

PROGRESS IN PRIMARY ALDOSTERONISM

Mineralocorticoid receptor antagonists and management of primary aldosteronism in pregnancy

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Abstract

Primary aldosteronism (PA) is the most common cause of secondary hypertension. In this review, we discuss the diagnosis and management of PA during pregnancy based on the literature. As aldosterone and renin are physiologically increased during pregnancy and confirmation tests are not recommended, the diagnosis of PA during pregnancy relies on a repeatedly suppressed plasma renin level. Mineralocorticoid receptor antagonists (MRAs) are the most effective drugs to treat hypertension and hypokalemia in patients with PA. However, spironolactone (FDA pregnancy category C) might lead to undervirilization of male infants due to the anti-androgenic effects. Although data in the literature are very limited, treatment with spironolactone is not recommended. Eplerenone (FDA pregnancy category B) is a selective MRA without anti-androgenic potential. If MRA treatment is required in pregnancy, eplerenone appears to be a safe and effective alternative, although symptomatic treatment with approved antihypertensive drugs and supplementation with potassium is the first choice. In case of aldosterone-producing adenoma, laparoscopic adrenalectomy is a therapeutic option in the second trimester of pregnancy.

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Physiological changes in the renin–angiotensin–aldosterone system during pregnancy

In pregnancy, the renin–angiotensin–aldosterone system (RAAS) plays an important role for the equilibrium of salt and water in mother and child. All components of the RAAS are altered during pregnancy (1, 2). Renin concentrations are elevated due to extra-renal secretion in decidua and ovaries through estrogen stimulation (2). An increase in angiotensinogen production in the liver is observed in pregnant women. By contrast, the angiotensin-converting enzyme is reduced. These changes result in an elevation in aldosterone and angiotensin II (ANGII) levels (3). Increased aldosterone secretion is also a physiological response to sodium loss in response to high progesterone concentrations, a competitive inhibitor of aldosterone at the renal tubulus (4). Therefore, owing to this peculiar balance between progesterone and aldosterone, no increase in blood pressure is found in healthy pregnant women. Additionally, ANGII is not as effective as in non-pregnant women through changes in the AT₁-receptor sensitivity, elevated progesterone levels, and elevated prostacyclin levels (5). Besides the systemic renin–angiotensin–system (RAS), a local extra-renal RAS is suggested to be in site in the placenta regulating the feto-placental circulation (6). Pre-eclampsia is a disease in pregnant women characterized by the combination of hypertension and proteinuria. Besides placental abnormalities, alterations in the RAAS system are assumed to play a major role for its pathogenesis. In patients with pre-eclampsia, decreased levels of renin, ANGI, ANGIIL, and aldosterone are found (1, 7) and the ANGIIL sensitivity is increased through AT₁ receptor heterodimers (8, 9). Although the pathogenesis of pre-eclampsia remains quite unclear, autoantibodies stimulating the AT₁ receptor (AT₁-AA) and/or placental hypoxia may contribute to the development of pre-eclampsia (10, 11). This concept is supported by experiments in rodent models. AT₁-AA injections in pregnant mice lead to hypertension and proteinuria (12). After reduction of uterine perfusion pressure, AT₁-AA was detectable together with pre-eclamptic symptoms in pregnant rats (13, 14). Recently, Rossitto *et al.* (15) and Kem *et al.* (16) reported high titers of AT₁-AA, especially in PA patients with aldosterone-producing adenoma (APA). Therefore, the underlying pathophysiology of pre-eclampsia and APA might be partially similar. However, further investigations are necessary.

PA and pregnancy

Hypertensive disorders affect 6–8% of all pregnant women and are leading causes of maternal and perinatal mortality and morbidity (17, 18, 19).

It is difficult to estimate as to how many of these pregnant women are affected by primary aldosteronism (PA). However, assuming that ~10% of all hypertensive disorders are caused by PA, 0.6–0.8% of all pregnant women would suffer from PA. Indeed, to our knowledge, only 41 PA patients with 47 pregnancies (excluding familial forms) have been published in the literature regarding PA and pregnancy (20, 21, 22, 33) (methods for literature review, see [Supplementary data](#), see section on [supplementary data](#) given at the end of this article). PA is mostly caused by idiopathic bilateral hyperplasia of the adrenal gland (IAH) or APA, whereas APA might be more frequent than IAH as shown in the PAPY study and in our own data (34, 35). In PA, the median age at diagnosis is ~50 years. However, the onset of PA might be earlier as the diagnosis is often delayed (34). Therefore, most female patients are diagnosed after the reproductive period. However, there are a few familial forms of PA (types I, II, and III) in ~1% of the PA patients (36). Familial hyperaldosteronism is important in the context of PA and pregnancy, as women are affected in the reproductive period due to its early onset.

