Preterm birth, early growth and adult metabolic health

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11 General discussion

Summary of the main findings

Effect of perinatal growth retardation on long-term height gain

According to current legislation, children born small-for-gestational-age (SGA) who fail to show postnatal catch-up growth are candidates for growth hormone (GH) therapy (1;2). At present, very preterm infants born appropriate-for-gestational-age (AGA) who grow poorly as neonates, resulting in an "SGA condition at term", are excluded from GH therapy if their small size evolves toward a short stature in childhood. Chapter 3 shows that the growth patterns of very preterm infants born SGA and those born AGA with a small size near term are virtually indistinguishable from the age of 3 months post-term onwards and, thus, extension of the SGA indication for GH therapy with short children with a history of neonatal growth retardation after preterm birth is recommended, provided the results are monitored until such extension is conclusively validated.

Effects of prematurity per se on the adult metabolic profile

Recently, it was found that 7-year-olds born prematurely were more insulin-resistant, assessed with an intravenous glucose tolerance test, than age-matched normal controls (3). In line with these observations, chapter 6 shows that the survivors of very preterm birth were relatively insulin-resistant at age 19 years. Furthermore, chapters 4 and 8 show that these subjects had a more central pattern of fat distribution and higher blood pressure, respectively. The clustering of cardiovascular risk factors in survivors of very preterm birth resembles the effects of permanent activation of the hypothalamus-pituitary-adrenal (HPA) axis, analogous to persons born with a lower birth weight (chapter 10). In prematurely born subjects, this may have contributed to improved neonatal survival, or, alternatively, it may be a consequence of the very preterm birth. Chapter 8 suggests that this phenotype may, in part, result from selective survival, because insulin resistance and adequate blood pressure regulation could optimize the fitness of the very preterm newborn. Insulin resistance may offer protection against neuroglycopenia, and raised blood pressure may, in the absence of an adequare cerebral autoregulation, prevent cerebral hypoperfusion, potentially life-threatening conditions which are commonly observed in the early neonatal course of very preterm infants. Chapter 9 shows that carriers of the 23K variant in the glucocorticoid receptor gene, associated with a mild glucocorticoid resistance (4;5), had a normal stature during childhood and in adulthood, and were less insulin-resistant than non-carriers. This suggests that the 23K variant protects against postnatal growth failure and insulin resistance after very preterm birth. Whatever the explanation, selective survival or causation, the price of neonatal survival after very preterm birth is to be paid in later life.

Effects of early growth on the adult metabolic profile

Effects of early growth on the risk, in the general population, of developing cardiovascular disease and type 2 diabetes are well described. However, at the start of the studies presented

in this thesis, little was known about the effects of early growth on the propensity to these diseases after preterm birth. Analogous to persons born after a term pregnancy, the path of early growth contributes to the onset of metabolic disease in very preterm subjects. Chapter 6 shows that overweight subjects after a lower birth weight for gestational age were more insulin-resistant at age 19 years than subjects with a similar fat mass after a higher birth weight. It has been argued for term individuals that the metabolic changes associated with low birth weight are usually insufficient to produce an increased risk of disease. Rather, a second hit, such as greater fat mass, is required for developing insulin resistance. According to Reaven et al, insulin resistance (hyperinsulinaemia) is fundamental in the development of many of the features of the metabolic syndrome (6). In our studies, early growth was unrelated to blood pressure, the serum lipid profile, or carotid intima-media thickness at age 19 years (chapters 5 and 7), probably because it takes many years more for these sequelae to develop after a prolonged period of hyperinsulinaemia. Therefore, continuing follow-up of the Project On Preterm and Small-for-gestational-age infants (POPS) cohort, as well as other preterm populations, is warranted.

Methodological considerations

Selection bias

In the POPS-19 study, selection bias could have been introduced at different levels. First, in 1983, there may have been a difference between participating and non-participating hospitals in the quality of the neonatal care provided. However, the far majority of Dutch hospitals were involved in the cohort retrieval in 1983, leading to the inclusion of 94% of all very preterm and/or very-low-birth-weight infants born in that year. Second, 28% of children were deceased before the age of 19 years (7), of whom were the majority (27%) in the first year (8). In the original cohort, in-hospital mortality was strongly related to gestational age and, accordingly, to the incidence and severity of the respiratory distress syndrome (8). As suggested by chapter 8, it seems plausible that there is a possible link between factors associated with neonatal mortality and some outcomes at age 19 years, such as blood pressure and parameters of insulin resistance. Third, the response at 19 years was 62%. Non-response was associated with male gender, non-white ethnicity, and lower socio-economic status but it was unrelated to gestational age or birth weight (9). A possible relationship between birth weight and the adult outcomes would be concealed if the lower birth weight subjects with a high risk of disease selectively declined to participate. This seems not very likely.

