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Children Born Small for Gestational Age (SGA): Growth and Clinical Assessment at age 4 to 6 years and Treatment with Recombinant Growth Hormone In Children Born SGA without Catch Up Growth

THESIS SUBMITTED FOR THE DEGREE
DOCTOR OF MEDICINE
BY RESEARCH

By

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2009

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DECLARATION

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Signed: Susan O'Connell

Date: 15th May 2009

DEDICATION

To my husband Enrique and our daughter Maria for your patience, and for reminding me of the most important things in life.

Thank you to my parents for your constant support and encouragement.

In memory of Elaine Quinn who was always an inspiring member of the Endocrinology nursing team and who is sadly missed by her patients and colleagues.

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SUMMARY

Small for gestational age (SGA) is a descriptive term used to describe a baby who is born smaller than expected for its gender and gestation. By international consensus the current definition is a birth weight $\geq$ 2 standard deviation scores (SDS) below the mean for that gender and gestation using appropriate population reference standards. As this approximates to the 2nd centile we would expect the incidence of SGA to be roughly 2% of all births. Although the definition has many limitations, given that fetal growth is a spectrum, it appears to be the most appropriate to detect those infants born pathologically rather than constitutionally small.

As being born SGA is associated with adverse perinatal outcomes, postnatal growth failure, short stature and future adult health problems, this is an area which has attracted widespread interest and research across a variety of disciplines ranging from obstetrics, neonatology and paediatrics to epidemiology and public health. Various socioeconomic and lifestyle factors such as smoking and ethnicity have been identified as risks for SGA; however, there are also a variety of medical/obstetric characteristics which contribute to poor fetal growth. The medical management of children born SGA has been a subject of intense debate, controversy, and clinical challenge. This is due in part to inconsistent diagnostic and treatment criteria and poor understanding of the mechanisms that lead to inappropriate postnatal weight gain and insulin resistance in some, and persistent short stature in others. Possible genetic factors such as growth hormone receptor genotype, mutations in genes involved in the insulin-like growth factor (IGF) pathways, insulin receptors or as-yet-unidentified isolated gene defects are proposed to play a role. Human epidemiological data have demonstrated that adaptive responses made by the fetus in response to a poor nutritional environment may be deleterious to adult health if the postnatal nutritional environment is one of nutritional excess. In the light of current growing prevalence of childhood obesity there is evidence to suggest that some of the metabolic consequences of intrauterine growth retardation in children born SGA can be mitigated by ensuring early appropriate catch-up growth, while avoiding excessive weight gain. Current infant nutritional practices are now the subject of increasing interest especially in preterm infants although little is known on what is optimal growth velocity in the context of antenatal growth restriction.

Growth hormone (GH) has recently been licensed in children born SGA who have persistent short stature by age 4 years, and who are growing at a lower than average velocity. Initial concerns related to unknown efficacy and risks of deterioration in insulin sensitivity and to fears about potential adverse effects by stimulation of the IGF system. Recent data, however, suggest that long-term treatment with GH does not increase the risk of type 2 diabetes mellitus and the metabolic syndrome in young adults born SGA, and various studies have shown positive effects on linear and head growth, body composition, blood pressure and lipid profiles.

Large studies on risk factors for fetal growth restriction and SGA using the definition agreed by international consensus, and studies of outcomes in children born SGA in Ireland are lacking. The aims of this study were to:- identify the population of children born SGA in a large Dublin maternity hospital and evaluate possible contributory risk factors; evaluate growth and clinical data on a cohort of Irish children born SGA at ages 4-6 years and identify those with short stature or risk of obesity and metabolic syndrome; identify the population of children born SGA with persistent short stature in the community; and collate new important data on the use of GH in children born SGA in relation to efficacy and safety.

This study examined a large cohort of over 14,000 births from a 2 year period (mid 1999-2001) and identified 284 infants without known congenital anomalies who were born SGA at over 28 weeks gestation. It analysed obstetric and perinatal data and compared them with non-SGA infants. This study then attempted to trace all 284 SGA infants identified from the cohort and to assess them in terms of auxological and clinical status at age 4-6 years.

Markers of lower socio-economic grouping ($p < 0.001$), nulli-parity ($p < 0.03$), maternal smoking ($p < 0.001$), smaller maternal size ($p < 0.001$), and pregnancy induced hypertension ($p < 0.001$), were clearly associated with the SGA births when compared to non-SGA births. Infants born SGA were more likely to be delivered earlier in gestation ($p < 0.001$), and by operative delivery (37% versus 17%) ($p < 0.001$), with higher rates of fetal distress (29% versus 19%) ($p < 0.001$). This study identified low rates of breastfeeding overall (32%), with lower rates being recorded in the infants born SGA (19%). Being born SGA was associated with higher rates of admission to the Special Care Baby Unit (61% versus 17%) but not with higher rates of ventilation (9% versus 13%) ($p = 0.24$), respiratory (9% versus 16%) ($p = 0.04$), neurological (4% versus 8%) ($p = 0.06$) or gastrointestinal problems (3% versus 8%) ($p = 0.05$). Despite difficulties in tracing the mothers of these infants, a sample of 56 (20%) children attended for clinical and auxological assessment (mean age 5.3 years). The majority of these children were found to have grown to within the normal range, with mean height (-0.7 SDS), weight (-0.9 SDS), body mass index (-0.6 SDS) and head circumference (-0.9 SDS). No significant gender difference was found. However, there were significant differences observed in height and weight at 4-6 years between children born preterm (< 37 weeks gestation) and children born at term (≥ 37 weeks), with those born preterm being shorter (height SDS -1.4 versus -0.6) and lighter (weight SDS -1.7 versus -0.7) at 4-6 years. In total, 5 children were identified with short stature, 3 of whom had severe short stature for which growth hormone was indicated. One patient was found to be overweight (BMI +2.7 SDS) and thus at risk for metabolic syndrome. One child with low weight was found to have coeliac disease.

In this first Irish study of GH use in short children born SGA, 20 extremely short prepubertal children (height < -2.5 SDS) were identified from various referral sources, who fulfilled the criteria for GH treatment. To date, 15 children have been on treatment, for varying durations ranging from three months to two and a half years. At the end of one year of treatment in 12 children, all had responded to treatment (mean baseline height = -3.2 SDS, mean height at one year = -2.3 SDS), without evidence of adverse effects on BMI, insulin sensitivity or inappropriate advancement of bone age. Positive effects on body composition ($p < 0.001$) and bone mineral content ($p = 0.003$) were also observed. The results to date are encouraging and the study is ongoing which will allow future pooling of data as part of a European multicentre clinical trial of GH use in short children born SGA.

International consensus recommends that children born SGA should have length, weight, and head circumference measured every 3 months in the first year, and every 6 months thereafter and that those who remain short by 2 years of age should be investigated for causes of poor growth. However, despite the fact that 10-15% will not catch up in growth by age 2 years, current low referral rates of children born SGA to Paediatric Endocrinology clinics would indicate that these recommendations are not being routinely implemented in Ireland. Although overall growth in children born SGA was found to be within the normal range, the 9% rate of failure of catch-up growth is consistent with similar studies of follow-up growth in children born SGA. In addition only one case of obesity was detected, however due to low response rates, concerns remain about the growth and health of those children born SGA who were not assessed. This also suggests a lack of awareness among parents and health professionals of the medical problems associated with being born SGA.

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CHAPTER ONE

INTRODUCTION

CHAPTER 1 INTRODUCTION

1.1 INTRODUCTION

Size at birth has been a subject of intense interest in the literature, not least over the past 3 decades due to its association with both perinatal morbidity and health in later life such as cardiovascular disease, insulin resistance and obesity (Rich-Edwards et al., 1997, Barker, 2004a, Barker, 2005). In addition, with advancing techniques in fetal ultrasonography, fetal growth has demanded attention with impact in the fields of obstetrics, neonatology and paediatrics, given the knowledge that suboptimal growth in utero increases risk of stillbirth (Gardosi et al., 2005) preterm delivery (Lackman et al., 2001, Marsal et al., 1996), perinatal morbidity and mortality (Zhang et al., 2007) (Figueras et al., 2007). In addition, size at birth and rates of early postnatal growth patterns predict subsequent disease risk as well as final adult height and body composition (Ong and Dunger, 2004). A key underlying mechanism implicated in the associations between early size or growth rate is nutrition in early life, and its impact on the developmental course. Influences which may be involved range from epigenetic influence on DNA expression, the development of hormonal axes, and effects on body composition which are implicated in induction of adult diseases (Wells, 2007). Furthermore, accelerated postnatal weight gain, especially after intrauterine growth restriction and lower birthweight for gestational age is associated with decreased insulin sensitivity even in childhood (Soto et al., 2003, Ong et al., 2004a). However the risk is less clear for children born small for gestational age who do not show catch-up growth and who are treated with GH for short stature (Saenger et al., 2007).

