Current management and outcome of pregnancies in women with adrenal insufficiency: experience from a multi-center survey

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Abstract

Context: Appropriate management of adrenal insufficiency (AI) in pregnancy can be challenging due to the rarity of the disease and lack of evidence-based recommendations to guide glucocorticoid- and mineralocorticoid dosage adjustment.

Objective: Multi-center survey on current clinical approaches in managing AI during pregnancy.

Design: Retrospective anonymized data collection from 19 international centers from 2013-2019.

Setting and Patients: 128 pregnancies in 113 women with different causes of AI: Addison disease (44%), secondary AI (25%), congenital adrenal hyperplasia (25%) and acquired AI due to bilateral adrenalectomy (6%).

Results: Hydrocortisone (HC) was the most commonly used glucocorticoid in 82.9% (97/117) of pregnancies. Glucocorticoid dosage was increased at any time during pregnancy in 73/128 (57%) of cases. In these cases, difference of the daily dose of HC equivalent between baseline and the third trimester was 8.6±5.4 [range: 1, 30] mg. Fludrocortisone dosage was increased in fewer cases (7/54 during the first trimester, 9/64 during the second trimester and 9/62 cases during the last trimester). Overall, an adrenal crisis was reported in 9/128 (7%) pregnancies. Caesarian section was the most frequent mode of delivery at 58% (69/118). Fetal complications were reported in 3/120 (2.5%) and minor maternal complications in 15/120 (12.5%) pregnancies without fatal outcomes.

Conclusions: This survey confirms good maternal and fetal outcome in women with AI managed in specialized endocrine centers. An emphasis on careful endocrine follow up and repeated patient education is likely to have reduced the risk of adrenal crisis and resulted in positive outcomes.

Précis: Good maternal and fetal outcome can be expected in appropriately managed AI.

Introduction

Adrenal insufficiency (AI) is a potentially life-threatening condition that can be caused by destruction of adrenocortical cells, by inborn alterations of steroidogenesis or by impairment of pituitary or hypothalamic stimulation of the adrenal cortex (1). AI is associated with an increased mortality risk and a reduced quality of life, as well as reduced ability to work (2). As AI predominantly affects women in their reproductive age, course and outcome of pregnancy may be affected. While the exact prevalence of AI in pregnancy is unknown, a recent population-based study from the United States reported an increase in prevalence of Addison disease (AD) from 5.6 per 100,000 in 2003 to 9.6 per 100,000 in 2011 in a cohort with 7.7 million births (3).

Prior to the introduction of glucocorticoid replacement therapy, AD was associated with a high maternal mortality (4). However, modern glucocorticoid replacement therapy and improved obstetric care have both contributed immensely in reducing maternal as well as fetal morbidity and mortality. In patients with primary AI, replacement of both glucocorticoid and mineralocorticoid are usually necessary, while in secondary or tertiary AI, only glucocorticoid substitution is required. However, it might be necessary to replace other deficient hormones in both primary AI, if it occurs as a part of polyglandular autoimmune syndrome (5) as well as in secondary AI, if other pituitary axes are affected (6). Particularly, women with secondary AI may need assisted reproduction techniques for conception (7). Accordingly, a population-based study on patients with primary AI from Sweden has indicated a persistently reduced parity, increased rate of preterm birth and low birth weight (8). While these studies have offered many important insights on a population basis, they fail to provide information on therapeutic strategies currently applied in this patient group.

Pregnancy can be considered as a state of hypercortisolism due to the upregulation of the whole hypothalamic-pituitary-adrenal (HPA) axis. Furthermore, bound cortisol levels are increased due to increased corticosteroid binding globulin under the high estrogen-state of pregnancy (9). Several biochemical parameters such as morning cortisol, adrenocorticotropic hormone (ACTH), plasma sodium and renin change physiologically in pregnancy and are therefore not reliable in dosage titration of replacement therapies. Diagnosing new onset AI in pregnant women is further complicated as many indicators suggestive of AI could be potentially mistaken as symptoms of pregnancy. Nevertheless, clinical information such as general well-being, appropriate weight gain during the course of pregnancy, blood pressure and potassium levels may help in adjusting glucocorticoid- and mineralocorticoid dosage. Ongoing follow-up during pregnancy, ideally from an endocrinologist, can be expected to facilitate the appropriate management of AI to ensure self-adjustment of glucocorticoid dosage in response to potential stress events (10). Furthermore, improved obstetric care and increased awareness among physicians regarding the importance of individualized dosage adjustment of glucocorticoid and or mineralocorticoid replacement have likely contributed in improving outcomes in this rare disease. The clinical guidelines from the Endocrine Society suggest an empirical increase in hydrocortisone dosage by 20-40% in the last trimester (11,12). However, this suggestion is based on low level of evidence. Therefore, the aim of our multicenter retrospective survey was to analyze the current management approaches of dosage adjustment in pregnant women with AI in specialized centers and to assess the maternal and fetal outcome.