Most of the data on pregnancy and PA were obtained from patients with glucocorticoid-remediable aldosteronism (GRA). Responsible for GRA is a hybrid gene caused by unequal crossing resulting in a fusion of the 5' regulatory region of the CYP11B1 and the coding region of the CYP11B2. Therefore, the expression of aldosterone synthase is adrenocorticotropin sensitive and patients are treated with low-dose dexamethasone. However, physiological elevation in the adrenocorticotropin level caused by production of corticotropin-releasing hormone in the placenta may lead to an exacerbation of blood pressure (37). In a large retrospective study, Wyckhoff *et al.* described 35 pregnancies in 16 females with GRA. Hypertension was present in 26 of the 35 pregnancies and two (6%) were complicated by superimposed pre-eclampsia. This rate is not higher than that in the general population (2.5–10%) (18). In a Sardinian family, none of the 29 pregnancies in eight GRA-affected mothers were complicated by severe hypertension or pre-eclampsia (38). However, 39% of women developed an aggravated hypertension during pregnancy, which was associated with a lower birth weight; 23% had to be treated with medication including α -methyl dopa, potassium-sparing diuretics, β -blocker, and thiazide diuretics.

Unfortunately, in patients with PA caused by APA or IAH, no studies in large cohorts exist – therefore, the evidence is based on single case reports. The course of hypertension during pregnancy in patients affected by sporadic PA appears to be highly variable and not predictable: case reports describe worsening of hypertension and hypokalemia as well as spontaneous improvement or even normotension independent of the PA subtype (39). The interaction between plasma aldosterone and its physiological antagonist progesterone may explain this variable course. Ronconi *et al.* hypothesized that the clinical consequences of PA, hypertension and hypokalemia, during pregnancy only develop if the amount of progesterone is unable to compensate the aldosterone excess. Therefore, the authors suggest calculating the progesterone-to-aldosterone ratio as a measure of mineralocorticoid excess during pregnancy. In healthy pregnant women, this ratio increases during pregnancy (values between 18 and 80 pmol/l/pmol/l) as progesterone increases ~1000 times and aldosterone approximately ten times. Shortly after delivery, the progesterone-to-aldosterone ratio falls to very low values (4). In the single case described by Ronconi *et al.*, a ratio below 20 pmol/l/pmol/l was associated with hypertension. Therefore, a ratio above this cutoff might be useful as a predictor for a favorable outcome (39). This is an interesting observation and should be evaluated in a larger cohort.

The outcome of mother and child mainly depends on the blood pressure. Case reports describe uneventful pregnancies with healthy newborns (e.g. (40, 41)). Nevertheless, end-organ damage, preterm delivery, and placental abruption are potential complications (39).

Diagnosing PA during pregnancy

Diagnosing PA during pregnancy is challenging. Therefore, it is the first step to consider PA as a reason for hypertension in pregnancy. Hypokalemia and/or severe hypertension in a pregnant woman should lead to screening for PA, especially if the onset is before pregnancy or before the 20th week of gestation. After the 20th week of gestation, the probability of developing pre-eclampsia associated with non-PA causes is higher. According to the guidelines, pre-eclampsia is defined as hypertension with proteinuria or hypertension with associated laboratory abnormalities, pulmonary edema, or neurological symptoms (42). However, superimposed pre-eclampsia develops in 13–40% of women with chronic hypertension.

