Management and Outcomes of Primary Aldosteronism in Pregnancy:

A Systematic Review

Short running title: Hyperaldosteronism in pregnancy

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Abstract

Primary aldosteronism (PA) in pregnancy (PAP) can be a serious condition and is challenging to diagnose. This study was conceived to help in the diagnosis of PAP and provide suggestions on management of PAP based on evidences retrieved using a **P**opulation, **I**ntervention, **C**omparison and **O**utcome (PICO) search strategy. Based on the changes of aldosterone and renin occurring in normal pregnancies, we developed a nomogram that will allow to identify PAP cases. Moreover, we found that published PAP cases fell into 4 main groups differing for management and outcomes: i) unilateral medically treated, ii) unilateral surgically treated, iii) bilateral medically treated and iv) familial forms. Results showed that complications involved 62.2% of pregnant women with non-familial PA and 18.5% of those with familial hyperaldosteronism type I. Adrenalectomy during pregnancy in women with PAP did not improve maternal and foetal outcomes, over medical treatment alone. Moreover, cure of maternal hypertension and mother and baby outcome were better when unilateral PA was discovered and surgically treated before or after pregnancy. Therefore, fertile women with arterial hypertension should be screened for PA before pregnancy and, if necessary, subtyped to identify unilateral forms of PA. This will allow to furnish adequate counselling, a chance for surgical cure and, therefore, for a pregnancy not complicated by aldosterone excess.

KeyWords: Hypertension; Pregnancy; Primary Hyperaldosteronism; Aldosterone-producing adenoma; Adrenalectomy during pregnancy.

Non-standard Abbreviations and Acronyms

ARR: aldosterone-renin ratio

AVS: adrenal venous sampling

BP: blood pressure

C-section: caesarean section

DRC: direct renin concentration

FH: familial hyperaldosteronism

HT: hypertension

ICU: intensive care unit

IUGR: intrauterine growth restriction

MRA: mineralocorticoid receptor antagonist

PA: primary aldosteronism

PAC: plasma aldosterone concentration

PAP: primary aldosteronism in pregnancy

Introduction

Primary aldosteronism (PA) is a common cause of high blood pressure (BP) [1]. Most cases are sporadic; familial forms caused by with germ-line mutations usually resulting in bilateral adrenocortical hyperplasia are much rarer. PA can often involve young fertile women, [2] who are exposed at high risk of complications because of severe hypokalaemia, drug-resistant hypertension (HT) and preeclampsia/eclampsia.

Currently, the cut-off values of plasma aldosterone concentration (PAC), direct active renin concentration (DRC) and the aldosterone-renin ratio (ARR) that allow to diagnose PA in pregnancy (PAP) are uncertain. Moreover, it remains controversial if sporadic unilateral PA discovered during the 2nd trimester of pregnancy, when HT can become severe and/or drug-resistant, should be treated medically or surgically. Likewise unsettled is the best management in pregnancy of familial hyperaldosteronism (FH), except for the most common type 1 (FH-1), for which suggestions have been recently provided [3].

Since only narrative reviews exist [4–12], guidelines for PA [13], even the most recent for HT in pregnancy [14], devoted scant, or no, attention to the management of PA in pregnancy (PAP), we herein aimed at providing an appraisal of normal changes of PAC, DRC, and the ARR during pregnancy, and the clinical features and management of PAP, moving from a systematic structured search of the information available in public databases, and from recent data on diagnosis of PA in young patients [15]. This search unveiled several findings that can serve as a basis for the diagnosis and management of this condition.

Methods

We searched the literature for studies that reported the changes of plasma renin activity and PAC during normal pregnancy. As the direct chemiluminescent assay of active renin (DRC) has replaced plasma renin activity, we calculated the corresponding DRC values from plasma renin concentration, and the ARR during each week of pregnancy (as DRC=PRA*0.05269-0.0476) by the ARR-app [16].

We then determined the 95% confidence interval (CI) of the normal values of PAC, and DRC and ARR. Details of the structured search of available information are given in the Supplemental materials (see 'Complete Methods' section).

Results

Changes of PAC, renin and ARR during normal pregnancy and diagnosis of PAP

A painstaking study by Wilson et al. [17] depicted the changes in BP values, PAC, and plasma renin concentration, from the 8th to the 38th week of pregnancy, in a multiethnic cohort of women at a normal sodium intake (100-150 mEq/day). It allowed us to determine the normal values of PAC, DRC, and the ARR and their changes in normal pregnancy (Figure 1) and also to calculate values exceeding by three-fold the 95% upper (for PAC and ARR) and lower (for DRC) normal confidence values.

Results showed that PAC increased less than renin; therefore, at least until the 32th week, the ARR cut-off value suggesting the presence of PAP (because it surpasses by three-fold the 95% CI upper normal limit) was lower than 20.6 ng/mIU, which is the value identified for the diagnosis of PA [18]. Figure 1 shows a nomogram depicting the range of values (dashed areas) suggestive of PAP for these variables.

PAP features

We found 618 papers (Figure S1) that contained the terms reported in Table S1. Of them, 36 that entailed 83 patients (56 cases with sporadic PA and 27 with FH-1) were relevant for this analysis.

The reported PAP cases fell into 4 main groups that differed for management and outcomes (Table S2): i) unilateral medically treated, ii) unilateral surgically treated, iii) bilateral medically treated and iv) familial forms (Table S3). They were analyzed and compared for outcomes with young fertile women with unilateral PA treated with surgery before or after pregnancy.

i) Unilateral medically treated PA

31 women with HT presumed to have unilateral PAP based on imaging alone and treated medically were reported thus far. In 3 unilaterality of the disease was uncertain [19,20], leaving 28 cases for this analysis. These women mainly received labetalol and/or methyldopa and/or calcium channel blockers [1]. The mineralocorticoid receptor antagonist (MRA) eplerenone (50 mg BID), added from the 27th gestation week, was given only one case. [21] 27 women underwent adrenalectomy after pregnancy, around 19.5 months after delivery.

61% of pregnancies were complicated; 46% ended prematurely, mostly by urgent caesarean section (C-section) owing to preeclampsia and foetal distress. 22% of the foetuses had intrauterine growth restriction (IUGR); 7% of the newborns needed intensive care unit (ICU) (Table 1) and 7% died [22].

After pregnancy, subtyping was suboptimal: only 32% of the patients received adrenal venous sampling (AVS)-guided surgery. Notwithstanding this, HT was cured in 85% of the women (Figure S2A). Biochemical cure was claimed in all, but follow-up data were available only in 52% of the cases. All cases showed an adenoma, but aldosterone synthase (CYP11B2) expression [23,24] was immuno-histochemically confirmed in the tumor only in 2 cases [25,26].

ii) Unilateral surgically treated PA during pregnancy

Ten women with unilateral PAP underwent adrenalectomy. The diagnosis was made before conception in 3, but surgery was not done because pregnancy was discovered before adrenalectomy could be planned. In 7 cases unilateral PA was only presumed based on magnetic resonance. AVS was performed during pregnancy in one case [27], which ended at 30th week for preeclampsia. Notwithstanding X-ray exposure, the newborn showed no malformations.

Only one of the 10 women, with AVS done before conception [28], showed cure of HT after adrenalectomy (Figure S2B).

After adrenalectomy, normalization of the ARR in the 3rd trimester was reported only in another patient, in whom the high BP values did not normalize and required drug treatment: pregnancy ended at 30th week with urgent C-section for foetal distress and IUGR [29].

Immuno-histochemical demonstration of aldosterone synthase (CYP11B2) expression in the tumor [23,24] was performed in one case [30].

6 of the 10 pregnancies were complicated (Table 1) and ended prematurely between the 26th and the 35th week of gestation, mostly by urgent C-section, because of preeclampsia or foetal distress (Figure S3). Half of the foetuses had IUGR and one third needed ICU stay (Figure S4). The baby death rate was 20%: in one case due to miscarriage at the 26th gestational week, and in the other to sepsis after prolonged ICU stay because of significant growth retardation.

After adrenalectomy, the overall rate of HT cure was low (10%) and the number of drugs needed to control the high BP during the 2nd trimester decreased a from 2.25 to 1.0, but raised again after delivery (Figure S2B).

iii) Bilateral medically treated PA

15 women were presumed to have bilateral PAP based on imaging, which was diagnosed before conception in 13 and after pregnancy in 2. Bilaterality was only presumed in 27% of the cases, as AVS was performed in 11 cases that showed no lateralization.

66.6% of the PAP were complicated by preeclampsia, impaired umbilical artery flow or premature membrane rupture and ended prematurely, mostly by urgent C-section. The newborn death rate was 13.3% (Table 1): one baby died by miscarriage at the 12th gestational week, another one at the 20th; 35.7% of the foetuses had IUGR.

During gestation the women required medical treatment because of high BP. They received labetalol, methyldopa, calcium channel blockers (mainly nifedipine or verapamil), but surprisingly no MRA.

iv) Familial forms

Thus far, 4 types of familial hyperaldosteronism have been identified (for rev. [31]), but only cases of FH-1 in pregnancy were reported [32]. Therefore, recommendations on management in familial forms can be made only for FH-1 in pregnancy.

FH-1 is an autosomal dominant disorder characterized by HT of different degree and high prevalence of cardiovascular and cerebrovascular events before age 50 years in pedigrees. Acquisition of the adrenocorticotropic hormone (ACTH) responsive elements of 11-β hydroxylase (CYP11B1) in a chimeric gene entailing aldosterone synthase (CYP11B2), as a result of homologous gene recombination, explains the lowering of high BP values with dexamethasone treatment. As the management of FH-1 in pregnancy has been recently reviewed [3], we have summarized the key messages in the Supplemental materials (see 'FH-1 overview' section).

Diagnosis of PA before and after pregnancy

Laparoscopic adrenalectomy generally shows the highest rate of HT cure in young women with a short history of HT [33]. In women with unilateral PAP adrenalectomized after delivery, the cure rate was 8.5-fold higher (85% vs 10%) than in women adrenalectomized during pregnancy. This striking difference could be, at least in part, because the responsible adrenal gland can escape detection during gestation leading to unnecessary or wrong adrenalectomy, since AVS is unfeasible in pregnancy.

Anti-hypertensive treatment

The choice of medical treatment for PAP stands on anecdotal evidence. MRAs have been rarely used [34] with only 3 cases reported: one in the medically treated group (eplerenone up to 50 mg BID from the 27th gestation week) [21] and 2 in the surgically treated. In one case eplerenone was up titrated to 200 mg day [35]; in the other, the dose of spironolactone was 50 mg/day [27]. Noteworthy, the MRA did not control hypokalemia and the high BP values. One case needed urgent C-section at 35th week and the others adrenalectomy during pregnancy because of drug-resistant HT. These pregnancies ended prematurely, despite surgery, at 28th [35] and 30th [27] week with urgent C-section performed because of

preeclampsia and IUGR. The babies needed ICU stay for months after delivery because of significant growth retardation, and one died of sepsis after 3 months [35].

These poor outcomes could be accounted for by a greater severity of PA in these cases; however, studies are needed to clarify if adequately up-titrated MRAs are more beneficial than harmful.

Discussion

In normal pregnancy, the increased production of vasodilatory prostaglandins [36] and of progesterone, which antagonizes aldosterone on the mineralocorticoid receptor, can lower, and even normalize, high BP during the 1st trimester [17]. Due to utero-placental renin production, DRC increases up to week 32 (Figure 1) and, because of oestrogen-stimulated production of angiotensinogen in the liver, angiotensin II increases up to almost 4-fold by the 8th week of pregnancy and 7-fold at term [17,37]. Notwithstanding this, PAC and the ARR increase less [17] (Figure 1); therefore, during gestation the interpretation of the ARR values should be guided by knowledge of the normal changes that are shown in Figure 1. At each week of pregnancy, values falling in the dashed area for these variables, which comprises values three-fold higher (for PAC and ARR) and lower (for DRC) than the 95% CI, should be regarded as suspicious of PAP with some words of caution. In fact, it is currently unknown what proportion or plasma renin is of utero-placental origin and what originates from juxtaglomerular cells, and also if these production sites undergo a similar regulation by volume expansion.

Because of the more prominent increase of renin than PAC, the ARR remains lower than 20.6 ng/mIU (Figure 1, dotted grey line) until the 32th week of pregnancy. This implies that the diagnosis of PAP can be concealed if one would apply the standard ARR cut-off values used to identify PA and might explain why only relatively few cases, likely the most florid ones, were recognized in pregnancy and why most reported cases were diagnosed late, after the onset of severe and/or resistant-HT and/or preeclampsia/eclampsia. In a recent Australian study, PAP was diagnosed in 9 women (37.5% with preeclampsia) among 42 screened over 2 years, by a combination of an ARR > 14.4 ng/mIU and DRC < 20 mU/l, i.e. an ARR is lower than the usual one (20.6 ng/mIU) and a renin non suppressed.

88.9% of these PAP women could not be diagnosed with unilateral PA and in other 8 with similarly elevated ARR the diagnosis, albeit likely, was not confirmed, thus illustrating the challenges of diagnosis PAP [34].