Material and methods

Patients and pregnancies

We collected data on 128 pregnancies in 113 women with AI from 19 centers with varying number of pregnancies per center (range 1-28 per center). Data collection was restricted to pregnancies between 2013 and 2019. Minimal clinical annotations for inclusion in the study were patient's age, etiology of AI, maternal and fetal outcome, presence of adrenal crisis during pregnancy and mode of delivery. Pre-defined data points were collected by each center for each individual patient. Upon anonymization, data were transferred for central analysis. The central ethical Committee of the University of Zurich approved this study and provided a waiver of consent to collect retrospective data from different centers in an anonymized form. Where required, centers obtained additional local ethical approval for data collection.

We assessed clinical and biochemical parameters before pregnancy and during all three trimesters [first (1^{st}) trimester weeks 1-13, second (2^{nd}) trimester weeks 14-27 and third (3^{rd}) trimester weeks 28-40 of pregnancy]. Main clinical parameters included weight, height, body mass index (BMI), blood pressure and main biochemical parameters were serum sodium and potassium. Maternal outcome was classified as good, with complications or fatal. Likewise, fetal outcome was defined as good, with complications or fatal.

We converted glucocorticoid medication to equivalent dose of immediate release HC dosage, as follows: 1mg dual - release HC as 1mg HC equivalent, 1mg prednisone and prednisolone as 4mg of HC, 1mg cortisone acetate as 0.8 mg HC, and 1 mg dexamethasone as 25mg (13). The mineralocorticoid potency of 100µg fludrocortisone was defined as 1 mineralocorticoid unit (MCU). For the glucocorticoids, we calculated 1mg immediate and dual release HC as a mineralocorticoid

potency of 0.054 MCU, 1mg prednisone or prednisolone as 0.013 MCU, 1mg cortisone acetate as 0.0432 MCU, respectively, while dexamethasone was regarded as 0 MCU (14).

Statistical analysis

Each individual pregnancy was considered as independent cases including the ones occurring in the same patient. The retrospective, case- based form of the study resulted in missing data in different variables that could be explained either by lack of documentation or incomplete follow-up of the patient by the participating centers. Further missing data across all pregnancies are explained by miscarriages or ongoing pregnancies. Data were gathered from participating centers in an anonymized form. Statistical analysis was performed using IBM SPSS Statistics for Windows (Released 2017, Version 25.0., IBM Corp, Armonk, NY). Graphs were generated using GraphPad Prism 5 (GraphPad Software, La Jolla, CA, United States). Variables were assessed for normality by evaluation of histograms and by Kolmogorov-Smirnov test. Differences between groups were assessed using Fisher's exact test for categorical variables, Mann-Whitney U-test for quantitative non-normally distributed variables and Student's t-test for normally distributed variables. Overall, comparisons of continuous variables between groups were carried out by using ANOVA or the Kruskal-Wallis test. Correlations were assessed by Pearson's or Spearman's correlation coefficient (r). For paired data, the Wilcoxon's test was used. A probability value of $p<0.05$ was considered statistically significant for all tests. If not stated otherwise, $p<0.05$ were denoted with one star (*), $p< 0.01$ with two stars (**), and $p<0.001$ with three stars (***), respectively.

Results

Description of patients with AI

The cause of AI was AD in the context of 56 pregnancies (44%), secondary AI in 32 pregnancies (25%), and congenital adrenal hyperplasia (CAH) in 32 pregnancies (25%). In eight pregnancies (6%), the cause was bilateral adrenalectomy performed for treatment of bilateral pheochromocytoma or therapy resistant ACTH dependent Cushing syndrome.

The mean age of women at the time of AI diagnosis differed significantly among the subgroups with 26 years ([range 14-35], n=48) for primary AI, 26 years ([range 8-44], n=31) for secondary AI, 9 years ([range 0-38], n=29) for CAH and 30 years ([range 23-37], n=6) for other causes of AI ($p<0.001$, Table 1). In contrast, the mean age at the time of pregnancy was similar among different groups with 33±4.5 years in women with AD, 32±5.5 in women with secondary AI, 32±6.1 in CAH and 35±3.8 in AI due to other reasons ($p=0.470$, Table 1). In most pregnancies (125/128, 98%), the diagnosis of AI had been established before pregnancy. In two cases, AI was diagnosed during the third trimester (in the 28^{th} and 34^{th} week of gestation).

