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Essential Hypertension in Children: New Mechanistic Insights

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Abstract

Paediatric hypertension is on the rise accompanied by concomitant increase of childhood obesity. The origin of paediatric hypertension however remains unknown. New epidemiological evidence suggests that environmental insult in utero or postnatally may lead to hypertension later in life. Independent associations have been reported between maternal obesity and cardiometabolic disorders in the offspring. In the first part, I will focus on functionally mechanistic pathways of essential hypertension with an attempt to elucidate the rather complex interplay of autonomic dysfunction, leptin, melanocortin-4 receptor (MC4R), inflammation, genetic and epigenetic predispositions. In the second part, the standalone risk factors will be integrated in a flow chart in attempt to understand the deeper meaning of this regulatory machinery in paediatric hypertension. I will refer to the pathophysiology of early sympathetic-mediated hypertension arising from maternal obesity. Maternal diet-induced obesity in rodents permanently resets the responsiveness to leptin-induced SNS in rat offspring via the hypothalamic paraventricular nucleus (PVN)-MC4R pathway. The stimulus that mediates Leptin-SNS-MC4R activity and promotes hypertension is still unknown and remains as a key for future investigations. Future research needs to identify effective preventive measures in the pregnant mother and child to reduce the risk of paediatric hypertension and prevent future cardiovascular disease.

Keywords: essential hypertension, maternal obesity, leptin, melanocortin system, sympathetic activity, hypothalamus

1. Introduction

Hypertension in children and adolescence is becoming an increasing health problem. The prevalence of pre-hypertension is approximately 14% in boys and 6% in girls (age 8–17 years)

[1, 2], and the prevalence of hypertension is estimated to be 3–4% (age 3–18 years) [3, 4]. One in three of the hypertensive children develops end-organ damage, including ventricular hypertrophy [5], chronic kidney disease [6] and vascular changes [7] and cognitive impairment [8, 9], all predictors for premature morbidity and mortality. Accumulating evidence supports the theory that elevated blood pressure levels in adolescence are a precursor of elevated blood pressure in adulthood, and an important risk factor for future cardiovascular diseases [10]. Another factor is the coexistent epidemic of childhood obesity, which in the US rose from 5 to 11% from the 1960s to the 1990 [11, 12], becoming a concomitant cardiovascular risk factor. Childhood BMI has strong positive concordance with blood pressure [13]. Children who are overweight demonstrate 4.5 and 2.3 times higher risk of developing increased systolic blood pressure and diastolic blood pressure, respectively [14], consistent findings were obtained by Sorof et al. [15] with a three-fold prevalence of childhood hypertension in obese versus lean at school age. Blood pressure in children may also vary by age, sex, race and height [4] but not as solid as BMI, all these inclusion criteria of risk being underdiagnosed [3]. Children within the “normotensive” range of blood pressure demonstrate elevated left ventricular mass [16] and greater risk of developing hypertension in adulthood [17]. Thus, blood pressure in children diverges from adults in that an underestimation of risk may cause severe cardiovascular diseases in adulthood [18]. Recent report indicates that more than 90% of children evaluated for hypertension have no underlying cause identified [19], which suggests that prevalence of essential hypertension is increasing. This revives the discussion of the aetiology and pathogenesis research of essential hypertension to identify important targets of prevention.

2. Pathophysiology of childhood hypertension

The origin of paediatric hypertension evolves a cluster of metabolic and haemodynamic disorders identifies as a polyfactorial disease. Unfavourable metabolic profiles, such as hyperinsulinaemia and dyslipidaemia, at a young age with abnormalities of vascular structure and function leads to adverse cardiovascular outcome [12, 20, 21]. The adverse metabolic profile may originate from an unbalanced autonomic nervous system (ANS). ANS is known as the major adaptor for stress responses which regulate the two neural efferent pathways the parasympathetic and sympathetic system [22]. Long-term increase to stress may lead to increased sympathetic activity and decreased parasympathetic activity, contributing to obesity, insulin resistance, dyslipidaemia and hypertension [23–25]. Dysregulation of ANS may therefore predict metabolic abnormalities [26, 27] and hypertension [22]. In children, these associations have barely been investigated. Childhood obesity has been associated with lower parasympathetic activity [28–31], but more conflicting results regarding the influence of the sympathovagal balance and sympathetic hyperactivity [31–33]. Possible confounding factors and differences in methodology and sample size might explain these differences. Latchman et al. [32] showed that normotensive obese 9-year-old children exhibited reduced baroreflex sensitivity, parasympathetic control as well as increased sympathetic control compared with normotensive lean children. Thus, suggest that autonomic dysfunction may precede the hypertension in obese children. Obesity is associated

with increased sympathetic nervous system (SNS) activity, with impaired heart rate variability [34]. The resting heart rate is positively correlated with sub-capsular skinfold thickness in children [35]. Similar findings have been obtained in early origin of cardiometabolic disease. Foetuses born to obese mothers demonstrate increased foetal sympathetic activation [36], which may predict long-term cardiovascular outcome.