This survey also unveiled four main categories of PAP that were associated with different mother and baby outcomes (Table 1). In the medically treated unilateral PAP, even though there were no reported maternal deaths, 61% of the pregnancies were complicated and the baby death rate was high (7%). In women with unilateral PAP, who underwent adrenalectomy in pregnancy, the complication rate was similar (60%), but the baby death rate was around 3-fold higher (Figure 2). Moreover, surgery in pregnancy cured HT in only 10% of the women, likely because it was performed in the most severe cases requiring immediate surgery, and also because, being non AVS-guided, it exposed to the risk of wrong or unnecessary adrenalectomy. Planning and performing surgery before pregnancy could furnish a much better outcome, as adrenalectomy guided by the information obtained with AVS leads to biochemical cure in 98% of PA young nonpregnant women [38,39]. In line with this, when performed after delivery, adrenalectomy cured HT in 85% and furnished biochemical cure in all the cases that had follow-up data. However, the latter comprised only a fraction of the women, which testifies the difficulty of collecting information in these (often) lactating women.

Pharmacologic treatment of PA in pregnancy

The evidence supporting the choice of medical treatment of PAP is anecdotal: only 3 women were reported to receive MRA, which failed to control hypokalaemia and the high BP values, suggesting that MRAs are under used and under dosed possibly due to concerns on their safety, because they cross the placenta and, due to their off-target actions on the androgen receptor, theoretically could affect genital differentiation in male foetuses. As the latter is complete by weeks 12th to 14th, MRAs are probably safe in the second half of gestation, i.e. when their administration is most useful and needed. When MRAs were used during all trimesters in pregnant women with Bartter's (spironolactone up to 400 mg [40]) and Gitelman's syndrome [41], two channelopathies with marked

secondary aldosteronism and severe hypokalemia, no signal for feminization and genital ambiguity was seen. Likewise, no male feminization was seen in two babies from women with PAP treated with eplerenone [21,35], which has less oestrogen-like effects than spironolactone [42]. To date, clinical experience with newer MRAs, as aparexone, exarenone and finerenone, lacks; however, the latter has been found to reduce placental weight and induce signs of embryo-foetal toxicity in in rats [43].

Labetalol, methyldopa, calcium channel blockers are approved for HT in pregnancy and were used in bilateral PA [1], where unilateral adrenalectomy shows inconsistent benefits [44]. However, since in two-thirds of the women with bilateral PA, pregnancy was complicated notwithstanding medical treatment, these women should receive counselling on their increased risk with pregnancy.

FH-1 women have a relatively benign course during pregnancy, as discussed elsewhere [3]. Most of them (75%) did not need anti-hypertensive treatment; others were treated pharmacologically. In our experience in one case, where dexamethasone was restarted from the second half of gestation to control BP and potassium levels [45], no negative effects on birth weight and baby hypothalamic-pituitary axis development were reported (see 'FH-1 overview' section in the Supplemental materials). In another woman, who was recently diagnosed with FH-1 20 years after pregnancy, no complications occurred in spite of no treatment (Prof Rossi personal communication).

Do women with PAP carry a higher risk for complications than pregnant women with essential hypertension?

This question cannot be answered conclusively because secondary forms of HT are not systematically excluded in young fertile women. Therefore, since it remains uncertain whether HT is essential or not in most of the studies conducted in pregnancy [46], a meaningful comparison in terms of outcomes between PA and essential HT women was precluded.

Considering that: i) the complication rate generally raises with increasing BP levels [47]; ii) a large randomized clinical trial of women with mild chronic HT showed better pregnancy outcomes by targeting a blood pressure of < 140/90 mmHg than by reserving treatment only for severe

hypertension [48]; iii) women with PAP show substantial increase of high BP values; iv) over 20% of them can become resistant to treatment in the 3rd trimester, the conclusion is offered that women with PAP are at higher risk of complications. In line with this contention, in 211 women, where a secondary form of HT was excluded before pregnancy [49], the rates of preeclampsia/eclampsia (18%), preterm delivery (28.9%), IUGR (17.5%) and baby death (3.8%), were all much lower than those (28.8%, 53.3%, 31.8% and 11%, respectively) recorded in women with sporadic PAP (Figure 3).

Limitations of the study

This review has an intrinsic limitation due to the fact that only 83 women with PAP were reported thus far. Likely, this reflects two facts: i) the underdiagnosis of PA in young fertile women in general and even more so during pregnancy for the reasons discussed above; ii) a publication bias as investigators cared to report only the most severe cases.

Conclusions

Available evidence indicates that undetected PAP is a severe condition, requiring close monitoring of BP and serum potassium levels, particularly during the second half of pregnancy.

The following recommendations for the management of women with PAP seem, therefore, reasonable (Figure 4): all fertile women with arterial hypertension, who consider a pregnancy, should be screened for PA. Detection of a raised ARR should be followed by subtyping with AVS, because an imaging-only strategy based on magnetic resonance overlooks unilateral surgically curable PA in over 47% of the women younger than 45 years of age [50], and also because X-rays exposure, and thus AVS [39], is not feasible in pregnancy. The ultimate goal of this strategy is to detect and treat surgically curable unilateral PA before pregnancy. It should be mentioned that the AVIS-2 Young study showed an accurate identification of the culprit adrenal gland, thus permitting adrenalectomy without performing AVS in young PA patients in the presence of hypokalemia concurrent with a unilateral adrenal nodules > 5 mm in size and a normal contralateral adrenal gland. Unfortunately, such criteria apply to only 32% of the women aged 45 years or younger [15].

At variance with non-pregnant women with unilateral PA, in whom removal of the responsible adrenal is the treatment of choice, the limited available evidence suggests that adrenalectomy performed during the 2nd trimester in women with a suspected unilateral adenoma did not improve and even worsened maternal and foetal outcomes compared to medical treatment alone. These findings reinforce the proposition that PA should be identified and resolved before conception.

Women with the surgically incurable bilateral PA should be warned about the risk of a further pregnancy and should receive a selective MRA, as part of their therapy, during the second half of pregnancy, a stage when the risk of feminization is negligible.

Finally, women who have a strong family history of HT and/or stroke at young age should be screened for the chimeric gene of FH-1 and, if positive, treated with low dose dexamethasone, which effectively controls high BP, as discussed in depth elsewhere [3].

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Supplemental materials

List of Content:

Supplemental text

Complete Methods

FH-1 overview

Foetal outcomes in medically treated PA women: unilateral vs bilateral forms

Foetal outcomes in unilateral PA forms: medical vs surgical treatment during pregnancy

Characteristics of medically treated women with PAP: complicated vs non-complicated pregnancies

Subsequent pregnancies

Supplemental Tables and Figures

Tables S1-S6

Figures S1-S4

References

1. Rossi GP, Bisogni V, Bacca AV, Belfiore A, Cesari M, Concistrè A, Del Pinto R, Fabris B, Fallo F, Fava C, et al. The 2020 Italian Society of Arterial Hypertension (SIIA) practical guidelines for the management of primary aldosteronism. *Int. J. Cardiol. Hypertens.* 2020;5:100029.

2. Monticone S, Burrello J, Tizzani D, Bertello C, Viola A, Buffolo F, Gabetti L, Mengozzi G, Williams TA, Rabbia F, et al. Prevalence and Clinical Manifestations of Primary Aldosteronism Encountered in Primary Care Practice. *J. Am. Coll. Cardiol.* 2017;69:1811–1820.

3. Sanga V, Seccia TM, Rossi GP. A systematic review of pathophysiology and management of familial hyperaldosteronism type 1 in pregnancy. Endocrine. 2021;74:5–10.

4. Landau E, Amar L. Primary aldosteronism and pregnancy. *Ann. Endocrinol. (Paris).* 2016;77:148–160.

5. Webb JC, Bayliss P. Pregnancy complicated by primary aldosteronism. *South. Med. J.* 1997;90:243–245.

6. Matsumoto J, Miyake H, Isozaki T, Koshino T, Araki T. Primary aldosteronism in pregnancy. J. Nippon Med. Sch. = Nihon Ika Daigaku zasshi. 2000;67:275–279.

7. Okawa T, Asano K, Hashimoto T, Fujimori K, Yanagida K, Sato A. Diagnosis and management of primary aldosteronism in pregnancy: Case report and review of the literature. *Am. J. Perinatol.* 2002;19:31–36.

8. Morton A. Primary aldosteronism and pregnancy. *Pregnancy Hypertens.* 2015;5:259–262.

9. Riester A, Reincke M. Mineralocorticoid receptor antagonists and management of primary aldosteronism in pregnancy. Eur. J. Endocrinol. 2015;

10. Affinati AH, Auchus RJ. Endocrine causes of hypertension in pregnancy. *Gland Surg.* 2020;9:69–79.

11. Kamoun M, Mnif MF, Charfi N, Kacem FH, Naceur BB, Mnif F, Dammak M, Rekik N, Abid M. Adrenal diseases during pregnancy: Pathophysiology, diagnosis and management strategies. *Am. J. Med. Sci.* 2014;347:64–73.

12. Manoharan M, Sinha P, Sibtain S. Adrenal disorders in pregnancy, labour and postpartum–an overview. J. Obstet. Gynaecol. (Lahore). 2020;40:749–758.

13. Funder JW, Carey RM, Mantero F, Murad MH, Reincke M, Shibata H, Stowasser M, Young WF. The management of primary aldosteronism: Case detection, diagnosis, and treatment: An endocrine society clinical practice guideline. *J. Clin. Endocrinol. Metab.* 2016;

14. Garovic VD, Dechend R, Easterling T, Karumanchi SA, Baird SMM, Magee LA, Rana S, Vermunt J V., August P. Hypertension in Pregnancy: Diagnosis, Blood Pressure Goals, and Pharmacotherapy: A Scientific Statement From the American Heart Association. Hypertension. 2022;79:E21–E41.

15. Rossi GP, Crimì F, Rossitto G, Amar L, Azizi M, Riester A, Reincke M, Degenhart C, Widimsky J, Naruse M, et al. Feasibility of Imaging-Guided Adrenalectomy in Young Patients With Primary Aldosteronism. *Hypertension*. 2021;79:187–195.

16. Rossi GP, Bisogni V. A useful tool to improve the case detection rate of primary aldosteronism: The aldosterone -renin ratio (ARR)-App. *J. Hypertens.* 2016;34:1019–21.

17. Wilson M, Morganti AA, Zervoudakis I, Letcher RL, Romney BM, Von Oeyon P, Papera S, Sealey JE, Laragh JH. Blood pressure, the renin-aldosterone system and sex steroids throughout normal pregnancy. *Am. J. Med.* 1980;68:97–104.

18. Rossi GP, Ceolotto G, Rossitto G, Seccia TM, Maiolino G, Berton C, Basso D, Plebani M.

Prospective validation of an automated chemiluminescence-based assay of renin and aldosterone for the work-up of arterial hypertension. *Clin. Chem. Lab. Med.* 2016;54:1441–1450.

19. Piccoli GB, Mannucci C. Preeclampsia: A diagnosis-nondiagnosis that is too easily made: the case of primary hyperaldosteronism. *Kidney Blood Press. Res.* 2020;45:363–367.

20. August P. Hypertension in a pregnant patient: How I treat. *Clin. J. Am. Soc. Nephrol.* 2019;14:1655–1657.

21. Cabassi A, Rocco R, Berretta R, Regolisti G, Bacchi-Modena A. Eplerenone use in primary aldosteronism during pregnancy. *Hypertension*. 2012;59.

22. Benbrahim OF, Agudo RG, Cadenas FC, Calero AM, González-Spínola J. Diagnóstico de una hipertensión arterial secundaria en una gestante en el primer trimestre como causa de un aborto espontáneo. *Nefrologia*. 2011;31:229–231.

23. Gioco F, Seccia TM, Gomez-Sanchez EP, Rossi GP, Gomez-Sanchez CE. Adrenal histopathology in primary aldosteronism: Is it time for a change? Hypertension. 2015;66:724–730.

24. Williams TA, Gomez-Sanchez CE, Rainey WE, Giordano TJ, Lam AK, Marker A, Mete O, Yamazaki Y, Zerbini MCN, Beuschlein F, et al. International Histopathology Consensus for Unilateral Primary Aldosteronism. *J. Clin. Endocrinol. Metab.* 2021;106:42–54.

25. Eguchi K, Hoshide S, Nagashima S, Maekawa T, Sasano H, Kario K. An adverse pregnancy-associated outcome due to overlooked primary aldosteronism. *Intern. Med.* 2014;53:2499–2504.

26. Teo AED, Garg S, Haris Shaikh L, Zhou J, Karet Frankl FE, Gurnell M, Happerfield L, Marker A, Bienz M, Azizan EAB, et al. Pregnancy, Primary Aldosteronism, and Adrenal

382 CTNNB1 Mutations . *N. Engl. J. Med.* 2015;373:1429–1436.

383 27. Shiraishi K, Kikuta K, Nitta Y, Matsuyama H. Laparoscopic adrenalectomy due to primary
384 aldosteronism during pregnancy. *Acta Urol. Jpn.* 2014;60:381–385.

385 28. Shekhar S, Haykal R, Kamilaris C, Stratakis CA. Curative resection of an aldosteronoma
386 causing primary aldosteronism in the second trimester of pregnancy. 2020;

387 29. Nursal TZ, Caliskan K, Ertorer E, Parlakgumus A, Moray G. Laparoscopic treatment of
388 primary hyperaldosteronism in a pregnant patient. *Can. J. Surg.* 2009;52:188–190.

389 30. Shigematsu K, Nishida N, Sakai H, Igawa T, Suzuki S, Kawai K, Takahara O. Primary
390 aldosteronism with aldosterone-producing adenoma consisting of pure zona glomerulosa-
391 type cells in a pregnant woman. *Endocr. Pathol.* 2009;20:66–72.

