performed to differentiate between uni- and bilateral forms of PA due to ambiguous finding on CT. Patients with the unilateral disease were scheduled for laparoscopic adrenalectomy, except for 1 patient diagnosed in 1999, in whom open adrenalectomy was performed. Diagnosis of APA was confirmed by histopathology in all subjects who underwent adrenalectomy and further by normalization of kalemia, aldosterone to renin ratio, and either improvement or normalization of BP postoperatively [9]. Hormonal reevaluation was performed mostly immediately postoperatively; BP was checked within 6–12 months postoperatively, either by direct contact or at least by telephonic interview. Three adenomas were subjected to mutational analysis of the *KCNJ5* gene.

Pregnancy-Related Complications

Delivery reports from the maternity hospital were used for evaluation of the pregnancy course (pregnancy-related complications: intrauterine growth restriction, preeclampsia), and a detailed pregnancy history was obtained from each subject. Hypertension was evaluated as chronic if occurring until week 20 of pregnancy. Hypertension occurring after 20 weeks of gestation was referred to as gestational hypertension [10]. We considered preeclampsia to be early onset if it occurred before 34 weeks, and late onset if it occurred after week 34 of gestation [11].

Results

Baseline and Hormonal Characteristics

We identified a total of 14 female patients with PA who presented with hypertension either before or during pregnancy (Table 1). A detailed description of each case is shown in the online supplementary material (see www.karger.com/doi/10.1159/000506287 for all online suppl. material). At the time of PA diagnosis, patients were 32.2 ± 4.2 years old and had suffered from hypertension for 5.4 ± 3.6 years. The longest interval from the diagnosis of hypertension and the diagnosis of APA was 12 years, the shortest was 5 months. All but 1 subject presented with severe hypokalemia (2.7 ± 0.4 mmol/L; the lowest was 1.75 mmol/L). Eight subjects suffered from hypokalemia-related symptoms, mostly muscle weakness or fatigue. Two subjects presented with muscle cramps before the diagnosis of PA was made (patients #2, #3 with rhabdomyolysis). Nine subjects presented with moderate hypertension, 3 with severe hypertension and the remaining 2 subjects with mild hypertension.

Hormonal analysis revealed markedly elevated serum aldosterone values and suppressed either plasma renin or plasma renin activity values in all subjects. The final diagnosis of PA in 13 cases was APA, and in 1 subject IHA. Microadenoma was found in only 2 subjects (#8, #10); macroadenoma (the largest tumor diameter was 25 mm) was diagnosed in the remaining 11 subjects. After tumor removal, plasma potassium values and aldosterone to renin ratio normalized in all subjects. Hypertension improved in 3 subjects and, in the remaining 10 subjects, BP levels normalized (Table 1).

Pregnancy-Related Complications

Patients were 28.8 ± 3.8 years old at the time of pregnancy (patients #2, 4, and 6 were pregnant twice, patient #8 three times) and had suffered for 3 (0, 4) years from hypertension

Table 1. Baseline characteristics of subjects with primary aldosteronism

Patient	Age at diagnosis, years	Duration of hypertension, years	Before operation		lowest K ⁺ , mmol/L	aldosterone, ng/dL	R, pg/mL PRA, µg/L/h	Final diagnosis	Tumor diameter, mm		After operation		R, pg/mL PRA, µg/L/h	severity of hypertension
			severity of hypertension	symptoms							K ⁺ , mmol/L	aldosterone, ng/dL		
1	36	0.75	Moderate	0	2.6	48.9	0.58 (R)	APA	13		3.8	4.7	2.24	Normotension
2	39	6	Mild	Tiredness, cramps, nocturia	2.4	38.6	3.3 (R)	APA	20		4.7	9.7	6	Normotension
3	38	12	Moderate	Muscle weakness, cramps, rhabdomyolysis, heart failure	1.75	63.8	4.8 (R)	APA	17		5.1	3.4	28	Mild hypertension
4	33	6	Moderate	Tiredness, ankle swellings, nocturia	2.3	99.2	2.8 (R)	APA	20		3.8	2.6	7	Normotension
5	33	7	Moderate	0	2.8	82.9	2.1 (R)	APA	21		4	2.2	22.1	Normotension
6	34	10	Moderate	Nocturia	2.5	43.3	0.5 (R)	APA	19		4.4	2.5	5.9	Normotension
7	32	0.3	Moderate	Fatigue	3.4	29.9	0.5 (R)	APA	12		4.3	2.1	0.32	Normotension
8	33	10	Moderate	0	2.7	40.3	0.7 (R)	APA	7		4.6	4.6	5.7	Normotension
9	32	4	Mild	Tiredness, ankle swellings	2.8	53.4	0.34 (PRA)	APA	25		4.7	2	1.18	Normotension
10	31	5	Severe	0	2.9	34.8	0.59 (PRA)	APA	5		4.7	3.7	0.24	Moderate hypertension
11	28	3	Moderate	Muscle weakness	3.2	37.8	0.26 (PRA)	APA	11		4.5	8.6	1.14	Normotension
12	22	3	Severe	0	2.3	64.1	0.15 (PRA)	APA	18		4.1	2.5	0.66	Normotension
13	29	0.5	Severe	Headache, dyspnea	2.9	47.1	0.6 (PRA)	APA	20		4.6	2.3	0.44	Mild hypertension
14	31	7	Moderate	0	2.7	73.8	0.29 (PRA)	IHA	16±5.9		4.4±0.4	2.6 (2.3, 4.6)	6 (4, 14.6)/0.7±0.4	
	32.2±4.2	5.4±3.6			2.7±0.4	54.1±20.2	1.9±1.6/0.4±0.2							