Among women with secondary AI, 45% (14/31) had at least one additional hormonal deficiency. Thyroid dysfunction was the most commonly reported additional comorbidity with 46.8% (52/111) having hypothyroidism. Hypothyroidism coexisted in primary AI as primary hypothyroidism in 55% (26/47) and as secondary hypothyroidism in women with secondary AI in 55% (17/29) of cases. In contrast, fewer patients with CAH had hypothyroidism (21%). Some women had other diseases of the thyroid, e.g., multinodular goiter (n=1), thyroid nodules (n=2), hyperthyroidism that was not otherwise specified (n=1), Graves disease (n=1) and papillary thyroid carcinoma (n=2).

Reproductive history of patients with AI

28.3% (36/127) of the women had at least one miscarriage in the past medical history. The percentage of miscarriages was significantly higher among CAH patients (43.8%, 14/32) compared with AD (27.3%, 15/55) and was considerably lower in patients with secondary AI (15.6%, 5/32) or due to other diseases (25%, 2/8)(all $p<0.001$). The exact week of miscarriage was recorded in 28 cases with 75% of miscarriages occurring in the first trimester and 25% in the second trimester. From 2013 onwards, three miscarriages were reported, two in the 9th week and one in the 15th week of gestation.

Management of glucocorticoid and mineralocorticoid substitution therapy during pregnancy

Glucocorticoid substitution

At baseline, immediate release HC was the most commonly used glucocorticoid (67/100, 67%) with considerably fewer patients treated with other single medication (18/100, 18% dual release HC; 8/100, 8% prednisolone; 2/100, 2% dexamethasone, 2/100, 2% cortisone acetate) or combinatory therapies (2/100, 2% immediate release HC with dexamethasone and 1/100, 1% immediate release HC with prednisolone). Treatment data at baseline were not available for 26 pregnancies while in further two cases, AI was first diagnosed during pregnancy. Of note, in one case, immediate release HC was given continuously through a subcutaneous pump throughout pregnancy (15).

During the 1st trimester, in 80/117 (68.4%) pregnancies the reported glucocorticoid was immediate release HC, in 15/117 (12.8%) dual release HC, in 2/117 (1.7%) a combination of both, in 11/117 (9.4%) prednisolone, in 7/117 (6.0%) cortisone acetate and in 2/117 (1.7%) combination of

prednisolone with HC. In contrast, no cases of dexamethasone treatment were reported. The split of the dosage for the immediate release HC formulation was twice per day in 28/80 (35.0%) cases and three times per day in 51/80 (63.7%) of the pregnancies and four times per day for one pregnancy (1/80, 1.3%). Of note, in two pregnancies with dual release HC (2/15, 13.3%), the treatment scheme was 20mg in the morning supplemented with another 5mg in the afternoon.

Applied glucocorticoid during the further course of pregnancy remained comparable with those of the 1st trimester (data not shown). Of note, dexamethasone was added as the only glucocorticoid in two patients with CAH during the 17th and the 32nd week of pregnancy, respectively.

Glucocorticoid dosage was not adapted uniformly in line with existing guidelines. Instead, data revealed individualized dosage adaptation during the different trimesters following no certain pattern but there were also cases where the dosage was not changed during the whole course of pregnancy (Figure 1). In none of the cases with a decrease of the dosage, the occurrence of an adrenal crisis was reported. During the last trimester, 5/109 patients (4.6%) had a decrease in daily dosage by 5-10 mg of HC equivalent due to the development of hypertension. Among the different subgroups, those with AD tended to receive the highest substitution dosage (Table 2).

Mineralocorticoid substitution

Before pregnancy, 95% (37/39) of patients with AD, 42% (13/31) of patients with CAH and 80% (4/5) of patients with AI due to other diseases were receiving fludrocortisone treatment. As expected, none of the patients (0/32) with secondary AI had mineralocorticoid substitution. During the whole course of pregnancy, fludrocortisone dosage was adapted in some cases but to a lesser extent in comparison to the HC adaptation (Figure 1). The reason for decrease in fludrocortisone dosage was

not recorded; particularly no correlation with increased blood pressure or onset of preeclampsia was documented.

