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Mini Review

Hypertension Since Birth (or Neonatal Period) to Adulthood

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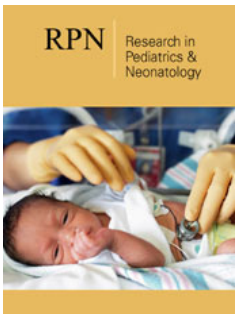
ISSN: 2576-9200



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Submission: May 20, 2024
Published: June 10, 2024

Volume 8 - Issue 3

How to cite this article: Maria Agostina Grillo* and Jorge R Ferraris*. Hypertension Since Birth (or Neonatal Period) to Adulthood. Res Pediatr Neonatol. 8(3). RPN. 000687. 2024. DOI: 10.31031/RPN.2024.08.000687

Abstract

Preterm newborns and small for gestational age (SGA) are particularly vulnerable to the development of hypertension (HTN) and chronic kidney disease (CKD). Fetal programming of HTN occurs in response to an insult during intrauterine life, which leads to adaptations by the fetus to allow fetal survival, but also results in permanent structural and physiological changes with long-term consequences such as an increased risk for cardiovascular disease and HTN. The mechanisms involved are: Renal alterations, vascular dysfunction, oxidative stress and epigenetic changes. Diagnosis and treatment of neonatal HTN remain challenging, with global incidence from 0.2%-3%, and there are a multitude of causes of neonatal hypertension. Most prematurity-related neonatal HTN resolves but the compensation mechanisms responsible may leave them at risk of later cardiovascular and kidney disease, in later childhood or adulthood, with a prevalence of HTN in children/adolescents born preterm up to 25%, diagnosed with both health check and ambulatory blood pressure monitoring. In adulthood gestational age is inversely associated with ischemic heart disease risk. They could present altered cardiac shape characterized by increased right and left ventricular mass, reduced right and left ventricle lengths, and smaller internal cavity diameters. Up to 10% of the population are preterm individuals, so we are facing a "silent epidemic" of CKD and HTN in these patients; preventive strategies should be implemented early to avoid the progression of these and CVD.

Keywords: Preterm neonates; Low birth weight; Arterial hypertension; Fetal programming; Small for gestational age; Cardiovascular disease

Introduction

Preterm birth (those born before 37 weeks gestational age) affects ~11% of births worldwide, similar to an annual prevalence of prematurity in Argentina between 8 and 9%, with the survival of infants born at 22 or 23 weeks with birth weights close to 500gr thanks to the new therapeutics and the increasing complexity of neonatal intensive care units [1-3].

Preterm newborns and small for gestational age (SGA) (birth weight of less than 10th percentile for gestational age) are particularly vulnerable to the development of hypertension (HTN) and chronic kidney disease (CKD). In the former, there is premature exposure to the conditions of extrauterine life, in organs that are not yet prepared for it, where the premature arrest of the development of the vascular tree results in stiffer and narrower arteries, which predisposes to glomerular and endothelial damage, structural alterations due to glomerular hyperfiltration, and increased systolic blood pressure (SBP) in children and adults [3,4]. SGA infants may be at increased risk of higher BP later in life, which may be in part due to a decreased nephron development as well as other factors, such as exposure to intrauterine stress that generates an altered fetal programming, placental insufficiency, or altered vascular system.

Although the morbidity and the complications of the appearance of arterial HTN in the neonatal period has not been completed established, it could be a predisposing factor for the appearance of cardiovascular and renal disease in the long term, hence this is an important disease that needs to be recognized and addressed prior to Neonatal intensive unit care discharge.

We consider that we are facing a "silent epidemic" of CKD and HTN in these patients, so preventive strategies should be implemented early to avoid the progression of these and CVD.

Pathophysiology

There are few mechanisms linking impaired fetal growth and the increased risk of CVD and HTN in adulthood.

Fetal programming of HTN occurs in response to an insult during intrauterine life, which leads to adaptations by the fetus to allow fetal survival, but also results in permanent structural and physiological changes with long-term consequences such as an increased risk for CVD and HTN [5,6]. The intensity, timing and nature of the fetal insult are critical to the phenotypic outcome.