Confounding

It has been argued that the relation between lower birth weight and the adult metabolic profile is due to confounding by socio-economic status (10;11), since maternal smoking is associated

with lower birth weight of her offspring, and, on the other hand, smoking, drinking and eating habits, and physical exercise influence the propensity to cardiovascular disease and type 2 diabetes. A sedentary life style is more common among persons with a lower socio-economic status. However, in the studies described in this thesis adjustment for parental socio-economic status did not alter the strength of the associations between early growth and the adult outcomes, implying that confounding by socio-economic status is not likely to explain the observations.

Inappropriate statistical adjustment for current size

Early size predicts later size. In our population, it was found that birth weight SDS was positively associated with BMI and fat-free mass at age 19 years (chapter 4). Also, weight gain in infancy was positively associated with BMI, and absolute and relative fat mass, and abdominal fat distribution. Adult fatness, in turn, is always positively associated with insulin resistance and blood pressure. In the past, adjusting for current size has been justified on the grounds that birth weight is positively related to later size, and later fatness to the outcome of interest, and if not adjusted for could obscure a negative relation between birth weight and the outcome variable (12). Tu et al examined with computer simulations the impact of adjusting for different correlations between current weight and birth weight and between current weight and blood pressure to assess their impact on associations between birth weight and blood pressure (13). Regardless of the direction of association between birth weight and blood pressure (positive, inverse or absent), adjustment for current weight created or exaggerated inverse associations between birth weight and blood pressure ("reversal paradox"). Therefore, the analyses presented in this thesis were not corrected for current size.

External validity

Due to improved perinatal care, especially the widespread application of maternal glucocorticoid treatment for impending preterm delivery and the introduction of synthetic surfactant, neonatal mortality of very preterm infants has improved dramatically between 1983 and 1996-1997: from 30 to 11% (14). The sicker individuals survive nowadays. This increasing survival rate has resulted in greater numbers with respiratory failure necessitating mechanical ventilation (14). Ventilated infants occasionally need dexamethasone treatment to wean them off the ventilator. Short- and possibly also long-term height gain is impaired in dexamethasone-treated infants (15-17). Furthermore, it can be inferred from animal experiments that high-dosed dexamethasone has the potential to produce life-long deleterious effects on HPA axis activity and cardiac function (18;19). Improved survival has also led to a rising incidence of bronchopulmonary dysplasia (14). Obviously, for those reasons, the results in this thesis may not be fully representative for the current generation of prematurely born children.

Relevance and implications

From a public health perspective, our primary attention should focus on reducing the number of preterm births. Factors amenable to intervention are older maternal age at first birth, now on average 29.4 years in The Netherlands (20), and maternal smoking.

In situations where preterm delivery cannot be avoided, a single course of maternal betamethasone treatment is effective in reducing neonatal mortality and the incidence of the respiratory distress syndrome and related conditions (21). Fear for possible long-term side effects of this therapy is not necessary. Previous studies have demonstrated that there were no differences between betamethasone exposed and unexposed subjects in later lung function, cognitive performance, psychiatric morbidity, and psychosexual development (22;23). We have added that maternal betamethasone 24 mg does not adversely influence the adult metabolic health in her offspring. Thus, obstetricians should continue to use a single course of betamethasone for the prevention of the neonatal respiratory distress syndrome.

Very preterm infants with neonatal growth retardation grow in a way that has previously been described for children born SGA (24;25). These long-term findings strengthen the plausibility of extending the SGA indication for GH therapy in such a way that this group of preterm infants are no longer excluded if they have a persistent short stature. However, the effectiveness of GH therapy remains to be explored in such children.

Like full-term children born SGA, very preterm infants are at risk for developing (abdominal) obesity, type 2 diabetes, and hypertension. Very preterm infants born SGA who become overweight as young adults have the greatest risk for developing type 2 diabetes. As obesity tracks from childhood to young adulthood (26), paediatricians and primary health care workers should be aware of fat accumulation in the follow-up of very preterm infants, especially of those born SGA. Weight reduction should be advised, though it is unclear whether this can reverse the metabolic alterations associated with very preterm birth. As the expression of type 2 diabetes and hypertension is strongly dependent on life style factors, physical exercise should be promoted and smoking be discouraged.

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