Clinical course and adrenal crisis during pregnancy

Blood pressure measurements as well as serum sodium and potassium remained in the normal range during the course of pregnancy in the majority of cases (Table 3 and Figure 2). Hypertensive values (defined as values above 140/90 mmHg) were reported in 6/94 (6.4%) at baseline, in 2/102 (2%) in the 1st trimester, in 2/102 (2%) during the 2nd trimester and in 7/100 (7%) in the 3rd trimester. No relevant differences were noted among the subgroups. Similarly, no significant differences in systolic and diastolic blood pressure were evident during pregnancy in comparison to baseline levels (Figure 2). In contrast, sodium concentrations decreased significantly compared to baseline (139.0±3.1 [range: 125-145] mmol/l) in the 1st trimester (136.3±2.7 [range: 130-144] mmol/l, p<0.001), 2nd (136.7±2.9 [range: 132-145] mmol/l, p<0.001) and 3rd trimester (137.7±2.8 [range: 129-145] mmol/l, p=0.0036). Low serum sodium concentrations (<135 mmol/L) were reported in 3/79 (3.8%) at baseline, in 21/94 (22.3%) in the 1st trimester, in 22/91 (24.2%) in the 2nd trimester and in 9/82 (11.0%) in the 3rd trimester.

With regard to serum potassium levels only minor changes were observed between baseline (4.2±0.4 [range: 3.0-5.5] mmol/l) and 2nd trimester (4.0±0.4 [range: 3.0-5.0] mmol/l, p=0.0234; Figure 2). Low serum potassium levels (<3.5 mmol/L) were reported in 2/79 (2.5%) at baseline and in 3/94 (3.2%), 5/91 (5.5%) and in 5/82 (6.1%) during 1st, 2nd and 3rd trimester, respectively.

No case of hypernatremia (>145mmol/L) or hyperkalemia (>5.5 mmol/L) was reported at any time point. When taking into consideration the mineralocorticoid substitution and serum electrolytes in the 3rd trimester of pregnancy, a negative correlation between the total mineralocorticoid potency and serum sodium (R=-0.217, p=0.047) and a positive correlation for serum potassium were observed (R=0.281, p=0.011 Figure 3). In contrast, no significant correlation was found at any other time point before or during pregnancy (Figure 3).

In 9/128 (7%) of pregnancies, an adrenal crisis was reported without any relationship to the etiology of AI (Table 4). In one case, adrenal crisis was precipitated by an influenza A infection, which was successfully managed. One patient experienced four recurring episodes of adrenal crisis due to hyperemesis gravidarum during the first trimester. In one case, the trigger was gastroenteritis during the 1st trimester. One patient was diagnosed with new AI when she presented with adrenal crisis in the 3rd trimester. In the other five cases, no further data regarding onset and cause of adrenal crisis was available.

Delivery management and outcome

Overall, 25/117 (21.4%) deliveries were reported as preterm without significant differences between the subgroups. Among those preterm births in patients with CAH 1/10 (10%) was defined as extremely preterm (25th week) in the context of chorioamnionitis. A further early preterm birth (28th week) in a patient with AD was reported but no further details of the etiology were available. The remaining preterm births were moderate to late preterm (28th to 32nd week).

Information regarding administration of stress dosage of glucocorticoid during delivery was available in 90/128 cases (70.3%), of whom 83/90 cases (92.2%) glucocorticoids were administered intravenously. In the seven cases where no stress dosage was provided, no adverse events were reported. In 54/90 cases, the exact dosage of substitution medication was available. The majority of these cases (36/54, 66.7%) received 100mg hydrocortisone, but overall a wide range of dosages of HC supplementation were used ranging from 50 to 300 mg.

Mode of delivery was CS in 69/118 (58%) of the cases. However, only a few cases had emergency CS (n=4) due to preeclampsia. Vaginal delivery was slightly more common in patients with AD (52%, 26/50). CS was more common in patients with secondary AI (20/29, 69%), patients with CAH (20/31, 65%), and patients with other types of AI (5/8, 63%). The exact reason for CS was not documented in these cases.

In 15/120 (12.5%) cases, maternal complications were reported: anemia (n=2), severe postpartum hemorrhage (n=4), mild to severe pre-eclampsia (n=7) and chorioamnionitis (n=1). However, no adverse fetal outcomes were reported in these cases. In three cases, miscarriage was documented, two in 9th week and one in 15th week of pregnancy. Two pregnancies were ongoing at the time of study completion. In three cases, fetal complications occurred with two premature babies requiring intensive care and one having macrosomia and shoulder dystocia in a woman with type 1 diabetes. No maternal or fetal fatalities occurred.

Discussion

To our knowledge, this is the first retrospective multicenter survey with a detailed analysis of course, management and outcome of a large number of pregnancies in women with AI of different etiologies. As these women had regular follow-up at specialized endocrine units during the course of their pregnancy, it was possible to collect and analyze information that sheds light on the current treatment and management of this rare clinical condition and to provide insights on the outcome of affected mothers and their offspring.