1.2 DEFINITION OF SGA

"Small for Gestational Age" (SGA) is a descriptive term, used when fetal size; weight and or length at birth, are less than expected (compared with appropriate population standards for both gender and gestation), regardless of the cause. It refers to the size at birth, irrespective of the growth velocity in utero. As SGA is associated with significant antenatal and postnatal pathology, accurate definition of small for gestational age is essential for both immediate postnatal care and follow up in infancy and childhood.

The precise definition of SGA itself is nebulous due to lack of agreement amongst members of the Obstetric, Neonatal and Paediatric specialities. Impaired fetal growth is influenced by a wide range of factors that act on the maternal-uterine environment such as maternal parity and smoking during pregnancy and also by familial or heritable factors (such as maternal genetic factors in the mother or fetal placenta, paternal height and fetal genes and demographic factors). Thus SGA infants are not a homogeneous group but consist of several subgroups with distinct aetiologies. The variety of definitions used in clinical practice has made comparisons between studies of outcome and follow up difficult. This area of research is also complicated by difficulties in accurate establishment of gestational age, consistent records of birth auxology, measurement of body composition in large epidemiological studies, and by challenges in interpretation of life-course data when some traits may be both confounding factors and simultaneously key outcomes (Wells, 2007).

1.2.1 Historical background

Estimates of intrauterine or fetal growth were first presented in 1963 by Lubchenco in the form of centile curves (10th,25th,50th,75th and 90th for males and females together and separately) based on birth weights in 5635 live born Caucasian infants 24-42 weeks of gestation (Lubchenco et al., 1963). Later standards on intrauterine growth in length and head circumference were made available (Lubchenco et al., 1966). Several limitations acknowledged in the analysis included "undeterminable bias" due to premature birth itself. A subsequent paper (Battaglia and Lubchenco, 1967), introduced the concepts of small for gestational age (SGA), appropriate for gestational age (AGA) and large for gestational age (LGA), which are now defined by international consensus as birth weight and or birth length ≤ 2 SD, within 2 SD or ≥ 2 SD of the mean for gestational age respectively. Since then there has been publication of a number of body weight by gestational age curves for various populations, ethnic groups and geographic locations (Ehrenkranz, 2007).

Due to the trend of increasing birth weight in Western societies, which possibly reflects changes in maternal care prior to and during pregnancy, it is recommended that birth weight for gestational age standards be updated every 5-10 years (Arbuckle et al., 1993). From an Irish perspective, this is backed up by studies of obstetric trends over the past 30 years in one Irish maternity hospital showing that the proportion of infants weighing more than 4kg has increased from 12% to 17%. In contrast however, the proportion of infants weighing more than 4.5kg has remained relatively static ranging between 1 and 3% (Mahony and O'Herlihy, 2003).

1.2.2 Low Birth Weight

The World Health Organization (WHO) definition of low birth weight (LBW) is birth weight at term under 2,500g however this definition does not take into account either gender or precise gestational age (World Health Organization, 1992). Hence premature infants with weight and length that is appropriate for gestational age fall under the definition of LBW. However, a birthweight less than < 2,500g in itself, regardless of gestation, has been found to be associated with increased incidence of infant mortality and morbidity both within and beyond the neonatal period (McCormick, 1985). Therefore this broad classification allows for international comparison of neonatal and public health and the WHO estimates that, depending on the geographical region, between 8 and 26% of all infants worldwide are born with LBW (World Health Organization, 2005).

1.2.3 Different Definitions of Small for Gestational Age

More precise cut-off definitions of SGA which have been used are:

- birth weight < 10th centile for gender and gestation
- birth weight < 3rd centile for gender and gestation
- birth weight and or birth length ≥ 2 SDS below the mean for gender and gestation. In addition, as one may distinguish an infant as being small for weight, for length, or for both weight and length (Clayton et al., 2007).

The latter definition approximates to the 2nd centile. It is estimated that 50-70% of fetuses born weighing less than the 10th centile for gestational age are constitutionally small (Ott, 1988, Wilcox, 1983), with fetal growth appropriate for parental size and ethnicity. These are usually associated with normal placental function and have a

normal outcome (Illanes and Soothill, 2004). However, the lower the cut-off is for defining SGA, the higher the likelihood of fetal growth restriction being present. Hence SGA fetuses with BW $\geq$ 2 SDS below the mean for gender and gestational age have a higher likelihood of being growth restricted (de Jong et al., 1998).

For the purpose of this study the definition of SGA used is a birth weight $\geq$ 2 SDS below the mean for gender and gestation using the cross sectional height and weight reference curves for the UK 1990 as the reference population (Freeman et al., 1995). There are three reasons for choosing this definition: (i) This is the widely accepted definition by international consensus in 2001 and again in 2007 (Lee et al., 2003, Clayton et al., 2007). (ii) It represents the most severe end of the spectrum and thus would have a high rate of "true positive" and low rate of "false negative" SGA babies below this cut-off (i.e. the minimum number of "normal small" or constitutionally small babies within the cohort and maximum number of "true SGA" babies). (iii) Growth Hormone (GH) is licensed for treatment of children born with a birth weight $\geq$ 2 SDS below the mean for gender and gestation who fail to catch up by age 4 years.

1.2.4 Calculation of Gestational Age

Gestational age is calculated on the basis of the date of the first day of the last menstrual period (LMP) and ideally confirmed by ultrasonography if available in the first trimester ($\leq$ 12 weeks). Using LMP to calculate gestational age assumes regular menstrual cycles and a cycle length of 28 days. Although this is a simple non-invasive clinical marker of gestation, clearly there are inherent problems with this method given that not all women have regular menstrual cycles, and indeed the duration of normal menstrual cycles varies between 21 and 35 days in length (Mishell, 2001). In addition, problems arise with women's accurate recall of LMP and cycle length (Small et al., 2007, Jukic et al., 2008). When compared to ultrasound dating, the

distribution of menstrual dating error is positively skewed (i.e. expected date of delivery is earlier with the menstrual-based gestational age) (Taipale and Hiilesmaa, 2001, Morin et al., 2005). Therefore many birth weight points at term appear at a later gestational age than the actual gestational age, leading to an artificial flattening of the growth curve and an apparent increase in 'post-term' births (Gardosi, 2006) (Gardosi et al., 1997). Studies hence indicate that ultrasound dating of pregnancy is more accurate than menstrual dating. Fetal ultrasound measurements are the basis for accurate determination of gestational age and detection of fetal growth abnormalities. However, the validity of indices used in ultrasound such as crown-rump length (CRL) and biparietal diameter (BPD), in determining gestational age is dependent on accurate recordings being made throughout gestation (Degani, 2001, Saenger et al., 2007). Selection of the most useful single biometric parameter depends on the timing and purpose of measurement and is influenced by specific limitations. The best parameter for early dating of pregnancy is CRL. In the second trimester BPD maintains the closest correlation with gestational age; however, due to variability in the shape of the skull, absolute reliance on BPD for estimation of gestational age has become less common (Degani, 2001). Later on in pregnancy abdominal circumference is the most useful dimension to evaluate fetal growth, and femur length is the best parameter in the evaluation of skeletal dysplasia (Degani, 2001). There are conflicting reports in the literature as to whether use of multiple predictors improves the accuracy of estimates (Degani, 2001) or not (Taipale and Hiilesmaa, 2001). In addition, anomalies in fetal growth can invalidate any predictions which are based on these measurements, thereby leaving the date of LMP as a chief predictor of gestational age (Degani, 2001).

1.2.2 Problems with defining Small for Gestational Age

Two limitations which influence birth weight means, standard deviations, and percentile values have been acknowledged: (i) inaccurately determined gestational age (ii) the computational procedures used to assign or estimate a gestational age (Platt, 2002). There are also a number of problems with using standard deviation scores as cut-offs for birth weight: birth weight does not follow a normal distribution and "Term" in a pregnancy is a five week period from 37 to 42 weeks gestation and as birth weight itself is limited biologically, theoretically there should be some negative skewness in distribution of birth weight for gestation curves (Gardosi, 2006).

Hence defining SGA relies on a number of important variables (Clayton et al., 2007):

(i) Accurate dating of gestational age (ideally based on a first trimester ultrasound scan)

(ii) Accurate measurements and documentation of birth weight, birth length and head circumference.

(iii) The use of an appropriate reference population.

