

# Mechanisms of growth in small preterm infants and early life origins of adult cardiovascular disease

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## ABSTRACT

*Background.* The improved prognosis of early preterm birth has created a generation of surviving small preterm infants whose health needs in adulthood are poorly known. Epidemiological studies in subjects born at term have repeatedly shown an association between small size at birth and increased risk of adult cardiovascular disease. While considerable variation in this risk is already related to small differences within the normal range of size at birth, small preterm infants frequently exhibit severe postnatal or prenatal growth retardation, or both, and are often exposed to growth-inhibiting treatments such as glucocorticoids. There is thus reason for serious concern about increased cardiovascular risk when surviving small preterm infants become older.

Endocrine programming – lifelong effects of early nutrition and hormonal milieu on endocrine systems such as the insulin-like growth factor (IGF) system and the hypothalamic-pituitary-adrenal axis (HPAA) – is likely to play a major role in linking size at birth with adult disease. Because direct assessment of late-life health in small preterm infants would require decades of follow-up, we studied endocrine mechanisms of growth in two distant parts of the life span: in small preterm infants and in 65- to 75-year-old adults with birth and childhood measurements recorded. Our secondary aim was to find a biochemical indicator of growth velocity for small preterm infants.

*Subjects and methods.* Cord vein IGFs and IGF-binding proteins (IGFBPs) as well as markers of collagen turnover were studied in 98 infants born at <32 weeks' gestation. Forty-eight infants with birthweight < 1500 g underwent a 9-week follow-up with repeated determinations of these factors and a rigorous protocol of frequent, accurate weight and lower leg length measurements (knemometry). In 107 infants of <32 weeks' gestation, placental 11 $\beta$ -HSD2 activity [enzyme converting active cortisol (F) to inactive cortisone (E)] was measured together with cord vein F and E concentrations.

In the adult study, 421 men and women born at term, now aged 65 to 75 years, underwent total and free F, IGF-I and IGFBP-1 measurements in conjunction with a detailed clinical examination.

*Results.* In small preterm infants, IGF-I and IGFBP-3 were associated with relative birthweight ( $r=0.58$ ,  $p<0.0001$  and  $r=0.44$ ,  $p<0.0001$ , respectively) and postnatal growth velocity, and IGFBP-1 was inversely correlated with relative birth weight ( $r=-0.50$ ,  $p<0.0001$ ). In adults, high IGF-I and low IGFBP-1 were associated with impaired glucose tolerance and elevated blood pressure, whereas low IGF-I was associated with increased waist circumference and percentage body fat. IGF-I was unrelated to birth measurements, while IGFBP-1 was correlated with birthweight ( $r=0.11$ ,  $p=0.03$ ). Tall height and high body mass index at 7 years predicted low IGF-I and high IGFBP-1 in adulthood, but only in subjects of low adult lean body mass.

The most robust indicator of growth velocity in small preterm infants was the ratio of marker of type I collagen degradation to a marker of its synthesis (ICTP / PINP ratio), which may be sufficiently sensitive and specific for clinical use in detecting slow growth.

In small preterm infants, reduced inactivation of F to E by placental  $11\beta$ -HSD2 was associated with low relative birth weight ( $r=0.56$ ,  $p<0.0001$ ) and severe foetal distress ( $p=0.02$ ). Findings in adults showed complex interactions in the early determinants of adulthood F concentration. In subjects born between 37 and 39 weeks' gestation, low birthweight was associated with high fasting total ( $p=0.02$ ) and free ( $p=0.09$ ) F in adulthood, whereas in subjects born after 40 weeks' gestation, the trend was inverse: low birthweight predicted low fasting total ( $p=0.06$ ) and free F ( $p=0.002$ ) ( $p$  for interaction = 0.01 for total and 0.003 for free cortisol).

*Conclusions.* Differences in circulating IGFs and IGFBPs as well as cortisol in 65- to 75-year-old subjects relate to minor variation in birth measurements and childhood growth. These hormonal parameters show marked aberrations in small preterm infants, who frequently suffer from pre- or postnatal growth restriction. This suggests that early life programming of adulthood disease has the potential of becoming a major health burden when the present-day small preterm infants become older. Our findings urge for systematic long-term follow-up studies in small preterm survivors to assess the risk of cardiovascular disease and other adverse health consequences and to search for preventive means.

## LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, referred to in the text by their Roman numerals:

- I Kajantie E, Hytinen T, Koistinen R, Risteli J, Rutanen EM, Seppälä M, Andersson S. Markers of type I and type III collagen turnover, insulin-like growth factors, and their binding proteins in cord plasma of small premature infants: relationships with fetal growth, gestational age, preeclampsia, and antenatal glucocorticoid treatment. *Pediatr Res* 49:481-489, 2001.
- II Kajantie E, Dunkel L, Risteli J, Pohjavuori M, Andersson S. Markers of type I and III collagen turnover as indicators of growth velocity in very low birth weight infants. *J Clin Endocrinol Metab* 86:4299-4306, 2001.
- III Kajantie E, Dunkel L, Rutanen EM, Seppälä M, Koistinen R, Sarnesto A, Andersson S. IGF-I, IGF binding protein (IGFBP)-3, phosphoisoforms of IGFBP-1, and postnatal growth in very low birth weight infants. *J Clin Endocrinol Metab* 87:2171-2179, 2002.
- IV Kajantie E, Phillips DIW, Andersson S, Barker DJP, Dunkel L, Forsén T, Osmond C, Tuominen J, Wood PJ, Eriksson J. Size at birth, gestational age and cortisol secretion in adult life: foetal programming of both hyper- and hypocortisolism? *Clin Endocrinol (Oxf)* 57:635-641, 2002.
- V Kajantie E, Dunkel L, Turpeinen U, Stenman UH, Wood PJ, Nuutila M, Andersson S. Placental 11 $\beta$ -hydroxysteroid dehydrogenase-2 and fetal cortisol / cortisone shuttle in small preterm infants. *J Clin Endocrinol Metab* (in press).
- VI Kajantie E, Fall CHD, Seppälä M, Koistinen R, Dunkel L, Ylihärsilä H, Osmond C, Andersson S, Barker DJP, Forsén T, Holt RIG, Phillips DIW, Eriksson J. Serum IGF-I and IGFBP-1 in elderly people: relationships with cardiovascular risk factors, body composition, size at birth, and childhood growth. *J Clin Endocrinol Metab* (in press).