Miscarriages were relatively prevalent in the past medical history of included women, being highest among those with CAH. A high rate of miscarriages among patients with CAH has previously been described in a German cohort that included 39 patients with either classical or non-classical form of CAH (16) and were attributed to a combination of androgen excess and cortisol insufficiency. A Swedish study reported increased rates of therapeutic abortions among 62 patients with CAH, while the rate of spontaneous abortions were not higher in comparison to a control population (17).

Interestingly, in the current dataset, women with secondary AI had the lowest rate of spontaneous abortion, but this could be explained by the usage of assisted reproduction methods for conception often guided by frequent follow-up during pregnancy. Overall, the reasons of reduced fertility in women with secondary AI are believed to be caused by additional hormonal deficiencies such as hypothyroidism and or secondary hypogonadism (7). Almost one out of three patients with AD reported a miscarriage in the past medical history but the reasons could not be determined in the context of the present study. However, overall, this rate is within the range (15-30%) of the normal population (18,19).

In the past, many cases of primary AI were reported to result in maternal and fetal death but recent reports correlate adverse events mostly with poor compliance (20). In the present study, the rate of miscarriages among patients with AD, CAH and AI due to other etiologies was comparable with the reported rate in a similar study of patients with primary AI in the German population (16). Of note, in that study, all miscarriages were reported among patients that suffered from primary AI in the context of autoimmune polyendocrine syndrome type 2. This information was not available in our dataset and we could not access the incidence of miscarriages in parallel with other manifestations of the syndrome, for example in combination with hypothyroidism.

The objective of the follow-up of a woman with AI during pregnancy is to keep the replacement therapy at levels that avoid effects of over-treatment (e.g. gestational diabetes, excessive weight gain, arterial hypertension) and of under-treatment (adrenal crisis, electrolyte imbalance). In keeping with the general recommendation from the Endocrine Society (11), glucocorticoids were in most instances increased during the course of pregnancy in a range between 5 and 25 mg hydrocortisone equivalents. However, adjustment of glucocorticoid dosage varied significantly among patients and centers emphasizing that current practice is a rather individualized approach.

Likewise, fludrocortisone dosage was adjusted in almost a quarter of patients, without a clear relationship with potassium concentrations or blood pressure measurements. Electrolyte balance during pregnancy is affected by the mineralocorticoid antagonistic action of progesterone (21,22). To counterbalance the effects of increased progesterone levels during pregnancy, higher doses of a mineralocorticoid receptor agonist are required (22,23). Proper adjustment of mineralocorticoid dosage is accomplished by evaluating blood pressure and assessment of blood electrolytes, as active renin cannot be used as a reliable indicator for the treatment during pregnancy (14). Despite the

observed tendency of increasing mineralocorticoid potency during the course of pregnancy in the majority of cases, serum sodium showed an initial decrease in the first trimester. Afterwards, there was no further change in serum sodium and serum potassium remained stable during the course of pregnancy. Our findings support an earlier report that pregnant women with primary AI have an increasing requirement for fludrocortisone substitution as pregnancy advances to maintain blood pressure and serum potassium in the normal range (24). However, also during normal pregnancy despite increased sodium retention the increase in plasma volume results in mildly reduced serum sodium concentrations. Accordingly, reference intervals of a pregnant women are approximately 2-5mmol/L lower those outside of pregnancy (25). Therefore, the observed reduced mean serum sodium levels during pregnancy could be explained by a combination of physiological effects of pregnancy and modulation by mineralocorticoid action implemented by the substitution treatment. It is interesting to note, that the current data for the 3rd trimester indicated a negative correlation between the total mineralocorticoid potency and serum sodium while it was positive for serum potassium levels. This pattern provides indirect evidence that changes in electrolytes had been the trigger for an increase in substitution therapy while it was less likely to be explained by steroid overdosage.

The reported rate of adrenal crisis of around 7% in the current study is within an expected range considering the high incidence of adrenal crisis even among educated populations based on recent studies (10,26). To avoid development of an adrenal crisis during delivery, the endocrinologist should provide the obstetric team with a written therapeutic plan regarding intravenous glucocorticoid coverage. This should be started before the active phase of labor with a recommended initial bolus of 100 mg hydrocortisone followed by continuous infusion or bolus dosages every 6 hours (27). However, there is no universal agreement regarding the timing and dosage adaptation of glucocorticoid substitution peri- and postpartum. In fact, in the vast majority of

cases of the current evaluation, glucocorticoid in stress dosage was administered intravenously. However, a wide scatter of hydrocortisone dosage was evident during labor and individual cases reported of missing or delayed stress coverage.