Nevertheless, if the signs described above for pre-eclampsia are missing, and especially in the presence of

hypokalemia, PA should be ruled out. To confirm or rule out the diagnosis of PA in pregnant women is a challenge as well. As the plasma aldosterone level is physiologically elevated in pregnancy, the only way to diagnose PA is via the suppressed plasma renin concentration, which is physiologically elevated in pregnancy. Therefore, in healthy pregnant women, the aldosterone-to-renin ratio (ARR) is low, whereas in pregnant women with PA the ARR is elevated. However, it might be false negative (43). Confirmation tests as saline infusion tests or captopril tests are not recommended in pregnancy due to risks associated with volume expansion or toxic effects (44). Therefore, the diagnosis of PA has to be based only on suppressed renin and elevated ARR (see Fig. 1). Subtype diagnosis during pregnancy is based on imaging as the prevalence of hormone-inactive adenoma in young patients below 40 years is very low and adrenal vein sampling is not recommended due to radiation exposure. Imaging of the adrenal gland with MRI or ultrasonography may be performed during pregnancy. However, if blood pressure and hypokalemia are well controlled during pregnancy, postponing the subtype diagnosis including adrenal vein sampling after delivery is recommended (45).

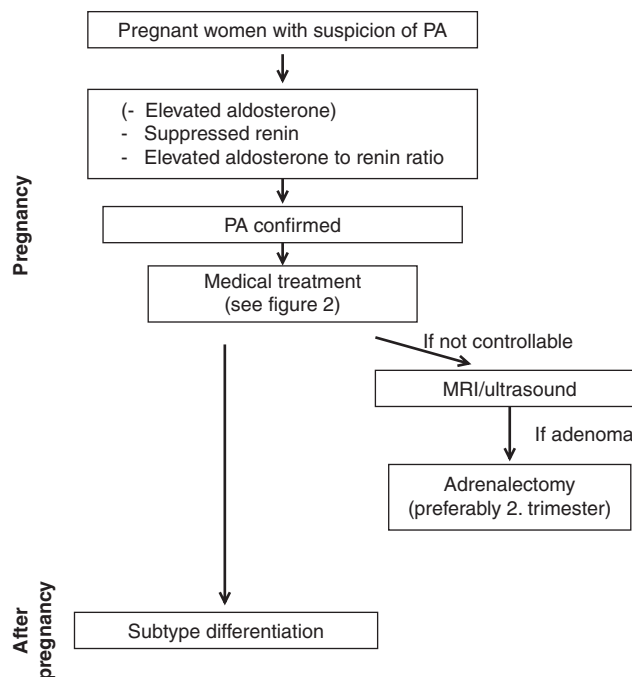


Figure 1

Diagnosis of primary aldosteronism during pregnancy.

PA, primary aldosteronism; MRI, magnetic resonance imaging; MRA, mineralocorticoid receptor antagonist.

Treatment with antihypertensive drugs or even adrenalectomy in these newly diagnosed patients depends on clinical presentation and does not differ from the approach in already diagnosed patients as described below.

In patients with inconclusive results, we recommend the diagnostic work-up including confirmation tests after delivery and after the breastfeeding period.

Mineralocorticoid receptor antagonist treatment in pregnancy and breastfeeding period

Mineralocorticoid receptor antagonists (MRAs) are the first choice for medical treatment of PA. Unfortunately, spironolactone is classified as FDA pregnancy category C: animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans. Eplerenone, on the other hand, is classified as pregnancy category B: no adequate and well-controlled studies in pregnant women are available. In the following paragraphs, the existing data on the use of these drugs in pregnancy are discussed.

Spironolactone in pregnancy

Spironolactone was introduced in 1960 as the first MRA and is widely used in different indications such as liver

cirrhosis with ascites, heart failure, hypertension, and PA (46, 47). However, spironolactone was never proved to be safe in pregnancy. Nevertheless, as indicated by Morton *et al.* (48), spironolactone was commonly used in hypertension, pre-eclampsia, liver disease, and myasthenia gravis in pregnancy before 1980. Two trials exist investigating the effect of spironolactone treatment on the RAAS and the excretion of different steroids in pregnant women with edema (49, 50). It is known that spironolactone crosses the placenta (44) and therefore might have an impact on the fetus. As testosterone is necessary for male morphogenesis, the anti-androgenic activity of spironolactone has to be considered. In an experiment on rats, Rose *et al.* (51) failed to show the effects of spironolactone on male genital development with an equivalent to the 100 mg adult human regimen. However, 5 years later, Hecker *et al.* (52) published a first study describing feminization in male rat fetuses after treatment of female rats (body weight of ~200 g) from the 13th to the 21st day p.c. with a higher dose of spironolactone (40 mg/day). In the FDA report of aldactone, teratology studies on mice, rats, and rabbits are mentioned (http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/012151s071lbl.pdf, 30 May 2014). No teratogenic or embryotoxic effects could be observed in mice. However, in rats treated with very high doses (200 mg/kg per day), feminization of male fetuses was observed. In rabbits

Table 1 Spironolactone as a therapeutic drug in pregnancy.