392 31. Lenzini L, Prisco S, Caroccia B, Rossi GP. Saga of familial hyperaldosteronism yet a new
393 channel. *Hypertension*. 2018;71:1010–1014.

394 32. Lifton RP, Dluhy RG, Powers M, Rich GM, Cook S, Ulick S, Lalouel JM. A chimaeric llβ-
395 hydroxylase/aldosterone synthase gene causes glucocorticoid-remediable aldosteronism and
396 human hypertension. *Nature*. 1992;355:262–5.

397 33. Zarnegar R, Young WF, Lee J, Sweet MP, Kebebew E, Farley DR, Thompson GB, Grant
398 CS, Clark OH, Duh QY. The aldosteronoma resolution score predicting complete resolution
399 of hypertension after adrenalectomy for aldosteronoma. *Ann. Surg.* 2008;247:511–518.

400 34. Vidyasagar S, Kumar S, Morton A. Screening for primary aldosteronism in pregnancy.
401 *Pregnancy Hypertens.* 2021;25:171–174.

402 35. Gunganah K, Carpenter R, Drake WM. Eplerenone use in primary aldosteronism during
403 pregnancy. *Clin. Case Reports*. 2016;4:81–82.

36. Eschler DC, Kogekar N, Pessah-Pollack R. Management of Adrenal Tumors in Pregnancy. Endocrinol. Metab. Clin. North Am. 2015;44:381–397.

37. Escher G. Hyperaldosteronism in pregnancy. Ther. Adv. Cardiovasc. Dis. 2009;3:123–132.

38. Rossi GP, Cesari M, Cuspidi C, Maiolino G, Cicala MV, Bisogni V, Mantero F, Pessina AC. Long-term control of arterial hypertension and regression of left ventricular hypertrophy with treatment of primary aldosteronism. *Hypertension*. 2013;62:62–69.

39. Rossi GP. Primary Aldosteronism: JACC State-of-the-Art Review. J. Am. Coll. Cardiol. 2019;

40. Groves TD, Corenblum B. Spironolactone therapy during human pregnancy. Am. J. Obstet. Gynecol. 1995;172:1655–1656.

41. De Arriba G, Sánchez-Heras M, Basterrechea MA. Gitelman syndrome during pregnancy: A therapeutic challenge. *Arch. Gynecol. Obstet.* 2009;280:807–809.

42. Kolkhof P, Jaisser F, Kim SY, Filippatos G, Nowack C, Pitt B. Steroidal and novel non-steroidal mineralocorticoid receptor antagonists in heart failure and cardiorenal diseases: Comparison at bench and bedside. In: Handbook of Experimental Pharmacology. Handb Exp Pharmacol; 2017. p. 271–305.

43. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/215341Orig1s000IntegratedR.pdf.

44. Sukor N, Gordon RD, Yee KK, Jones M, Stowasser M. Role of unilateral adrenalectomy in bilateral primary aldosteronism: A 22-year single center experience. *J. Clin. Endocrinol. Metab.* 2009;94:2437–2445.

45. Sanga V, Lenzini L, Seccia TM, Rossi GP. Familial hyperaldosteronism type 1 and

pregnancy: successful treatment with low dose dexamethasone. *Blood Press.* 2021;30:133–137.

46. Bramham K, Parnell B, Nelson-Piercy C, Seed PT, Poston L, Chappell LC. Chronic hypertension and pregnancy outcomes: Systematic review and meta-analysis. *BMJ*. 2014;348.

47. Wu DD, Gao L, Huang O, Ullah K, Guo MX, Liu Y, Zhang J, Chen L, Fan JX, Sheng JZ, et al. Increased Adverse Pregnancy Outcomes Associated with Stage 1 Hypertension in a Low-Risk Cohort: Evidence from 47 874 Cases. *Hypertension*. 2020;772–780.

48. Tita AT, Szychowski JM, Boggess K, Dugoff L, Sibai B, Lawrence K, Hughes BL, Bell J, Aagaard K, Edwards RK, et al. Treatment for Mild Chronic Hypertension during Pregnancy. *N. Engl. J. Med.* 2022;386:1781–1792.

49. Lecarpentier E, Tsatsaris V, Goffinet F, Cabrol D, Sibai B, Haddad B. Risk Factors of Superimposed Preeclampsia in Women with Essential Chronic Hypertension Treated before Pregnancy. *PLoS One*. 2013;8.

50. Rossi GP, Crimì F, Rossitto G, Amar L, Azizi M, Riester A, Reincke M, Degenhart C, Widimsky J, Naruse M, et al. Identification of Surgically Curable Primary Aldosteronism by Imaging in a Large, Multiethnic International Study. *J. Clin. Endocrinol. Metab.* 2021;106:E4340–E4349.

51. Santos CMDC, Pimenta CADM, Nobre MRC. The PICO strategy for theresearch question construction and evidence search. Rev. Lat. Am. Enfermagem. 2007;15:508–511.

52. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and

elaboration. *PLoS Med.* 2009;6.

53. Quinkler M, Diederich S. Difference of in vivo and in vitro antimineralocorticoid potency of progesterone. *Endocr. Res.* 2002;28:465–70.

54. Zelinka T, Petrák O, Rosa J, Holaj R, Štrauch B, Widimský J. Primary Aldosteronism and Pregnancy. *Kidney Blood Press. Res.* 2020;45:275–285.

55. Krysiak R, Samborek M, Stojko R. Primary aldosteronism in pregnancy. *Acta Clin. Belg.* 2012;67:130–134.

56. Albiger NM, Sartorato P, Mariniello B, Iacobone M, Finco I, Fassina A, Mantero F. A case of primary aldosteronism in pregnancy: Do LH and GNRH receptors have a potential role in regulating aldosterone secretion? *Eur. J. Endocrinol.* 2011;164:405–412.

57. Lu W, Zheng F, Li H, Ruan L. Primary aldosteronism and pregnancy: A case report: Clinical-Scientific Notes. *Aust. New Zeal. J. Obstet. Gynaecol.* 2009;49:558.

58. Al-Ali NA, El-Sandabesee D, Steel SA, Roland JM. Conn's syndrome in pregnancy successfully treated with amiloride. *J. Obstet. Gynaecol. (Lahore).* 2007;27:730–731.

59. Takehiko Murakami, Eriko Watanabe Ogura, Yuji Tanaka MY. Case report High blood pressure lowered by pregnancy. 2000;356:2000.

60. Nezu M, Miura Y, Noshiro T, Inoue M. Primary aldosteronism as a cause of severe postpartum hypertension in two women. *Am. J. Obstet. Gynecol.* 2000;182:745–746.

61. Kreze A, Kothaj P, Dobáková M, Rohoň S. Primary aldosteronism caused by aldosterone-producing adenoma in pregnancy - Complicated by EPH gestosis. *Wien. Klin. Wochenschr.* 1999;111:855–857.

62. Fujiyama S, Mori Y, Matsubara H, Okada S, Maruyama K, Masaki H, Yonemoto T, Nagata

T, Umeda Y, Matsuda T, et al. Primary aldosteronism with aldosterone-producing adrenal adenoma in a pregnant woman. *Intern. Med.* 1999;38:36–39.

63. Saito Y, Omoto T, Fukuda M. Lobular pattern of choriocapillaris in pre-eclampsia with aldosteronism. *Br. J. Ophthalmol.* 1990;74:702–703.

64. Kosaka K, Onoda N, Ishikawa T, Iwanaga N, Yamamasu S, Tahara H, Inaba M, Ishimura E, Ogawa Y, Hirakawa K. Laparoscopic adrenalectomy on a patient with primary aldosteronism during pregnancy. *Endocr. J.* 2006;53:461–466.

65. Shalhav AL, Landman J, Afane J, Levi R, Clayman R V. Laparoscopic adrenalectomy for primary hyperaldosteronism during pregnancy. *J. Laparoendosc. Adv. Surg. Tech. - Part A*. 2000;10:169–171.

66. Solomon CG, Thiet MP, Moore F, Seely EW. Primary hyperaldosteronism in pregnancy: A case report. *J. Reprod. Med. Obstet. Gynecol.* 1996;41:255–258.

67. Baron F, Sprauve ME, Huddleston JF, Fisher AJ. Diagnosis and surgical treatment of primary aldosteronism in pregnancy: A case report. *Obstet. Gynecol.* 1995;86:644–645.

68. Aboud E, De Swiet M, Gordon H. Primary aldosteronism in pregnancy - Should it be treated surgically ? *Ir. J. Med. Sci.* 1995;164:279–280.

69. Ronconi V, Turchi F, Zennaro MC, Boscaro M, Giacchetti G. Progesterone increase counteracts aldosterone action in a pregnant woman with primary aldosteronism. *Clin. Endocrinol. (Oxf).* 2011;74:278–279.

70. Campino C, Trejo P, Carvajal CA, Vecchiola A, Valdivia C, Fuentes CA, Delgado JF, Lagos CF, Aglony M, Carrasco C, et al. Pregnancy normalized familial hyperaldosteronism type I: A novel role for progesterone. *J. Hum. Hypertens.* 2015;29:138–9.

71. Hamilton E, O'Callaghan C, O'Brien RM, Stowasser M, Gordon R, Zajac J, Grossmann M.

Familial hyperaldosteronism type 1 in pregnancy. *Intern. Med. J.* 2009;39:135–6.

72. Mulatero P, Cella SM Di, Williams TA, Milan A, Mengozzi G, Chiandussi L, Gomez-Sanchez CE, Veglio F. Glucocorticoid remediable aldosteronism: Low morbidity and mortality in a four-generation Italian pedigree. *J. Clin. Endocrinol. Metab.* 2002;87:3187–91.

73. Wyckoff JA, Seely EW, Hurwitz S, Anderson BF, Lifton RP, Dluhy RG. Glucocorticoid-remediable aldosteronism and pregnancy. *Hypertension*. 2000;35:668–72.

Tables and Figures Legends

Figure 1: Changes in plasma aldosterone concentration (PAC, ng/dl), direct active renin concentration (DRC, mIU/l), and aldosterone-renin ratio (ARR, ng/mIU) from the 8th to the 38th gestational week in a multiethnic cohort of women on a normal sodium intake (100-150 Na^+ mEq/day) during normal pregnancy. Values were re-elaborated with the ARR-app [16] from Wilson et al. [17]. The square symbols show mean and 95% confidence interval. The grey circles and lines indicate values three-fold higher (for PAC and ARR) or lower (for DRC) than the 95% confidence interval. The dashed areas indicate values that should raise the suspicion of PAP. Please note that as the spread of the values increased toward the end of pregnancy, the dashed areas narrowed. Please also note that up to the 32th gestational week the proposed ARR cut-offs are lower than the 20.6 ng/mIU (identified here by the horizontal line) used to identify PA before and after pregnancy [18].

Abbreviations: ARR: aldosterone-renin ratio; DRC: direct renin concentration; n. pat.: number of patients; PAC: plasma aldosterone concentration.

Figure 2: Maternal and foetal complications rate in pregnancy in women with unilateral medically treated PA, unilateral surgically treated PA during pregnancy, bilateral medically treated PA and FH-1. The overall rate of complications was compared with Chi-square test. For comparisons between groups on overall complications see Table S5.

519 Abbreviations: C-section: caesarean section; IUGR: intrauterine growth restriction; n: number.

520 Figure 3: Maternal and foetal complications rate in pregnancy in women with sporadic PA vs
521 essential hypertension [49]. For comparisons between groups on overall complications see Table S6.

522 Abbreviations: EH: essential hypertension; IUGR: intrauterine growth restriction.

523 Figure 4: Proposed algorithm for the screening and management of women with hypertension and
524 possible hyperaldosteronism.

525 * Corresponding values are 26 (ng/mL)/(mg/mL/hour). For conversion use the ARR-app [16].

526 Abbreviations: ARR: aldosterone-renin ratio; AVS: adrenal venous sampling; BP: blood pressure;
527 FH-1: familial hyperaldosteronism type 1; HT: hypertension; MRA: mineralocorticoid receptor
528 antagonist; PA: primary aldosteronism.

529 Table 1: Characteristics of the women with PAP and results of the analysis of the cases reported from
530 1990 to 2021. For extended version of this table see Table S4.

531 Abbreviations: ARR: aldosterone-renin ratio; AVS: adrenal venous sampling; BP: blood pressure; C
532 section: caesarean section; CT: computed tomography; dexa.: dexamethasone; FH-1: familial
533 hyperaldosteronism type 1; HT: hypertension; ICU: intensive care unit; IUFD: intrauterine foetal
534 death; IUGR: intrauterine growth restriction; LA: laparoscopic adrenalectomy; MR: magnetic
535 resonance; MRA: mineralocorticoid receptor antagonist; n: number; N/A: not available; NA: not
536 applicable; PA: primary aldosteronism; PE: preeclampsia; pregn.: pregnancy; SGA: small for
537 gestational age; tr.: trimester; US: ultrasound; w.: gestational week.

