# Urinary Sodium and Pregnancy Induced Hypertension; A Unsolved Mystery

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## ABSTRACT

*Objective:* to know the connection between Sodium intake/urinary Sodium excretion and the tendency to develop hypertension during pregnancy.

*Study design:* Prospective longitudinal study.

*Place and Duration of Study:* Combined Military Hospital Kharian, District Gujrat Pakistan from Jul 2019 to Dec 2020.

*Methodology:* The included population was divided into two equal Groups (Normotensive and hypertensive). Blood pressure was measured at a pre-determined interval starting from the initial prenatal visit before 18 weeks of pregnancy to the 36th week of gestation. Urinary Sodium secretion was determined in 24-hours urine accumulated at three stages between 18 and 36 weeks of gestation. The main outcome actions were the implication of the difference in mean between urinary Sodium and alterations in maternal BP.

*Results:* The mean age of our study population was 32 years ± 6.96 years, and it ranged from 31 to 48 years. The mean urinary sodium was 141.00±24.879, 140.00±29.73 and 139.00±15.17 mEq/day in the normotensive group, which was 142.00±21.90, 143.00±32.03 and 139.00±14.27 mEq/dl in the hypertensive group. In the hypertensive group, systolic Blood pressure was also high with mean systolic BP of 143.00±12.10, 141.00±12.47 and 148.00±16.82 respectively during the three trimesters. As expected, it was normal in the second group.

*Conclusion:* There was no significant association between sodium intake and pregnancy-induced hypertension.

**Keywords:** Blood pressure, Pregnancy, Sodium, Urinary sodium excretion.

## INTRODUCTION

Hypertensive disorders of pregnancy are one of the very common complications of pregnancy, contributing to a lot of morbidity and multi-level mortality in pregnant females. First, high blood pressure in pregnancy may manifest long-lasting hypertension pregnancy, or it may be some complication developed specifically during pregnancy leading to elevated blood pressure, known as pregnancy-induced hypertension.[1,2] In addition, the combination of new proteinuria with elevated blood pressure is labelled as pre-eclampsia.

In non-pregnant women, it is well-known that dietary Sodium intake and urine excretion of Sodium strongly correlate with the development of chronic hypertension.[1-3] Later, it was also discovered that low Sodium in the diet leads to control or at least improvement in blood pressure. However, the exact impact of Sodium consumption is not known. Most world researchers agree that high Sodium intake is associated with elevated blood pressure, especially over long periods.[2,4] Similarly, it is believed that pregnancy-induced hypertension has a multifactorial aetiology, and one of those factors may be related to various electrolyte intake. Since the turn of the century, there has been much discussion about the Sodium content of food.[3,4] However, the association between Sodium consumption and elevated blood pressure during pregnancy remains elusive. De Snoo, a famous Dutch obstetrician, was the first person to make comments about the important role played by Sodium ingestion and elevated blood pressure during pregnancy.[4,5] However, after many years of research, carried out so far, none has been able to establish a clear role for Sodium intake and elevated blood pressure during pregnancy.[6,7] Most of these studies were either underpowered or carried out only late in pregnancy, so their results never established the critical role played by Sodium in pregnancy-induced hypertension.[8,9] Therefore, we tried to bridge this knowledge gap and studied the changes in urinary Sodium secretion and their connection to blood pressure. We tried to study urine Sodium excretion and its relationship to pregnancy-induced HTN at three stages in pregnancy, at 18th, 28th and 36th weeks of pregnancy.

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## METHODOLOGY

This prospective longitudinal study was carried out from July 2019 to December 2020 at the Combined Military Hospital Kharian Pakistan. It is a tertiary care hospital with a fully established gynaecology and obstetrics department. It provides medical facilities to three main districts of Punjab. Permission of the Ethical Committee was taken (via Letter No KHN/ 1100/adm/02).

**Inclusion Criteria:** All nulliparous and parous ladies with singleton pregnancies coming for prenatal care after the 16th week of gestation were included in the study.

**Exclusion Criteria:** Patients with the communication barrier and non-consenting ladies were also excluded from the study.