APA, aldosterone-producing adenoma; IHA, idiopathic hyperaldosteronism; R, plasma renin; PRA, plasma renin activity. Values in the last line are shown as mean ± SD or median (interquartile range).

before pregnancy (in 6 subjects, hypertension developed only in pregnancy; the longest interval from hypertension diagnosis to pregnancy was 8 years: patients #6 and 8). After delivery, hypertension persisted in 12 subjects and, in 2 subjects, was transiently resolved (#7 and 13) (Table 2).

Fourteen pregnancies were delivered at term, and 5 prematurely (gestational age 27, 29, 33, 36, and 36 weeks). The reason for preterm delivery was early-onset preeclampsia (#5, #12, #14) in 3 cases, significant BP elevation without concomitant proteinuria (#3) in 1 case, and premature rupture of membranes (#9) also in 1 case. The remaining subjects delivered spontaneously at term in 7 cases (#2, 13; twice #4 and #8), 3 spontaneously with induction (#2 at week 40 due to intrauterine growth restriction; #6 twice due to late-onset preeclampsia), and 5 subjects by Caesarean section for different reasons (#1 herpes genitalis, #7, #8 breech presentation, #10 fetal hypoxia and intrauterine growth restriction, #11 increase in BP).

A favorable hypertension course (= without significant BP increase) was present in 9 pregnancies (#1, #2 [twice], #4 [first pregnancy], #7, #8 [three times], and #13). Significant BP elevation in the second trimester occurred in 4 pregnancies (#5, #12, #14 who developed preterm preeclampsia, and in subject #6 in her first pregnancy). The remaining 6 pregnancies presented with significant BP increase during the third trimester of gestation – #3, #4 (second pregnancy, admission to the hospital 10 days before delivery), #6 (second pregnancy), and #9, #10, and #11 (Table 2).

In subject #10, hypokalemia was already known (and supplemented with 3 g potassium chloride during gestation), but examination for secondary cause of hypertension was initiated almost 1 year after delivery. Patient #5 was followed by a nephrologist for hypokalemia. In subject #1, hypokalemia was found immediately after the end of puerperium, and a diagnosis of PA was subsequently made. In patient #7, hypertension reoccurred within 6 months after delivery, which was followed by screening of secondary hypertension.

Targeted molecular tumor examination for the *KCNJ5* gene was performed in 3 subjects and was positive in all cases: mutation c.451 G>A was found in subject #1 and c.503 T>G in subjects #2 and #6. Two patients became pregnant after adrenalectomy, and their pregnancies were uneventful without any BP elevation (#9 and 11) (Table 2).

Discussion

In this retrospective study from one institution, we showed a high incidence of hypertension-related pregnancy complications in subjects in whom diagnoses of PA were subsequently made.

On one side, 3 (16%) of pregnancies developed severe early-onset superimposed preeclampsia, resulting in Caesarean section at gestational age 27, 31, and 33 weeks. A further 7 pregnancies were complicated with BP elevation at the end of pregnancy, leading either to spontaneous delivery with induction, early hospital admission, or Caesarean section. On the other side, only 10 pregnancies presented with mild hypertension without any BP-related complication.