1.2.3 Birth Length and Ponderal Index

Ideally SGA should be defined and sub-classified by birth length also, as prognosis in SGA varies depending on what sub-classification the baby falls into – SGA_W (weight), SGA_L (length), SGA_{WL} (weight and length). This also allows calculation of ponderal index, defined as birthweight/length^3. A low ponderal index is associated with thinness at birth, and has been often referred to by Barker in follow up studies into adulthood as a marker of poor outcome (Barker, 2004a). In addition, risk for short stature varies depending on whether an infant was born short, light or short and light for gestation (Karlberg and Albertsson-Wikland, 1995). However, as accurate birth

length measurements (using a calibrated infant stadiometer) are not routinely available in Ireland and the UK, in reality SGA can only be defined by birth weight alone in these countries.

Metabolic Syndrome and insulin resistance are associated not only with low birth weight but also with thinness at birth, as measured by a low ponderal index (birthweight/length^3) (Phillips et al., 1994a). Babies who are thin at birth lack muscle as well as fat, and muscle in adult life is the peripheral site of insulin action. Such small or disproportionate newborns have increased risk of cardiovascular disease, high blood pressure, high cholesterol levels and abnormal glucose-insulin metabolism. These relationships are not shown to be associated with length of gestation, suggesting they are linked to fetal growth restriction rather than to premature birth (Godfrey and Barker, 2000).

1.3 FETAL GROWTH

1.3.1 Regulation of fetal growth

Fetal development or growth should be considered as optimum preparation of the fetus for ex-utero life. This complex process depends on interactions between the fetal genome, availability of nutrients and oxygen to the fetus, maternal nutrition and various growth factors and hormones of maternal, fetal and placental origin. However, the growth of the fetus has to be constrained by the size (height or pelvic dimensions) of the mother (maternal constraint); otherwise normal vaginal birth could not occur (Barker 2004). Early in fetal life, the fetal genome is the major determinant of growth,

but nutritional, environmental and hormonal factors (in particular the IGF system) increase in importance as gestation continues (Gicquel and Le Bouc, 2006). The concept that GH-independent IGF production had a role in fetal growth emerged from studies of mice with defective genes for IGFs or their receptors (Rosenfeld, 2003). IGF-2 is the primary growth factor supporting embryonic growth, with the importance of IGF-1 increasing later in gestation. Serum IGF-2 concentrations are much higher than serum IGF-1 concentrations in late gestation; however, fetal and cord serum IGF-1 concentrations have been found to correlate more with birth weight (Gicquel and Le Bouc, 2006). In growth restricted fetuses, IGF-1 and IGFBP-3 concentrations are decreased in utero and at birth, but IGFBP-1 and IGFBP-2 concentrations are increased (Giudice et al., 1995) (Hills et al., 1996). Babies born following IUGR have higher IGFBP-1 levels which are negatively correlated with birth weight and decrease the availability of IGF for fetal growth (Gicquel and Le Bouc, 2006). Conversely, IGF-1 and IGFBP-3 concentrations are increased in LGA neonates (Fowden, 2003, Nayak and Giudice, 2003). Restriction of nutrients decreases IGF levels, the IGF-1 gene showing greater sensitivity to changes in nutritional status in late gestation than the IGF-2 gene (Fowden, 2003, Gluckman and Pinal, 2003). Periconceptual undernutrition may have epigenetic effects and it is also a determinant of IGF and IGFBP levels later in mid-gestation (Gluckman and Pinal, 2003). In contrast to what is observed after birth, GH has relatively little effect on the fetal IGF axis, as GH receptors are generally expressed at low levels in fetal tissues (Gicquel and Le Bouc, 2006). At birth there is a shift from IGF-2 predominance to IGF-1 predominance, the production of which then becomes GH-dependent. This then ensures appropriate postnatal growth in the new nutritional environment by resetting the mechanisms regulating growth.

In addition, human placental lactogen (hPL) and placental GH may act together to regulate maternal metabolism and fetal development (Freemark, 2006). Pregnancies complicated by IUGR show reductions in maternal and fetal hPL concentrations and maternal placental GH levels at mid-gestation and at term, and birth weight correlates with maternal placental GH levels. In contrast, maternal hPL and fetal IGF-1 concentrations are elevated in women with gestational diabetes (Caufriez et al., 1993). From animal studies reduced IGF-1 in the presence of high cord blood GH levels suggest that human IUGR may represent a state of GH resistance (Woodall et al., 1996).

1.3.2 Fetal growth restriction versus small for gestational age

Intrauterine growth retardation (IUGR) is defined as decreased growth velocity in utero as documented by two or more intrauterine ultrasound growth measurements. This in utero decreased growth velocity prevents a fetus, which may have initially had normal size for gestational age up to a certain point, from obtaining its complete genetic growth potential and causes it to be born smaller than it was originally destined to be. In contrast, as the definition of SGA relies on an absolute cut-off for birth weight (and/or birth length), this also includes babies with constitutional smallness or "small normal" babies who have not experienced IUGR, and who are not at increased risk of problems when compared with AGA babies.

Small for gestational age does not necessarily equate with intrauterine growth restriction. Even if birthweight remains within the normal range, this may conceal a birthweight significantly below the infant's genetic potential as a result of sub-optimal maternal or fetal nutrition. However, such "non-SGA" babies born following IUGR are often at risk for the same neonatal and childhood growth problems despite many

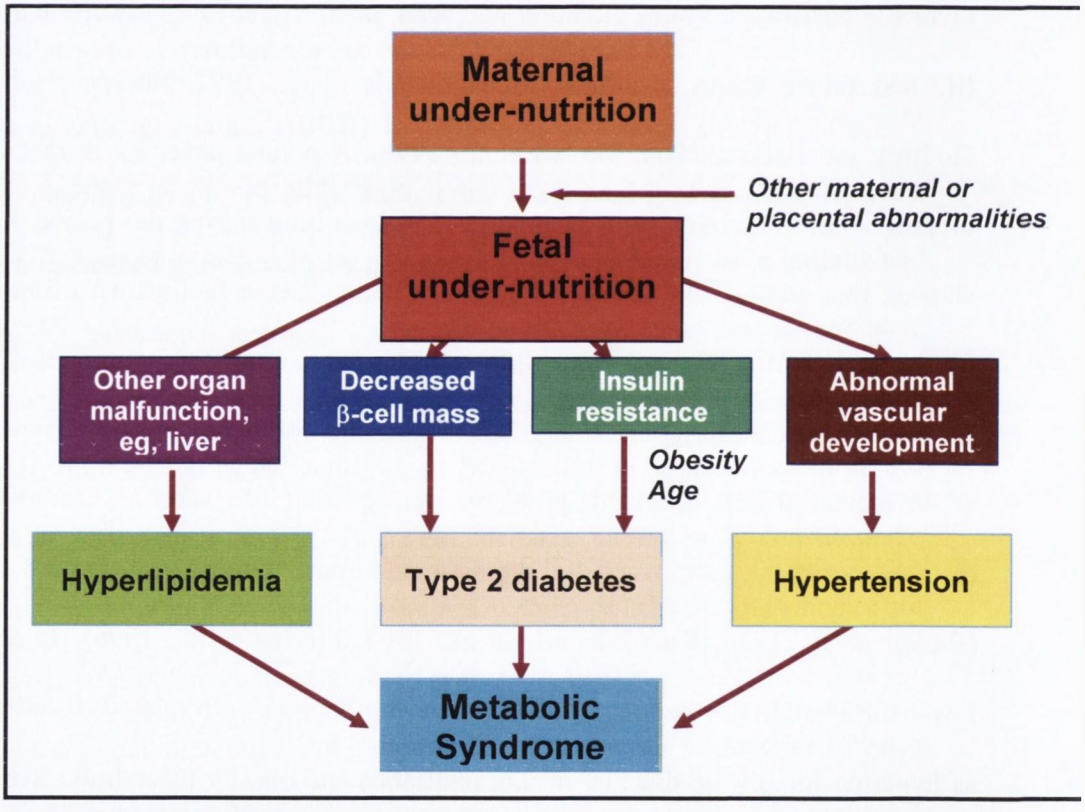
being born within the normal birth weight range for gender and gestation. Therefore, IUGR babies irrespective of birth size may require ongoing surveillance (Clayton et al., 2007, Freeman et al., 1995, Stephenson and Symonds, 2002). Hence it has been suggested that the term "IUGR" should be used to describe only those fetuses with inadequate growth due to placental dysfunction and that other causes of SGA fetuses, such as chromosomal abnormalities and congenital infections, should be considered before this diagnosis is made (Alberry and Soothill, 2007).