Tables and Figures

Figure 1:

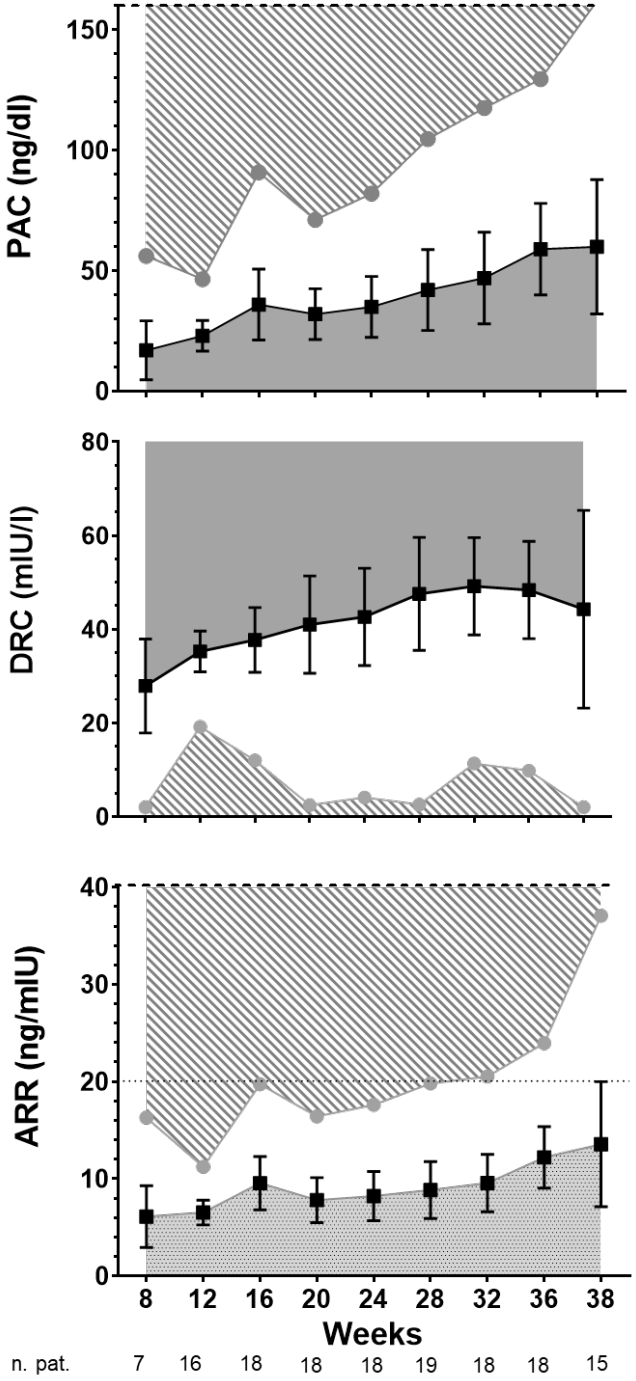


Table 1:

	N. of cases	Mean age (ys)	Previous pregnancies	HT discover (timing and BP increase in pregnancy)	PA diagnosis (timing)	Adrenalectomy (timing)	AVS guided (n)	Histological confirmation	HT cure after adrenalectomy (clinically / biochemically)
Unilateral medically treated PA	28	30.7	7/28 (2/7 complicated)	12 before pregnancy 14 during pregnancy → BP increase during 2nd trimester (mean 20.8 w, ranging from 8 to 35 w) 2 in the first weeks after delivery	1 before conception (AVS confirmed) 3 during pregnancy 24 after pregnancy (8 AVS confirmed)	27/28 after pregnancy (19.5 months after delivery) (one woman is waiting for surgery)	9/28 (32%)	27/27 (100%)	23/27 (85%) / 14/14 (100%)
Unilateral surgically treated PA during pregnancy	10	27.7	4/10 (4/4 complicated)	8 before pregnancy 2 during pregnancy → BP increase around 11-12 w	3 before conception 7 during pregnancy (in Shiraishi et al. case [27] ACTH-stimulated AVS was performed during pregnancy before 24th w)	10/10 during 2nd trimester (range 14-26 w)	2/10 (20%)	10/10 (100%)	1/10 (10%) / 1/1 (100%)
Bilateral medically treated PA	15	30.7	3/7 (2/3 complicated) (unknown for 8 women)	15 before pregnancy → BP increase mainly during the 2nd – 3rd trimester (mean 24 w)	13 before conception (9 AVS confirmed) 2 after pregnancy (both AVS confirmed)	0/7	11/15 (73%)	NA	NA
FH-1	27	26.2	12/27 (not known if complicated)	most of the cases before → generally good BP control during pregnancy without medications	most of the cases before pregnancy	0/27	NA	NA	NA

(continued…)

	Mean n. of anti-HT drugs before pregnancy	Mean n. of anti-HT drugs 1st trimester	Mean n. of anti-HT drugs 2nd trimester	Mean n. of anti-HT drugs 2nd trimester after LA	Mean n. of anti-HT drugs 3rd trimester	Mean n. of anti-HT drugs at follow-up after LA	MRA use	Delivery (preterm --- miscarriage)	Complicated pregnancies	C-section	Foetal mortality	IUGR	Newborn ICU stay
Unilateral medically treated PA	1 (data available for 4 women)	0.67	1.27	NA	1.44	0.37	1/28 no male foetus feminization	13/28 (46.4%) (mean 34.5 w) --- 1/28 (3.6%) (at 10th w)	17/28 (60.7%) (8 cases by PE, 4 by foetal distress, 2 by premature membrane rupture, 1 by HELLP syndrome, 1 by abruptio placentae, 1 by herpes genitalis, 1 by breech presentation, 1 by miscarriage)	17/27 (63%) (14/17 urgent)	2/28 (7%) (1 miscarriage at 10th w; 1 baby died after 3 months ICU stay after urgent C-section at 27 w for PE)	6/27 (22%)	2/27 (7.4%)
Unilateral surgically treated PA during pregnancy	1.5 (data available for 5 women)	1.50 (at least 6 women over 10 needed a drug)	2.25	1.00	1.00	2	2/10 no male foetus feminization	6/10 (60%) (mean 33.9 w) --- 1/10 (10%) (at 26th w for failure in placenta blood flow)	6/10 (60%) (3 cases by PE, 2 by impaired umbilical artery flow with foetal distress, 1 by miscarriage)	6/9 (66.7%) (4/6 urgent)	2/10 (20%) (1 miscarriage at the 26th gestational w; 1 baby died after 3 months ICU stay for sepsis after urgent C-section at 28 w for PE)	5/10 (50%)	3/9 (33.3%)
Bilateral medically treated PA	1 (6 women over 7 needed at least 1 drug, 1 no drugs)	0.4 (data available for 5 women)	1.3	NA	0.8 (data available for 5 women)	NA	0/15	10/15 (66.6%) (mean 33.3 w) --- 2/15 (13.3%) (at 12th and at 20th w)	10/15 (66.6%) (5 cases by PE, 2 by impaired umbilical artery flow, 2 by miscarriage, 1 by premature membrane rupture and antepartum hemorrhage)	11/14 (78.6%) (7/11 urgent)	2/15 (13.3%) (one miscarriage at the 12th and one at the 20th w)	5/14 (35.7 %)	2/14 (14.3%)
FH-1	1	0.1	0.04 (data were available only for half patients)	NA	0.18	NA	0/27 (3 cases took K^+-sparing diuretics not better defined)	2/19 (10.5%) --- 0/27 (0%)	5/27 (18.5%) (1 PE, 1 chorioamnionitis, 1 failure of placental separation, 2 consistent blood loss during delivery)	7/27 (26%) (4/7 urgent)	0/27 (0%)	0/27 (0%)	N/A
Non-familial PA (excluding FH-1 cases)								29/53 (54.7%) --- 4/53 (7.5%)	33/53 (62.2%) (PE 16 cases: 30.2%)	34/50 (68%)	6/53 (11.3%)	16/51 (31.4 %)	7/50 (14%)

Figure 2:

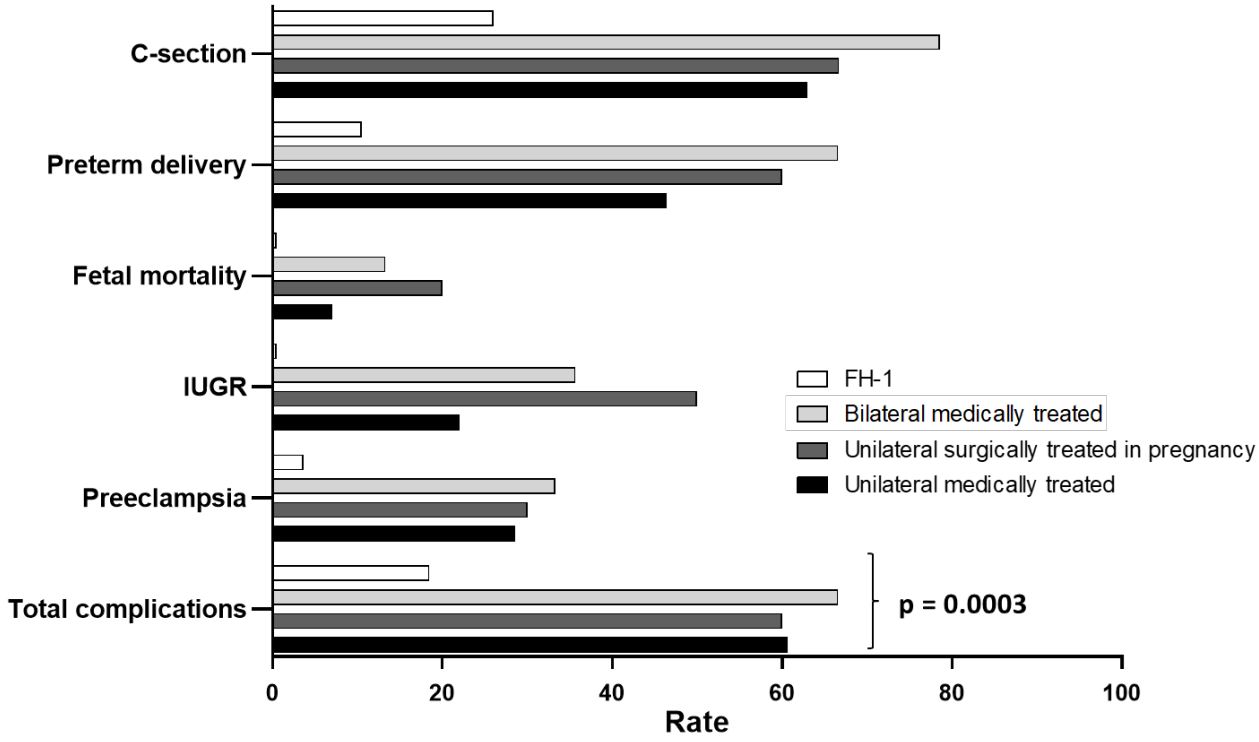


Figure 3:

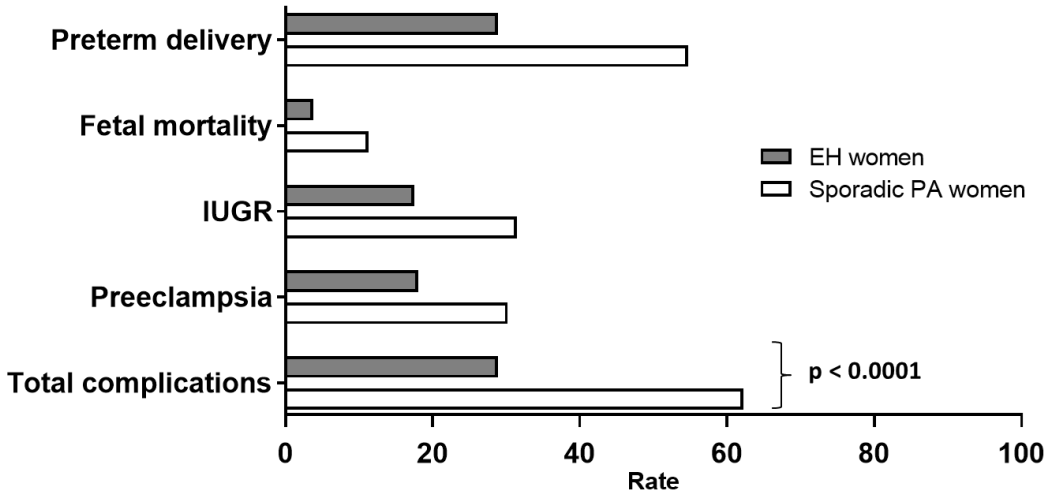
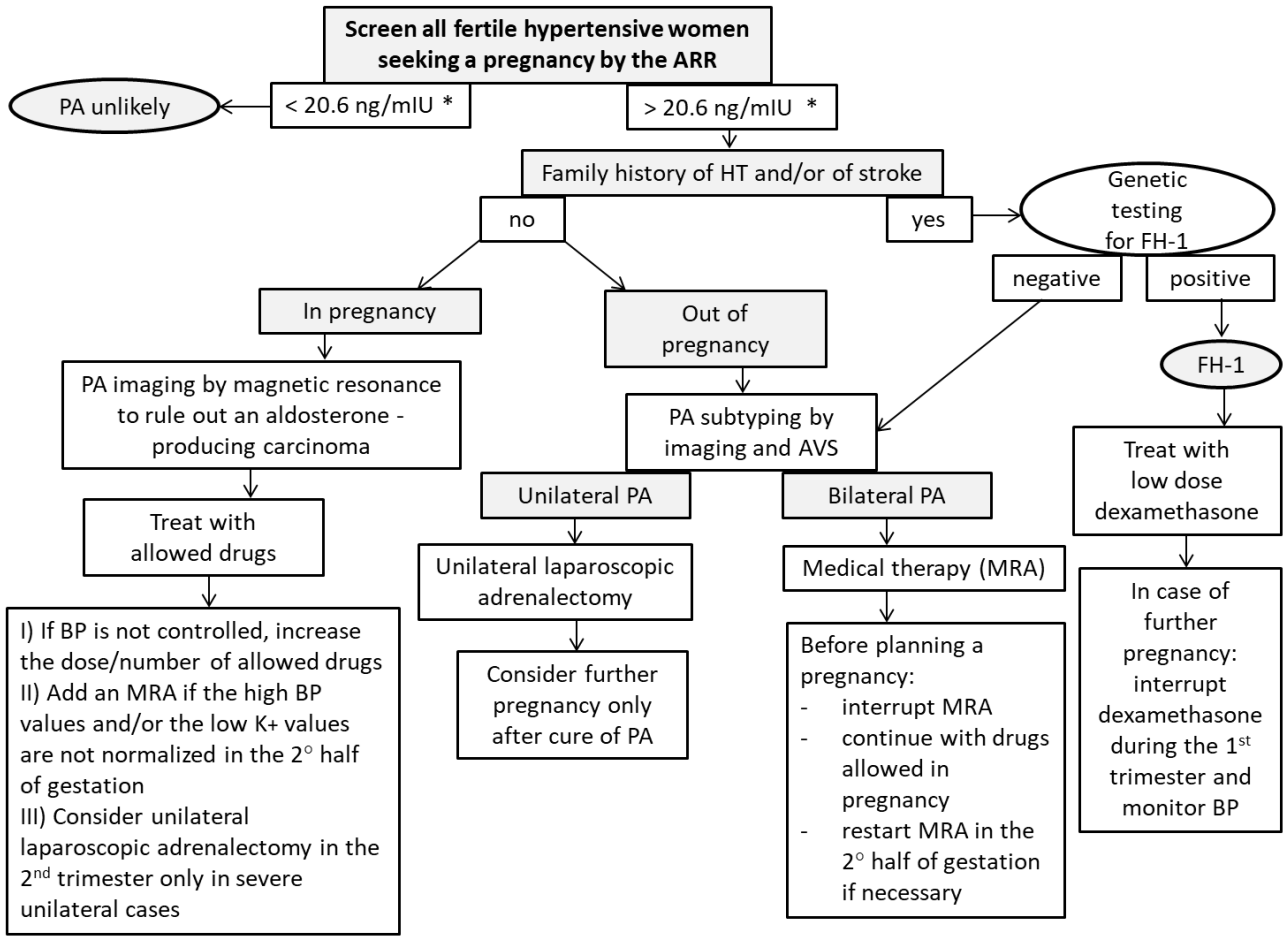