First author	Year of publication	Reasons	Dosage per day (mg)	Weeks of gestation	No. of pregnancies	Infants	Outcomes and comments
Crane (59)	1964	PA	800	32 (only for 2 days)	1	1 male	Stillbirth 32nd week of gestation, abruptio placentae
Levy (57)	1971	PA		~ ≥ 12	1	1 male	CS, hyperkalemia of the infant after potassium infusion peripartal
Lammintausta (50)	1979	Pregnancy edema	100	≥ 24 (for ≥ 2 weeks)	10	10	–
Lotgering (58)	1986	PA	300	≥ 22	1	1 female	SGA
Groves (41)	1995	Bartter syndrome	≤ 400		3	2 males, 1 female	No complications
Rigo (40)	1995	Bartter syndrome			2	1 male, 1 female	No complications
Nohira (54)	2001	Bartter syndrome		≥ 31	1	1 female	SGA
De Arriba (55)	2009	Gitelman syndrome		0–17 and 25–35	1	1 male	Oligohydramnion, CS
Shah (53)	2011	PCOS		0–5	1	1 male	Ambiguous genitalia
Rusavy (56)	2012	Gitelman syndrome		30–39	1	1 female	Diagnosis at 30th week of gestation, healthy infant

CS, Cesarean section; PA, primary aldosteronism; SGA, small for gestational age.

treated with 20 mg/kg, a lower number of live fetuses was described. Overall, using an extensive PubMed and Google Scholar research, we found one case report describing an ambiguous genitalia in a human newborn of a mother treated with spironolactone until the 5th week of gestation for PCOS (53). By contrast, there are a few case reports describing healthy newborns of mothers treated with spironolactone during pregnancy (see Table 1): case reports describe six children of three women with Bartter syndrome showing no anti-androgenic effect in three male and three female newborns (40, 41, 54). Similarly, two case reports of mothers with Gitelman syndrome treated with spironolactone describe a healthy boy with normal growth but oligohydramnion (55) and a healthy girl respectively (56). In three case reports of PA patients, the administration of spironolactone is mentioned (57, 58, 59). Additionally, the German database Embryotox lists three pregnancies with spironolactone treatment resulting in three healthy newborns (two males and one female) (<http://www.embryotox.de/spirobeta.html>, 30 May 2014).

Taken together, in each single case, it has to be discussed whether the benefits of spironolactone to control hypokalemia and hypertension outweigh the feared but only once described risk of undervirilization in male newborns. As the most important steps of sex differentiation take place in the first trimester, the anti-androgenic effects of spironolactone might only be important in the first weeks of gestation. However, especially in late pregnancy, spironolactone administered in high doses may lead to a decrease in the plasma volume due to the natriuretic effect of spironolactone, and that might result in a higher risk of intrauterine growth retardation (40).

Eplerenone in pregnancy

Eplerenone was introduced ~10 years ago as a selective MRA. In contrast to spironolactone, no anti-androgenic effects are described. As no adequate studies in pregnant women are available, the pregnancy category B has been assigned (60). In animal models, no teratogenic effects

were observed (FDA report Inspra Eplerenone, http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021437s006lbl.pdf, 30 May 2014). We found one case report describing an uneventful pregnancy under treatment with eplerenone in a woman with APA delivering a healthy boy with a follow-up of 2 years (21). Additionally, a safe and effective use of eplerenone was reported in a mother with Gitelman syndrome (48) as well as in a mother with a diastolic heart failure (61) (see Table 2).

Breastfeeding under MRA treatment

To our knowledge, no case reports are available on treatment of PA in breastfeeding mothers. Canrenone, the major and active metabolite of spironolactone, appears in human breast milk (Aldactone, FDA report). The relative dose for the newborn is 1.2% of the daily dose of the nursing mother. Therefore, an impact on the newborn is not expected (<http://www.embryotox.de/spirobeta.html>, 30 May 2014). For eplerenone, no data on human breast milk are available. Preclinical data show that eplerenone is detectable in rat breast milk with a peak concentration at 30–60 min after oral dosing (eplerenone, FDA report).

Taken together, based on the presented data, we recommend the use of eplerenone in pre-pregnancy, pregnancy, and breastfeeding situation, if MRA treatment is necessary.

