

DIETARY SALT INTAKE IN PREGNANCY AND HYPERTENSIVE PREGNANCY DISORDERS – NARRATIVE REVIEW

Živka Dika^{1,5*}, Josip Juras^{2,5}, Ivan Vukoja^{3,6}, Boris Lovrić⁴, William Migo⁵

¹Department of Nephrology, Arterial Hypertension, Dialysis and Transplantation; University Clinical Hospital Centre Zagreb, Zagreb, Croatia

²Department of Gynaecology and Obstetrics, University Clinical Hospital Centre Zagreb, Zagreb, Croatia

³Gastroenterology and Nephrology Department, General County Hospital Požega, Požega, Croatia

⁴Department of Gynaecology and Obstetrics, General Hospital Nova Gradiška, Nova Gradiška, Croatia

⁵School of Medicine, University of Zagreb, Zagreb, Croatia

⁶Faculty of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia

review paper

Summary

Salt is crucial for human health, but its excess is associated with the development of many diseases including arterial hypertension which is a major feature of hypertensive pregnancy disorders (*HPDs*). Maternal nutrition during pregnancy can affect cardiometabolic disease development during pregnancy and later in life, but it can also affect fetal growth and disease development in adulthood. Recent studies suggest that excessive salt intake often combined with low potassium intake throughout pregnancy, can suppress renin-angiotensin-aldosterone system (*RAAS*) with adverse effects on fetoplacental development and can increase the risk of *HPDs*. Although salt restriction has been considered potentially harmful in the non-pharmacological treatment of arterial hypertension in pregnancy and current guidelines do not recommend it during pregnancy to prevent *HPDs*, especially gestational hypertension and the development of preeclampsia, its role should be reconsidered in light of the recent evidence. However, one key question remains: How much salt, upper and lower limit of daily intake, in a balanced diet is not harmful in uncomplicated pregnancies as well as *HPDs* in general?

Keywords: hypertension, pregnancy, hypertensive pregnancy disorders, preeclampsia, salt

Dietary salt intake in general population and in pregnancy

Salt (sodium chloride, *NaCl*), is crucial for human health, however, its excess is associated with the development of many diseases, namely: cardiovascular diseases (Aburto et al., 2013; Cogswell et al., 2016; He et al., 2013), gastric cancer (D'Elia et al., 2012; Ge et al., 2012; Poorolajal et al., 2020), nephrolithiasis (Lin, 2020), kidney disease (McMahon et al., 2013) and osteoporosis (Caudarella et al., 2009; Teucher et al., 2008). Sodium is the main chemical component in table salt and an essential nutrient necessary for the maintenance of fluid and acid-base balance, and cellular homeostasis in the human body. The recommended dietary salt intake is less than 5 g (or 2 g of sodium) per day for adults and less than 3 g (1.2 g sodium) for children under 7 years of age, and even less than 2 g (0.8 g sodium) for those under 4 years of age (Campbell et al., 2014; Campbell et al., 2015; WHO, 2016). The amount of sodium needed to maintain homeostasis in adults is very low (<500 mg) (He et al., 2009; Holbrook et al., 1984) compared to current global average intake of 2.4-4.8 g per day (WHO, 2016; WHO, 2020). According to the *US Centers for Disease Control and Prevention (CDC)* and *European Food Safety Authority (EFSA)*,

approximately 70-75% of the sodium intake is in the food we buy (Anderson et al., 2010; Centers for Disease Control and Prevention, 2012; European Food Safety Authority, 2005), while 11% comes from sodium added at the table or cooking at home (Harnack et al., 2017). Salt is mainly in food due to its role in sensory appreciation, processing technology and preservation (Elias et al., 2019). High salt intake is often accompanied with high consumption of sugar and fat (Hu, 2013; Gupta et al., 2018). Interestingly, the preference for sweetness and saltiness significantly increases during pregnancy peaking highest during the third trimester (Oh et al., 2011). Cioffi et al. (2018), have shown that pregnant women were more likely to consume salt and sugar than nonpregnant women of the same age. There are a growing number of studies showing increased prevalence of cardiometabolic diseases related to high salt and sugar consumption in pregnant and nonpregnant populations (Ponzo et al., 2021; Seo et al., 2020).

