Extreme Birth Weight and Metabolic Syndrome in Children

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Contributor: Teofana-Otilia Bizerea-Moga

Small and large birth weights (BWs) for gestational age (GA) represent extremes, but the correlation between extreme BW and metabolic syndrome (MetS) has not been fully elucidated.

metabolic syndrome | extreme birth weight | gestational age | obesity | children

1. Introduction

Extreme birth weight (BW), involving babies born small for gestational age (SGA) or large for gestational age (LGA), has been associated with an increased metabolic risk in adulthood. In the first two years of life, children born outside the normal BW range tend to return to their genetically determined growth trajectory. “Catch-up” and “catch-down” growth usually compensate for both restricted and excessive intrauterine fetal growth, respectively [1][2].

Rapid weight gain during the catch-up growth phase in SGA infants occurs due to an increase in fat mass at the expense of lean mass [3][4][5]. The “catch-up fat” phenomenon significantly increases the risk of childhood obesity in these children, thereby linking low BW to insulin resistance (IR), impaired glucose tolerance (IGT), type 2 diabetes, hypertension, and cardiovascular disease [3][6][7][8].

LGA infants who do not enter the catch-down phase have increased adiposity, a higher body mass index (BMI), and a higher risk of developing early obesity [9]. Furthermore, some evidence shows that LGA babies are more likely to be overweight regardless of catch-down growth [10]. Consequently, being born LGA represents a considerable cardiovascular and metabolic risk [11][12].

The prevalence of SGA and LGA births fluctuates significantly in developed countries: 4.6–15.3 and 5–20%, respectively. This variation for SGA births becomes more pronounced and prevalent in developing countries where it is estimated between 27 and 41.5% [13]. In contrast, the proportion of LGA newborns in developing countries tends to be lower (1–14.9%), compared to Nordic countries, where it is as high as 20% [14].

In a systematic review, Friend et al., concluded that the median prevalence of metabolic syndrome (MetS) in children was notably higher in overweight and obese children, with an occurrence of 11.9 and 29.2%, respectively. In contrast, in the whole population, the MetS criteria was met by 3.3% of cases [15]. Another review published by

Reiner reported a range of MetS from 30 to 72% [16]. Two studies on the prevalence of MetS in obese children from Romania found it to be between 12.47 and 58% [17][18].

It was demonstrated that obese SGA children have an overall higher prevalence of MetS compared to those born appropriate for gestational age (AGA) (11 versus 9%), and it increases with age. This finding can be best observed in the adolescent group, where those born SGA had the highest prevalence of MetS (26.31%) compared to 16.84% of those born AGA [18]. The same tendency was described by Meas et al. in adults born SGA, who showed an increased risk of developing MetS compared to those born AGA. By the age of 30, 4.45% of AGA and 6.77% of SGA individuals met three MetS criteria; only 0.43% of AGA and 2.08% of SGA individuals met four MetS criteria [19].

Obese children born LGA are more prone to developing MetS, as observed in a study published by Wang et al., who found that the 65%prevalence of MetS in obese children born LGA, was significantly higher than for the 42.3% of obese children born AGA [20].

2. Extreme BW and Obesity

The prevalence of extreme BW related to GA mentioned the in literature is wide-ranging. Taal et al. [9], in a study of 3941 children of normal weight, found no significant percentage differences between the BW extremes (191 SGA subjects representing 4.84% and 199 LGA subjects accounted for 5.04% of the total). Two other prospective studies conducted on a normal-weight population both found SGA prevalence to be 26.6%, but the LGA prevalence varied significantly. Chiavaroli et al. [21] recorded 34.4% LGA patients (31 of 90 total patients), representing a higher percentage compared to the SGA group, whereas Lurbe et al. [22] discovered a much lower percentage (14.4%) in the LGA patients. Another study conducted between 1993 and 2013 on a pooled total of 5896 live births did not find significant differences regarding the incidence of SGA or LGA births twenty years apart (8.3 and 10.8% in 1993 versus 7.6 and 11.7% in 2013, respectively) [13]. In the current study, the prevalence of SGA was 7.85% and that for LGA was 16.82%. The same bias in favor of LGA (20% LGA compared to 7% SGA) was described by Hill et al. [23] in their study, which was also conducted on obese patients.

The slightly increased median BMI value in the oLGA group can be explained by the finding that LGA-born children who did not “catch down” maintained their excess weight throughout growth and development. This observation was reinforced by the finding that the combined effect of increases in BW and age led to a BMI increase in 30.7% of study subjects. This finding was in agreement with other research findings [9][11][12][14][24][25]. In their study, Hill et al., found a positive correlation between BMI and BW for GA in adolescents diagnosed with obesity [23]. A follow-up study performed by Lurbe et al. on 139 children at 5 years of age found that out of the 27% of subjects that developed obesity, 50% were born LGA, 25% SGA and 18% AGA [22]. Other authors claimed that both BW extremes for GA were linked to an increased risk of obesity later in life. Although a correlation between LGA and persistent overweight throughout childhood and adolescence seems more logical, weight catch up in SGA-born children in the first years of life can also lead to excessive adipose tissue deposition and visceral adiposity [24]. In LGA-born children, overweight and obesity appear at a younger age compared to SGA-born children [26]. The

contradictory research results as well as the finding that only one-quarter of patients' BMI values were influenced by BW and age combined to indicate the need to extend research by conducting a prospective study to follow normal-weight children from infancy to adolescence, following both the presence of MetS components and lifestyle habits.