The renal alterations that have been reported in fetal programming of HTN include small kidney size at birth (reduced nephron number), kidney disfunction, and alterations in sodium transport, renin-angiotensin aldosterone system (RAAS), and sympathetic renal nerves.

In subjects preterm or low birth weight has been demonstrated a lower nephron number with a smaller glomerular filtration area, causing compensatory glomerular hyperfiltration and hypertrophy, and eventually glomerulosclerosis with kidney injury favoring the development of HTN [3,5-7]. Alterations in the RAS appear to contribute to hypertension programmed in response to certain fetal insults, with different impact and with tissue specific effects [6]. For example, in one animal model, late gestational exposure to glucocorticoids leads to an increase in fetal pulmonary angiotensin converting enzyme (ACE) expression associated with an increase in blood pressure [8]. On the contrary, another experimental animal study (sheep) shows that placental insufficiency leads to suppression of the fetal renal RAS, and this could alter the activity of the intrarenal RAS and so affect growth and development of the kidney [9].

Another mechanism involved in the fetal programming of hypertension is vascular dysfunction. Fetal stress may affect vasculo-genesis and cause vascular remodeling. This process is characterized by changes such as an alteration in wall thickness and lumen diameter, which may develop or be precursors of HTN later in life. In the case of intrauterine growth restriction, elastin synthesis is altered during the fetal stage, reducing arterial elasticity [10,11]. Preterm birth results in a restricted vascular bed, impaired endothelial function, narrowed and stiffer arteries, predisposing to endothelial dysfunction and arterial hypertension[6].

On the other hand, it has been proposed that oxidative stress produced by vascular, immune, and enzyme systems may account for several organ system alterations, such as endothelial dysfunction with increased vascular tone. Maternal deprivation, sodium overload during pregnancy, and placental dysfunction are associated with higher oxygen radicals being one of the plausible mediators between adverse fetal growth and higher risk for CVD and HTN [6,12,13].

In addition, studies suggest that epigenetic changes are one of the mechanisms responsible for fetal programming that may explain both organ system alterations and vascular dysfunction and HTN in the offspring. These epigenetic changes consist in modifications in genes related to the RAAS, angiotensin type 1 receptor, vascular tone, ion channels, epithelial sodium channels, Na+-K+-2Cl- cotransporter, an increased expression of micro-RNA that regulates the translation of angiotensin converting enzyme-1, micro-RNA associated with cardiac injury, angiogenesis, and cell changes, modifications in endothelial nitric oxide synthase (eNOS), and DNA modifications in important genes in endocrine hypertension [5,14].

Neonatal hypertension

Diagnosis and treatment of neonatal HTN remain challenging, due to the scarcity of normative data on neonatal blood pressure values, the relative rarity of the condition, and exclusion of neonates from clinical trials of antihypertensive medications [15]. The global incidence ranges from 0.2%-3%, but these values may change according to population studied, being higher in preterm newborns who were in critical condition [16].

The gold standard for blood pressure measurement remains to be the invasive intra-arterial measurement; this is most commonly done in a NICU and measured with an umbilical artery catheter. However, the majority of umbilical arterial catheters are not placed to monitor for hypertension. In this population the method of choice is oscillometric devices, which have a good correlation between oscillometric and umbilical or radial artery BP, are easy to use and provide the ability to follow BP trends over time [17,18].

HTN is defined as systolic and/or diastolic BPs persistently equal to or greater than the 95th percentile according to the tables for gestational age and postmenstrual or postconceptional age [15,16,19]. Dionne [18], created tables which provide derived systolic and diastolic BP percentiles based on post-menstrual age [18] (Table 1).

Table 1: Blood pressure values at weeks gestational age in the newborn from 26 to 44 weeks SBP: systolic blood pressure; SBP: diastolic blood pressure; MAT: mean arterial pressure. Reproduced from Arterial hypertension in the newborn, Comité Nacional de Nefrología, Comité de Estudios Feto Neonatales (CEFEN), 2020, with authorization. Adapted from Dionne [18].

