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Foreword

Up to 10% of all live-born neonates are small for gestational age (SGA). Although the vast majority of these children show catch-up growth by 2 years of age, approximately 1 in 10 will experience poor growth throughout childhood. It is increasingly recognized that children who are born SGA may be at risk of developing metabolic disease in later life. In September 2005, 200 of the world's leading paediatricians and paediatric endocrinologists met in Montreux, Switzerland, for *SGA 2005: Understanding the biology and therapeutic consequences*. The meeting was designed to highlight the causes of being born small and the long-term growth, developmental and metabolic sequelae of being SGA.

These Proceedings comprise papers based on presentations given at *SGA 2005*. Each manuscript has been reviewed by the Editors as well as the Editorial Board of *Hormone Research*. Our aim, in publishing these Proceedings, is to increase awareness of the adverse consequences of being born SGA and the need to develop guidelines for treatment and future research.

As outlined in the introductory lecture, observed fetal growth may not reflect the true growth potential, and definitions of growth impairment should focus on deviation from the optimal growth trajectory for a particular life course. The current concept is that impaired growth and increased intra-abdominal obesity in childhood are outcomes of adaptive responses of the fetus to an adverse in-utero environment, which have evolved to optimize the chances of perinatal survival and later potential to reproduce. These adaptive processes may be inappropriate in today's society, as there may be a mismatch between evolutionary adaptation to a poor intrauterine environment and exposure to an extrauterine environment in which nutrients are plentiful. This mismatch may be a causal factor in the high risk of type 2 diabetes and the metabolic syndrome observed among contemporary populations of adults born SGA.

Size at birth is believed to be highly heritable; however, fetal growth is complex and is affected by both maternal and fetal genes as well as the maternal intrauterine environment. In the session on human fetal growth, the confounding factors that impact on growth in utero were discussed, including the effects of imprinting (an epigenetic modification in which an allele of either maternal or paternal origin is selectively inactivated) on the expression of fetal genes and their interactions with the uterine environment. These complex interactions highlight the importance of accurate definitions of SGA that are customized to the individual and which reflect maternal factors such as ethnicity, parity and complications of pregnancy.

The role of imprinting in fetal growth and placental development was examined further in the session on the biology of fetal growth. The insulin-like growth factor (IGF) system has a critical role in fetal and placental development; for example, the paternally expressed imprinted gene *IGF2*, which encodes IGF-II, affects both placental growth and the supply of nutrients to the growing fetus. Maternal metabolism also affects the nutrient supply to the fetus. Maternal fat storage increases in early to mid-gestation and, during late gestation, these maternal energy reserves are mobilized, following changes in maternal insulin production and action, to provide an increased supply of nutrients to the fetus. The fetal requirements for long-chain polyunsaturated fatty acids, in particular, are enhanced during late gestation, when the fetal growth rate is maximal. These fatty acids are hydrolysed in the placenta, allowing their diffusion into the fetal plasma. The genetic, epigenetic, hormonal and environmental interactions involved in optimal fetal growth

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are complex and further research is necessary before they are fully understood.

In children born SGA, several hormonal and metabolic changes are observed, and an appreciation of these may improve our understanding of the links with adult disease. The short-term consequences of being born small were discussed in the session on early postnatal growth. Children born SGA show subtle abnormalities in the growth hormone (GH)-IGF axis, the hypothalamic-pituitary-adrenal axis and thyroid function. Infants born SGA have elevated GH levels in the newborn period, but a high subsequent incidence of GH deficiency has been reported. In addition, being born SGA is associated with a higher ratio of fat mass to lean mass in infancy and later development of central adiposity and insulin resistance. The particular contributions of prenatal growth restriction and postnatal catch-up are yet to be determined. Experience in infants born prematurely suggests that there may be a link between accelerated postnatal weight increases and higher rates of morbidity and premature death.