3. Maternal obesity and offspring cardiovascular complications

A large body of epidemiological literature supports the link between an adverse intrauterine environment and disease in later life, showing inverse association between low birth weights (poor nutrition) with subsequent hypertension [37–40]. Similar findings have been demonstrated in animal models of maternal malnutrition and uterine growth restriction (IUGR) [41]. Despite the worldwide obesity epidemic, relative few studies have investigated the influence of maternal obesity on offspring health, with only recent emerging human data suggesting detrimental effects with preterm mortality in the offspring [42]. Epidemiological study demonstrates associations between maternal BMI and increased systolic blood pressure (SBP) in 7-year-old children [43]. The Amsterdam Born Children and their Development (ABCD) study recently reported that maternal pre-pregnancy BMI, in 3074 women, was positively associated with childhood diastolic blood pressure (DBP) and SBP at the age of 5–6 [44]. In the Jerusalem perinatal study (JPS), both gestational weight gain (GWG) and pre-pregnancy BMI were related to cardiovascular risk factors including SBP and DBP in adult offspring, at the age of 32 [45]. A stronger association for maternal pre-pregnancy BMI than paternal BMI with adverse cardiometabolic health in offspring suggests a direct intrauterine mechanisms, instead of life-style-related characteristics or genetic factors [46]. However, the causation is difficult to establish in human cohort studies. Interestingly, a recent study demonstrated an increased risk for cardiovascular mortality in children born to obese mothers, and this association remained after removing the child BMI [42]. Thus, suggests a direct effect of maternal obesity on child cardiovascular function, independent of childhood obesity [42]. The WHO Global Burden of Disease database currently identifies a rapid rise in maternal obesity in the past two decades. In the US, 64% of women of reproductive age are overweight and 35% are obese [47], with a similar pattern in Europe [48] and the rest of the world [49–51]. Obese pregnant women not only develop a higher risk of preeclampsia, preterm labour, stillbirth, caesarean deliveries, there are also a higher incidence of developing diabetes and hypertension in the offspring [52]. The increasing rate of maternal obesity may therefore provide a major challenge to future generations' health. Children born to obese mothers not only are prone to develop obesity but also essential hypertension which is the primary risk factor for developing other cardiovascular diseases leading to premature death. Whilst further randomised controlled clinical trials of improved design are indicated, there is an important task to revisit the basic science of autonomic function using experimental models that mimics the human condition of essential hypertension.