Maternal nutrition during pregnancy can affect cardiovascular disease development during pregnancy and later in life, but it can also affect fetal growth and disease development in adulthood (Arvizu et al., 2020; Fogacci et al., 2020; Gluckman et al., 2008). Women of reproductive age have a relatively low prevalence

of arterial hypertension, 8–9 % (Azeez et al., 2019; Bateman et al., 2012). Arterial hypertension in pregnancy may be chronic (predating pregnancy or diagnosed before 20 gestational weeks) or *de novo* (either preeclampsia or gestational hypertension) (Brown et al., 2018). Hypertensive pregnancy disorders (*HPD*) are among the most common medical complications and affect 5-10 % of all pregnancies worldwide (Hutcheon et al., 2011; Umesawa et al., 2017). In the case of associated comorbidities, the incidence increases up to 15 % (Umesawa et al., 2017). These hypertensive disorders include preexisting (chronic) arterial hypertension, gestational hypertension (*GH*) and pre-eclampsia (*PE*). *PE* itself is now defined as persistent arterial hypertension (systolic pressure ≥ 140 mmHg or diastolic pressure ≥ 90 mmHg) that develops after 20 gestational weeks or during the post-partum period, associated with proteinuria (≥ 300 mg in 24 h) and/or other maternal organ dysfunction (Brown et al., 2018). Of note, pregnant woman with chronic arterial hypertension may develop *PE* superimposed on chronic arterial hypertension. *HPDs* are a major cause of maternal, fetal, and neonatal morbidity and mortality (Cantwell et al., 2011; Chappell et al., 2021; Khan et al., 2006; Stevens et al., 2015).

Nutritional interventions during pregnancy for the prevention or treatment of maternal morbidity and preterm delivery often result in reduced energy intake and reduced micro and macronutrient consumption (Villar et al., 2003). Van der Maten (1995) has shown that the restriction of salt consumption (low sodium intake) in pregnant women also causes a significant reduction in the intake of proteins, carbohydrates, fat and minerals.

Current national and international guidelines do not recommend salt restriction during pregnancy to prevent *GH* and the development of *PE* (ACOG, 2013; Hanson et al., 2015; NICE, 2010; WHO, 2011; Magee et al., 2014; Regitz-Zagrosek et al., 2018).

The role of renin-angiotensin-aldosterone system in normal pregnancy and hypertensive pregnancy disorders

Pregnancy is characterized by normal blood pressure (*BP*) and elevated circulating levels of renin, angiotensin II (*Ang II*), and aldosterone (Brown et al., 1997; Langer et al., 1998; Uddin et al., 2015). Hyperactivation of renin-angiotensin-aldosterone system (*RAAS*) in pregnancy is necessary for an increase in the circulating maternal plasma volume (*PV*) which is crucial in maintaining sufficient uteroplacental perfusion (Verdonk et al., 2014). *PV* correlates positively with fetal birth weight, while

reduced *PV* correlates with intrauterine growth restriction (Brown et al., 1989). During normal pregnancy, there is a compensatory decline in peripheral vascular resistance to maintain normal maternal *BP*. This happens due to the vasodilating effect of progesterone (Hill et al., 2008) and decreased sensitivity to *Ang II* vasoconstriction (Elsheikh et al., 2001; Irani et al., 2011; Langer et al., 1998). In preeclampsia, *RAAS* is suppressed, circulating maternal *PV* is reduced, and vascular reactivity to *Ang II* is increased compared to normal pregnancy (Brown et al., 1997; Langer et al., 1998; Uddin et al., 2015; Washburn et al., 2015). Furthermore, decreased secretion and utilization of aldosterone in pregnancy can lead to insufficient fetoplacental development, and thus the development of perinatal complications and poorer maternal and fetal outcomes (Bellamy et al., 2007; Birukov et al., 2019; Gennari-Moser et al., 2011; Todkar et al., 2012).

Relation between renin-angiotensin-aldosterone system and salt intake

RAAS activity during pregnancy is influenced by dietary sodium and potassium intake (Birukov et al., 2019; Nielsen et al., 2016), importantly adrenal aldosterone synthesis is stimulated directly by potassium. In a randomized, cross-over, double-blinded, dietary interventional study by Nielsen et al. (2016), high-salt intake decreased renin and *Ang II* concentrations significantly in healthy pregnant and nonpregnant women, however preeclamptic patients failed to demonstrate the same effect. Decreased aldosterone and increased brain natriuretic peptide (*BNP*) were observed in all groups (Nielsen et al., 2016). Importantly, findings from other authors showed that pregnant women who later developed *PE* retained more of a given sodium load than those with uncomplicated pregnancies (Brown et al., 1988; Scaife and Mohaupt, 2017), even after furosemide administration (Brown et al., 1994). This suggests an impaired kidney ability to excrete sodium in *PE* despite suppressed *RAAS* and arterial hypertension, which normally promotes natriuresis (Kjolby et al., 2008). Renal hyperreabsorption of sodium at a site distal to the thick ascending limb of Henle's loop could be explained by abnormal activity of apical sodium transport proteins, i.e. epithelial sodium channels (*ENaC*) (Nielsen et al., 2016). Preeclamptic women display an abnormal presence of plasmin in the urine which activates collecting duct *ENaCs*. This is achieved by cleavage of the apical exodomain of the α -subunit of the *ENaC* (Buhl et al., 2012; Svenningsen et al., 2009). Enhanced renal sodium retention in preeclamptic women could explain subsequent

suppression of RAAS and salt-sensitive hypertension. Furthermore, Martillotti et al. (2013), showed that BP response to salt was significantly increased in women with a history of PE compared with controls.