1.3.3 The Barker Hypothesis – The fetal origins of disease

Over the past two decades attention has been given to the link between intrauterine life and future health in adults (Rich-Edwards et al., 1997, Barker et al., 1989, Godfrey and Barker, 2000, Martyn et al., 1996). A pivotal paper by Barker in 1989 looking at birth weights in a cohort of 5,654 men born during the period 1911-30, showed that adults who developed coronary heart disease had grown differently to other people during fetal life and childhood. This led to a new "developmental" model for the disease (Barker et al., 1989). Infants who are born small are now known to be at an increased risk of health problems during adult life such as coronary heart disease, non-fatal cardiovascular diseases and narrowing of the carotid arteries (Barker et al., 1989, Rich-Edwards et al., 1997, Martyn et al., 1996). In addition, lower birthweight has been associated to varying degrees with related disorders such as hypertension, dyslipidaemia, insulin resistance and obesity (Metabolic Syndrome) (Newsome et al., 2003, Lauren et al., 2003, Huxley et al., 2004, Huxley et al., 2000). This is thought to be due to "programming" of these diseases by an inadequate supply of nutrients or oxygen in utero or immediately after birth. This phenomenon whereby under-nutrition in early life leads to permanent alteration of body structure and

function, is well documented in animals (Barker, 1994). The *thrifty phenotype* hypothesis postulates that poor nutrition in utero or early postnatal life results in decreased ß cell function and insulin resistance in muscle (Figure 1.1). According to this hypothesis, the endocrine alterations induced by intrauterine malnutrition are intended to divert the limited nutrient supply to maintain survival and development of vital organs, such as the brain, at the expense of glucose transport into the muscles for muscle growth (Barker, 2004a).

Figure 1.1 Fetal Origins of the Metabolic Syndrome



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Hence if a fetus is undernourished the result is persisting defects including reduced cell numbers in tissues and organs, modified organ structure, selection of particular clones of cells and altered settings of key hormonal axes (Barker, 1994) (Figure 1.1).

As an alternative explanation to intrauterine programming, Neel (Neel, 1962) and Hattersley and Tooke (Hattersley and Tooke, 1999) propose that insulin resistance is genetically mediated. In contrast to the thrifty phenotype hypothesis discussed above, the *thrifty genotype* hypothesis postulates that a genetically programmed ineffective insulin action in utero results in poor fetal growth and subsequent impaired glucose tolerance in later childhood and adulthood. Indeed, a genetic explanation for the association between birthweight and Type 2 diabetes is plausible (Hattersley and Tooke, 1999). In pathophysiological terms, as insulin has a central role in regulation of fetal growth, genetic factors which impair insulin secretion or decrease insulin action (both features of type 2 diabetes), would be expected to reduce fetal growth (Phillips, 2004).

It should also be noted that much of the original data published by Barker and colleagues, associating low birth weight to metabolic and cardiovascular disease in later life, is based on weight at 1 year of age and lacks data on birth weight (Saenger et al., 2007). In addition, ultrasonographic data are not available, therefore it is difficult to distinguish premature from SGA infants in these studies. Recent systematic analyses of the numerous studies associating birth weight with adult disease would suggest that the strength of such associations may have been overestimated due to selective emphasis on specific measures from particular studies, and may have been confounded by inappropriate adjustment for current weight and other variables (Saenger et al., 2007). For example, in a review by Newsome et al, the relationship of birth weight with insulin secretion was inconsistent in studies of adults (Newsome et al., 2003). Furthermore, in Lauren et al's review, there was no consistent relationship between size at birth and blood lipid levels; the one exception

being triglyceride concentration, which showed statistically significant negative or U-shaped, but not positive, relationships with birthweight (Lauren et al., 2003). In addition, a review by Huxley et al suggests that impaired fetal growth does not have effects on blood cholesterol levels that would have a material impact on vascular disease risk (Huxley et al., 2004).

1.3.4 Management of Fetal Growth Restriction

Prenatal and postnatal growth restriction poses a variety of challenges for obstetricians and neonatologists. In the absence of successful intrauterine therapy, the timing of delivery may be the single most important aspect of the antenatal management of IUGR (Baschat and Hecher, 2004). When infants with congenital malformations are excluded, late fetal deaths in extremely SGA fetuses can account for more than 50% of all late fetal and infant deaths in Sweden from 1983-1992. The very strong relationship between late fetal death and SGA fetuses highlights the fact that an extremely SGA fetus must be closely monitored (Cnattingius et al., 1998). Factors associated with differences in rates of late fetal death in extremely small for gestational age fetuses are maternal age > 35 years, maternal height ≥ 175 cm, singleton pregnancy and non-hypertensive pregnancy.

Placental dysfunction occurs in approximately 3% of pregnancies and its obstetric management remains a major problem in developed countries (Kupferminc et al., 2000). Both placental metabolism and transport are altered in IUGR as a result of adaptive changes which take place in both placenta and fetus (Tabano et al., 2006). Fetal growth restriction also has significant long-term health consequences which extend into childhood and adult life. The management of a fetus with growth restriction involves balancing the risks of chronic intrauterine hypoxia associated with

continued pregnancy, and the short and long-term risks of preterm delivery (Alberry and Soothill, 2007). Interventions are guided by severity of the fetal condition and gestational age at presentation (Baschat and Hecher, 2004). Management is more complicated in pregnancies between 25 to 32 weeks gestation, where each day gained in utero may improve survival by 1-2% (Soothill et al., 1986). Hence an individual approach to each pregnancy is recommended for fetal growth assessment (Degani, 2001).

Management should depend on umbilical artery Doppler studies (Royal College of Obstetricians and Gynaecologists, 2002). Using fetal Doppler studies, a combination of umbilical artery, middle cerebral artery and precordial vein Doppler can show the degree of placental disease, level of redistribution and degree of cardiac compromise respectively (Alberry and Soothill, 2007). As fetal death can ensue as a result of adaptive changes within the placenta, staging of placental disease is fundamental to appropriate timing of delivery. Arterial and venous Doppler studies aim to define three critical aspects of IUGR 1) correct diagnosis of IUGR 2) documentation of a fetal compensatory response 3) evidence of fetal decompensation. Changes in venous Doppler precede abnormalities on cardiotocography, which occur late during the course of fetal growth restriction (Kupferminc et al., 2000).

1.3.4.1 Estimated fetal weight growth curves

As fetal ultrasound techniques have improved over the past 25 years, many studies have the explored their accuracy by comparing predicted weights estimated by fetal growth models to postnatal birth weight by gestational age charts. There is an increasing body of evidence which indicates that intrauterine growth curves derived from ultrasonographically estimated fetal weight are more appropriate than neonatal

growth curves to detect fetuses and neonates at higher risk of adverse perinatal outcome (Zhang et al., 2007) (Figueras et al., 2007) (McCowan et al., 2005). On the other hand, fetuses who are small for dates may be protected from adverse programming by early expulsion from the uterus (Barker, 1994). Not surprisingly, the birth weights of the majority of the preterm infants fall below the mean-gestational age related estimated fetal weight (EFW), and as gestational age decreases the incidence of fetal growth restriction based upon EFW curves increases (Lackman et al., 2001, Marsal et al., 1996). Fetal growth standards are normally distributed throughout gestation (Marsal et al., 1996) and this may improve detection of fetuses with IUGR at risk for adverse outcomes (Lackman et al., 2001). Therefore, compared to body weight-gestational age intrauterine growth standards, EFW intrauterine growth standards will classify more infants as having experienced fetal growth restriction (Ehrenkranz, 2007) (Ott, 1993) which has both obstetric and neonatal implications. In addition, recent data analysis using the methodology of Cole (Cole, 1990) has been used to develop LMS parameters for the Fenton preterm growth chart to facilitate the calculation of z-scores. In the future these should permit more precise assessment of growth of infants who are born preterm (Fenton and Sauve, 2007).

1.3.4.2 Customised fetal growth curves

In order to adjust for the physiological variation between different babies due to maternal height, weight, parity, ethnicity and gender which are associated with normal variation in birth weight, "customised fetal growth curves" have been developed. These growth curves are designed to adjust the variables above in order to calculate more accurately the true growth potential of the individual fetus. Although this

method for calculating growth potential has been validated in a number of international studies (Figueras et al., 2007, Gelbaya and Nardo, 2005, Gardosi, 2006), the growth curves are not being implemented routinely in an Irish setting to date (personal communication). Co-efficients are currently being developed for more ethnic groups, to broaden the international applicability of individualised standards, and work is also underway to incorporate the customized birth weight percentile as the starting point of the infant growth curves (Gardosi, 2006). In addition, individually adjusted birth weight percentiles are better correlated with Apgar scores and neonatal morphometry indices and the association between SGA and adverse outcomes has been shown to be independent of the gestational age at delivery using this method (Figueras et al., 2007).