A further surprising finding was the predominantly high rate of CS as delivery mode among patients with secondary AI. Because of the retrospective nature of the data retrieval, the indications for CS remain uncertain. In accordance with previous findings, the rate of CS among patients with CAH was high, for which some percentage can be assumed to be related to earlier genital surgery (16,20,27). Furthermore, the increased rate of CS could also be related to the overall frequency of CS in large tertiary care hospitals (28).

Independent of the mode of delivery, most deliveries were without complications. Likewise, our study revealed good maternal and fetal outcomes for the overall patient cohort. Children born preterm were reported in all groups but were more frequent among patients with CAH. Similarly, the mean weight and height of these children tended to be lower. In a comparable study from Germany, children born to CAH patient weighed significantly less and had a tendency to be smaller compared to the general population (16). As our study lacked information regarding the sex of the children, we were unable to report the number of children born small for gestational age. Furthermore, considering the multi-centric nature of the study with data from different countries, a clear comparison to the respective general population was not possible.

Limitations of our study include possible missing data, over- or under-reporting of some aspects of baseline or follow-up parameters, and selection bias. In particular, it should be noted that those centers that took part in the current study are specialized in the diagnosis and treatment of patients

with AI and are more likely to be integrated into multidisciplinary teams as well as to provide patient management based on their clinical experience in addition to the existing guidelines. Therefore, it is possible that data gathered from expert centers will not be representative for the overall patient population. The strengths of our study include the availability of an extensive and recent dataset reflecting the current clinical management of pregnancies in women with AI from a variety of countries.

Taken together, this survey confirms good maternal and fetal outcome of pregnancies in AI treated in specialized centers. These data provide a reassuring ground for counselling of women with known AI and motivation for regular endocrine follow-up to adjust glucocorticoid and mineralocorticoid dosage during the course of pregnancy. Regarding the etiology and the prevention of miscarriages among patients with AI further prospective studies are required.

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Tables

Table 1: Baseline characteristics of pregnant patients with adrenal insufficiency.

	AD (n=56)	**Secondary AI (n=32)**	**CAH (n=32)**	**Other reason for AI (n=8)**	**P-value**
Age at diagnosis (years)	26 [14,35]	26 [8,44]	9 [0,38]	30 [23,37]	**<0.001**[a]
Age at pregnancy (years)	32.7±4.5	32.0±5.5	31.8±6.1	34.9±3.8	0.470[b]
Baseline BMI (kg/m^2)	24.3±4.5	27.5±6.9	25.7±4.6	24.3±6.0	0.143[a]

AD, Addison Disease; AI, adrenal insufficiency; CAH, congenital adrenal hyperplasia; BMI, Body Mass Index; Values are given as median [range] or mean±SD; [a] Kruskal- Wallis test, [b] One-way ANOVA

Table 2: Hydrocortisone equivalent dosage and total mineralocorticoid factor before pregnancy and per trimester divided in different subgroups of patients with adrenal insufficiency.

	AD	Secondary AI	CAH	Other reasons of AI	P-value[a]
Before pregnancy					
Daily HC equivalent dosage (mg)	22.4 [15.0-31.4] n=39	18.1 [7.5-40.0] n=25	21.8 [6.3-50.0] n=31	18.5 [15-20] n=5	**0.012**
Total MCU	2.0 [0.8-3.4] n=39	0.9 [0.0-2.2] n=26	1.5 [0.1-4.2] n=29	1.9 [1.1-2.5] n=5	**<0.001**
1st trimester					
Daily HC equivalent dosage (mg)	24.0 [15-40] n=53	18.8 [7.5-40] n=25	21.8 [7.5-45] n=30	23.8 [20-30] n=8	**0.02**
Total MCU	2.1 [0.0-4.2] n=56	0.7 [0.0-2.2] n=32	1.3 [0.0-4.2] n=31	2.3 [1.4-3.1] n=8	**<0.001**
2nd trimester					
Daily HC equivalent dosage (mg)	27.4 [15-70] n=50	21.6 [10-60] n=28	23.9 [7.5-45] n=30	25 [20-30] n=7	0.24
Total MCU	2.4 [0.9-5.8] n=51	1.0 [0.5-2.2] n=28	1.4 [0.1-4.2] n=29	2.6 [1.4-4.6] n=7	**<0.001**
3rd trimester					
Daily HC equivalent dosage (mg)	26.6 [10-40] n=50	23.0 [10-50] n=27	25.6 [7.5-50] n=28	25.7 [20-35] n=7	0.053

Total MCU	2.4 [0.9-4.1] n=50	1.1 [0.5-2.2] n=27	1.8 [0.1-5.6] n=26	2.7 [1.4-4.4] n=7	**<0.001**

AD, Addison Disease; AI, adrenal insufficiency; CAH, congenital adrenal hyperplasia; HC, hydrocortisone; MCU, mineralocorticoid unit; Values are given as median [range] or mean±SD

[a] Kruskal- Wallis test

Table 3: Development of blood pressure and serum electrolytes during pregnancy in patients with adrenal insufficiency.