The frequency of pregnancy-related complications in this study is in agreement with previous reports focused on the course of PA during pregnancy, showing the prevalence of preeclampsia in about 25% of pregnancies, Caesarean section in about 39–44%, or preterm birth in 51% [7, 12]. The risk of superimposed preeclampsia in patients with subsequently diagnosed PA may be even higher than in subjects with chronic hypertension with an estimated risk of about 17–25% [13].

PA is characterized by suppressed renin due to autonomous aldosterone secretion, which is associated with elevated BP levels, hypokalemia, and hypernatremia without concomitant

Table 2. Pregnancy-related complications in subjects with primary aldosteronism

Patient	Age at gravidity, years	Hypertension before pregnancy, years	BP during pregnancy	Gestational age at delivery, weeks	Birth weight (centile)*, g (%)	Type of delivery			Complications	Hypertension after puerperium	Pregnancy after adrenalectomy
						S	SI	CS			
1	35	0	Mild gestational hypertension	40	3,690 (50–90)			1	Herpes genitalis	Yes	
2	34 36	1 3	Mild BP increase Mild BP increase at the end of gravidity	41 40	3,650 (50–90) 2,710 (5–10)	1		1	0 IUGR	Yes Yes	
3	26	0	Significant BP increase at week 36 of gestation	36	3,550 (>95)			1	0	Yes	
4	27 30	0 3	Mild gestational hypertension Moderate BP increase	40 39	3,710 (50–90) 3,220 (10–50)	1 1			0 Admission to the maternity hospital 10 days before delivery	Yes Yes	
5	29	4	Gradual BP elevation	27	860 (10–50)			1	Early-onset superimposed preeclampsia	Yes	
6	30 32	6 8	BP decompensation during the 2nd trimester BP decompensation during the 3rd trimester	39 39	4,350 (>95) 3,550 (50–90)	1 1			Late-onset superimposed preeclampsia Late-onset superimposed preeclampsia	Yes Yes	
7	31	0	Mild gestational hypertension	40	3,100 (10–50)			1	Breech presentation	No	
8	23 26 31	1 4 8	Mild hypertension Mild hypertension Mild hypertension	40 40 40	3,970 (90–95) 3,490 (50–90) 3,830 (50–90)	1 1 1			0 Breech presentation 0	Yes Yes Yes	
9	28	2	Significant BP increase during the 8th month of gestation	36	2,410 (10–50)			1	Premature rupture of membranes	Yes	Normotensive, CS due to herpes genitalis
10	26	3	Moderate BP increase	40	2,640 (<5)			1	IUGR, fetal hypoxia	Yes	
11	25	0	Significant BP elevation at the end of gravidity	39	3,450 (50–90)			1	0	Yes	Normotensive, spontaneous delivery
12	22	3	BP decompensation during the 2nd trimester	31	1,310 (10–50)			1	Early-onset superimposed preeclampsia	Yes	
13	27	0	Mild gestational hypertension	40	3,620 (50–90)	1			0	No	
14	29 28.8±3.8	5 3 (0, 4)	BP decompensation during the 2nd trimester	33	1,800 (10–50)			1	Early-onset superimposed preeclampsia	Yes	

BP, blood pressure; S, spontaneous delivery; SI, spontaneous delivery with induction; CS, caesarean section; IUGR, intrauterine growth restriction. * Centiles of normal birth weight are shown according to Kučera et al. [30]. Values in the last line are shown as mean ± SD or median (interquartile range).

development of edema because of a rise of natriuretic peptides [14, 15]. In pregnancy, we see the activation of the RAAS and its antagonists, nitric oxide/atrial natriuretic peptide. This leads to plasma volume expansion due to continuous sodium retention by the kidney on one side, and to peripheral vasodilatation on the other side to maintain a high rate of placental perfusion for substrate supply and fetal fluid volume balance. Plasma volume expansion and a decrease in systemic vascular resistance associated with BP decrease, and increased renal flow and glomerular filtration are detectable as early as 6 weeks after conception. Since increase in plasma volume expansion is seen throughout a pregnancy, reaching <30% above the nonpregnant value [16], systemic vascular resistance reaches its maximal decrease of up to 40% in the mid-second trimester [17]. BP reaches its nadir at the 20–24th gestational week, with a subsequent increase until the end of pregnancy [18].