3.1. Autonomic dysfunction and paediatric hypertension

The autonomic nervous system (ANS) has two principal divisions, the parasympathetic pathway and the sympathetic pathway which acts either in synergy or in opposition synergy. The autonomic system continuously controls heart rate and blood pressure, respiratory rate and gut motility, body temperature and other essential functions. The autonomic function interacts with the primitive brain, including the limbic system (memory function), brain stem and hypothalamus [53]. Neurons within hypothalamic nuclei, particularly the paraventricular nucleus (PVN) and dorsomedial hypothalamus (DMN), make direct or indirect connection with sympathetic and parasympathetic preganglionic neurons and interfere with autonomic balance, sympathetic hyperactivity and neurogenic hypertension [53]. Early stages of hypertension, particularly in children, are defined by autonomic dysfunction [54]. Excessive sympathetic activity and/or withdrawal of parasympathetic balance are assessed by HR variability (HRV), using the ratio of low to high frequency (LF/HF) power. Pioneering studies conducted by Urbina et al. showed altered HRV in 39 male adolescences and reported trends of higher LF/HF ratio with higher BP, but did not reach statistical significance [65]. In a larger cohort, Sorof et al. [20] reported increased HR and BP variability in obese children with isolated systolic hypertension assessed by office HR/BP measurement and ambulatory blood pressure monitoring (ABPM). Interestingly, obese hypertensive children had higher HR than non-obese hypertensive children, suggesting that obesity is independently related with SNS activation [20]. These initial findings of SNS hyperactivity in hypertensive children, measured by indirect methods, were later confirmed by direct measurement of sympathetic activity using micro-neurography [55]. Zhou et al. [56] demonstrated altered vagal and sympathetic activity in hypertensive children, with a greater influence of systolic blood pressure (SBP) than diastolic blood pressure (DBP) on HRV [57]. Genovesi et al. [58] demonstrated baroreflex impairment, in both hypertensive and pre-hypertensive children. Autonomic dysfunction is therefore considered a critical feature in pre-hypertensive children which may predict future cardiovascular health. In children with arterial hypertension, the increase of sympathetic activity during sleep correlate with increase left ventricular mass and left ventricular mass index [59]. Moreover, HRV can predict the severity of children with pulmonary arterial hypertension [60]. This is particular worrisome as historical reference data on child HRV by Massin et al. [61] with current child HRV in Germany [62] showed change in children's ANS in the last 15 years. These changes constitute reduced vagal activity and a shift towards sympathetic dominance [62]. The authors suggest that these changes might be related to the rise in childhood obesity, with a negative association between BMI and ANS activity [62]. The historical samples of Kauzuma et al. [63], however, featured a comparable overweight rate (17%), but still reported much lower mean sympathetic activity. Additional factors including physical inactivity or nutrient composition may influence ANS [64, 65]. Maternal BMI, which recently been associated with the offspring ANS activity, may be another important determinant [66]. Several different mechanisms leading to and maintaining central sympathetic hyperactivity in essential hypertension have been identified. An impaired vagal heart rate control exerted by arterial baroreflex impaired volume-sensitive cardiopulmonary reflex, arterial chemoreceptors as well as humoral factors such as leptin and angiotensin II with direct central sympathoexcitatory effects have all been shown to play at least partial roles in essential hypertension.

3.2. Leptin and childhood obesity and hypertension

Experimental models of maternal obesity in sheep, non-human primate and rodents provide evidence for the adverse influence on offspring cardiovascular function [67]. In rodents, the perinatal exposure to metabolic milieu of maternal obesity may permanently change the central pathways involved in blood pressure regulation [66]. Leptin, an adipocyte-derived hormone, promotes weight loss by reducing appetite and increasing energy expenditure through hypothalamic sympathetic stimulation to brown adipose tissue [68] and kidney [69] which results in increased arterial pressure [70]. This has been confirmed in chronic infusion of leptin in rats developing increased blood pressure [71]. Transgenic mice overexpressing leptin develops overt obesity with elevations of blood pressure [72]. Selective leptin resistance of the appetite and weight reducing effect of leptin [73], and preservation of the sympathetic action of leptin, been implicated in obesity-related hypertension [74]. In humans, high plasma leptin concentration has been associated with arterial pressure [75] and muscle sympathetic nerve activity [76]. Leptin is also thought to have a neurotrophic role in the development of the hypothalamus [77], and altered neonatal leptin profiles secondary to maternal obesity are associated with permanently altered brain hypothalamic structure and function. In rodent studies, maternal obesity confers persistent sympathoexcitatory hyper-responsiveness and hypertension acquired in the early stages of development [78]. Unrevealing the mechanisms controlling hypothalamic development may help to identify the nature of the hypothalamic dysfunction and develop future therapies. High leptin in cord blood from foetuses of obese mothers [79] might cause permanent changes of the hypothalamic circuits leading to heightened leptin-induced sympathetic activity and blood pressure in juvenile offspring, prior to obesity and metabolic dysfunction [70].

3.3. The role of the central melanocortin system

The melanocortin system is an essential pathway in central regulation of metabolic and cardiovascular function. Central pro-opiomelanocortin (POMC) containing neurons in the arcuate nucleus (ARC) of the hypothalamus and the brain stem (e.g. nucleus of the tractus solitaries, NTS) project to other brain regions involved in energy homeostasis but also cardiovascular regulation [80]. The POMC neurons stimulate melanocortin receptor subtype 3 (MC3R) and 4 (MC4R) and reduce appetite and increase energy expenditure, SNS activity and BP [80]. Mutation of the melanocortin-4 receptor (MC4R) or pro-opiomelanocortin (POMC) gene estimates for 5–6% of early onset obesity in human [81]. Pharmacological blockade of MC4R causes pronounced obesity in rodents [82], whereas activation of MC4R promotes weight loss by reducing appetite and increase energy expenditure [83, 84]. Conversely, chronic MC4R activation causes sustained increased in BP despite reducing food intake and promoting weight loss [85]. MC4R-deficient rodents demonstrate reduced SNS activity and BP, independent of obesity [86]. Similar observations have been shown in humans, and MC4R deficiency leads to obesity but exhibits lower BP and reduced 24-h noradrenaline excretion compared with obese subjects with normal MC4R function [87, 88]. We and others have also demonstrated a critical role for the POMC-neurons MC4R axis in mediating appetite-suppressing and blood pressure effects of leptin [89, 90]. Rahmouni et al.

