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Case Report

Blood pressure reduction in pregnancy by sodium chloride

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Volume expansion in the presence of elevated aldosterone availability is a hallmark of normal pregnancy. Intravascular volume depletion characterizes severe pregnancy-associated disease conditions such as intra-uterine growth retardation, chronic hypertension or pre-eclampsia [1]. Two hypotheses have been forwarded to explain volume depletion in pregnancy: the first hypothesis charges inappropriate sensing of vascular 'overfilling', resulting in an increased transendothelial loss of fluid to the extravascular compartment. In contrast, the second hypothesis focuses on vascular 'underfilling' due to inappropriately low aldosterone levels. The second hypothesis is based on the assumption that a compensatory increase in the circulating fluid volume is required in normal pregnancy to support fetal substrate delivery. According to the second concept, maternal blood pressure increases due to counter-regulatory mechanisms when placental blood supply is reduced [2]. In support of the 'underfilling' hypothesis are observations that a compromised volume status before pregnancy or a reduced ability to retain sodium by pregnant women predicts a complicated pregnancy outcome. The relevance of intravascular volume expansion during normal pregnancy is also supported by the clinical observation that further reduction of fluids by prescribing either diuretics or salt restriction does not prevent or improve the course of the disease [3]. On the contrary, acute volume expansion in overt pre-eclampsia has been observed to transiently decrease blood pressure [4]. Assuming low aldosterone availability to be the cause rather than the consequence of pre-eclampsia [5], we recently observed an association between a reduced 18-methyl oxidase, the rate limiting enzymatic step of aldosterone synthase (CYP11B2), an increased frequency of polymorphisms in the gene of the same enzyme and pre-eclampsia [6]. Likewise, patients with inborn corticosterone methyl oxidase deficiency are known to decompensate at times of sodium deprivation. Here, we demonstrate for the first time the utility of prescribing supplemental NaCl for a woman with neither the increase in aldosterone production nor the blood pressure drop expected during pregnancy.

Case report

A 33-year-old woman had received a diagnosis of essential arterial hypertension 15 years ago. Renin activity was normal. She was followed at the Department of Nephrology and Hypertension of the University of Berne. Her blood pressure was well-controllable by dual antihypertensive treatment (calcium channel and β-blocker) at 123 and 84 mmHg systolic and diastolic, respectively, during the 6 month period prior to conception. Throughout pregnancy, office blood pressure readings were taken at twice-weekly scheduled follow-up visits using the first and fifth Korotkoff sound and according to current guidelines. Office blood pressure measurements were supplemented by three home self-measurements per day performed by the patient herself using an automated device, which had been calibrated and controlled at our clinic. Blood pressure recordings were collected using the patient's blood pressure diary and our outpatient's clinics files. Weekly means were derived from the daily averages of typically three independent measurements. At five weeks of gestation in her first pregnancy, the patient stopped all antihypertensive drugs. The average blood pressure increased to 132 and 87 mmHg systolic and diastolic, respectively, and remained within this unusual first trimester range for the consecutive weeks (Figure 1). Twenty-four hour urinary samples were analysed by gas chromatography–mass spectroscopy for urinary steroid metabolites, as described earlier [6]. High ratios indicate low enzyme activities. In normal pregnancy, tetrahydroaldosterone excretion increases, indicating a high aldosterone production. In the patient presented, tetrahydroaldosterone excretion remained low compared with normal pregnant women (Table 1).