1.4 FACTORS INVOLVED IN THE AETIOLOGY OF SGA

As size at birth is such a strong determinant of perinatal survival intense genetic selection pressure has clearly played a role during human history (Dunger et al., 2006). Although up to 30% of cases of SGA may be caused by genetic abnormalities (e.g. chromosomal aberrations), the remaining cases result from environmental influences (Bernstein and Divon, 1997). Size at birth for gestational age is a marker of fetal growth rate, a dynamic process which can only be assessed by repeated ultrasound measurements. Causes of SGA have traditionally been subdivided into fetal, placental and maternal; however in some cases more than one cause of SGA can be implicated and accurate prenatal assessment of fetal growth is not without

difficulties. In up to 40% of cases the cause will remain unidentified (Bernstein and Divon, 1997).

1.4.1 Congenital Anomalies & Syndromes

Proposed explanations for the relationship between IUGR and congenital anomalies are: (i) IUGR is a secondary effect of certain anomalies, (ii) IUGR can predispose the fetus to certain fetal anomalies and (iii) IUGR can coexist with congenital anomalies and syndromes due to common aetiological factors.

Anatomical and chromosomal abnormalities of the fetus and abnormal placental vascular development are responsible for most cases of IUGR in singleton pregnancies (Baschat and Hecher, 2004) (Khoury et al., 1988) and fetal growth restriction arising from chromosomal abnormalities is often observed early in the pregnancy. Karyotypic abnormalities, such as trisomy 21 or 18, are estimated to contribute to up to 5% of the cases of fetal growth restriction (Neerhof, 1995).Other chromosomal abnormalities such as ring chromosomes and autosomal deletions, also contribute to this incidence. Other conditions that involve congenital anomalies, such as Potter's syndrome, cardiac anomalies and any group of major malformations, are frequently associated with abnormal fetal growth (Bernstein and Divon, 1997). The frequency of IUGR among infants with multiple congenital anomalies increases with the number of defects – from 20% for infants with two defects to 60% for infants with nine or more defects (Khoury et al., 1988).

1.4.2 Genetics of fetal growth

Birth size is the result of fetal growth. The fetal experience of growth is unique and influenced by maternal constraint, paternal, placental and fetal factors, and it is likely that there are complex interactions between the genetic and environmental factors of all three. This results in a complex balancing act where the interests of the mother (to physically deliver the infant through the birth canal) may conflict with those of the father (for its progeny to have an optimal birthweight for survival) over fetal growth rates (Moore and Haig, 1991). Epidemiological studies estimate that genetic influences account for 38-80% of birthweight variance (Johnston et al., 2002, Magnus et al., 1984, Magnus, 1984). Maternal genes have a greater influence on fetal size than paternal genes (Johnstone and Inglis, 1974). In addition significant correlation between parental birth weights and birth weight in offspring has been demonstrated (Magnus et al., 1997).

Interestingly, the glucokinase gene defects, which have maturity onset diabetes of the young (MODY) type 2, influence birth weight up or down, depending on whether the mother or the fetus has the mutation respectively (Hattersley et al., 1998).

Naturally occurring mutations in the IGF system are rare in humans despite its critical role in fetal growth. Polymorphisms within the IGF-1 genome have been associated with low birth weight and low serum IGF-1 levels (Vaessen et al., 2002, Arends et al., 2002). However, there have only been several reported patients with deletion or mutation of the IGF-1 gene to experience severe pre- and postnatal growth retardation (Woods et al., 1996, Bonapace et al., 2003), (Walenkamp et al., 2005). In addition, very few cases of IUGR with postnatal growth failure have been attributed to defects

in the IGF1R gene (Gicquel and Le Bouc, 2006), (Abuzzahab et al., 2003, Jain et al., 1998). The common polymorphism H19+2292 variant of the maternally-expressed gene H19, which regulates the imprinting of IGF-2 and has been associated with size at birth, is also associated with increased levels of cord blood levels of IGF-2 and maternal blood glucose levels during pregnancy (Petry et al., 2005).

1.4.2.1 The role of Genomic Imprinting in fetal growth

Genomic imprinting is an epigenetic phenomenon by which the expression of a gene is determined by its parental origin and only one allele of the imprinted gene is expressed. Imprinting is controlled by DNA methylation in such a way that a difference in methylation between the maternal and paternal alleles correlates with different expression of the two parental alleles. Over 70% of imprinted genes are thought to regulate fetal growth and brain development (Reik and Walter, 2001). Imprinted genes are the targets of molecular defects in particular rare genetic conditions, including Beckwith-Wiedemann syndrome, Angelman syndrome, Prader-Willi syndrome and Albright hereditary osteodystrophy.

There are no described mutations of the IGF-2 gene associated with IUGR however there is evidence of IGF-2 over-expression in Beckwith-Wiedemann syndrome (BWS), a disorder associated with fetal and postnatal overgrowth. Hypermethylation of the tumor suppressor gene H19 locus is a major cause of the clinical features of gigantism and/or asymmetry seen in BWS or an isolated hemi hypertrophy. Given the role of the 11p15 imprinted region in the control of fetal growth, attention has turned to the hypothesis that dysregulation of genes at 11p15 may be involved in syndromic intrauterine growth retardation (Gicquel et al., 2005). Loss of paternal methylation at the 11p15 imprinted region is thought to be responsible for relaxation of imprinting

and biallelic expression of the tumor suppressor gene H19 and downregulation of the IGF-2 growth factor. Overall, epigenetic defects in 11p15, resulting in silencing of IGF-2, are found in approximately 50% of patients with Silver Russell syndrome (which is associated with IUGR and postnatal growth failure) (Gicquel et al., 2005). Hypomethylation of the H19 promoter region was recently reported in a series of patients with clinical features of Silver Russell Syndrome (SRS) (Bliek et al., 2006). In another recent study of 51 SRS patients, approximately 31% patients were found to have epi-mutations in ICR-1 (the telomeric imprinting centre region of 11p15) and the authors suggest that in growth-retarded patients with only minor or without further dysmorphic features, a general involvement of 11p15 changes should be considered (Eggermann et al., 2006). There is also evidence for the ICR-2 imprinting centre in the aetiology of SRS, showing that SRS presents a picture with epigenetic defects opposite to that of BWS (Schonherr et al., 2007).

The reports of assisted reproduction techniques (ART) such as in-vitro fertilization (IVF) associated with Beckwith-Wiedemann syndrome suggest up to a six-fold increase in the risk of Beckwith-Wiedemann syndrome against a background incidence of about 1.3/100, 000 newborns, (Halliday et al., 2004, Gosden et al., 2003, Sutcliffe et al., 2006). However, before firm aetiological conclusions can be reached, further studies are needed to understand the relationship between imprinting, imprinting-related disorders and IVF. Children conceived using ART are also at risk of IUGR via an unknown mechanism, however it has not yet been determined whether the growth retardation induced by ART involves the disruption of imprinted genes (Schieve et al., 2002) (Gicquel and Le Bouc, 2006) hence this is clearly an area deserving of ongoing research.

1.4.2.2 Placental genetics

In most cases the placenta is genetically identical to the fetus, but in 1 to 2% of conceptuses a cytogenetic abnormality is detected in the placenta and not in the fetus (confined placental mosaicism) (Kalousek and Dill, 1983, Lestou and Kalousek, 1998).Up to 20% of idiopathic SGA term deliveries have confined placental mosaicism (Kalousek and Dill, 1983, Wilkins-Haug et al., 1995).

1.4.3 Maternal socio-demographic characteristics

The literature has explored various aspects of pregnancy and perinatal outcomes and their relationship with socio-demographic factors such as marital status, occupation, and maternal educational achievement. In particular, over the past 50 years various studies have identified many important associations between the socio-demographic characteristics of mothers and the birth weight of infants. In general, increasing social disadvantage has been associated with decreasing birthweight (Spencer et al., 1999, Elmén, 1996). Given the importance of birthweight for infant, childhood and adult health, a 150 to 200g social gradient in mean birthweight and 30% of births less than 2500g being attributable to social inequalities (Spencer et al., 1999) this is a key public health issue (Spencer and Logan, 2002). Early life exposure to poor socioeconomic circumstances in turn may lead to biological vulnerability in later life (Wadsworth, 1997) and adult health behaviours, which also may have effects on fetal well-being, appear to have socioeconomic roots early in life (Lynch et al., 1997). For example, a woman whose parents were disadvantaged is more likely to have been born low birth weight herself, to have experienced more childhood ill-health, to have had a less nutritious diet with suboptimal growth, to have started smoking in adolescence and be less likely to stop smoking in early pregnancy, and to become

pregnant at an earlier age (Spencer and Logan, 2002). Some of the maternal characteristics (age, parity, marital status and education) which have been identified in those women at lowest risk of giving birth to a low birth weight infant are maternal age 20 to 39 years, 12 years of education for mother and their spouses, early prenatal care, gravida 2 or 3 and no previous fetal loss (David and Collins, 1997). Not surprisingly, the risk factors for preterm birth are similar to those for low birth weight although there are some distinctions. When it comes to race difference in the rate of premature birth in the USA, four economic, demographic, and behavioural predictors have been identified: age less than 20 years, single marital status, receiving welfare support, and not having graduated from high school (Lieberman et al., 1987).