During pregnancy, renin is produced not only by the kidney but also by the uterus. The factors regulating renin production by the uterus are unknown. Increased levels of angiotensin II are counterbalanced by decreased responsiveness to angiotensin II, which extends to the renal circulation [19]. Aldosterone levels at the end of pregnancy may increase up to 10 times compared to baseline levels [7]. Despite marked activation, intact RAAS responds appropriately to volume change in pregnant females [20]. The decrease in sodium excretion is mediated by an increased abundance of α -subunit of the epithelial sodium channel in the aldosterone-sensitive distal nephron [21]. However, progesterone plays a more significant role in potassium homeostasis, acting as a competitive aldosterone inhibitor on the mineralocorticoid receptor, leading to the increase of potassium reabsorption in the collecting duct [22]. Progesterone action may be counterbalanced by 21-hydroxylation, which leads to a huge increase in sodium-retaining deoxycorticosterone [23].

Preeclampsia contributes to preterm birth and Caesarean delivery, while it is associated with induced early delivery, placental abruption, and fetal growth abnormalities [13]. In preeclampsia, a decrease in RAAS and plasma volume precedes BP elevation [24]. Increased angiotensin II sensitivity is mediated by AT_1 - B_2 receptor heterodimers, which were detected in preeclampsia [25]. Stimulation of the AT_1 receptor may also be mediated by AT_1 receptor autoantibodies, which were also detected in preeclampsia and contribute to abnormal uterine perfusion, increased resistance index and placental hypoxia [26]. Elevated levels of these autoantibodies were found in subjects with PA expressing higher titers in APA than in IHA [27]. The course of pregnancy may also be modified by the presence of gonadotropin-releasing hormone/luteinizing hormone-responsive aberrant regulation of aldosterone secretion, which was present in at least 30% of studied APAs in the study by Gagnon et al. [28].

All subjects presented with a severe form of PA (hypokalemia was present in all subjects; in the vast majority of cases, symptomatic, and in 2 subjects even leading to muscle cramps). Unfortunately, the combination of profound hypokalemia and hypertension was either known but left without further examination (patients were treated with usual antihypertensives and potassium chloride supplementation) or was not diagnosed (general practitioners do not regularly screen for potassium levels even in younger hypertensive subjects in our country). Although hypokalemia is not a sensitive tool for PA screening in the general population [8], we would recommend that checking of potassium levels in all pregnant hypertensive subjects should be performed, in particular in those with moderate and severe hypertension. Those patients with hypokalemia should be referred for further evaluation to Hypertension Centers experienced in PA diagnosis (Fig. 1). Diagnosis of PA during pregnancy may be difficult because of unpredictable renin stimulation due to possible activation of RAAS, which may lead to renin increase and the subsequent decrease of the aldosterone to renin ratio (Fig. 1). The importance of early PA diagnosis with subsequent tumor removal is stressed not only by hypertension cure but also by the normal pregnancy course after APA removal, as shown in 2 cases.

Fig. 1. Flowchart of the diagnosis and treatment of primary aldosteronism during pregnancy. Adapted from Riester and Reincke [29]. ALDO, aldosterone; ARR, aldosterone to renin ratio; BP, blood pressure; K⁺, potassium; KCl, kalium chloratum; MR, mineralocorticoid receptor; MRI, magnetic resonance imaging; PA, primary aldosteronism.

This study has some limitations. Firstly, labeling of pregnancy-related complications was done only from delivery reports which, in the vast majority of cases, are very brief with very limited data available. Secondly, severity of hypertension was judged mostly from a personal history. Thirdly, we have not performed molecular tumor analysis for the presence of somatic mutations systematically, in particular of the *KCNJ5* gene which is associated with female gender, younger age, and larger tumor dimension. At least, the preliminary results suggest a high frequency of mutations of the *KCNJ5* gene in this group of subjects, which corresponds with previous reports.

In conclusion, this study shows the high frequency of BP-related pregnancy complications in subjects who were subsequently diagnosed with PA. APAs were the dominant type of PA in this study. Successful treatment of PA led not only to hypertension improvement or cure, but also to a normal pregnancy course. As all subjects presented with hypokalemia, potassium testing and awareness of PA as a cause of hypertension and hypokalemia would be the best prevention of these pregnancy-related complications. These subjects should be immediately referred to Hypertension Centers experienced in PA diagnosis.

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Statement of Ethics

All patients gave their informed consent for inclusion in the study. As this study reports only routine patient care, no approval of the Ethical Commission of our institution was necessary according to Czech Law.

Disclosure Statement

The authors have nothing to disclose.

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Author Contributions

T.Z.: data acquisition, data analysis, writing, and manuscript editing; O.P., J.R., R.H., B.Š., J.W.: data acquisition, and manuscript editing.

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