Postconceptional Age		Percentil 50	Percentil 95	Percentil 99
44 weeks	IT	88	105	110
	At that time	50	68	73
	COMPLETE	63	80	85
42 weeks	IT	85	98	102
	At that time	50	65	81
	COMPLETE	62	76	81

40 weeks	IT	80	95	100
	At that time	50	65	70
	COMPLETE	60	75	80
38 weeks	IT	77	92	97
	At that time	50	65	70
	COMPLETE	59	74	79
36 weeks	IT	72	83	92
	At that time	50	65	70
	COMPLETE	57	72	71
34 weeks	IT	70	85	90
	At that time	40	55	60
	COMPLETE	50	65	70
32 weeks	IT	68	83	88
	At that time	40	55	60
	COMPLETE	48	62	69
30 weeks	IT	65	80	85
	At that time	40	55	60
	COMPLETE	48	65	68
28 weeks	IT	60	75	80
	At that time	35	50	54
	COMPLETE	45	58	63
26 weeks	IT	55	72	77
	At that time	30	50	56
	COMPLETE	38	57	63

In term and preterm infants, blood pressure (BP) increases with gestational age and postmenstrual age, along with birth weight [15-17], and in the first ones, the strongest predictor of BP appears to be postmenstrual age, with a rise in the first 3-7 days of age in both systolic and diastolic BPs that is considered normal [17].

In this sense, BP values change rapidly over the first days of life, especially in those born preterm [20]. Pejovic [21] in a prospective study found that in infants born <28 weeks, the mean BP increases by 26% in the first week and >50% over the first month of life. Also showed the most premature and lowest weight neonates having the lowest blood pressures at birth, however demonstrated the most rapid rate of increase in BP in the most premature infants [6,21]. For most term infants, BP increases significantly from the first to second day of life but less so on subsequent days [19], with a less marked rise in BP (by >20% over the first month of life) [20].

It is not entirely defined at what level birth weight influences or determines blood pressure. In one study of preterm infants, BP inversely correlated with birth weight in those born with SGA, especially in the first week of life; on the other hand, the infants born with an appropriate weight for gestational age had a positive correlation [3,22].

While intrauterine growth restriction (IUGR) (when a fetus does not achieve the expected in utero growth potential due to genetic or environmental factors, estimated fetal weight <10th percentile) is considered as a possible risk factor for kidney damage and high BP in later life, one recently study did not observe any significant differences in BP values and urinary protein/creatinine ratios between between IUGR and non-IUGR neonates and young infants [21].

The most common causes of neonatal hypertension are umbilical artery catheter-associated thromboembolism, kidney disease, and chronic lung disease [23]; however numerous other causes and coexisting conditions have been identified in infants with HTN: antenatal steroid exposure, maternal HTN, acute kidney injury, extracorporeal membrane oxygenation (ECMO) therapy, congenital or acquired renal disease, parenteral nutrition (volume, calcium and salt excess), coarctation of the aorta and disorders of the endocrine system [15-17,24-26]. Historically, the leading cause of hypertension has been renal abnormalities (polycystic kidney diseases) [17], however in up to 50% of cases of neonatal HTN, no cause is detected [16,17,27] (Table 2). Considering causes associated with renal abnormalities, the AWAKEN study has shown a significant association with acute kidney injury (AKI) and neonatal hypertension [28]. From 10% to 20% of newborns with AKI have hypertension, usually associated with hypervolemia, so treatment focuses on correcting fluid overload with furosemide if needed [29]. The diagnosis of AKI is mostly based on imperfect parameters including serum creatinine levels and urine output; in neonates obtaining accurate glomerular filtration rate (GFR) is challenging as SCR values has several drawbacks, at the beginning reflect maternal creatinine levels, is also cleared by tubular secretion and GFR increases in the first days of life [30]. Other endogenous or exogenous markers for GFR exist, but are rarely

used in daily clinical care [30]. The evaluation with complementary studies to reach an etiological diagnosis can be guided by the tests proposed in Table 3.

Table 2: Causes of neonatal Hypertension (HTN).