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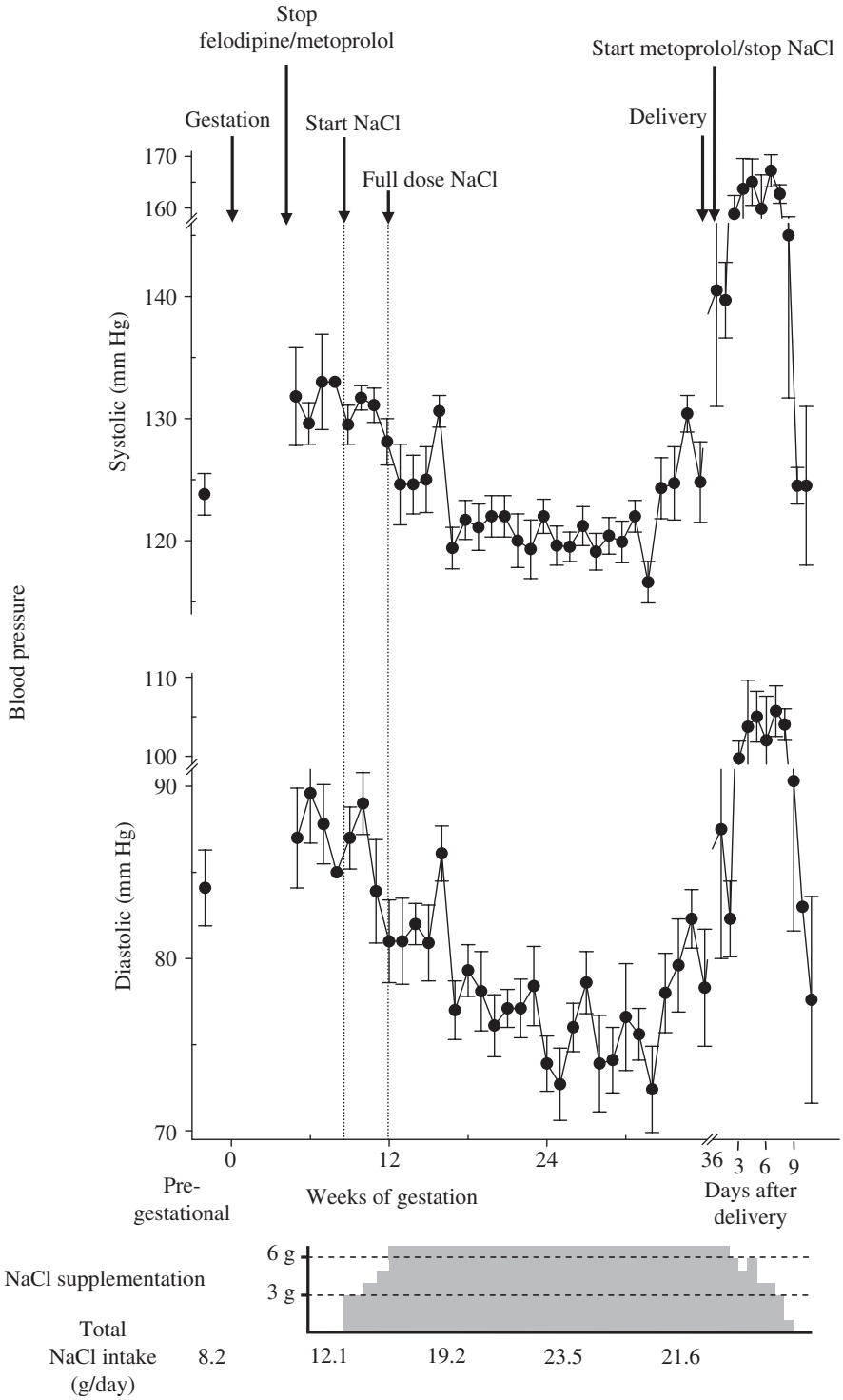

Fig. 1. Systolic and diastolic blood pressure is presented. Pre-gestational blood pressure is the mean ± SEM of monthly office cuff measurements during six proceeding months. Gestational blood pressure is presented as weekly mean ± SEM of triplicate daily measurements verified by office measurements every other week. After delivery, daily means ± SEM of three to five measurements are given. The NaCl supplementation is indicated at the bottom. Total (supplemental and dietary) NaCl uptake as calculated from urinary 24 h Na^+ excretion in g/day.