Figure 4:


Screen all fertile hypertensive women seeking a pregnancy by the ARR
PA unlikely
< 20.6 ng/mIU *
> 20.6 ng/mIU *
Family history of HT and/or of stroke
no
yes
Genetic testing for FH-1
negative
positive
FH-1
In pregnancy
Out of pregnancy
PA imaging by magnetic resonance to rule out an aldosterone - producing carcinoma
PA subtyping by imaging and AVS
Treat with low dose dexamethasone
Treat with allowed drugs
Unilateral PA
Bilateral PA
Unilateral laparoscopic adrenalectomy
Medical therapy (MRA)
I) If BP is not controlled, increase the dose/number of allowed drugs
II) Add an MRA if the high BP values and/or the low K+ values are not normalized in the 2° half of gestation
III) Consider unilateral laparoscopic adrenalectomy in the 2nd trimester only in severe unilateral cases
Consider further pregnancy only after cure of PA
Before planning a pregnancy:
- interrupt MRA
- continue with drugs allowed in pregnancy
- restart MRA in the 2° half of gestation if necessary
In case of further pregnancy: interrupt dexamethasone during the 1st trimester and monitor BP

ONLINE-ONLY DATA SUPPLEMENT

Management and Outcomes of Primary Aldosteronism in Pregnancy: A Systematic Review

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Complete Methods

We searched the PubMed and EuropePMC databases using a **P**opulation, **I**ntervention, **C**omparison and **O**utcome (PICO) strategy [51] (Table S1) and the **P**referred **R**eporting **I**tems for **S**ystematic reviews and **M**eta-**A**nalyses Statement (PRISMA) method [52]. The following boolean operators ['Primary aldosteronism' OR 'Hyperaldosteronism'] AND ['Pregnancy' OR 'Pregnant'] (Table S1) were used to identify available information on management of PA in pregnancy (Figure S1). Table S2 provides comprehensive data on the key information that were extracted from the retrieved papers.

FH-1 overview

In FH-1, BP values fell during the 1st trimester along with the generally modest increase of aldosterone production, the antagonist action of progesterone on the mineralocorticoid receptor [53] and the prostaglandin-induced resistance to angiotensin II [36].
Immediate withdrawal of dexamethasone in those, who become pregnant, is advised, followed by careful monitoring of BP values and serum K^+ levels during the 1st and 2nd trimester [3], when both PAC and BP values rose. Very low- to low-dose dexamethasone can be used in these women if BP rises during the 2nd and/or the 3rd trimester, with dose titration to normalize high BP, PAC, renin and serum K^+ levels. Our preference goes to dexamethasone, which potently suppresses the ACTH drive on the chimeric gene, and proved to be safe for both the mother and the baby in a recent case [45].

Foetal outcomes in medically treated PA women: unilateral vs bilateral forms

In medically treated women with unilateral PA, foetal mortality rate (7% vs 13.3%) and IUGR rate (22% vs 35.7%) were half as common as in women with bilateral PA (Table 1). The rate of miscarriage rate was much lower in unilateral than in bilateral forms (3.6% vs 13.3%). However, in both conditions, a high proportion of preterm delivery occurred (46.4% vs 66.6%). The worse outcome seen in bilateral than in unilateral forms is not explained by treatment differences and, more likely, probably reflects the greater severity of the disease as both cohorts were similarly treated pharmacologically.

Foetal outcomes in unilateral PA forms: medical vs surgical treatment during pregnancy

In patients with unilateral PA, foetal outcomes were better in medically treated than in surgically treated women: the rate of baby death (7% vs 20%), IUGR (22% vs 50%) and of miscarriage (3.6% vs 10%) were lower (Table 1 and Figure 2). However, preterm delivery occurred in a high rate (46.4% vs 60%) in both treatment groups.

Characteristics of medically treated women with PAP: complicated vs non-complicated pregnancies

The complication rate of medically treated women with unilateral or bilateral PAP was 63%. Compared to non-complicated women, women with complications had a history of prior complicated pregnancies two-fold higher (13.6% vs 7%); their HT was diagnosed at a slightly younger age (26 vs 28.4 years old) and the BP increase occurred earlier during pregnancy (24.9 vs 30 week). Age (30.7 vs 30.8 years age) and the average number of anti-hypertensive drugs taken before conception (around 1 drug) were identical, but during pregnancy the mean number of anti-hypertensive drugs was three-fold higher in complicated than in non-complicated women (1.48 vs 0.54). Thus, on the whole, complicated cases seem to show a more severe form of HT than uncomplicated women.

Subsequent pregnancies

Reported PAP cases provided scant or no information and/or conflicting data on subsequent pregnancies. In 3 women, who were adrenalectomized after gestation a second pregnancy after some years was uncomplicated [25,54]; in another woman, who was not cured by adrenalectomy during gestation, but showed good control of high BP values with 3 antihypertensive agents, a new pregnancy was complicated by preeclampsia that required an emergency C-section [35]. In three women with bilateral PA, a new pregnancy was complicated: two women developed preeclampsia [8,54]; the third required C-section [55].

Supplemental Tables and Figures

Table S1: PICO strategy applied for the research of clinical cases of patients with PA during pregnancy (articles from 1990 to 2021).

	Description
Population	[Primary aldosteronism OR hyperaldosteronism] AND [Pregnancy OR pregnant]
Intervention	Surgical OR Medical treatment
Comparison	Surgically vs Medically treated Primary aldosteronism
Outcome	Maternal outcomes (hypertension cure, complications, etc), foetal outcomes (survival, weight, ICU stay, etc)

Table S2: Parameters considered for the analysis.

	Parameters considered
Maternal features	Ethnicity Maternal age Previous pregnancies Comorbidities HT diagnosis (timing) PA identification (timing and diagnostic approach)
Pregnancy course and complications	Complicated pregnancies rate Miscarriage Preeclampsia (new-onset hypertension [blood pressure > 140/90 mmHg] plus new unexplained proteinuria [> 300 mg/24 hours or a urine protein/creatinine ratio of ≥ 0.3] after 20 weeks) Eclampsia (unexplained generalized seizures in patients with preeclampsia) Preterm delivery (before 37th gestational week) Delivery week C-section rate, urgent C-section rate
Maternal outcomes	BP before, during, and after pregnancy Biochemical values before, during, and after pregnancy (direct renin, aldosterone, serum potassium, others) Drugs treatment before, during, and after pregnancy (HT drugs and potassium supplementation; use of MRA in pregnancy) Surgical therapy with adrenalectomy (timing and approach) Histological confirmation HT cure after adrenalectomy (clinically / biochemically)
Foetal outcomes	Survival rate Weight at birth and weight centile IUGR rate ICU stay Permanent disability

Abbreviations: BP: blood pressure; C-section: caesarean section; HT: hypertension; ICU: intensive care unit; IUGR: intrauterine growth restriction; MRA: mineralocorticoid receptor antagonist; PA: primary aldosteronism.

Table S3: Cases available in the literature (from 1990 to 2021) of patients affected by PA who underwent a pregnancy: treatment, BP control and outcomes.

	N. of cases	References	Diagnosis confirmation	Anti-hypertensive treatment during pregnancy	HT discovery timing and blood pressure course	Delivery	FH-1 testing	Baby outcome
Unilateral medically treated PA	31	1) Zelinka et al 2020 (case 1) [54] 2) Zelinka et al 2020 (case 2) [54] 3) Zelinka et al 2020 (case 3) [54] 4) Zelinka et al 2020 (case 4) [54] 5) Zelinka et al 2020 (case 5) [54] 6) Zelinka et al 2020 (case 6) [54] 7) Zelinka et al 2020 (case 7) [54] 8) Zelinka et al 2020 (case 8) [54] 9) Zelinka et al 2020 (case 9) [54] 10) Zelinka et al 2020 (case 10) [54] 11) Zelinka et al 2020 (case 11) [54] 12) Zelinka et al 2020 (case 12) [54] 13) Zelinka et al 2020 (case 13) [54]	1) CT scan after delivery 2) CT scan 3 years later 3) CT scan 12 years later 4) CT scan 3 years later 5) CT scan 1 year later 6) CT scan 1 year later 7) CT scan 6 months later 8) CT scan and AVS 1 year later 9) CT scan 3 years later 10) CT scan and AVS 9 months later 11) CT scan and AVS 1 year later 12) CT scan 6 months later 13) CT scan and AVS after delivery 14) CT scan after delivery (surgical workup ongoing)	1) No therapy 2) No therapy 3) No therapy until end of gestation, when methyldopa was started with poor effect 4) No therapy until 3rd trimester, when methyldopa was started with poor effect 5) She started therapy from 1st trimester; at 27 w new BP increase not responsive to nitroprussiate 6) Monotherapy 7) Methyldopa was started during pregnancy 8) N/A 9) Amlodipine 10) Escalating antihypertensive treatment (higher doses of alpha-methyldopa and metoprolol) 11) No therapy 12) Increasing number and doses of antihypertensives 13) No therapy 14) No therapy 15) Nicardipine 100 mg/d and labetalol 200 mg/d 16) Nifedipine 90 mg extended release and labetalol 1200	1) HT found at the 4th month of pregnancy and defined as white-coat HT; APA diagnosed after delivery 2) BP increase at the end of gestation; APA diagnosed 3 years after delivery 3) BP increase at 35 w; APA diagnosed 12 years after delivery 4) BP normalization in the 1st trimester which allowed drugs cessation; then, BP increase in the 3rd trimester with poor control despite methyldopa; APA diagnosed 3 years later 5) HT found at 1st trimester; BP increase at 27 w despite therapy, associated with PE; APA diagnosed 1 year later 6) BP improvement during 1st trimester; BP increase in the 3rd trimester, complicated by PE; APA diagnosed 1 year after delivery 7) HT found in pregnancy; BP normalized after delivery; APA diagnosed 6 months	1) C section at term (40 w) 2) Spontaneous delivery with induction (40 w); IUGR 3) C section for uncontrolled HT and PE (36 w) 4) Spontaneous delivery (40 w) 5) C section for PE and foetal hypoxia (27 w) 6) Spontaneous delivery with induction for PE (39 w) 7) C section for breech presentation (40 w) 8) Spontaneous delivery (40 w) 9) C section for premature membrane rupture (36 w)	1) N/A 2) N/A 3) N/A 4) N/A 5) N/A 6) N/A 7) N/A 8) N/A 9) N/A 10) N/A 11) N/A 12) N/A 13) N/A 14) N/A 15) N/A 16) N/A 17) N/A 18) N/A 19) N/A 20) N/A 21) N/A 22) N/A 23) N/A 24) N/A 25) N/A 26) N/A 27) N/A 28) N/A 29) N/A 30) N/A	1) normal 2) female neonate weight 5-10th centile 3) normal 4) normal 5) male neonate weight 15-20th centile 6) normal 7) normal 8) normal 9) male neonate weight 10-25th centile 10) male neonate < 5th centile 11) normal 12) female neonate < 5th centile 13) normal 14) normal 15) neonate weight 2nd centile, followed by 5 months stay in ICU