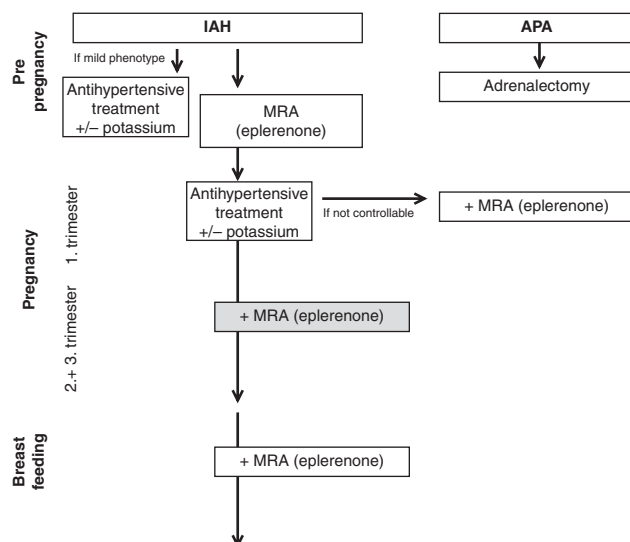
Recommendations for treatment of PA in pregnancy and in the pre-pregnancy period

Treatment of PA in pregnancy is challenging. Before planning pregnancy, it is highly recommended to perform adequate subtype differentiation by adrenal vein sampling (AVS). If APA is diagnosed, surgical cure by adrenalectomy should be aspired before planning pregnancy to avoid complications during pregnancy. However, the situation is more difficult in patients with IAH. In these patients, it is favorable to achieve normotensive values before pregnancy. Depending on the severity of hypertension,

Table 2 Eplerenone as a therapeutic drug in pregnancy.

First author	Year of publication	Reasons	Dosage per day (mg)	Weeks of gestation	No. of pregnancies	Infants	Outcomes and comments
Hutter (61)	2006	Diastolic heart failure		> 32	1	1	Healthy infant
Morton (48)	2011	Gitelman syndrome	100	0–39	1	1 female	Healthy infant
Cabassi (21)	2012	PA	50	27–35 (end)	1	1 male	Healthy infant

PA, primary aldosteronism.

**Figure 2**

Treatment of primary aldosteronism in pregnancy. IAH, idiopathic adrenal hyperplasia; APA, aldosterone-producing adenoma; MRA, mineralocorticoid receptor antagonist.

different approaches are possible (Fig. 2). In normokalemic patients with well-controlled or mild hypertension, the termination of MRA treatment should be discussed. Alternatively, antihypertensive drugs with a good safety profile during pregnancy, such as α -methyldopa and β -blockers, should be initiated already in the planning period. Nevertheless, these patients have to be monitored closely. In patients with severe PA including WHO hypertension grades 2 and 3 and hypokalemia, the termination of MRAs before pregnancy seems to be inadequate as the time of conception is not predictable. In this situation, spironolactone therapy should be continued using a low effective dose (25–50 mg of spironolactone per day). Alternatively, MRA therapy can be switched to eplerenone. As soon as the pregnancy is confirmed, we recommend stopping spironolactone as the first trimester is the most sensitive period for sex differentiation and spironolactone might lead to disturbance as described above.

If hypertension or hypokalemia are not controlled before conception or during the first trimester, we recommend the use of eplerenone as a selective MRA. In patients with APA, adrenalectomy could be considered if hypokalemia and hypertension are uncontrollable (22, 26, 44). In these cases, a laparoscopic approach in the second trimester is recommended. PA patients could be treated again in the second and third trimesters with MRAs if necessary.

In guidelines dealing with the treatment of hypertension in pregnancy, sodium restriction is not recommended as a treatment option. Notably, the recommended blood pressure in hypertensive pregnant patients is between 120/80 and 160/105 mmHg. In hypertensive pregnant patients with evidence of end-organ damage, the recommended blood pressure level is below 140/90 mmHg (42).

In summary, the evidence for diagnosing and treating PA with MRAs during pregnancy and breastfeeding is limited. Recommendations given in this review are mainly based on case reports and toxicity data generated in animal studies. The paucity of data on adverse outcomes during pregnancy despite being on the market for more than 50 years is remarkable and might indicate a better safety profile than anticipated from the known anti-androgenic activities of spironolactone.

Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/EJE-14-0444>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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