The sample size was calculated using the Raosoft sample size calculator. Taking a confidence level of 95%, the margin of error of 5%, reported prevalence of 2-7% of pregnancy-induced hypertension,[1,3,9] our sample size was just over 200. However, technically it was a difficult study as 24-hour urine collection was tedious and had to be repeated at least three times in 9 months. Many patients left the study in the middle or did not consent. Several patients were unable to adhere to the 24-hour urine collection technique. Ultimately, we included a relatively modest number of patients who completed the study.

Informed permission was taken prior to registration. The gestational period was established from the best approximate corresponding to menstrual history or ultrasonic calculations in early pregnancy. Since standard mercury sphygmomanometer is subject to observer bias error,[10] BP evaluation was standardised using a computerised device, the Hana and UUI, China). This device uses oscillometry for measuring BP. We validated it for use in pregnancy. Blood pressure was measured once in the woman sitting position and with the cuff at the cardiac level. These harmonised blood pressure dimensions were noted during the prenatal visits at booking and 18th, 20th, 28th, and 36th weeks of gestation. All the participating ladies were asked to collect a urine sample of 24-hours urine at 18th, 28th and 36th weeks of gestation. To avoid inaccuracies, the women received written guidelines for every visit beforehand. Residents of the Gynaecology ward gave verbal instructions. Urine was collected in 2-litre plastic bottles without preservatives and investigated in the Central Pathology Laboratory in CMH Kharian. Gestational HTN was demarcated as a diastolic pressure of 90 mm Hg or above on two successive occasions at a minimum of four hours apart in the subsequent half of pregnancy of an earlier normotensive woman.[11]

Pre-eclampsia was identified as gestational HTN with proteinuria of 300 mg/24 hour or more on a particular occasion.[12] For every lady, the mean urinary Sodium and creatinine were estimated from the sample given by the females. From these samples mean for Sodium and urinary creatinine excretion were computed for the entire study population. Urine samples with a volume below 500 ml were incomplete 24-hour compilations and thus eliminated from the analysis. In addition, urine compilations with a volume higher than 3000ml were omitted as being over-complete. For these ladies, the variation in urinary Sodium secretion was estimated from 18th, 28th and 36th weeks. Variations in systolic and diastolic BP were also defined for the same pregnancy periods. The main outcomes were the significance of fluctuations in Sodium secretion with changes in BP. These values were estimated for the entire entire study population, as well as for nulliparous and parous females individually, and each of the three gestational periods. Nulliparous and parous women were matched by employing the unpaired t-test. The *p*-value of ≤ 0.05 was deemed to suggest statistically significant. Ladies with and without Pregnancy induced HTN were compared with each other through the unpaired t-test for the sequential values of BP and Sodium secretion.

## RESULTS

Our study included 60 patients distributed in two identical groups of 30 each. The mean age of our study was 32.00±6.96 years, ranging from 31 to 48 years. The age comparison between two study groups was shown in the Table-I.

**Table-I: Age Comparison between two Study Groups (n=60)**

| Parameters | Study Groups n (%5) | | p-value |
|---|---|---|---|
| | Group-A (Normotensive) (n=30) | Group-B (Hypertensive) (n=30) | |
| **Age n (%)** | | | |
| <30 years | 20 (63) | 12 (38) | 0.038 |
| >30 years | 10 (36) | 18 (64) | |

Mean urinary Sodium at 18, 28, and 36 weeks was 142.00±21.90, 143.00±32.03 and 139.00±14.27 mmol/l, respectively, in the whole study population. Mean urinary Sodium remained 141.00±24.87, 140.00±29.73 and 139.00±15.17 mmol/l at 18, 28 and 36 weeks of

gestation (Table-II). Mean systolic blood pressure in normotensive group was 119.00± 7.133 mmHg, 118.00 ±7.45, and 116.00± 18.16 mmHg. At the same time diastolic blood pressure at 18, 28 and 36 weeks of gestation was 75.00±6.14 mmHg , 75.00±6.009, and 80.00±6.59 mmHg .It was not significantly different.