Renovascular	Thrombosis, compression, stenosis of renal artery
	Renal venous thrombosis
	Mid-aortic coarctation
	Thromboembolism
Renal Parenchymal Disease	Polycystic kidney disease
	Multicystic-dysplastic kidney disease
	Tuberous sclerosis
	Ureteropelvic junction obstruction
	Congenital nephrotic syndrome
	Renal Hypoplaplasia
	Acute kidney injury
	Acute tubular necrosis
	Cortical necrosis
	Interstitial nephritis
	Hemolytic-uremic syndrome
	Obstruction (stone, tumors)
Cardio-pulmonary	Aortic coarctation
	Bronchopulmonary dysplasia
	Pneumothorax
Endocrine	Congenital adrenal hyperplasia
	Hyperaldosteronism
	Hyperthyroidism
	Pseudohypoaldosteronism type II
Neurologic	Pain
	Intracranial hypertension
	Seizures
	Familial dysautonomia
	Subdural hematoma
Neoplasic	Wilms tumor
	Mesoblastic nephroma
	Neuroblastoma
	Pheochromocytoma
Miscellaneous	Parenteral nutrition
	Closure of abdominal wall defect
	Hypercalcemia, Nephrocalcinosis
	Extracorporeal membrane oxygenation
	Birth asphyxia
Medications	Dexamethasone, adrenergic agents, vitamin D intoxication, theophylline
	caffeine, phenylephrine

Table 3: Complementary studies for neonatal hypertension DTPA: diethylenetriamine penta acetic acid; Mag-3: mercaptoacetyltriglycerine.

Initial/Routine Testing	Secondary Testing
Serum creatinine or cystatin, and electrolytes (with calcium), blood and platelet count.	Serum thyroid and cortisol levels Plasma renin and aldosterone
Urine analysis, Urine albumin/ creatinine ratio, urine culture.	Urinary vanillylmandelic acid and homovanillic acid
Kidney and bladder ultrasound with doppler, Echocardiogram, abdominal ultrasound, chest x-ray.	Voiding cystourethrogram, Head ultrasound Nuclear medicine scan (DTPA o MAG-3), magnetic resonance imaging, renal angiography.

Raj Sahu et al., in a retrospective study showed that term infants were diagnosed with HTN significantly earlier, with higher incidence of resistant HTN, some requiring greater than 3 medications to control their blood pressure and shorter duration of stay than preterm infants. The major risk factors for preterm infants were bronchopulmonary dysplasia and iatrogenic factors (ex. chronic steroids), and in term infants they were cardiac and other systemic disease [26].

Treatment aimed at reducing the BP (objective below the 90th percentile) needs to be considered carefully, guided by the pediatric nephrologist. There are wide options of pharmacological treatments, however the literature on treatment of neonatal hypertension is limited [17].

For most neonates diagnosed with HTN, the long-term outcomes should be good, and HTN will resolve over time; one study indicates that most infants will be off medication by 6 months of age. Infants with HTN associated with bronchopulmonary dysplasia almost universally resolve by 2 years of age. However, long-term outcome studies of infants with neonatal HTN are needed [15,25].

Long-term monitoring of infants with neonatal HTN is essential, with periodic monitoring of BPs and renal function, at least until the HTN has resolved, it is unclear how long and what follow-up is required. Serial ultrasonography may be helpful to follow renal growth, or the evolution of renal parenchymal disease [15].

Hypertension in children and adolescents born preterm

Most prematurity-related neonatal hypertension resolves but the compensation mechanisms responsible for the improvement may leave them at risk of later cardiovascular and kidney disease [31].

Several publications highlight the relationship between fetal growth restriction, low birth weight, preterm delivery and elevated BP later in life [3,32].

One publication reported a prevalence of HTN in children and adolescents born preterm ranged from 6 to 25% [33,34].

Rodriguez [35] showed in children aged 1-7 years with a history of PTN and SGA, increased systolic BP (SBP) in 21% and diastolic BP (DBP) in 37% of patients, with mean SBP and DBP between 10 and 15mmHg above the mean of healthy term newborns. They

have associated a decreased glomerular filtration rate (GFR) (78 ± 26.8ml/min/1.73m2) and Umicroalbuminuria/Ucreatininuria (85 ± 187 mg/gr) [35].