Interestingly, fifteen percent of the decline in the rate of moderately low birth weight (between 1500g and 2500g) among whites in the USA has been attributed to favourable changes in maternal characteristics (primarily an increase in educational level) (Kleinman and Kessel, 1987) and the sharp increase in risk of low birth weight in black women with increasing maternal age in the USA is attributed to the high prevalence of disadvantage in the population of over 96,000 births studied by Rich-Edwards et al (Rich-Edwards et al., 2003).

1.4.4 Ethnic Origin

Genetic factors associated with ethnicity that confer a perinatal advantage or disadvantage clearly influence birth weight. As concluded by the 1967 National Collaborative Perinatal Project "race behaves as a real biological variable in its effect on birthweight" (Naylor and Myrianthopoulos, 1967). Black women in the United States of America have a substantially higher risk (13.1% v 4.8%) of giving birth to

low birth weight infants (<2,500g) than white women (David and Collins, 1997) (Fang et al., 1999). However, after controlling for socioeconomic and medical characteristics, the risks of low birth weight for Caribbean- and African-born black mothers had birth outcomes generally similar to and, in poor communities, even more favourable than those for whites. Looking at the black subgroups in a recent cohort of New York City births there was substantial variation in the risks of preterm birth and low birth weight with all of the groups having lower risks than the American black reference group (Howard et al., 2006). This study also showed that births to foreign-born black women were less likely to be preterm or low birth weight than births to US-born women. Similarly, foreign-born Mexican American women, despite having many demographic and socioeconomic risk factors, have similar rates of LBW infants and infant mortality to those of white women. Conversely, despite their high socioeconomic status and early entry into prenatal care, foreign-born Asian Indian women in the USA have a paradoxically higher incidence of LBW infants and fetal deaths when compared with US-born whites, and protective factors in white women are not protective among Asian Indian women (Gould et al., 2003). However, a limitation of these observations in the context of this Irish study is that gestational age was not taken into account. In New Zealand, Indian women have more than a three-fold risk of delivering an infant with birthweight <10th centile (using New Zealand population references) compared to European women (Thompson et al., 2001).

1.4.5 Maternal smoking in pregnancy

The association of smoking with a reduction in birthweight has been well established (Kramer, 1987). A number of studies have found an association between maternal smoking and lower birth weights with estimates of the reduction ranging from 100 to

300g (Horta et al., 1997, Cliver et al., 1995) (Macmahon et al., 1965, Meyer and Comstock, 1972). The effect of maternal smoking on low birthweight seems to be attributable to intrauterine growth restriction (OR 2.07) rather than to preterm delivery (Horta et al., 1997). Looking at the causal impact of late-term (8th month of gestation) maternal smoking on birthweight, on average smokers have been found to give birth to infants weighing 348g less than those of non-smokers (Hamilton, 2001). A dose-response relationship has been demonstrated with the degree of impaired fetal growth and with the average weight deficit of 458g in infants born to heavy smokers. In addition, passive smoke exposure during pregnancy plays a role and can result in an average weight deficit of 192g (Horta et al., 1997, Roquer et al., 1995). However, some authors have argued that the effects of smoking are confounded by lifestyle and physiological factors associated with both maternal smoking and birthweight (Yerushalmy, 1971, Hickey et al., 1978). The effect of exposure to cigarette smoking during pregnancy has been shown to be modified by advancing maternal age in an American study by Fox et al., although number of cigarettes per day and years of smoking were not examined (Fox et al., 1994).

It is hypothesised that the aetiology of the observed impairment in fetal growth is due to a combination of carbon monoxide exposure (decreased fetal haemoglobin oxygen-carrying capacity) and of nicotine (inducing release of maternal catecholamines). This results in repetitive episodes of reduced maternal perfusion of the placenta. Using the definition for SGA of birth weight less than the gender specific 10th percentile for gestational age at birth (in term infants >37 weeks), in the Auckland Birthweight Collaborative Study the population attributable fraction for smoking suggested that up to 18% of SGA infants born could be related to maternal smoking (Thompson et al., 2001).

1.4.6 Alcohol consumption

The association between alcohol and birthweight is more complex. High levels of alcohol consumption (two or more drinks per day) may affect fetal growth (Zuckerman and Hingson, 1986); however studies of the effect of alcohol consumption can be difficult due to confounding variables such as maternal smoking and maternal nutrition (Walpole et al., 1990). The effects of prenatal exposure to alcohol have been found to have an influence not only on growth of the fetus but also on that of the infant and child (Day et al., 1990, Jones and Smith, 1973, Day et al., 1994, Carter et al., 2007). Low birth weight, decreased head circumference and birth length are associated with prenatal maternal alcohol consumption especially during the first 2 months of the first trimester (Day et al., 1989). In one study, children at six years of age who had been exposed to alcohol prenatally were found to be significantly smaller in weight, height, head circumference and palpebral fissure width (Day et al., 1994). These effects on size were mediated by the effect of prenatal alcohol exposure on the offspring, where alcohol use during the second and third trimesters of pregnancy and continuous use of alcohol throughout pregnancy were significantly related to lower weight, length, and head circumference in the exposed infants at the follow-up observations at 8 months of age (Day et al., 1990). In a recent study of fetal alcohol exposure, iron-deficiency and infant growth, maternal binge drinking ($\geq$ 4 drinks per occasion) was associated with an increased incidence of iron-deficiency anaemia at 12 months, lower birth weight and reduced weight and shorter length at 6.5 months and 12 months (Carter et al., 2007). Moreover, iron deficiency seemed to exacerbate the prenatal alcohol effects on growth as it was related to

reduced 12-month weight and head circumference and to slow growth velocity between 6 and 12 months. The authors proposed that the association of maternal binge drinking with an increased incidence of iron-deficiency anaemia reflected disruption of accumulation of fetal iron stores or postnatal deficiencies in iron uptake, absorption or intake (Carter et al., 2007). In contrast, in a prospective study of approximately 500 offspring, neither birthweight nor any later size measure was as useful an indicator of the enduring effects of prenatal alcohol exposure as were certain neuro-developmental outcomes through to age 14 years (Sampson et al., 1994).

Fetal alcohol syndrome (FAS), the most severe manifestation of the adverse effects of alcohol on fetal development, was first described in the French medical literature by Lemoine et al. in 1968. It was first reported as a syndrome by Jones and Smith in 1973 (Jones and Smith, 1973). They delineated the association between maternal alcohol abuse and a specific pattern of birth defects and provided diagnostic criteria for this condition. Several diagnostic systems have since been developed with a view to capturing the wide spectrum of physical and behavioural anomalies resulting from prenatal alcohol exposure; including growth deficiency, the characteristic FAS facial phenotype (short palpebral fissures, thin upper lip, smooth philtrum) and central nervous system damage/dysfunction (Astley and Clarren, 2000). Fetal growth retardation has been associated with FAS since its first description as a syndrome (Jones and Smith, 1973) and pre- and/or postnatal growth deficiency has been a characteristic included in many other definitions (Astley and Clarren, 2000). There are no specific tests for FAS and diagnosis may not be made until a pattern of delayed development shows up on developmental screening tests. However, any low birth-weight newborn, whose mother has a history of alcohol abuse during pregnancy, needs to be evaluated for alcohol effects. The classic phenotype of Fetal alcohol

syndrome (FAS) can be difficult to diagnose at birth, as the classical facial dysmorphism (mid-facial hypoplasia, small palpebral fissures, flattened philtrum, thin upper lip and low nasal bridge) may not be present, may be subtle, or may be overlooked, which has made follow-up studies of these children challenging and also because as the neurological and behavioural aspects manifest over time.

1.4.7 Maternal Size

Maternal height and weight are other known variables associated with fetal growth restriction, and as small maternal size is a factor in maternal constraint, smaller women tend to deliver smaller babies (Gluckman and Hanson, 2004, Bernstein and Divon, 1997, Thompson et al., 2001).

1.4.7.1 Maternal auxology

Maternal height is an important determinant of birth weight (Kramer, 1987) and, on average, mothers of SGA infants are shorter and lighter than mothers of AGA infants (Thompson et al., 2001). BMI is an index of maternal nutritional status which has an important role in fetal growth, and, in turn, size at birth in relation to gestational age is a marker of fetal nutrition (Harding, 2001, Barker, 2004b, Mitchell et al., 2004).