**Table-II: Mean Urinary Sodium and systolic Blood Pressure at 18-Weeks, 28-Weeks And 36-Weeks of Gestation (n=60)**

| Parameters | Minimum | Maximum | Mean±SD |
|---|---|---|---|
| UrinaryNa18 weeks umol/l | 110 | 200 | 142.70±21.97 |
| UrinaryNa28 umol/l | 105 | 245 | 142.05±32.03 |
| UrinaryNa36 umol/l | 120 | 165 | 139.23±14.42 |
| Systolic Blood pressure at 18 weeks (mmHg) | 100 | 175 | 130.70±15.47 |
| Systolic Blood pressure at 28 weeks (mmHg) | 105 | 180 | 129.47±15.84 |
| Systolic Blood pressure at 36 weeks (mmHg) | 30 | 180 | 132.20±23.47 |

On the other hand, in the Hypertensive Group, mean systolic blood pressure was 143 ± 12.102, 141 ± 12.473 and 148 ± 16.829.so the systolic blood pressure was significantly high in the second group with *p*< 0.05. At the same time, diastolic blood pressure was 99 ± 5.673, 100 ± 5.498 and 105 ± 5.796 mmHg at 18, 28 and 36th week of pregnancy in this group, which was expectedly to be higher than the Normotensive population of our study. Mean urinary Sodium was 141mday, 140 and 139 mmol/l in the Normotensive Group. While in a Normotensive Group, it was 142, 141, 147 mEq/dl. Although the difference was significant statistically and clinically, there was no significant difference in the 24-hour urinary Sodium of the two groups. Parity was significantly different between the two groups, as nulliparous women were more likely to develop pregnancy Induced hypertension *p*<0.05 (0.003). Blood pressure comparison of two groups was shown in the Figure.

## DISCUSSION

To our knowledge, very few studies have tried to find out the association between urinary Sodium elimination, which is the surrogate sign of dietary Sodium intake, and pregnancy-associated hypertension.[8,9] This is mainly because of the difficulty in the induction of the people in similar studies as the 24-hour urinary collection is a tedious job. Most of the patients either do not volunteer or leave the study in the midway.[10,11] we also faced similar problems with

sampling errors and dropouts. Our study failed to find any significant association between 24-hour urinary Sodium secretion and its association with pregnancy-caused hypertension. There was wide variation in the 24-hour urinary excretion of Sodium which is probably the result of extreme variation in daily intake of Sodium.
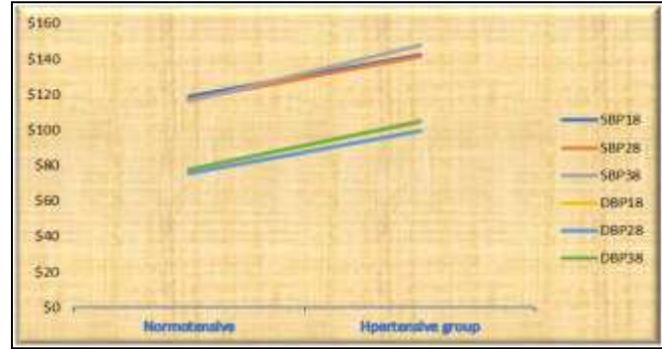

**Figure: Blood Pressure Comparison of Two Groups (n=60)**

Most of the people in Punjab take spicy food with much salt. No special specific attention is usually paid to control of blood pressure or dietary modification during pregnancy in these areas because of low education and adherence to various myths.[12,13] However, it cannot be concluded with certainty that the Sodium content of the diet is the only factor responsible for urinary Sodium excretion as other factors are believed to contribute at least partially to unity Sodium excretion in pregnancy.[14] Sampling inaccuracies cannot be excluded, as many 24-hours urine compilations are needed to reliably guess an individual's usual Sodium consumption.[15] Obviously, this was not possible in epidemiological studies. In addition, this education level is not very good in most countries, and patients find it difficult to follow the instructions. Samples are also analysed in the laboratory at different times by different people, which may be another contributing factor to Sodium results in urinary Sodium. Resultantly, not many researchers have travelled on this difficult path.[16] The studies mostly mentioned in the discussion of Sodium restraint in pregnancy are that of Franx *et al.* and Nielsen *et al.*[10,17] carried out that breakthrough trial in Dutch population and probably it was the first major detailed study analysing the parameters mentioned above in detail. Their study Group comprised 667 minimal-risk females with singleton pregnancies, of which 350 were nulliparous, and 317 stood parous. They measure BP at prearranged intervals from the first prenatal visit preceding 16 weeks of pregnancy and until delivery. They measure