In the same line, Mhanna [36] evaluated 204 patients over 3 years of age, who had been born weighing <1,000g, with gestational age of 26 weeks; they found a prevalence of HTN of 7.3%, associated with an increase in the body mass index (BMI) and with higher weight gain from birth [36].

One prospective observational case-control study showed children born preterm at <30 weeks GA had higher systolic and diastolic BPs, and higher prevalence of elevated BP beyond the 90th, especially in those with lower GA and younger age at last follow up. Albumin and calcium excretion in the urine were similar in preterm-born children and term-born controls [33].

Andrea Solís [37] carried out a descriptive study to evaluate the prevalence of HTN by ambulatory blood pressure monitoring (ABPM) in patients aged 5-7 years who were premature <32 weeks gestational age and less than 1500 grams of birth weight. Although the sample size is small (19 patients) and no diagnosis of HTN was made, stands out the presence of pathological findings as absence of systolic and/or diastolic nocturnal dipping (47%) [37]. In the same way, Bayrakci [38] assessed BP patterns with ABPM and found preterm children and adolescents had similar 24-hour and daytime blood pressure but higher nighttime blood pressure and less nocturnal dipping than term controls [38].

In pediatric patients, there are no studies that show a direct relationship between the absence of nocturnal dipping and target organ damage, but it is proposed that the presence of an alteration in the normal variation of pressure during the day would be a risk factor for progression to HTA [39].

Another analysis made in adolescents of median 14-year-olds that were born PTN (mean 27.8 weeks) with very low birth weight (mean 1048grs) compared to term peers, showed the first ones had higher SBP and DBP (3.5mmHg, 95% CI – 0.1 to 7.2 and 3.6mmHg, 95% CI 0.1 to 7.0). The preterm birth cohort also had a significantly greater rate of high blood pressure; the differences in DBP was greater in individuals without overweight/obesity. The PTN group had significantly higher rates of maternal hypertensive pregnancy, maternal smoking and cesarean section. There were no differences in weight, BMI, or rates of overweight [40]. In adolescents born with PTN, albumin-to-creatinine ratio was modestly greater in subjects with overweight; this suggests that the development of obesity during adolescence may compound the risk of developing renal disease in these individuals [40].

Being born intrauterine growth-restricted or SGA has been associated with higher rates of HTN later in life [31]. In a prospective study evaluating children between the ages of 6-10 years born term but SGA compared to adequate GA (AGA), by ABPM measurements, 18% SGA had HTN while none of the children born AGA. Also, elevated BP was found in 50% of the SGA children compared to only 16% in those born AGA and a significantly higher blood pressure load (systolic and diastolic) was found in the SGA patients [41]. In part, these differences could be attributed to vascular alterations in those born with SGA, that show more arterial stiffness and endothelial dysfunction [31]. However, other studies suggest that SGA children had significantly lower BP values than AGA, so it is difficult to clearly assess the impact of IUGR in preterm babies on BP values in future life [34].

The most frequently targeted organs damaged in childhood due to hypertension are the heart (left ventricular hypertrophy) and blood vessels such as the coronary, the cerebral and the kidney vessels.

In another study, one-third of children who had AKI during the neonatal period had at least one sign of long term kidney dysfunction (hypertension, proteinuria or hyperfiltration); the ones who had a worse stage of AKI tended to have a higher rate of ABPM hypertension, non-dipper patron or another abnormal ABPM results, although the differences did not reach statistical significance [42]. In this group, ABPM hypertension was more frequent in patients with a gestational age <32 weeks and birth weight <1,500g.

As a consequence of low nephron endowment, prematurity is associated with chronic kidney disease. Emerging evidence suggests that perinatal characteristics could be indicators of future risk of transplant [43]. One Canadian cohort investigated the degree to which maternal and neonatal complications of pregnancy were associated with the likelihood of requiring an organ or tissue transplant before 14 y of age. Preterm birth was associated with 6.30 times the risk of kidney transplant (95% CI, 3.23-12.31), compared with term birth, especially in children with urinary anomalies [43]. Other perinatal factors associated were neonatal sepsis, intubation, blood transfusion, oligohydramnios, and congenital anomalies.