We observed absence of the expected increase in aldosterone synthase activity in pregnancy as indicated by the following ratios [6]: deoxycorticosterone to tetrahydroaldosterone and total deoxycorticosterone to tetrahydroaldosterone (both reflecting all enzymatic steps of aldosterone synthase activity) and of 18-hydroxy-precursors of aldosterone, denoted by 18-hydroxy-tetrahydro-11-dehydrocorticosterone to

Table 1. Summary of analysis of steroid hormone urinary metabolites

Urinary ratios of steroid/creatinine (μg/mmol)	Non-pregnant		Pregnant	
	Index patient	Normal values as reported in [6]	Index patient	Normal values as reported in [6]
Tetrahydrocortisone (THE)	154	(201 ± 29)	465	(507 ± 62)
Tetrahydrocortisol (THF)	76	(103 ± 15)	175	(196 ± 62)
5α-tetrahydrocortisol (5αTHF)	29.4	(63.1 ± 11.3)	45.1	(49.4 ± 11.7)
Deoxycorticosterone (DOC)	0.0	(0.8 ± 0.2)	3.7	(2.3 ± 0.92)
(THDOC + DOC)	0.7	(1.5 ± 0.3)	217	(63.5 ± 14.7)
18-Hydroxy-tetrahydro-11-dehydrocorticosterone (18-OH-THA)	16.3	(7.0 ± 2.4)	12.0	(13.7 ± 3.9)
Tetrahydroaldosterone (THAldo)	1.7	(4.1 ± 0.6)	2.2	(37.9 ± 12.8)
THA	6.1	(8.2 ± 1.3)	9.4	(47.7 ± 8.1)
Tetrahydrocorticosterone (THB)	10.9	(10.8 ± 2.1)	13.7	(38.5 ± 8.3)
5αTHB	9.3	(19.8 ± 3.1)	17.0	(27.5 ± 3.0)

Normal values are given as mean ± SEM as reported in [6].

Table 2. Calculated ratios of steroid hormone urinary metabolites

Calculated ratios	Non-pregnant		Pregnant	
	KC	Normal values as reported in [6]	KC	Normal values as reported in [6]
11β-hydroxylase activity				
[tetrahydro-11-deoxycortisol/(THE + THF + 5αTHF)] × 100	1.38	(1.12 ± 0.12)	2.20	(7.50 ± 1.52)
(THDOC/(THE + THF + 5αTHF)) × 100	0.26	(0.2 ± 0.1)	31.1	(12.8 ± 4.3)
11β-hydroxysteroid dehydrogenase activity				
THB/THA	1.79	(1.30 ± 0.10)	1.46	(0.94 ± 0.17)
Aldosterone synthase activity				
DOC/18-OH-THA	0.04	(0.27 ± 0.07)	0.30	(1.01 ± 0.55)
(THDOC + DOC)/18-OH-THA	0.40	(0.5 ± 0.1)	18.1	(17.2 ± 6.3)
(THA + THB + 5αTHB)/(THE + THF + 5αTHF)	0.10	(0.11 ± 0.01)	0.06	(0.28 ± 0.04)
DOC/THAldo	0.00	(0.23 ± 0.07)	1.63	(0.15 ± 0.07)
(THDOC + DOC)/THAldo	0.40	(0.44 ± 0.07)	97.1	(4.04 ± 1.06)
18-OH-THA/THAldo	9.48	(2.26 ± 0.51)	5.37	(0.45 ± 0.09)

Normal values are given as mean ± SEM as reported in [6].