	AD	Secondary AI	CAH	Other reasons of AI	P-value[a]
Before pregnancy					
Systolic blood pressure (mmHg)	113.8 ± 13.4 n=39	115.4 ± 16.7 n=25	110.9 ± 11.2 n=26	107.5 ± 12.6 n=4	0.558
Diastolic blood pressure (mmHg)	72.4 ± 9.6 n=39	70.7 ± 10.3 n=25	70.0 ± 9.2 n=26	68.3 ± 6.2 n=4	0.690
Serum sodium (mmol/l)	138.5 ± 3.2 n=40	139.4 ± 3.7 n=25	139.5 ± 2.2 n=25	138.0 ± 1.4 n=5	0.449
Serum potassium (mmol/l)	4.3 ± 0.5 n=40	4.1 ± 0.4 n=25	4.2 ± 0.4 n=25	4.1 ± 0.1 n=5	0.342
1st trimester					
Systolic blood pressure (mmHg)	109.7 ± 11.8 n=46	114.7 ± 9.7 n=24	110.0 ± 12.4 n=26	116.8 ± 17.4 n=6	0.225
Diastolic blood	71.2 ± 9.93	70.4 ± 8.8	71.0 ± 8.6	75.0 ± 18.8	0.790

pressure (mmHg)	n=46	n=24	n=26	n=6	
Serum sodium (mmol/l)	135.2 ± 2.1 n=44	137.5 ± 2.9 n=15	137.6 ± 2.6 n=23	136.1 ± 2.7 n=7	**<0.001**
Serum potassium (mmol/l)	4.2 ± 0.3 n=43	4.1 ± 0.5 n=15	4.0 ± 0.4 n=23	4.3 ± 0.2 n=7	0.076
2nd trimester					
Systolic blood pressure (mmHg)	108.4 ± 11.1 n=45	114.9 ± 15.3 n=23	111.1 ± 9.4 n=27	120.6 ± 12.9 n=7	**0.034**
Diastolic blood pressure (mmHg)	66.0 ± 8.3 n=45	71.9 ± 8.1 n=23	69.1 ± 7.7 n=27	78.2 ± 10.4 n=7	**0.001**
Serum sodium (mmol/l)	135.9 ± 2.7 n=36	138.1 ± 2.5 n=18	136.3 ± 3.9 n=24	136.7 ± 2.8 n=6	0.052
Serum potassium (mmol/l)	4.1 ± 0.4 n=40	3.9 ± 0.5 n=25	4.0 ± 0.3 n=25	4.1 ± 0.4 n=5	0.415
3rd trimester					
Systolic blood pressure (mmHg)	111.4 ± 12.3 n=43	117.0 ± 16.7 n=25	118.7 ± 16.4 n=25	112.4 ± 12.0 n=7	0.487
Diastolic blood pressure	74.1 ± 11.9 n=43	75.7 ± 14.1 n=25	70.2 ± 8.6 n=25	71.7 ± 6.2 n=7	0.359

(mmHg)					
Serum sodium (mmol/l)	137.2 ± 2.9 n=35	138.6 ± 2.5 n=19	137.7 ± 2.7 n=22	137.8 ± 3.1 n=6	0.376
Serum potassium (mmol/l)	4.1 ± 0.4 n=35	4.0 ± 0.4 n=19	4.0 ± 0.4 n=22	4.1 ± 0.3 n=6	0.653

AD, Addison Disease; AI, adrenal insufficiency; CAH, congenital adrenal hyperplasia; BMI, Body Mass Index; Values are given as median [range] or mean±SD; [a] ANOVA

Table 4: Course and outcome of pregnancies in patients with adrenal insufficiency.