Hypertension in adults

Impaired fetal growth is associated with CVD in adulthood [44]. IUGR and preterm birth are both risk factors for the development of adult HTN, and IUGR or SGA are considered more associated with higher rates of HTN than prematurity alone [31,45], secondary to previously described renal and vascular compromise. This association both with prematurity and IUGR starts in early childhood and could become augmented in adulthood, at which stage blood pressures typically reach hypertensive ranges [46].

A meta-analysis including preterm-born adults concluded that the mean difference between preterm-born adults and controls was 4.2mmHg for SBP and 2.6mmHg for DBP. In another meta-analysis of 1,571 adults born with very low birth weight (defined according birth weight < 1,500g) vs. 777 full-term controls, mean blood pressure averages were higher for subjects <1,500g; they had 3.4mmHg higher SBP and 2.1mmHg higher DBP than controls. The only perinatal event associated with higher BP was maternal preeclampsia [3,47].

Along the same lines, in another study that included subjects born < 35 weeks and/or a birth weight below 2,000gr, birth weight was negatively associated with HTN, with the incidence being higher with smaller fetal size [48].

Brewer P [49] evaluated a group of women aged 50 to 79 years, self-reported being born preterm. Preterm status was statistically significant associated with prevalent HTN (37% vs 33.1%), early-onset HTN (<50 years), and taking more antihypertensive medications. Women born preterm without actual HTN had elevated coronary heart disease compared with women born full-term [49].

In a Swedish study cohort with median age 22.5 years, they showed that across all attained ages (0-43 years), gestational age at birth was inversely associated with HTN risk and each additional week of gestation was associated with a 4% lower risk of HTN. Persons born extremely premature had a 1.8-fold risk of HTN, and also have a major risk of ischaemic heart disease, heart failure, and cerebrovascular disease. The highest risk of HTN was observed among those exposed to both preterm birth and preeclampsia [50].

Different studies consistently show a dose-response relationship between degree of prematurity and increase in BP; with higher resting systolic BP in the range of 3.8-4.6mm Hg in individuals born preterm and an increase in diastolic BP of 2.6mm Hg which are clinically important differences in cardiovascular risk (stroke mortality and mortality from other vascular diseases) [51].

These findings suggest that infants who are born preterm have modestly elevated BP at young adulthood, but are susceptible to develop HTN with associated other cardiovascular and renal complications [52]. Several studies have demonstrated a link between low birth weight and Chronic Kidney Disease (CKD) [52]. In a meta-analysis low birth weight was associated with CKD with an overall odds ratio (OR) of 1.73 [52,53]. Superimposed SGA seems to increase the risk of cardiovascular and renal diseases [52].

ABPM also reveals higher 24-h BP in 114 preterm- and compared to 103 term-born young adults, showing higher 24-hour and awake systolic and diastolic BP, and higher sleep systolic BP in preterm birth below 34 weeks [54].

Impact of preterm heart

Preterm-born individuals are at greater risk of all-cause mortality in young adulthood, as well as cardiometabolic diseases, including type 1 and 2 diabetes mellitus, ischemic heart disease, HTN, pulmonary vascular disease and increased risk of heart failure [10].

Carr [55], published a study with the incidence rates of heart failure that were inversely related to gestational age at birth, with a 17-fold increased risk in those born extremely preterm compared with those born at term [55].

Crump et al in a Sweden cohort investigated the association between prematurity and increased risk of ischemic heart disease in adulthood. Gestational age was inversely associated with ischemic heart disease risk. Both preterm birth and early-term birth were associated with increased relative risks of ischemic heart disease (53% and 19%, respectively) [56].