Urinary Sodium secretion on at least four occasions. Franx et al.[10] recognised widely over the world, as they had conducted this difficult study design in a very professional and skilled manner. We tried to follow their study design but used simpler means because of resource limitations and financial constraints. However, our results were mostly in keeping with them. We could not establish any defini-tive correlation between urinary Sodium excretion and pregnancy-induced hypertension. Like their study, we also discovered that women ultimately developing gestational hypertension had considerably higher BP from the initial prenatal visit and remaining pregnancy. According to them, toxaemias of preg-nancy were greatest in the low salt Group. This finding was direct incongruity with our study. However, Robinson et al. study have obtained severe critiques for a few key methodological inadequacies: no effort was rendered to evaluate conformity to the prescribed diets, and 'toxaemia' was recognised in women with proteinuria and oedema with no hypertension. McEnery et al.[11] and contemporaries studied the consequences of short-term alterations of nutritional Sodium on BP in pregnancy. In their modest study, pregnant ladies were assigned to a randomly selected cycle of three diets, each for 7–10 days: minimal Sodium (10 mmol per day), high Sodium (300 mmol per 34 hours) and the women on a standard diet with routine Sodium intake. These short-term dietary manipulations generated no changes in heart rate or blood pressure. Plasma volume and plasma renin activity altered with altered Sodium intake, but these changes did not link with changes in blood pressure between low and elevated Sodium intake. Our study population was a bit larger, and we did not study any changes in Renin and aldosterone levels as they were beyond the scope of our research. In their study, urinary Sodium elimination showed some reduction during pregnancy. Normotensive nulliparous females had a mean Sodium output of 145 (45.3) mmol at 16 weeks and 115 (44.5) mmol at 36 weeks of pregnancy, reflecting a reduction of about 0.2 mmol. Similarly, we also noticed a decrease in Sodium in urinary Sodium of 141, 140, and 139 mmol at 18 and 28,36 weeks of gestation. This decline was more prominent in a normotensive group with values of 144, 144, and 139 mmol, as mentioned above. This topic remained ignored until 2018, when Jandee et al.[12] published their results in 2021. They included the Thai population and discovered that Spot U[Na+]/[Cr] and U[K+]/[Cr] proportions were inversely related to Blood pressures; weak relationships were found in pregnant ladies in southern Thailand. In their study, 327 pregnant females were included. Systolic and diastolic BPs decreased slowly from 14 weeks of pregnancy to 18–22 weeks and then went up until 30–34 weeks. Mean spot U[Na+]/[Cr] did not drastically change throughout the study period. Mean spot U[K+]/[Cr] augmented, and spot U[Na+]/[K+] ratios steadily reduced. According to them the association of spot U[Na+]/[Cr] and U[K+]/[Cr] ratios with Blood pressure was implau-sibly negative at all four-time points. Our results were in keeping with them, but we did not measure Serum Potassium. It is believed that glutathionylation by Na+/K+ ATPase Transporter plays a key role in BP response to salt (Sodium) intake.[18,19] However; we were mainly focused on establishing an association between Sodium intake and PIH. To establish etiological factors at the molecular level, analysis was beyond the scope of our study.

## LIMITATIONS OF STUDY

Our study was limited by poor compliance of the patients and a high dropout rate.24-hour urine collection was not acceptable to many females. They did not collect the samples at all, or most of them were either overfilled or under-collected. Many patients did not collect samples on all three different occasions and had to be removed from the study. Laboratory also had multiple issues with urinary Sodium measurement equipment. Therefore, all our results are like most of the world literature, which states that there is no or very weak clinical correlation between urinary Sodium and pregnancy-induced hypertension. However, larger studies with strong methodical techniques are needed to accept or refute this hypothesis.

## CONCLUSION

There was no significant association between Sodium intake and pregnancy-induced hypertension.

**Conflict of Interest:** None.

**Author's Contribution**

SNK: Management of obs related issues and data collection from obstetrics ward. patient counselling for study. coordination among patients, labs and study members , MIK: Principal investigator/researcher, RS: Data analysis, administrative support, JAK: Expert advice on medical management of the cases and dealing with medical causes of sodium imbalance. Pivotal role in study design, AN: Expert advice on Nephrology related aspects of Sodium disorders in pregnancy. Data collection from Nephrology ward, UA: Data collection, analysis and facilitation of sample collection from obs department. Typing the whole write up and partial statistical support.

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