Relation between hypertensive pregnancy disorders and salt intake

Arterial hypertension is a major feature of hypertensive disorders in pregnancy (Brown et al., 2018) and excessive salt is one of the proven causes of arterial hypertension (Blaustein et al., 2012; Kotchen et al., 2013; Mozaffarian et al., 2014). Moreover, excessive salt plays a role in endothelial dysfunction, induction of inflammation and has differential effects on immune cell activity (Asayama et al., 2018; Edwards, 2016; van der Meer et al., 2013). Inflammation is involved in the pathogenesis of PE (Michalczyk et al., 2020; Sanchez-Aranguren et al., 2014; Weissgerber et al., 2016). Gluckman et al. (2008), have demonstrated that impaired endothelial function is present in pregnant women who later develop PE.

The studies in pregnant and nonpregnant populations indicated that a combined effect of dietary sodium excess and potassium insufficiency is greater than either alone, as a mediator of high BP (Morris et al., 1999; Yilmaz et al., 2017). Furthermore, the decreased efficacy of lowering BP with low sodium and potassium intake has also been reported in the Dietary Approaches to Stop Hypertension (DASH) trial (Sacks et al., 2001). In a recent meta-analysis conducted by Binia et al. (2015), they found a significant correlation between reduced BP with daily urinary sodium to potassium ratio. Yilmaz et al. (2017), reported positive correlations between urinary sodium to potassium ratio and BP levels in pregnant women with PE. During this study the estimation of daily salt and potassium intake was based on a calculation of 24-hour urinary sodium and potassium excretion. The pregnant women with PE (n=150) were divided into tertiles according to urinary sodium to potassium ratio ($U[Na/K]$): low, medium and high Na/K groups. The mean systolic BP (SBP) and diastolic BP (DBP) levels were significantly lower in the low Na/K group compared with medium or high Na/K groups. The frequency of severe PE was lower in the low Na/K group compared with medium and high Na/K groups. Birth weight and gestational age at birth were higher in the low Na/K group compared with the high Na/K group (newborn weight difference mean was 306 g; 2 weeks difference in gestational age) (Yilmaz et al., 2017). These findings suggested that pregnant women with PE with high dietary sodium and low potassium intake had a greater maternal and neonatal morbidity

risk compared to their low dietary salt and high potassium intake counterparts. Additional analysis by Birukov et al. (2019) showed that salt intake > 6 g per day in pregnancy was associated with a greater risk of developing PE (hazard ratio: 5.68, 95 % CI: 1.51; 21.36). Further, a large analysis from the Danish National Birth Cohort (DNBC), carried out on 66,651 singleton pregnancies, demonstrated that women with the highest sodium intake (median 3.70 g/day (range: 3.52–7.52 g/day)) had a 54% (95 % CI: 16% - 104 %) higher risk of GH and a 20% (95 % CI: 1 % 42%) higher risk of PE than women with the lowest intake of sodium (median 2.60 g/day (range: 0.83–2.79 g/day)) (Arvizu et al., 2020). This indicated that salt intake during pregnancy was positively related to the occurrence of HPDs among pregnant Danish women.

Conclusion

Sodium intake and retention in the early stages of pregnancy is essential for physiologic maternal extracellular volume expansion, which regulates maternal blood pressure and uteroplacental circulation (Scaife and Mohaupt, 2017). Excessive salt intake often combined with low potassium intake throughout pregnancy, can suppress RAAS with adverse effects on fetoplacental development and can increase the risk of HPDs (Arvizu et al., 2020; Asayama et al., 2018; Bellamy et al., 2007; Birukov et al., 2019; Fogacci et al., 2020; Gennari-Moser et al., 2011; Nielsen et al., 2016; Todkar et al., 2012; Yilmaz et al., 2017). Women with a history of HPDs have increased risk of cardiovascular and cerebrovascular disease in later life (Bellamy et al., 2007; Honigberg et al., 2019; Umesawa et al., 2017). Cardiovascular risk after HPD is largely mediated by development of chronic arterial hypertension (Chappell et al., 2021; Haug et al., 2019). The risk of subsequent cardiovascular events increases with severity, parity and recurrence of HPDs (Chappell et al., 2021; Lykke et al., 2009). In addition to the increased risk of morbidity in women, HPDs seem to have a clinical impact on the health outcomes of offspring not only in the perinatal period, but also during childhood and adolescence (Jansen et al., 2019; Kanata et al., 2021). Offspring exposed to HPDs are more likely to have cardiovascular, renal, endocrine, gastrointestinal, immune and neurocognitive disorders (Jansen et al., 2019; Kanata et al., 2021). HPDs may affect fetal programming, namely neurohormonal adaptation (alterations in RAAS, hypothalamic-pituitary axis (HPA)), immune system, angiogenesis and fetal organ development (Kanata et al., 2021). These alterations may play a role in the future development of the diseases in the exposed offspring. According to current evidence, direct causal relations