[89] showed that acute effect of leptin-induced hypophagia and renal SNS activity which were attenuated and abolished in heterozygous and homozygous MC4R knockout mice, respectively. Intact POMC neurons-MC4R axis is also required in chronic leptin-induced SNS activity and BP regulation [91]. MC4R antagonism markedly reduced BP in juvenile offspring born to obese dams (OffOb) [90] and spontaneous hypertensive rats (SHR) [92] two experimental models of hypertension that is associated with increased SNS activity in the absence of obesity [70, 93]. MC4R antagonism also attenuates or abolishes the acute pressor responses to leptin that raises BP by SNS stimulation [92]. Collectively, these observations suggest that the MC4R plays a key role in contributing to elevated BP in several forms of hypertension that accompany SNS overactivity. Greatest abundance of MC4R is the paraventricular nucleus of the hypothalamus (PVN), lateral hypothalamus (LH), the amygdala, the NTS and the preganglionic sympathetic neurons, which are all important sites for regulation of autonomic function [80]. Although the specific contribution of MC4R in distinct CNS nuclei in mediating the actions of the brain melanocortin system on energy balance, appetite and glucose homeostasis has been the subject of intense investigation, the particular regions of the brain, where MC4R is the most important in regulation of SNS activity and BP, are still unclear. We have recently shown that the activation of MC4R in the PVN (using simcre genetic-modified mice) demonstrated increased BP in offspring of obese dams that were protected in the MC4R-mutated mice; suggest an important role for MC4R in PVN in contributing to early onset hypertension [90]. One study has also observed that specific neuronal populations including cholinergic preganglionic parasympathetic and sympathetic neurons are involved in MC4R-mediated hypertension [94]. The specific stimuli that mediate the effect of MC4R to evoke sustained increases in SNS activity to cardiovascular-relevant tissue and promote chronic increase in BP are still unknown and remain an important area for future investigations.

3.4. Common genetic traits in paediatric hypertension

There has been a great progress in elucidating molecular targets for hypertension from monogenic disorders [95]. Among the most significant findings has been from single-gene disorders with primary effect on blood pressure that acts via common pathway alterations including renin-angiotensin and melanocortin system [95]. Recent genome-wide association studies (GWASs), conducted mostly in Europeans, have identified >30 genomic loci associated with systolic/diastolic BP [96], including candidate genes angiotensinogen [97], angiotensin-converting enzyme (ACE) [98], and alpha 2 adrenergic receptor genes (ADRA2A) [98]. The GWAS analysis is, however, inconsistent between populations, with a great gene-environment interaction, that significantly contributes to the increased risk of hypertension [99]. Obesity is one of the most dominant risk factor of childhood hypertension with a common genetic traits in FTO [100] and downstream of MC4R [101]. Hypertension has been associated with the risk allele A for FTO rs9939609 and the risk allele C for MC4R rs17782313, independent of BMI [102, 103]. Recent study by Sun et al. demonstrated an association of the FTO rs9939609 and MC4R rs17782313 genes with nocturnal blood pressure in the Chinese Han population [104]. The effect sizes are, however, small for each individual genetic variant, typically 1 mmHg for SBP and 0.5 mmHg for DBP [105]. Even collectively, the 30 variants tested in one experiment explain

only 1–2% of SBP and DBP variance [105]. Heritability of hypertension is estimated to be between 30 and 40% which is approximately 25 times larger than the phenotypic variation and disease risk currently explained by GWAS SNPs. The observation that only little of the total heritability can be currently be explained by the GWAS has led to the term “missing heritability” [106]. It is expected that many more yet undiscovered loci, possible including variants in the rare allele spectrum that might have larger effects sizes, will contribute to explain the missing heritability [106]. It has been suggested that epigenetic changes may account for the missing heritability determinants of complex diseases, such as hypertension.