One explanation for this is that the most premature individuals (<28 weeks' gestation) may have the lowest cardiac endowment and thus the fewest overall number of cardiomyocytes and lower cardiac mass [10]. This individual could have impairments in both left and right ventricular myocardial functional reserve, which is likely to increase susceptibility to heart failure later in life, particularly with additional insults such as hypertension or myocardial infarction [10]. Preterm-born young adults present altered cardiac shape characterized by increased right and left ventricular mass, reduced right and left ventricle lengths, and smaller internal cavity diameters for both ventricles. These alterations were independent of elevations in BP and were proportional to the degree of prematurity [51].

Another study investigated the cardiac impact of being born preterm in young adulthood using cardiovascular magnetic resonance in 234 individuals, of whom 102 were born preterm with an average gestational age of 30 weeks. Of them, 14 preterm-born individuals had smaller left ventricular (LV) end-diastolic volumes, smaller internal LV cavity dimensions and lengths, as well as greater LV wall thickness and mass [57].

In the perinatal period, especially in UCIN, some interventions and complications including infection, accelerated postnatal weight gain, parenteral nutrition, and antenatal and postnatal steroids, have been shown to relate to increased vascular stiffness and may contribute to long term cardiovascular remodeling. However, further work is needed to determine the long-term effects of these early life interventions [10].

In the same line, one systematic review [58] indicates that premature birth during the past 50 years is associated with modestly increased mortality in early to mid-adulthood. Gestational age at birth was inversely associated with all major causes of death including respiratory, cardiovascular, endocrine (mostly diabetes), neurological, cancer, and external causes, across ages 0-45 years. In late adulthood there is a strong association with endocrine and respiratory mortality [58,59].

In one study with the longest follow-up, up to a maximum age of 86 years but born in earlier years (1915-1929), reported that gestational age at birth was inversely associated with risk of death from cerebrovascular disease and occlusive stroke, but not with ischemic heart disease or all-cause mortality [60].

There is limited data to suggest specific pharmacological therapeutic strategies in adults born preterm to treat HTN or modify heart failure risk. Considering that these diseases could be generated by elevated plasma levels of angiotensin I, low glomerular endowment with glomerular hyperfiltration, autonomic dysfunction and impaired heart rate recovery, could exist a potential role for angiotensin or adrenergic blockade, but these have not been specifically evaluated in preterm subjects.

Impact of maternal disorder

Maternal hypertensive disorders of pregnancy (preeclampsia or eclampsia, gestational hypertension, and pregestational hypertension) are associated with an increased risk of congenital heart disease and a number of risk factors of CVD in offspring, with a Denmark study reporting individuals born to mothers with these

disorders had a 23% increased risk of early onset CVD, especially of those mothers with a history of CVD or diabetes [61]. They also showed severity of preeclampsia influenced the association, being the strongest association for early-onset and severe preeclampsia [61]. In individuals born at term also severe preeclampsia was found to be an independent risk factor for cardiovascular morbidity [62]. A systematic review evidenced in utero exposure to preeclampsia was associated with higher systolic and diastolic blood pressure and higher BMI during childhood and young adulthood; there was no evidence of variation in lipid profile or glucose metabolism [62].

Conclusion

Preterm birth and being small for gestational age should be considered as a (new) risk factors for the development of arterial hypertension and cardiovascular morbidities, both in childhood (sometimes reversible) and in adulthood, associated with modestly increased mortality risks in early to mid-adulthood, considering likewise that fortunately most people who were born preterm survive into adulthood without major comorbidities.

For this, preterm birth should be recognized as a chronic condition and assessed as a CVD risk factor that requires long-term follow-up for preventive actions, monitoring, and treatment of potential health sequelae across the life course.

Preventive strategies involve efforts to improve global maternal gestational health and nutrition, prevent preterm birth and SGA, avoid repeated courses of antenatal steroids, promote maternal milk as first-line nutrition, avoid extra uterine growth restriction and avoid overgrowth after hospital discharge, limit exposure to nephrotoxic drugs from neonatal to adulthood, and to promote a healthy lifestyle including regular physical activity, avoid smoking, and overweight.

Statements and Declarations

Authors contribution

MG and JF: concept and design and drafting of the manuscript. MG and JF: acquisitions, analysis, and interpretation of data. JF: critical revision of the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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