1.4.7.2 Maternal weight and weight gain in pregnancy

Weight gain in pregnancy is also a predictor of infant birth weight, with low infant birthweight predicted by lower and higher than recommended weight gain (May, 2007) (Stotland et al., 2006). Guidelines for weight gain in pregancy generally allow

greater weight gain for lighter mothers in light of evidence that women with low pregnancy weight gains have a higher risk of having an infant with a below-average birth weight (Institute of Medicine, 1990, Cedergren, 2007). In a study based on pre-pregnancy BMI and birthweight outcomes, women were classified as underweight (12%), overweight (16%) or obese (31%). 42% of women gained more weight than recommended and 16% gained less than recommended (Abrams and Selvin, 1995). It is not clear whether maternal poor weight gain during pregnancy is a cause of fetal growth restriction or merely an associated finding (Bernstein and Divon, 1997). However, differences in dietary intake during pregnancy may also influence birthweight (Godfrey and Barker, 2000) (Stephenson and Symonds, 2002).

Maternal weight gain in pregnancy may also influence rates of overweight in childhood. In a study by Oken et al. of 1,044 mother-child pairs, women were divided into three groups based on whether their pregnancy weight gain was below, within, or above the values set by the USA Institute of Medicine. Excessive weight gain was noted in 51% of subjects, adequate weight gain in 35%, and inadequate weight gain in 14%. Mothers with excessive or adequate weight gain were roughly four times more likely than those with inadequate weight gain to have a child who was overweight by age 3 (Oken et al., 2007). Similar findings have been reported from a Portuguese study (Moreira et al., 2007). Increased risk of cardiovascular disease in the offspring has been shown when the mother was obese and the baby thin at birth (Forsen et al., 1997). This probably reflects in utero growth restraint as a consequence of maternal gestational hypertension, which can be up to five times higher in obese versus non-obese mothers (prior to pregnancy). Offspring of such obese mothers would be expected to show postnatal catch-up weight gain, as overall children of obese mothers are at four times increased risk of becoming obese themselves (Reilly et al., 2005).

1.4.8 Medical disorders in pregnancy

The most important maternal medical conditions that influence birthweight are diabetes and hypertension which also have risk for adverse perinatal outcome.

1.4.8.1 Gestational diabetes

Compared with offspring of non-diabetic obese mothers, offspring of mothers with gestational diabetes have increased fat mass at birth, but no difference in lean body mass (Catalano et al., 2003). A U-shaped birth weight association with risk of type 2 diabetes in the offspring exists particularly in populations with a high predisposition to type 2 and gestational diabetes, due to the association between large birth weight and risk of type 2 diabetes combined with the known risks of low birth weight (McCance et al., 1994).

The increased risk of type 2 diabetes is attributed to the combination of persisting increased adiposity, insulin resistance and reduced beta-cell capacity (Sobngwi et al., 2003) (Hunter et al., 2004). The fact that offspring of mothers who have diabetes during pregnancy are also at higher risk of type 2 diabetes and obesity during later life suggests that intrauterine influences provided by a diabetic mother might result in programming of the fetus for later risk of metabolic disease (Freinkel, 1980). For example, in populations with high rates of maternal diabetes during pregnancy, such as Pima Indians, the effects of these early environmental effects are of great importance to the health of the next generation, with maternal diabetes in utero being the single strongest predictor of type 2 diabetes in Pima children (Dabelea et al., 1998).

1.4.8.2 Maternal hypertension and pre-eclampsia

There has been international debate on the definitions and classification of hypertensive disorders of pregnancy due to the well documented associated maternal and perinatal morbidity and mortality. Women with hypertension, when compared with normotensive women, have been shown to have increased risks for preterm birth, LBW and SGA birth as well as for low Agpar scores, lower mean birthweight and shorter gestational age (Heard et al., 2004). Fetal growth restriction is known to increase 2-3 fold in the presence of chronic hypertension (Martikainen et al., 1989, Scott, 1981). It is not clear whether this is a result of the vasospastic characteristics of the disorder that leads to a chronic reduction of uterine blood flow, or the result of the increased incidence of pre-eclampsia among women with chronic hypertension. The severity of the hypertension directly correlates with increasing incidence of fetal growth restriction, however good control of blood pressure during early pregnancy has not been shown to change the incidence of fetal growth restriction among hypertensive women (Redman, 1976).

Pre-eclampsia is diagnosed when a pregnant woman develops high blood pressure (two separate readings taken at least 6 hours apart of 140/90 or more) and 300 mg of protein in a 24-hour urine sample (proteinuria). A rise in baseline BP of 20 systolic or 15 diastolic, while not meeting the absolute criteria of 140/90 is still considered important to note but no longer diagnostic. The association of pre-eclampsia (PET) and fetal growth restriction has a major effect on antenatal care, timing of delivery and perinatal mortality and morbidity (Walker, 2000). The presence of PET affects the prognosis of cases of IUGR, probably as an indicator of the severity of placental dysfunction and subsequent rapid fetal deterioration, as well as the risks to the

maternal condition. Increased risk of "SGA" defined by birthweight <10th centile, has been found with increasing severity of pregnancy-induced hypertension, from gestation hypertension (adjusted OR 1.55) to pre-eclampsia (adjusted OR 2.42) and those with pre-existing hypertension (prior to 20 weeks gestation) (adjusted OR 5.49) (Thompson et al., 2001). Superimposed pre-eclampsia has been shown to occur in approximately 40% of pregnancies of women with pre-existing hypertension and has the most severe outcomes (Heard et al., 2004). In addition, smoking worsens the outcome for hypertensive women in terms of SGA births (Vreeburg et al., 2004).

1.4.9 Parity and maternal constraint of fetal growth

As outlined previously (section 1.3.1 Regulation of fetal growth), growth of babies has to be constrained by the size of the mother, otherwise a normal birth would not be possible (Barker, 2004a). The major non-genetic factor which determines the size of the fetus at term is "maternal constraint", a term referring to a set of poorly defined processes whereby maternal and utero-placental factors act to limit fetal growth, presumably by limiting nutrient availability and/or the metabolic-hormonal drive to grow (Gluckman and Hanson, 2004).

Maternal constraint can be divided into supply-limited constraint (e.g. maternal size) and demand driven constraint (e.g. twinning). Maternal constraint acts in all pregnancies, but is greater in some situations, particularly those involving young maternal age, small maternal size, nulliparous and multiple pregnancies (Gluckman and Hanson, 2004). Some restraint of fetal growth by the maternal uterine environment is evident, particularly in first pregnancies, with first babies being thinner, having lower birth weights and preservation of head circumference and length, suggesting reduced adiposity (Dunger et al., 2006). Mothers' first pregnancies

are also associated with lower birth weight in their offspring and an increased risk of pregnancy-induced hypertension (Dunger et al., 2006). Proposed mechanisms by which maternal constraint occurs are by in utero programming of fetal metabolism (via the maternally transmitted mitochondrial genome) and inheritance of exclusively maternally expressed genes (silencing of paternal alleles by imprinting) (Dunger et al., 2006). The concept of inherent conflict between the mother's need to limit nutritional demands of the fetus and the father's interests in promoting fetal growth to increase chances of perinatal survival was put forward by Haig (Haig, 1996) however, there is only variable imprinting of some of the genes related to fetal growth.

Interestingly, fetal genes, and in particular paternally expressed genes, may have significant effects on fetal growth during pregnancies where maternal restraint of fetal growth is less evident. This is borne out by the observation that common variation in the insulin gene (INS) variable number tandem repeats - which regulates the transcription of insulin and IGF-II - has been associated with size at birth largely in second and subsequent pregnancies where maternal restraint is least evident (Dunger et al., 2006).