between aforementioned disorders and HPDs cannot be established. Thus, closer monitoring of this population and further studies are necessary.

Although salt restriction has been considered potentially harmful in the non-pharmacological treatment of arterial hypertension in pregnancy (Farese et al., 2006; Gennari-Moser et al., 2014) and current guidelines do not recommend it during pregnancy to prevent GH and the development of PE

(ACOG, 2013; Hanson et al., 2015; Magee et al., 2014; NICE, 2010; Regitz-Zagrosek et al., 2018; WHO, 2011), its role should be reconsidered in light of the recent evidence outlined in this article (Table 1). However, one key question remains: How much salt (upper and lower limit of daily intake) in a balanced diet is not harmful in uncomplicated pregnancies as well as HPDs in general?

Table 1. Studies on the effect of excessive salt intake on maternal, fetal and offspring morbidity and mortality outcomes during pregnancy and later in life

Study (First author and year)	Type of study	Study population	Outcomes	Note
Yılmaz et al. (2017)	Prospective case – control	200 pregnant women (50 control - healthy pregnancy, 150 with newly diagnosed PE)	Pregnant with PE with high dietary salt and low potassium intake had greater maternal and neonatal morbidity risk than pregnant with PE under low dietary salt and high potassium intake	Women at risk not included
Birukov et al. (2019)	Longitudinal, observational cohort	569 pregnant women from 29 gestational week	Salt intake > 6 g per day in pregnancy was associated with a greater risk of developing PE (HR: 5.68, 95 % CI: 1.51; 21.36).	Women with HPDs or GDM at the time of sampling not included
Arvizu et al. (2020)	Observational cohort	66 651 singleton pregnancies from 62 774 women	Women with the highest Na ⁺ intake (median 3.70 g/day) had a 54% higher risk of GH and a 20% higher risk of PE than women with the lowest intake of Na ⁺ (median 2.60 g/day)	Women with history of HPDs not included
Nielsen et al. (2016)	Randomized, cross-over, double-blinded, dietary interventional	22 pregnant women with singleton pregnancies in gestational weeks 28–38: PE patients (n=7), healthy pregnant women (n=15); and healthy nonpregnant women (n=13)	High-salt intake decreased renin and Ang II concentrations significantly in healthy pregnant and nonpregnant women, but not in PE ones.	
Brown et al. (1988)	Combined cross - sectional and prospective	158 primigravid women	Na ⁺ excretion after saline solution loading varied according to prestudy Na ⁺ intake and was reduced between the second and third trimesters, independent of dietary salt intake. Normal pregnant women retain more administered Na ⁺ in late pregnancy than in midpregnancy despite further increases in PV and no alterations to BP or GFR. Those with established proteinuric PIH (i.e. PE) retain Na ⁺ avidly without stimulation of PRA or PAC (i.e. RAAS).	
Brown et al. (1994)	Prospective, randomized	25 third-trimester pregnant and 16 non-pregnant women	Normal pregnant women exhibited natriuresis and stimulation of plasma renin after frusemide similar to that of non-pregnant women. PE women had significantly impaired renin stimulation after frusemide (blunted response), but a similar natriuresis to that of normal pregnant women.	All women were on an ad libitum diet. Pregnant women - 10 normal and 9 with PE received frusemide, and 6 control received saline. Non-pregnant women - 10 received frusemide and 6 received saline

Ang II – angiotensin II, BP - blood pressure, GDM- gestational diabetes mellitus, GFR - glomerular filtration rate, GH- gestational hypertension, HPDs – hypertensive pregnancy disorders, HR –hazard ratio; Na⁺ - sodium, PAC -plasma aldosterone concentration, PE- preeclampsia, PIH- pregnancy induced hypertension, PRA- plasma renin activity, PV - plasma volume, RAAS - renin - angiotensin - aldosterone system

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