		14) Piccoli et al. 2020 (case 1) [19] 15) Piccoli et al. 2020 (case 2) [19] 16) August 2019 [20] 17) Teo et al. 2015 (case 1) [26] 18) Eguchi et al. 2014 [25] 19) Cabassi et al. 2012 [21] 20) Albiger et al. 2011 [56] 21) Fikri Benbrahim 2011 [22] 22) Lu et al. 2009 [57] 23) Al-ali et al. 2007 [58] 24) Okawa et al. 2002 [7] 25) Matsumoto et al. 2000 [6] 26) Murakami et al. 2000 [59] 27) Nezu et al. 2000 (case 1) [60] 28) Nezu et al. 2000 (case 2) [60] 29) Kreze et al. 1999 [61] 30) Fujiyama et al. 1999 [62] 31) Saito et al. 1990 [63]	15) CT scan after delivery (no clear adenoma, probable unilateral hyperplasia; workup ongoing) 16) CT scan after delivery 17) CT scan after delivery 18) AVS confirmed after delivery 19) MR during pregnancy, CT scan after delivery 20) AVS confirmed after delivery 21) CT scan and MR after delivery 22) US scan during pregnancy, CT scan after delivery 23) AVS confirmed after delivery 24) CT scan and I-131 iodo-methyl-norcholesterol scintigraphy after delivery 25) AVS confirmed before pregnancy	mg/d (increasing doses during pregnancy) 17) Amiloride 15 mg 18) Methyldopa, hydralazine and nifedipine L with scarce efficacy 19) Nifedipine; at 24 w methyldopa was added; at 27 w eplerenone 50 mg/d was added, up titrated to 100 mg/d 20) Calcium channel blocker 21) Methyldopa 1500 mg/d 22) Nitroglycerine + nifedipine + labetalol + furosemide 23) Amiloride 15 mg/d; from 37 w: amiloride 20 mg/d + methyldopa 1g/d + labetalol 24) Dihydralazine (2 mg/h, intravenously) and methyldopa (1000 mg/day, p.o.) 25) Hydralazine chloride 90 mg/d and nifedipine 40 mg/d since 36 w 26) N/A 27) No therapy 28) No therapy 29) N/A; the patient refused adrenalectomy proposed during the 2nd trimester 30) Methyldopa 750 mg/d; at 30 w switched to hydralazine intravenously + nifedipine 40 mg/d for uncontrolled HT 31) N/A	after delivery when BP increased again 8) N/A 9) HT before pregnancy; BP increase at the 8th month of pregnancy 10) HT before pregnancy; worsened hypertension, despite escalating antihypertensive treatment 11) HT found in pregnancy; gradual BP increase 12) HT before pregnancy; worsened HT during 2nd trimester 13) Mild gestational hypertension (BP levels not exceeding 150/90 mmHg) 14) HT found at 25 w; BP not systematically measured during pregnancy; PA diagnosed after delivery 15) HT before pregnancy (diagnosed in a previous pregnancy complicated by PE); poor BP control during pregnancy; PA diagnosed after delivery 16) HT before pregnancy; BP not controlled in the 3rd trimester despite increasing doses of nifedipine and labetalol; APA diagnosed after delivery	10) C section for foetal hypoxia, uncontrolled HT and IUGR (40 w) 11) C section for HT (39 w) 12) C section for PE (31 w) 13) Spontaneous delivery (40 w) 14) Vaginal delivery (39 w) 15) C section for PE, severe IUGR and inversion of umbilical blood flow (27 w) 16) C section for PE (32 w) 17) Vaginal delivery (38 w) 18) C section for PE (30 w) 19) Delivery for persistent HT (35 w) 20) C section for uncontrolled HT (36 w) 21) Spontaneous miscarriage for persistent HT (10 w)	31) N/A	16) male neonate weight 5-10th centile 17) normal 18) SGA 19) male neonate weight 10-25th centile, with no evidence of feminization 20) normal 21) spontaneous miscarriage 22) N/A 23) normal 24) foetal growth retardation 25) male neonate weight 2.5-5th centile 26) N/A 27) N/A 28) N/A 29) deceased at the 9th day after delivery (27 w) (weight N/A) 30) foetal distress; female neonate weight 50-75th centile

			26) CT scan after delivery 27) CT scan and I-131 iodo-methyl-norcholesterol scintigraphy during dexa. administration after delivery 28) CT scan and I-131 iodo-methyl-norcholesterol scintigraphy during dexa. administration after delivery 29) N/A 30) CT scan, MR and I-131 iodo-methyl-norcholesterol scintigraphy during dexa. administration after delivery 31) CT scan after delivery		17) HT found at 17 w; BP increase at 37 w; APA diagnosed after delivery 18) HT before pregnancy; BP increase at 24 w; poor BP control with drugs; APA diagnosed after delivery 19) HT before pregnancy; BP increase to 155/110 mmHg at 21 w under nifedipine; APA suspected during pregnancy 20) HT found at 28 w; well controlled; APA diagnosed after delivery 21) HT found at 8 w; poor control with methyldopa; APA diagnosed after delivery 22) HT found at 20 w; poor control with several drugs; APA suspected during pregnancy 23) HT found at 17 w; good control until 37 w; APA diagnosed after delivery 24) HT before pregnancy; BP increase at 22 w (180/100 mmHg); despite medical treatment, BP remained uncontrolled 25) APA diagnosed before pregnancy not yet treated; BP increase at 31 w 26) HT diagnosed before pregnancy; BP improvement during pregnancy till	22) Emergency C section for HELLP, HT and placenta previa (25 w) 23) Vaginal delivery (38 w) (moderate PE at 37 w) 24) Elective C section for uncontrolled HT, foetal heart rate deceleration and foetal growth restriction (27 w) 25) Abruptio placentae (38 w) 26) At term 27) N/A 28) N/A 29) C section for PE (27 w) 30) C section for acute pulmonary edema of the mother + foetal distress (31 w) 31) C section for PE (34 w)		31) N/A

					normotension; APA diagnosed after delivery 27) Normotensive before and during pregnancy; BP increase 1 month post-partum and consequent APA diagnosis 28) Normotensive before and during pregnancy; BP increase 18 days post-partum and consequent APA diagnosis 29) Poor BP control; APA diagnosed in pregnancy 30) HT found at 24 w; uncontrolled HT under treatment, complicated by pulmonary edema; APA diagnosed after delivery 31) N/A; APA diagnosed after delivery			
Unilateral surgically treated PA during pregnancy	10	1) Shekhar et al. 2020 [28] 2) Gunganah et al. 2015 [35] 3) Shiraishi et al. 2014 [27] 4) Nursal et al. 2009 [29] 5) Shigematsu et al. 2009 [30] 6) Kosaka et al. 2006 [64] 7) Shalhav et al. 2000 [65]	1) AVS confirmed before pregnancy 2) MR during pregnancy 3) MR during pregnancy 4) MR during pregnancy 5) MR during pregnancy 6) MR during pregnancy 7) MR during pregnancy	1) Hydralazine 50 mg every 8 h and labetalol 300 + 400 mg from 5 w when pregnancy was discovered; for uncontrolled HT, she did adrenalectomy at 19 w; then, no need for anti-hypertensive medications 2) Amiloride, methyldopa and doxazosin from 10 w; for uncontrolled HT with this therapy, eplerenone was added at 18 w, starting at 50 mg and quickly titrating to 200 mg/d in divided doses; for uncontrolled	1) APA diagnosed before pregnancy; poor BP control, solved with adrenalectomy; after surgery, HT cured 2) HT before pregnancy; BP increase at 10 w; APA suspected during pregnancy; scarce control with therapy until adrenalectomy; after surgery, good control with drugs 3) BP increase from the beginning of pregnancy; APA suspected during	1) Preterm delivery by C section due to IUGR (35 w) 2) Urgent C section for PE (28 w) (Four years later, during her sixth pregnancy, despite well-controlled hypertension on three	1) N/A 2) N/A 3) N/A 4) N/A 5) N/A 6) N/A 7) N/A 8) N/A 9) N/A 10) N/A	1) IUGR 2) male neonate with significant growth retardation, but no evidence of feminization; after 3 months of ICU stay, he died from sepsis

		8) Solomon et al. 1996 [66] 9) Baron et al. 1995 [67] 10) Aboud et al. 1995 [68]	8) CT scan before pregnancy 9) MR during pregnancy 10) CT scan before pregnancy	HT at 20 w adrenalectomy was performed; after that, she continued with methyldopa and doxazosin 3) Spironolactone 50 mg/d, methyldopa 375-750 mg/d, nifedipine 20-60 mg/d; adrenalectomy at 24 w; then, methyldopa 375-750 mg/d, nifedipine 20-60 mg/d, doxazosin 2 mg/d 4) Methyldopa 2000 mg/d; adrenalectomy at 17 w; BP did not normalize after adrenalectomy, so she restarted methyldopa with good control 5) N/A; adrenalectomy at 26 w for hypokalemia 6) Nifedipine 40 mg/d + hydralazine 90 mg/d then surgery at 17 w for uncontrolled HT and severe hypokalemia; after surgery, she continued with nicardipine 20 mg/d 7) Amiloride 10 mg/d + nisoldipine 30 mg/d; she did adrenalectomy at 14 w (to prevent 3rd trimester BP peak); after surgery she continued with nisoldipine 40 mg/d until 34 w when BP increased and she was switched to methyldopa 750 mg/d + labetalol 100 mg/d 8) High doses of nifedipine and nadolol in the 1st trimester;	pregnancy; poor control during the whole pregnancy, also after adrenalectomy 4) HT before pregnancy complicated by intracranial hematoma 4 years before; APA suspected during pregnancy; BP increase at 19 w to 220/140 mmHg despite medical treatment; BP did not normalize after adrenalectomy, so therapy was restarted with good control 5) HT found at 11 w (168/99 mmHg); APA suspected during pregnancy 6) HT before pregnancy; APA suspected during pregnancy; BP increase at 14 w; BP control improved after surgery but medications were still required 7) HT found at 12 w (254/154 mmHg); APA suspected during pregnancy; BP increase at 34 w despite adrenalectomy and drugs 8) HT before pregnancy (APA suspected before pregnancy; she became pregnant before completion of evaluation); BP under control until 2nd trimester; after adrenalectomy, good control	antihypertensive agents, she developed pre-eclampsia and required an emergency cesarean section to deliver a healthy female infant) 3) C section for persistent HT (30 w) 4) C section for foetal distress (30 w) 5) C section (38 w) 6) IUFD (26 w) - stillborn 7) Induced delivery per persistent HT (34 w) 8) C section at term 9) Induced delivery (41 w) (mild PE) 10) Vaginal delivery at term		3) neonate weight 5th centile 4) SGA and foetal distress; weight at birth < 5th centile; he needed respiratory ventilation and developed pulmonary infection, but after 7 weeks of ICU he was discharged 5) normal 6) IUGR (21 w) --> IUFD (26 w) - stillborn 7) normal 8) normal 9) normal 10) normal

				adrenalectomy at 15 w for uncontrolled HT; after surgery, anti-hypertensive medication was withdrawn, with good control; new BP increase at 36 w that responded to bed rest 9) Labetalol 200 mg/d; adrenalectomy at 17 w; then, good BP control without medications 10) Interrupted spironolactone, enalapril and furosemide at 8 w when pregnancy was discovered; no other information was provided on therapy during gestation; in the 2nd trimester she did adrenalectomy, that normalize BP values	without medication until 36 w 9) HT before pregnancy; APA suspected in pregnancy; BP increase at 14 w; BP normalization after surgery 10) APA diagnosed before pregnancy; normotensive after adrenalectomy			
Bilateral medically treated PA	15	1) Vidyasagar et al. 2021 (case 1) [34] 2) Vidyasagar et al. 2021 (case 2) [34] 3) Vidyasagar et al. 2021 (case 3) [34] 4) Vidyasagar et al. 2021 (case 4) [34] 5) Vidyasagar et al. 2021 (case 5) [34] 6) Vidyasagar et al. 2021 (case 6) [34] 7) Vidyasagar et al. 2021 (case 7) [34] 8) Vidyasagar et al. 2021 (case 8) [34]	1) AVS confirmed before pregnancy 2) AVS confirmed before pregnancy 3) AVS confirmed before pregnancy 4) AVS confirmed before pregnancy 5) AVS confirmed before pregnancy 6) AVS confirmed before pregnancy 7) AVS confirmed before pregnancy 8) AVS confirmed before pregnancy	1) N/A but at least 1 drug, no MRA 2) N/A but at least 1 drug, no MRA 3) N/A but at least 1 drug, no MRA 4) N/A but at least 1 drug, no MRA 5) N/A but at least 1 drug, no MRA 6) N/A but at least 1 drug, no MRA 7) N/A but at least 1 drug, no MRA 8) N/A but at least 1 drug, no MRA 9) > 1 antihypertensive drugs 10) Interrupted amiloride 10 mg at 5 w when pregnancy was discovered; BP remained controlled without medication 11) Interrupted enalapril and nifedipine when pregnancy was discovered, switching to nifedipine 40 mg and labetalol	1) HT before pregnancy 2) HT before pregnancy 3) HT before pregnancy 4) HT before pregnancy 5) HT before pregnancy 6) HT before pregnancy 7) HT before pregnancy 8) HT before pregnancy 9) HT before pregnancy; BP increase from the 2nd trimester; bilateral PA diagnosed after pregnancy 10) bilateral PA diagnosed before pregnancy; normal BP values during pregnancy off treatment	1) Miscarriage at 12th w 2) Urgent C section before 37 w for PE 3) Urgent C section before 37 w for PE 4) Elective C section before 37 w for PE 5) Elective C section after 37 w 6) Elective C section after 37 w	1) N/A 2) N/A 3) N/A 4) N/A 5) N/A 6) N/A 7) N/A 8) N/A 9) N/A 10) N/A 11) N/A 12) N/A 13) N/A 14) N/A 15) N/A	1) Spontaneous miscarriage 2) SGA, ICU stay 3) SGA, ICU stay 4) normal 5) normal 6) normal 7) normal 8) normal 9) male neonate weight 5-10th centile 10) normal 11) growth below the 10th