The relationship between the in-utero environment and postnatal growth were further explored in the session on fetal nutrition and postnatal biology. Studies in rats have shown that both prenatal growth restraint, associated with reduced insulin secretion, and gestational diabetes, leading to hyperinsulinaemia and increased fetal adiposity, are linked to the subsequent risk of diabetes. Hyperinsulinaemia and insulin resistance in early postnatal life are accompanied by suppressed thermogenesis, which may be an early event in the drive for postnatal weight gain. Additionally, a rat model of fetal undernutrition has shown that fetuses that suffer intrauterine growth retardation have a decreased beta-cell mass, which persists postnatally and may result in glucose intolerance. Other abnormalities in growth-retarded neonates, such as programming of glucocorticoids, may also play a role in pancreas development in rodents and in the risk of adult disease in humans.

Being born SGA may also be associated with changes in the timing and duration of pubertal development. These alterations were examined in the session on the influence of size at birth on postnatal endocrine function. Rat studies have shown that prenatal nutrient restriction is associated with a delay in the onset of puberty in male and female pups. Human studies have shown that children with low birth weight have high levels of adrenal androgens compared with children of normal birth weight. Prenatal growth restraint may also be associated with higher follicle-stimulating hormone levels in adolescent girls, as well as changes in the timing and duration of menarche and risk of development of ovarian hyperandrogenism. In boys, low birth weight has been associated with increases in levels of adrenal androgens and in the risks of congenital hypospadias and cryptorchidism. Low birth weight has also been associated with later risk of testicular cancer. Few data are available, however, and further research is required before we fully understand the effects of being born SGA on puberty.

The relationships between small birth size and the risk of adult disease were discussed in the session on size at birth, postnatal growth and the metabolic syndrome. Reduced fetal growth has been shown to be independently associated with an increased risk of insulin resistance, which underpins the risk of cardiovascular disease and type 2 diabetes. These modifications are thought to be a consequence of catch-up in weight after fetal growth restriction. Studies have shown that reduced insulin sensitivity may be observed in children who were born prematurely; however, the relative importance of premature birth compared with growth restriction on risk of reduced insulin sensitivity is still to be determined. Although the association between fetal growth retardation and metabolic disease may be, in part, genetic, studies in male twins have shown that insulin resistance and type 2 diabetes have a non-genetic, age-dependent origin. Programming of muscle insulin action and signalling may represent an early mechanism responsible for this association.

In the session on the short child born SGA, the effects of GH therapy were reviewed. The available evidence demonstrates that GH therapy is a valid growth-promoting strategy in children born SGA, particularly if started early. GH treatment is also associated with improvements in body composition, cholesterol and lipoprotein levels and a reduction in systolic blood pressure. Further studies will increase our understanding of the long-term effects of GH treatment and may allow treatment to be tailored to the individual.

The safety of GH treatment in children born SGA remains a concern, as few long-term data are available. Data on adverse events reported in KIGS – Pfizer International Growth Database – were examined in the session on safety and benefits of GH therapy. Overall, adverse events were not reported more commonly in children born SGA than in children with idiopathic short stature enrolled in KIGS.

We have much still to learn about the mechanisms that underlie the development of obesity, the metabolic syndrome and type 2 diabetes in individuals who were born SGA. However, the majority of pathology is seen in adults

who showed spontaneous catch-up growth as children. The risk in individuals who do not show catch-up growth and who are treated with GH is less clear, although preliminary data are encouraging and suggest that the risk may be low, at least in the short term. The high-quality scientific content of this Symposium provides a fascinating insight into the genetic, epigenetic and environmental interactions that lead to the development of adult metabolic disease in children of low birth weight. It remains only for us to thank the Scientific Organizing Committee and Pfizer Endocrine Care for their clinical, scientific and financial support of the Symposium. It is hoped that, through the efforts of all involved, we have taken a step forward in being able to understand and reduce the long-term risks associated with being born SGA.

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