3. Extreme BW and Cardiometabolic Risk

Scientific evidence for the link between birth weight and blood pressure is controversial. Additionally, no consensus exists regarding the major determinant of hypertension, extreme BW, or subsequent weight gain. Some authors have stated that SGA is associated with elevated systolic BP [6][19][26][27], whereas others have claimed that LGA is strongly linked to high BP and increased cardiovascular risk [20][26][28]. The researchers did not find any correlation between BW and systolic or diastolic BP, which is consistent with the observations of other researchers who found no link between BW and hypertension [21][23]. Some prospective studies conducted on lean children and adults demonstrated a connection between weight gain rather than BW and high BP, respectively [22][29].

No detectable variations were found in the current study regarding the median fasting glucose and glucose levels at 2 h of an OGTT, between oSGA, oAGA, and oLGA groups. Other studies found differences between the plasma glucose concentration at 120 min during an OGTT of SGA-born individuals compared to those born AGA [19][27], whereas Xiao et al. found overall impaired glucose metabolism in SGA children [30]. A higher, but not large, BW appears to offer protection against glucose intolerance [31].

In this study, fasting insulinemia and the HOMA index describing IR had non-statistically significant higher median values among oSGA children compared to both oAGA controls and oLGA subjects, a finding that was consistent with the literature. Researchers agreed that SGA had a strong influence on later IR development [6][19][21][22][23][27]. However, some studies also reported a stronger correlation between LGA and IR compared to AGA [26][21][32][33]. The reseachers data did not show a higher IR in oLGA children compared to oAGA controls, as was also found by Huang et al. [34].

Whereas IR is associated with SGA, hypertriglyceridemia is associated with LGA. Three hypotheses are used to explain the development of IR in obese SGA children. The "thrifty phenotype" hypothesis refers to metabolic reprogramming caused by malnutrition in the embryo–fetal period. Under conditions of normal or excessive nutrition after birth, the children develop insulin resistance later in life. The "fetal salvage" postulation states that IR in an undernourished fetus develops to redistribute essential nutrients like glucose to vital organs, mainly the brain. Finally, the "catch-up growth" theory considers IR as a consequence of a sudden exposure to high concentrations of insulin and insulin-like growth factors in the postnatal period as a response to adequate or overnutrition, after intrauterine undernutrition and depletion of the two hormones [35].

The lipid profile did not show differences between the median values of total cholesterol in the groups. Lower values of HDL cholesterol were found among obese children born with extreme BW for GA compared to obese born AGA, but with no statistical significance. Whereas some studies did not find any detectable differences in the

lipid profile of SGA, AGA, or LGA children [21], others reported an inverse association between total cholesterol and BW [36]. Meas et al. found no differences between SGA and AGA children regarding total plasma cholesterol, but a significantly decreased plasma HDL cholesterol concentration was found in the SGA group compared to the AGA controls [19]. The same observation was reported by Lurbe et al., when comparing both AGA and LGA children to their SGA peers [22]. Extreme BW for GA in adults has been associated with dyslipidemia [37].

Current research data has shown that BW exerts a moderately positive effect on triglyceride values, with statistical significance. Thus, a higher BW will lead to higher triglyceride values. Other authors reached the same conclusion [22], whereas some reported a high prevalence of hypertriglyceridemia in SGA compared to AGA children [38].

Although the literature regarding the pathophysiological mechanism of hypertriglyceridemia in LGA children is scarce, this link is highlighted by many studies looking at the relationship between LGA, obesity, and MetS. The reseachers think that this relationship deserves further research as hypertriglyceridemia is an important biomarker of cardiometabolic risk in these children.

4. Obesity and Cardiometabolic Risk

Concerning the relationship among BMI, MetS, and its components, the reseachers found a statistically significant positive correlation among BP, fasting and 2 h glucose, IR (insulinemia and HOMA index) and triglycerides, but no correlation was observed regarding total cholesterol, and HDL and LDL cholesterol. Two studies conducted on Argentinean and Saudi children concerning the relationship between obesity and MetS reported similar findings [39] [40].

The mechanism through which obesity causes hypertension in children is not fully understood. A combination of mutually potentiating factors have been considered, including increased activity of the sympathetic nervous system and the renin–angiotensin–aldosterone axis, excessive secretory function of adipose tissue, insulin resistance, and vascular remodeling [41][42][43][44].

Decreases in glucose tolerance and insulin sensitivity accompany one another. As an important marker of cardiometabolic risk, IR is linked to both obesity and SGA. However, obesity plays the most important role in its development.

Triglycerides, another biomarker of cardio-metabolic risk, show an important positive correlation with both BW and current weight. In obese children, hypertriglyceridemia is determined by an impaired storage of triglycerides in the adipocytes and release of fatty acids [45].

5. Extreme BW, Obesity and MetS

In addition to obesity, the MetS components most prevalent in the children were hyperinsulinemia and impaired glucose tolerance. An important obesity-related imbalance is that of the carbohydrate metabolism, as ascertained

by the reseachers research as well as several other studies [46][47][48][49][50]. Although many authors proposed fasting glucose as a reliable parameter to describe impaired glucose tolerance, when defining the MetS components [47][48][50], in the reseachers study, glucose levels at two hours of an OGTT proved to be a more accurate marker in this regard. Other researchers, such as Viner et al. and Weiss et al., arrived at the same conclusion [51][49].

Dyslipidemia was predominant in oLGA children, where the highest prevalence of high total cholesterol, triglycerides, and low HDL cholesterol were detected.

The prevalence of MetS in the obese children was higher among those at both BW extremes for GA. Whereas some authors reported an increased influence of SGA on the development of MetS in childhood and adolescence [6][19][52][53][54], others found that this influence to be more pronounced in LGA [52][55][56].

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