3.5. Epigenetic traits in experimental model of hypertension

Recent years have shown a dramatic interest in the epigenetic trait of human disease. Phenotypic variation is regulated independent of changes in DNA sequence, such as DNA methylation, histone modification, chromatin remodelling and the action of small noncoding RNAs (microRNA) [107]. These epigenetic modifications change the accessibility of gene promoter sequence (by methyl donor) and binding domain [107]. Several animal studies have characterise epigenetic modification influenced by the intrauterine environment (maternal stress, nutrition and behaviour) [107]. In cardiovascular disease, recent studies of low-protein diet during pregnancy showed early onset hypertension in the offspring [108]. The renin-angiotensin system showed to be a main target as angiotensin receptor (AT1R) antagonist reversed the hypertension in the offspring [108]. Consistent with these finding, offspring showed a hypomethylated AT1R gene promoter along with the increased expression of AT1R [109], suggesting a role for specific AT1R hypomethylation in regulating elevated blood pressure in this model. Similar epigenetic modification has been shown in the hypothalamic POMC neurons in a rat model of neonatal overfeeding [110]. Hypothalamic POMC showed hypermethylated in the overfed neonates and consequently influence the set point of the melanocortin system which is critical for metabolic and cardiovascular regulation [110]. Fewer studies of epigenetic changes have been conducted in primates, and there is little direct evidence relating this to humans. One study showed a correlation of epigenetic RXRA (retinoid X receptor alpha—induces transcription of PPARs) promoter methylation with increased adiposity in children of mothers with lower carbohydrate intake in two independent cohorts [111]. Although this fails to confirm a causal relationship, it may provide an objective marker in identifying children at risk of obesity and hypertension-induced cardiac hypertrophy [112].

3.6. The role of central inflammation

Several reports have demonstrated enhanced inflammatory profile with paediatric hypertension [113, 114]. The C-reactive protein (CRP) which normally is involved in innate immune responses is heightened both in hypertensive and pre-hypertensive obese children, suggesting that systemic low-grade inflammation may precede hypertension [115]. This has been further confirmed in animal models of hypertension. Spontaneous hypertensive rats (SHR) a genetic model of essential hypertension demonstrate increased renal infiltration of lymphocytes and macrophages and activation of nuclear factor κ B (NF- κ B) in 3-week-old pre-hypertensive rats [116]. Serum CRP has also been associated with cardiovascular risk factors in children

including BP variability [117], intima media thickness [118], arterial stiffness [119], left ventricular hypertrophy [120]. Obese children and adolescence also demonstrate elevated serum concentration of pro-inflammatory cytokines interleukin-6 (IL-6) IL-1 β and ICAM-1 (intercellular cell adhesion molecule-1) with increased ambulatory BP [121]. The pro-inflammatory cytokines may also be increased due to obesity alone, independent of essential hypertension [122]. However, the highest concentration of these molecules was found in children with co-existing hypertension [114]. Mounting evidence suggests that the pro-inflammatory condition in mother may induce inflammation-induced hypertension in their offspring [123]. An overactive immune response during pregnancy, as shown in obese pregnancy [124], can lead to chronic neuro-inflammation in the foetus [125]. Activated microglia, resident immune cells in the brain, increases pro-inflammatory cytokines release from the PVN, which stimulate preganglionic nerve fibres and sympathetic nerve activity (SNA) [126]. Vice versa, SNA has a direct impact on microglia via adrenergic receptors [127] or indirect via regulating distribution and production of lymphocytes, or modulating the release of pro-inflammatory peptides. SNA is also involved in inflammatory cell recruitment and redistribution, and SNA mobilise inflammatory cells from spleen and bone marrow [128]. In addition, parasympathetic nervous system has anti-inflammatory effects [129]. Vagal afferents sense peripheral inflammation and feedback via the cholinergic anti-inflammatory pathway [129]. There are also important direct effects of cytokines and angiotensin II on the brain that certainly could contribute to SNA [129, 130]. Catheter-base renal denervation is a promising therapeutic approach to treat hypertension [131], and recent animal studies suggest