		9) Zelinka et al. 2020 (case 14) [54] 10) Morton et al. 2015 (case 1) [8] 11) Morton et al. 2015 (case 2) [8] 12) Morton et al 2015 (case 3) [8] 13) Morton et al. 2015 (case 5) [8] 14) Krysiak et al. 2012 [55] 15) Ronconi et al. 2011 [69]	9) AVS confirmed after pregnancy 10) N/A 11) N/A 12) N/A 13) N/A 14) AVS confirmed before pregnancy 15) AVS confirmed before pregnancy	600 mg with poor BP control; at 27 w nifedipine was increased to 80 mg a labetalol to 1200 mg 12) Nifedipine 60 mg from 30 w 13) Interrupted amiloride 10 mg at 5 w when pregnancy was discovered and switched to labetalol 400 mg/d 14) Methyldopa 750 mg/d; at 20 w uncontrolled HT despite administration of methyldopa, hydralazine, labetalol, diazoxide and nifedipine 15) Amlodipine dose was reduced during pregnancy till discontinuation	11) bilateral PA diagnosed before pregnancy; BP increase at 27 w despite medications 12) bilateral PA diagnosed before pregnancy; BP increase at 30 w 13) bilateral PA diagnosed before pregnancy; BP increase at 30 w 14) HT before pregnancy; good BP control until 19 w with methyldopa; at 20 w BP increase to 200/110 mmHg and IUGR; bilateral PA diagnosed after delivery 15) bilateral PA diagnosed before pregnancy; BP amelioration during pregnancy that allowed to discontinue amlodipine and maintain good BP control without medications	7) Vaginal after 37 w 8) Vaginal after 37 w 9) C section for PE (33 w) 10) Elective C section (38 w) 11) Urgent C section for absent end-diastolic flow and reduced cerebral flow (30 w) 12) C section after an abrupt BP increase and PE (36 w) (renal biopsy, after delivery, revealed IgA nephropathy) 13) Emergency C section because of premature membrane rupture and antepartum hemorrhage (30 w) 14) IUFD (20 w) --> stillborn 15) Vaginal delivery (39 w)		centile; absent end-diastolic flow and reduced cerebral flow (30 w) 12) normal 13) normal 14) IUGR; stillborn (20 w) 15) normal

FH-1	27	1) Sanga et al. 2020 [45] 2) Campino et al. 2015 [70] 3) Hamilton et al. 2009 [71] 4) Mulatero et al. 2002 [72] 5) Wyckoff et al. 2000 [73]		1) discontinued dexa. 0.50 mg once pregnancy was known; restarted dexa. 0.25 mg o.d. at the end of 2nd trimester 2) none (discontinued dexa. 0.25 mg once pregnancy was known) 3) none (discontinued verapamil once pregnancy was known) 4) not specified 5) 23% required ≥1 anti-hypertensive medications: methyldopa (n=2), potassium-sparing diuretics (n=3), beta-blockers (n=2), thiazides (n=5)			1) yes 2) yes 3) yes 4) yes 5) yes	

Abbreviations: ARR: aldosterone-renin ratio; AVS: adrenal venous sampling; BP: blood pressure; C section: caesarean section; CT: computed tomography; dexa.: dexamethasone; FH-1: familial hyperaldosteronism type 1; HT: hypertension; ICU: intensive care unit; IUFD: intrauterine foetal death; IUGR: intrauterine growth restriction; LA: laparoscopic adrenalectomy; MR: magnetic resonance; MRA: mineralocorticoid receptor antagonist; N/A: not available; PA: primary aldosteronism; PE: preeclampsia; SGA: small for gestational age; US: ultrasound; w.: gestational week.

Table S4: Characteristics of the PA patients who underwent a pregnancy and results of the analysis of the cases reported over 3 decades from 1990 to 2021.

	N. of cases	Ethnicity	Mean age (ys)	Previous pregnancies	HT discover (timing and BP increase in pregnancy)	PA diagnosis (timing)	Adrenalectomy (timing)	AVS guided (n)	Histological confirmation	HT cure after adrenalectomy (clinically / biochemically)
Unilateral medically treated PA	28	18 caucasic 9 asiatic 1 black	30.7	7 women with previous pregnancies (2/7 with complicated pregnancies) 21 women primigravida	12 before pregnancy (age 26.8 ys) → BP increase mainly during the 2nd – 3rd trimester (around 26.9 w) 14 during pregnancy → BP increase during 2nd trimester (mean 20.8 w, ranging from 8 to 35 w) 2 in the first weeks after delivery	1 before conception (AVS confirmed) 3 during pregnancy (2nd trimester) 24 after pregnancy (around 18 months after delivery, ranging from 1 to 144 months) (8 AVS confirmed)	27/28 after pregnancy (mean time after delivery 19.5 months) (1 case is waiting for LA [22])	9/28 (32%)	27/27 (100%)	Clinically: 23/27 (85%) Not cured: 3 cases did not reach the cure [54] (the diagnosis of APA was also AVS-confirmed in 2 of them) despite biochemical cure in all 3 cases; these 3 patients needed 2 anti-hypertensive drugs after adrenalectomy Biochemically: 14/14 (100%)
Unilateral surgically treated PA during pregnancy	10	5 asiatic 3 black 2 caucasic	27.7	4 women with previous pregnancies and they were complicated 6 women primigravida	8 before pregnancy (mean age at diagnosis 24.1 ys) → BP increase mainly during the 1st trimester 2 during pregnancy → BP	3 before conception 7 during pregnancy (through MR; in 1 case, also AVS was performed	10/10 (100%) during 2nd trimester (range 14-26 w)	2/10 (20%) (in 1 case AVS was done before pregnancy; in Shiraishi et al. clinical case [27] ACTH-stimulated AVS was	10/10 (100%)	Clinically: 1/10 (10%) (in this case, the diagnosis was done through TC, MR scan and AVS before conception [28]) Not cured: 6 showed persistent HT during 3rd trimester and beyond (1 with HT responsive to bed rest, 1 complicated by mild PE, 3 with

					increase around 11-12 w	during pregnancy)		performed during pregnancy before 24th w)		HT that needed 1-3 drugs, 1 with persistent HT where no information about administered therapy was provided) 2 had no resolution of HT after pregnancy Biochemically: 1/1 (100%)
Bilateral medically treated PA	15	15 caucasic	30.7	3 women with previous pregnancies, 2 of them with complications 4 women primigravida 8 unknown	15 before pregnancy (mean age at diagnosis 26.8 ys) → BP increase mainly during the 2nd – 3rd trimester (mean 24 w)	13 before conception (at least 9 AVS confirmed) 2 after pregnancy (both AVS confirmed)	0/15 (0%)	11/15 (73%)	not applicable	not applicable
FH-1	27	27 caucasic	26.2	12 women with previous pregnancies, not known if complicated 15 women primigravida	most of the cases before pregnancy → generally good BP control during pregnancy without medications	most of the cases before pregnancy	0/27 (0%)	not applicable	not applicable	not applicable

Abbreviations: ARR: aldosterone-renin ratio; AVS: adrenal venous sampling; BP: blood pressure; C section: caesarean section; CT: computed tomography; dexa.: dexamethasone; FH-1: familial hyperaldosteronism type 1; HT: hypertension; ICU: intensive care unit; IUFD: intrauterine foetal death; IUGR: intrauterine growth restriction; LA: laparoscopic adrenalectomy; MR: magnetic resonance; N/A: not available; PA: primary aldosteronism; PE: preeclampsia; SGA: small for gestational age; US: ultrasound; w.: gestational week.

(continued…)

	Mean n. of anti-HT before pregnancy	Mean n. of anti-HT drugs 1st trimester	Mean n. of anti-HT drugs 2nd trimester	Mean n. of anti-HT drugs 2nd trimester after LA	Mean n. of anti-HT drugs 3rd trimester	Mean n. of anti-HT drugs at follow-up after LA	MRA use	Delivery	Complicated pregnancies	C-section	Foetal mortality	IUGR	Newborn ICU stay
Unilateral medically treated PA	1 (data available for 4 women: 4 needed 1 drug)	0.67	1.27	not applicable	1.44	0.37	1/28 (no male foetus feminization)	Preterm 13/28 (46.4%) (mean 34.5 w) Miscarriage 1/28 (3.6%) (at 10th w)	17/28 (60.7%) (8 cases by PE, 4 by foetal distress, 2 by premature membrane rupture, 1 by HELLP syndrome, 1 by abruptio placentae, 1 by herpes genitalis, 1 by breech presentation, 1 by miscarriage)	17/27 (63%) (14/17 urgent)	2/28 (7%) (1 miscarriage at 10th w; 1 baby died after 3 months ICU stay after urgent C-section at 27 w for PE)	6/27 (22%)	2/27 (7.4%)
Unilateral surgically treated PA during pregnancy	1.5 (data available for 5 women: 2 needed 3 drugs, 2 no drugs)	1.50 (at least 6 women over 10 needed a drug)	2.25	1.00	1.00	2	2/10 (no male foetus feminization)	Preterm 6/10 (60%) (mean 33.9 w) Miscarriage 1/10 (10%) (at 26th w for failure in placenta blood flow)	6/10 (60%) (3 cases by PE, 2 by impaired umbilical artery flow with foetal distress, 1 by miscarriage)	6/9 (66.7%) (4/6 urgent)	2/10 (20%) (1 miscarriage at the 26th gestational w; 1 baby died after 3 months ICU stay for sepsis after urgent C-section at 28 w for PE)	5/10 (50%)	3/9 (33.3%)
Bilateral medically treated PA	1 (6 women over 7 needed at least 1 drug, 1 no drug; others unknown)	0.4 (data available for 5 women: 2 needed 1 drug, 3 no drugs)	1.3	not applicable	0.8 (data available for 5 women: 1 needed 2 drugs, 2 needed 1 drug, 2 no drugs)	not applicable	0/15	Preterm 10/15 (66.6%) (mean 33.3 w) Miscarriage 2/15 (13.3%) (one at the 12th and one	10/15 (66.6%) (5 cases by PE, 2 by impaired umbilical artery flow, 2 by miscarriage, 1 by premature membrane rupture and antepartum hemorrhage)	11/14 (78.6%) (7/11 urgent)	2/15 (13.3%) (one miscarriage at the 12th and one at the 20th w)	5/14 (35.7 %)	2/14 (14.3%)

								at the 20th w)					
FH-1	1	0.1	0.04 (data were available only for half patients)	not applicable	0.18	not applicable	0/27 (3 cases took K^+-sparing diuretics not better defined)	Preterm 2/19 (10.5%) Miscarriage 0/27 (0%)	5/27 (18.5%) (1 PE, 1 chorioamnionitis, 1 failure of placental separation, 2 consistent blood loss during delivery)	7/27 (26%) (4/7 urgent)	0/27 (0%)	0/27 (0%)	N/A
Non-familial PA (excluding FH-1 cases)								Preterm 24/45 (53.3%) Miscarriage 3/45 (6.7%)	28/45 (62.2%) (PE 13 cases: 28.8%)	29/43 (67.4%)	5/45 (11%)	14/44 (31.8 %)	5/43 (11.6%)

Table S5: Maternal and foetal complications rate in pregnancy in women with unilateral medically treated PA, unilateral surgically treated PA during pregnancy, bilateral medically treated PA and FH-1.

		FH-1	Sporadic PA women	Two-tailed p value *
Complicated pregnancies (n. over the total n. of pregnancies)	yes	5/27 (18.5 %)	33/53 (62.2 %)	0.0003
	no	22/27 (81.5 %)	20/53 (37.8 %)	

		Bilateral medically treated	Unilateral medically treated	Two-tailed p value *
Complicated pregnancies (n. over the total n. of pregnancies)	yes	10/15 (66.6 %)	17/28 (60.7 %)	0.7523
	no	5/15 (33.3 %)	11/28 (39.3 %)	

		Unilateral surgically treated in pregnancy	Sporadic medically treated PA	Two-tailed p value *
Complicated pregnancies (n. over the total n. of pregnancies)	yes	6/10 (60 %)	27/43 (62.8 %)	1.0000
	no	4/10 (40 %)	16/43 (37.2 %)	

		Unilateral medically treated	Unilateral surgically treated in pregnancy	Two-tailed p value *
Complicated pregnancies (n. over the total n. of pregnancies)	yes	17/28 (60.7 %)	6/10 (60 %)	1.0000
	no	11/28 (39.3 %)	4/10 (40 %)	

* Fisher test (calculated with MedCalc Software Ltd. Fisher exact probability calculator. https://www.medcalc.org/calc/fisher.php Version 20.027; accessed May 14, 2022)

Table S6: Maternal and foetal complications rate in pregnancy in women with sporadic PA vs essential hypertension [49].