	AD (n=56)	Secondary AI (n=32)	CAH (n=32)	Other reason for AI (n=8)	P-value
Spontaneous abortions (%)	15/55 (27.3)	5/32 (15.6)	14/32 (43.8)	2/8 (25.0)	**<0.001[a]**
Adrenal crisis during pregnancy (%)	5/56 (8.9)	2/32 (6.3)	2/32 (6.3)	0/8 (0)	0.607 [a]
Caesarean section (%)	24/50 (48.0)	20/29 (69.0)	20/31 (64.5)	5/8 (62.5)	0.224 [a]
Week of labor	37.9 ± 2.2	38.7 ± 1.8	37.0 ± 3.3	37.5 ± 2.2	0.075 [b]
Preterm births (%)	8/50 (16.0)	6/28(21.4)	10/31(32.3)	1/8(12.5)	0.335[a]
First APGAR score	8.3 ± 1.5	8.6 ± 1.8	8.7 ± 0.8	8.3 ± 1.0	0.739 [b]
Child height (cm)	48.7 ± 3.3	51.0 ± 5.1	48.1 ± 4.7	51.5 ± 0.7	0.337 [b]
Child weight (g)	3261 ± 606	3322 ± 674	2934 ± 696	2814 ± 344	0.063 [b]

AD, Addison Disease; AI, adrenal insufficiency; CAH, congenital adrenal hyperplasia; Values are given as median [range] or mean±SD; [a] Kruskal- Wallis test, [b] One-way ANOVA

Figure legends

Figure 1: Dosage adaptation for daily glucocorticoid (upper panel) and mineralocorticoid (middle panel) substitution therapy and calculated total mineralocorticoid potency (lower panel) during pregnancy for women with adrenal insufficiency. TM, trimester; HC, hydrocortisone. Stars denote significant differences in comparison to baseline (* = p<0.05; **=p<0.01; ***=p<0.001).

Figure 2: Systolic and diastolic blood pressure (upper panel) and serum electrolytes with sodium (middle panel) and potassium (lower panel) during pregnancy for women with adrenal insufficiency. TM, trimester. Stars denote significant differences in comparison to baseline (* = p<0.05; **=p<0.01; ***=p<0.001).

Figure 3: Relation between mineralocorticoid potency and serum electrolytes at baseline and during the three trimesters of pregnancy. AD, Addison disease; AI, Adrenal Insufficiency, CAH; Congenital Adrenal Hyperplasia.

Figure 1

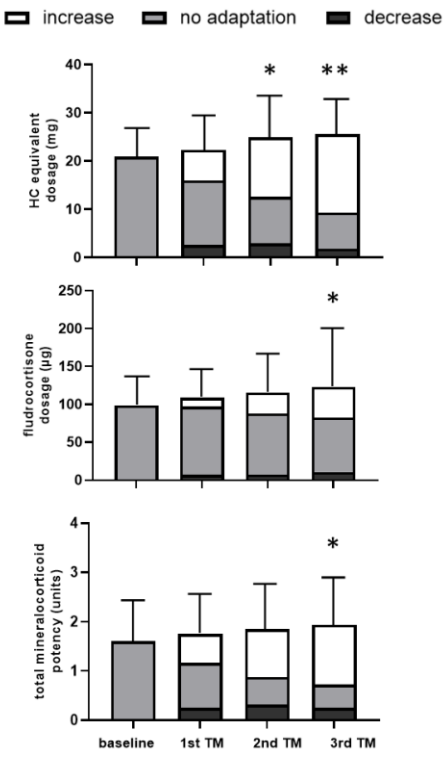

Figure 2

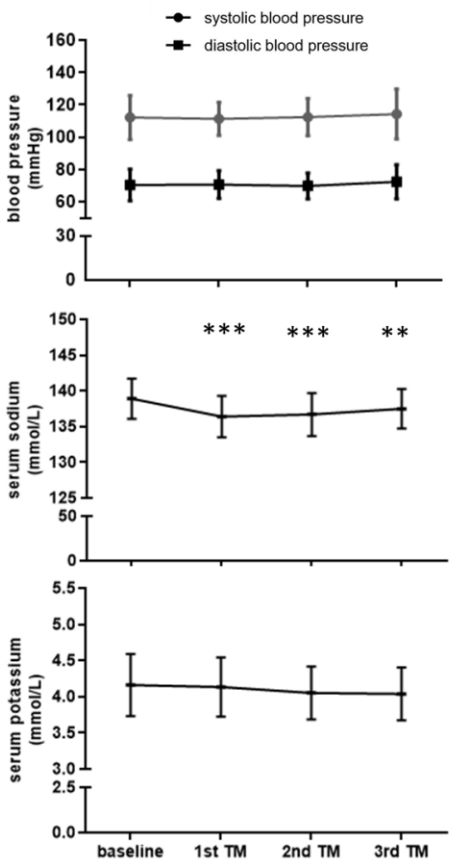

Figure 3