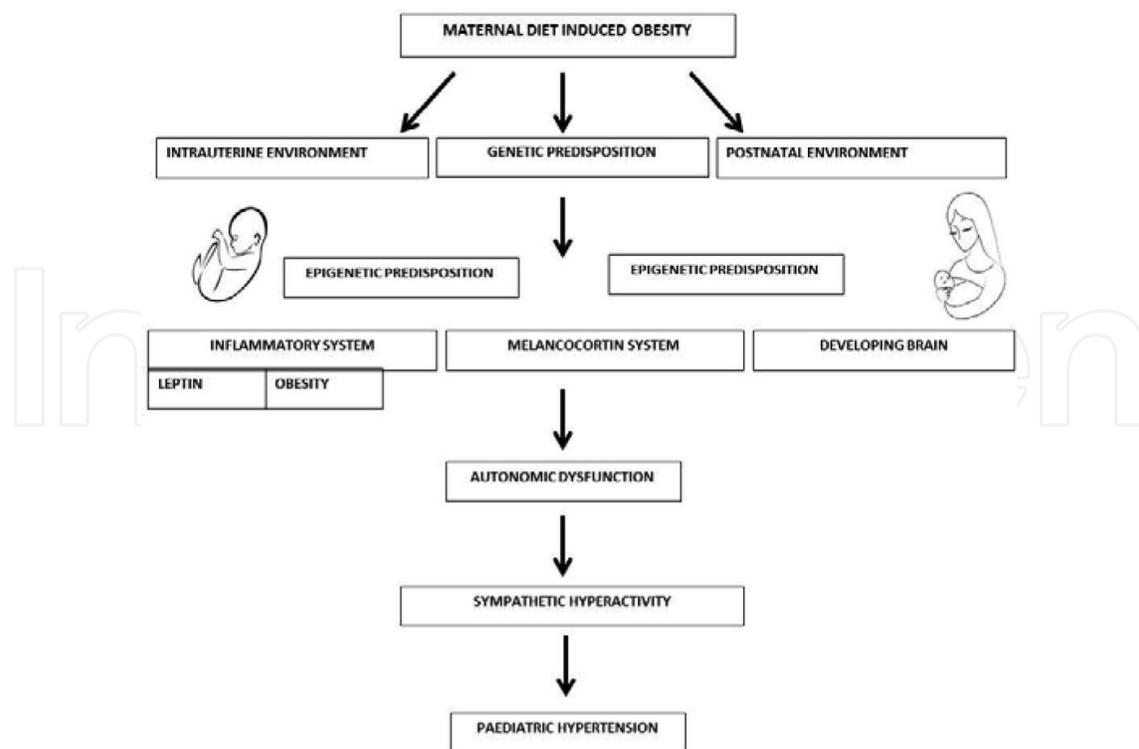


Figure 1. Mechanistic overview of the developmental origin of hypertension.

an improvement of renal inflammation with reduced renal macrophages and levels of cortical TNF-alpha and suggest a potential target for renal injury and dysfunction [132]. Minocyclin treatment, an anti-inflammatory antibiotic that crosses the blood brain barrier, has shown to prevent autonomic dysfunction and hypertension in experimental models of hypertension [126]. The reduction in blood pressure was associated with “de-activation” of the microglia in the PVN [126]. Overall, all these studies suggest a potentially important link between inflammation, melanocortin system, developing brain and autonomic dysfunction in the environmental and genetic predisposition of hypertension arising from maternal diet-induced obesity (Figure 1).

4. Future research and intervention strategies

Paediatric hypertension has been gaining significant attention in the last decade, mainly due to the increased prevalence worldwide. The estimated prevalence of paediatric hypertension is from 1 to 10%, with a steady rise over time. Alarming rate of childhood obesity and metabolic syndrome with the precondition of maternal obesity may worsen the future cardiovascular morbidity and mortality. This could be hypothetically prevented by early diagnosis and management in children before they even develop the pathophysiological progression state of hypertension. In fact, certain drugs may fail to reduce sympathetic hyperactivity as other stimuli of SNA have become predominant in elevating SNA, which are independent of the standard antihypertensive strategies. The progress and impact of preventive blood pressure screening for children could also inhibit adult hypertension and cardiovascular disease. Therefore, increased alertness to paediatric hypertension including several risk parameters (genetic, maternal, inflammatory, adiposity) and standardise sequential ABPM monitoring to avoid “white-coat” and “masked” hypertension in the diagnosis could improve future statistics in adverse cardiovascular outcome. Research effort should continue with the goal to clarify the aetiology, complexity and inheritable factors of paediatric hypertension. Research efforts should also focus on optimal treatment of these children and on effective preventive measures starting in the pregnant mother to the child at a young age.

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