		EH women	Sporadic PA women	Two-tailed p value *
Complicated pregnancies (n. over the total n. of pregnancies)	yes	61/211 (28.9 %)	33/53 (62.2 %)	< 0.0001
	no	150/211 (71.1 %)	20/53 (37.8 %)	

* Fisher test (calculated with MedCalc Software Ltd. Fisher exact probability calculator. https://www.medcalc.org/calc/fisher.php Version 20.027; accessed May 14, 2022)

Figure S1: PRISMA strategy applied for the research of clinical cases of patients with PA during pregnancy (articles from 1990 to 2021).

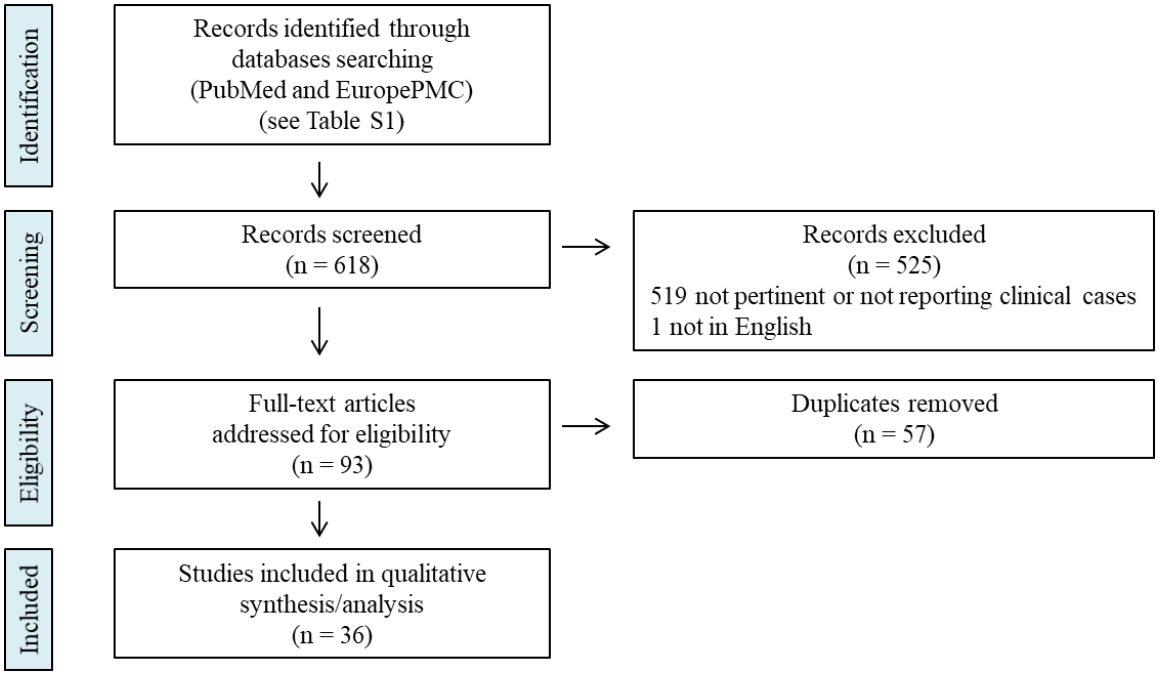
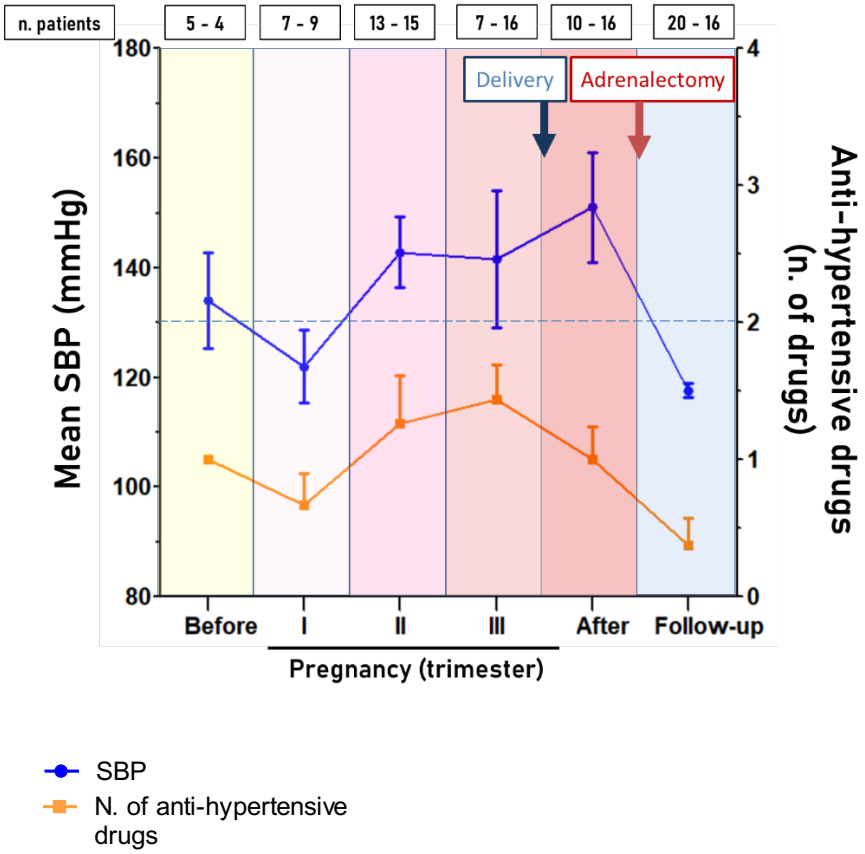


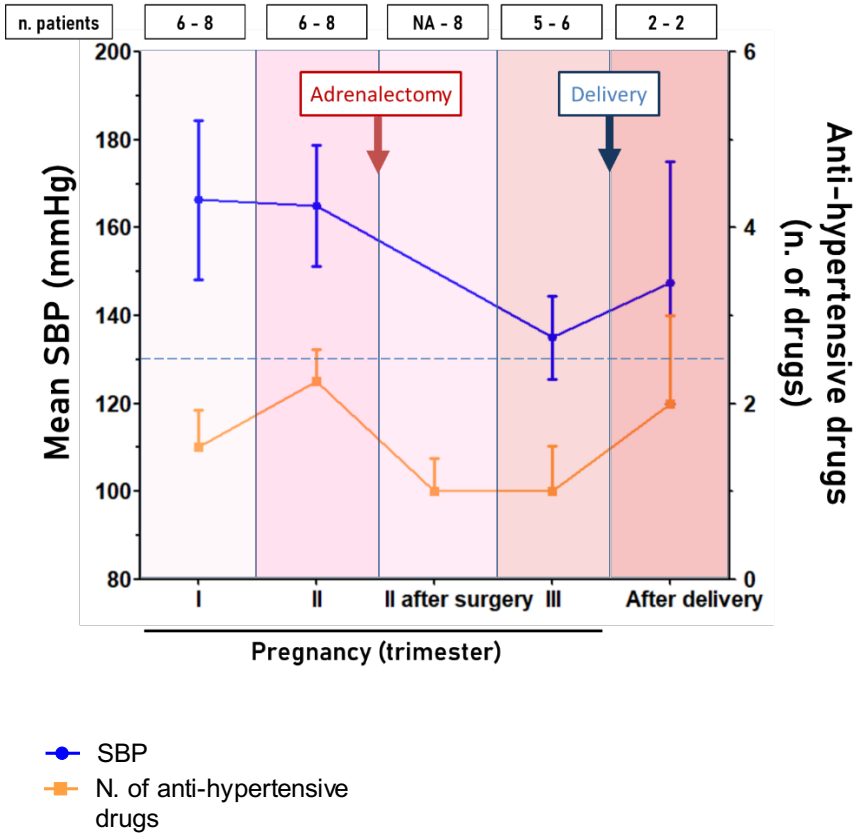
Figure S2:

A) Course of systolic BP (mean ± SEM) and number of anti-hypertensive drugs before, during and after pregnancy in unilateral medically treated PA patients during pregnancy. The last value refers to SBP after adrenalectomy performed after pregnancy. Please note the fall during the 1st trimester, the progressive increase during the 2nd and 3rd and the fall after surgery. B) Course of systolic BP (mean ± SEM) and number of anti-hypertensive drugs before, during and after pregnancy in unilateral surgically treated during pregnancy PA patients.
Annotation: the n. of patients indicated on the top of the figures refer to the n. of patient at every timepoint with available office SBP value (first number) and/or with information about the n. of anti-hypertensive drugs (second number). The cut-off for normal BP values was set at 130 mmHg, identified here by the blue horizontal line.

A



B



Abbreviations: n: number; SBP: systolic blood pressure.

Figure S3: Delivery/miscarriage time in unilateral medically treated PA patients, unilateral surgically treated during pregnancy PA patients and bilateral PA. The cut-off for a preterm delivery was set at 37 gestational week, identified here by the vertical line.

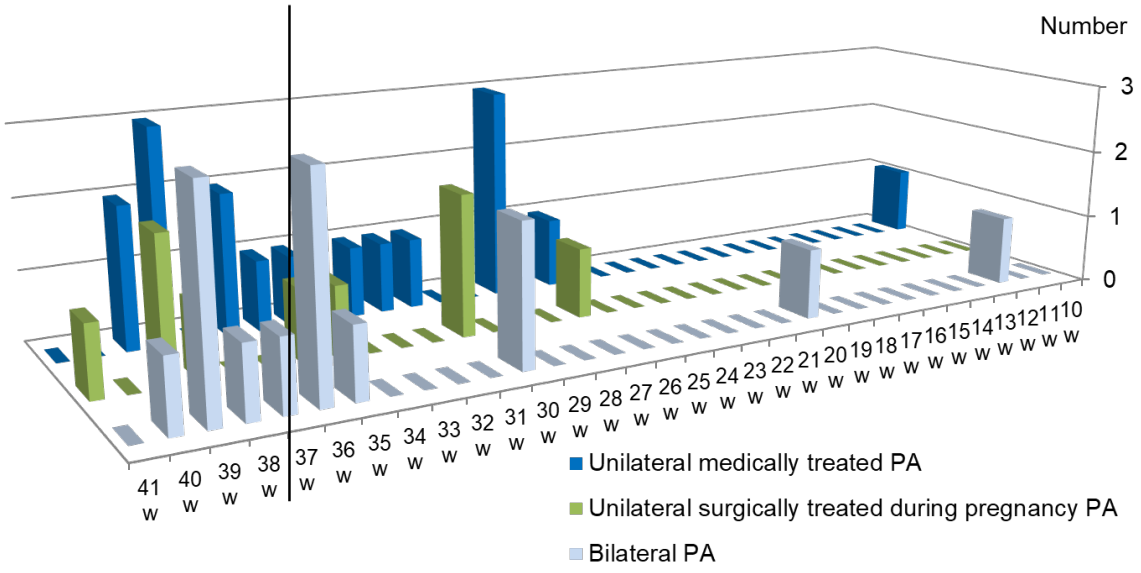
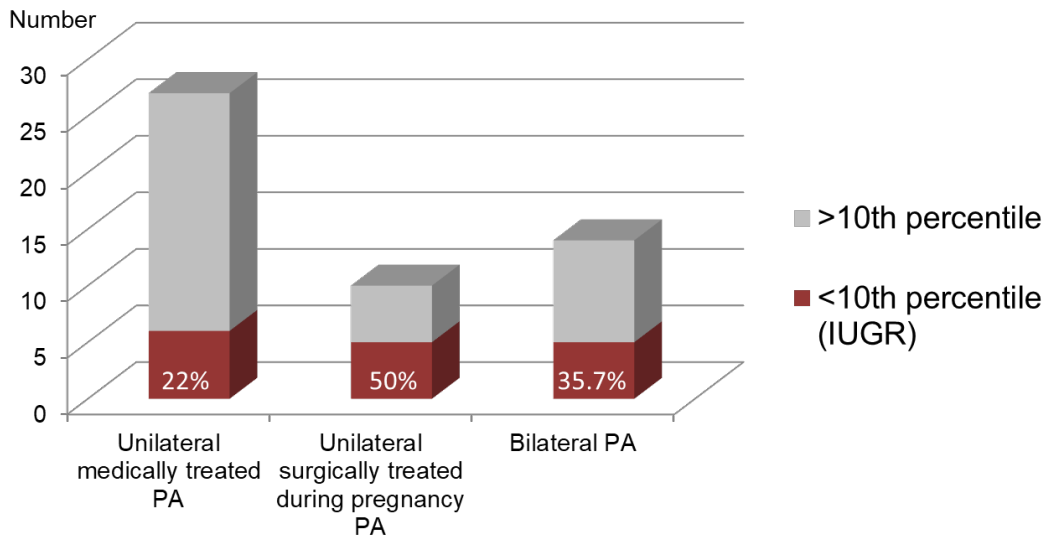


Figure S4: IUGR rate in unilateral medically treated PA patients, unilateral surgically treated during pregnancy PA patients and bilateral PA.



Abbreviations: IUGR: intrauterine growth restriction.