tetrahydroaldosterone (reflecting 18-methyl oxidase activity) (Table 2). Compared with regular pregnancies, this led to an 11.9-fold raised ratio of 18-hydroxy-tetrahydro-11-dehydrocorticosterone to tetrahydroaldosterone pointing towards a metabolic defect at the level of 18-methyl oxidase activity (Table 2). In contrast to non-pregnant urinary steroid hormone metabolites assessed 3 years ago, the missing switch to pregnancy-induced hyperaldosteronism is most prominent in these three ratios. The analysis of urinary steroid metabolites indicated no abnormalities with respect to the activity of 11β-hydroxysteroid dehydrogenase or 11β-hydroxylase (Table 2). Genetic analysis of the *CYP11B2* revealed homozygocity for a loss-of-function mutation as observed earlier by our group [6]. Given the hypoaldosteronism, sodium supplementation aiming at 20 g total NaCl intake per day as defined by the 24 h urinary sodium excretion was initiated and pursued throughout pregnancy (Figure 1). Mean systolic and diastolic blood pressure decreased by 16 and 12 mmHg, respectively throughout pregnancy, with just a limited increase not reaching initial values prior to delivery (Figure 1). Due to breech presentation, delivery was by primary caesarian section. The child had a normal birth weight of 2800 g at 37 weeks of gestation. After delivery, the maternal blood pressure rose to 165 and 105 mmHg systolic and diastolic, respectively. The NaCl supplementation was terminated and β-blockade reinstalled.

Discussion

Treatment of hypertension in pregnancy and prevention of pre-eclampsia by drugs and dietary manoeuvres are issues still unsatisfyingly approached in clinical practice. The blood pressure of the patient presented did not fall in early pregnancy, in contrast to the response expected in normal pregnancy even in women with chronic hypertension [7]. Interestingly, blood pressure was responsive to NaCl supplementation. This finding is in line with the hypothesis that intravascular volume depletion causes increased blood pressure in pregnancy. In a series reported recently by us and in the patient presented here, an inadequate increase in aldosterone production due to a

compromised aldosterone synthase activity was observed in pregnancy [6].

Aldosterone is produced by the aldosterone synthase, which comprises three enzymatic steps, the 11β- and 18-hydroxylation as well as the 18-methyl oxidation. The aldosterone synthase is 93% homologous to the 11β-hydroxylase, an enzyme, which has limited 18-hydroxylation activity, and which is unable to catalyse the last and rate limiting enzymatic step of aldosterone production, the 18-methyl oxidation. The absence of the expected increased aldosterone synthesis during pregnancy in this patient was associated with a homozygous, non-conservative mutation of the aldosterone synthase gene, V386A, similar to our earlier findings in a significant number of pre-eclamptic patients [6]. This mutation represents the sequence normally present in *CYP11B1* at a site of *CYP11B2* heterologous to this enzyme, potentially an ancestral gene conversion, and led *in vitro* to a reduced efficiency to produce aldosterone [6–8].

The presence of persistent hypoaldosteronism and reports emphasizing NaCl supplementation in corticosterone methyl oxidase deficiency led us to supplement salt in this woman. This salt supplementation was associated with a reduced blood pressure throughout the pregnancy. Support for a critical role of NaCl intake in pregnancy is provided by an early observation by Robinson, who found a reduced incidence of pre-eclampsia in pregnant women on a high salt diet [9]. In this early study, a reduced risk of developing pre-eclampsia by consuming ~20 g/day dietary NaCl was observed. The quasi randomized design introduced substantial potential for bias in this and two further studies performed 40 years ago on the utility of a high salt diet in pregnancy [10]. Two studies on low salt *vs* normal salt diet in pregnancy to prevent pre-eclampsia including 603 patients indicated an unchanged relative risk of developing pre-eclampsia [10]. These data suggest that salt restriction during pregnancy does not seem promising for the prevention of pre-eclampsia and that a large number of women would need to be randomized to detect a moderate to small beneficial effect. In summary, there is uncertainty with respect to the utility of salt intake during pregnancy. The report presented here indicates that pregnant women with even subtle signs of volume deficiency, probably in part attributable to a reduced capacity to produce aldosterone, might benefit from salt supplementation in pregnancy.

Conflict of interest statement. None declared.

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