1.4.9.1 Multiple Pregnancies

As discussed above, twinning is an example whereby maternal constraint is demand-driven (Gluckman and Hanson, 2004). Multiple gestations are associated with increased risk of pregnancy-induced hypertension, perinatal and obstetric complications and maternal mortality (Spellacy et al., 1990) (Kinzler et al., 2000). Fetal growth restriction can be particularly severe in multiple gestations where there is shared fetal circulation (Bernstein and Divon, 1997). However, the biology of twinning suggests that intrauterine growth in twins is different from that of singletons

and is subject to different constraints (Phillips et al., 2001) and birth weight disparity within twin pairs is not necessarily indicative of aberrant fetal growth but is a specific measure of intrauterine development in multiple gestations (Blickstein et al., 2000). There are conflicting studies looking at the influence of birth weight in terms of perinatal mortality risk with one study showing that at birthweights less than 2,500g twins are at lower risk of fetal or perinatal mortality compared to singleton infants but that at weights above 2,500g there is a greater risk to twins (Spellacy et al., 1990). Another study showed lower risk of late fetal death (Cnattingius et al., 1998). A further study of twin gestation showed that the optimum birth weight for twins in terms of perinatal mortality was 3,001-3,500g versus an optimum birthweight for singletons of 3,501-4,000g (Brown and Schloesser, 1990). In twin pregnancies fetal growth velocity has been found to decrease after 32 weeks gestation but to be independent of birth order, fetal gender, chorionicity and zygosity (Smith et al., 2001). Birthweight discordance is caused by inherent inter-twin biologic diversity and extrinsic determinants of fetal growth; however it is widely debated whether inter-twin birth weight discordance is a normal biologic variation or some form of growth restriction (Blickstein et al., 2000). Studies would suggest that at lower birth weights, discordance of birth weight may be more important than absolute birth weight (Blickstein et al., 2000, Yalcin et al., 1998). Greater birth weight discordance was associated with significantly more preterm deliveries as a result of intervention, low birth weight, NICU admissions, respiratory distress, fetal abnormalities and fetal deaths (Hollier et al., 1999). However, when twins surpassed the risks of preterm birth (i.e. delivery >37 weeks) and when the lighter twin weighed > 2,500g, no excess risk of adverse outcome for discordant twins has been shown (Blickstein et al., 1988).

Genetic factors are not part of the 'thrifty hypothesis' which proposes an association between fetal undernutrition, poor fetal growth and low birthweight with subsequent adult disorders such as type 2 diabetes, hypertension and coronary heart disease even though studies suggest that genetic factors are important factors in the variation of both birthweight and type 2 diabetes (Iliadou et al., 2004). Many studies have shown associations between low birth weight and the risks of cardiovascular diseases (Barker et al., 1989, Barker et al., 1990, Barker, 2004a, Barker, 1995); there is still debate as to whether such associations are caused by undernutrition in utero or whether they are mediated by genetic and/or shared environmental effects (Kramer, 2000, Paneth and Susser, 1995). Differences in birth weight between genetically identical, monozygous (MZ) twins must be due to differences in the fetal environment and feto-placental influences (such as differences in nutrient portioning and blood supply between twins, an extreme example of which is the twin-twin transfusion syndrome), but not to maternal factors which will be shared by both twins and are at play in both MZ and dizygotic (DZ) twin types (Phillips, 2004). Hence, studies within MZ twin pairs allow perfect matching for genetic influences. Iliadou's large Swedish study of 11,162 twins showed that between pairs there was a significant increase in risk of developing type 2 diabetes because the effect of low birth weight on type 2 diabetes is due to an in utero programming effect possibly caused by intrauterine undernutrition. However it did not exclude the possibility of a common genetic mechanism (Iliadou et al., 2004). Within-pair birth weight difference has also been shown to be a significant predictor of abnormal responses to OGTT and the metabolic syndrome (Bo et al., 2000); diabetes has been shown to occur more often among twins with the lower birth weight in which there were significant within-pair birth weight difference for both MZ and DZ twin pairs (Poulsen et al., 1997). These studies strengthen the hypothesis that

intrauterine environment may be responsible for metabolic abnormalities in adult life and that for future adult health risks within-pair birth weight difference is more important than an absolute low birthweight (Bo et al., 2000).

1.4.9.2 Birth order in twin gestations

Birth order is important in twin deliveries as the second twin at term is at increased risk of perinatal morbidity and mortality. Labour and delivery are associated with risks to the second twin at all gestations (Smith et al., 2007). A large Swedish study found that second twins had a four-fold risk of an Apgar score < 7 at five minutes (Thorngren-Jerneck and Herbst, 2001) and a Canadian study found that if the second twin was delivered vaginally there was a three-fold risk of morbidity but no excess risk if delivered by elective caesarean section (Armson et al., 2006). Similarly, a study of twin pregnancies in England, Northern Ireland and Wales from 1994-2003, has shown that among term births the second twin had a greater risk of dying from intrapartum anoxia if delivered vaginally compared with those delivered by caesarean section (Smith et al., 2007). In contrast, the authors found no association between birth order and the risk of death among infants born before 36 weeks gestation but other studies have shown an increased risk of fetal distress or perinatal morbidity for second twins born preterm (Hartley and Hitti, 2005). Other studies have identified risk factors for death of the second twin of twin pairs with discordant birthweights. In a study by Smith et al. the absolute discrepancy between birthweights was wider in twin pregnancies where the second twin had died at term; however the discrepancies were equally distributed between those in which the second was the smaller twin and those in which the second twin was the larger. However, due to small numbers involved, it

was not possible to establish a relationship between the direction of the birthweight discrepancy and the cause of death (Smith et al., 2002).

1.4.9.3 Intergenerational effects of intrauterine growth restriction

There is a recognized association between birth weight of offspring and maternal birth weight (Ounsted et al., 1988). In addition, a mother's risk of pre-eclampsia has also been related to her own birth weight (Innes et al., 2003). There is also a continuous relationship between maternal glucose levels and birth weight of the offspring. This variation in maternal glucose levels is thought to be partly transmitted down the maternal line as risk of gestational diabetes is also related to low maternal birth weight (Innes et al., 2002). Genetic inheritance may explain some of the cross-generational effect on birth weight but evidence suggests that the fetal genome plays a subordinate role in determining the growth achieved during pregnancy and it is the environment in which the fetus develops that dominates (Murrin et al., 2007). There is strong evidence of intergenerational effect of reduced intrauterine growth even when socioeconomic factors, smoking and BMI are taken into account. In human populations the influence of a woman's own birth weight on the birth weight of her child indicates that maternal nutritional status may affect subsequent generations. In a Swedish study by Selling et al., odds ratio for giving birth to SGA (BW SDS $\leq$ -2) (OR 2.68) and preterm infants (OR 1.30) was higher among mothers who themselves were born SGA (Selling et al., 2006). Mothers whose intrauterine growth was moderately reduced but who did not meet the criterion of being born SGA were also at higher risk of giving birth to both preterm and SGA infants respectively. In contrast, a consistent intergenerational effect of preterm birth has not been observed (Selling et al., 2006). Nutrition in pregnancy may exert its effect over a longer period

through an effect on maternal growth in childhood (Baird, 1980) and possibly through an intergenerational effect (Emanuel et al., 1992). The Dutch famine studies looking at the effects of starvation during pregnancy have shown that reduced caloric intake during the first 2 trimesters of pregnancy increases the risk of obesity in the offspring (Ravelli et al., 1976, Ravelli et al., 1999).

1.5 CLINICAL FEATURES OF SGA

1.5.1 Perinatal risks associated with SGA

IUGR is a major contributor to perinatal morbidity and mortality (Bernstein et al., 2000); however one problem encountered when comparing outcome studies of SGA infants is the range of definitions used for SGA (as discussed), confounding parameters such as prematurity, and antenatal detection of IUGR or lack thereof. Garite et al.'s retrospective study showed IUGR to be a serious problem associated with increased morbidity and mortality among prematurely born neonates, regardless of the definition used or whether the diagnosis was made before or after birth (Garite et al., 2004). IUGR fetuses, already compromised by variable durations of chronic hypoxia, are less resilient to the stress of delivery and thus, when compared with AGA infants of the same gestation, SGA infants have higher risk of intrapartum fetal distress and metabolic acidosis (Figueras et al., 2007). Hence, the type of delivery and, as previously discussed, timing of delivery in such infants is critical. The inherent dilemma is how long to leave a non-thriving fetus in a sub-optimal uterine environment versus iatrogenic premature delivery with all the known inherent risks for adverse perinatal outcome. In some cases there will be no option, with the risks of intrauterine death outweighing those of the complications of prematurity. In countries with low infant mortality rates, when infants with congenital malformations are excluded, late fetal deaths in extremely SGA fetuses can account for more than 50% of all late fetal and infant deaths (Cnattingius et al., 1998). In contrast, delaying delivery until fetal distress is evident in cases of IUGR may be associated with higher stillbirth rates but a lower neonatal mortality and, at very low gestational age, neonatal

mortality and cerebral palsy are competing short versus long-term outcomes (Baschat and Hecher, 2004, Jarvis et al., 2003). Other studies have shown both increased rates of neonatal mortality and adverse neonatal outcomes in infants with severe early IUGR (Aucott et al., 2004). All these known risks would be expected to have considerable influence on onset of labour, type of delivery, intrapartum problems, and rates of admission to neonatal intensive care units infants with IUGR or born SGA.

1.5.2 Neonatal period

Fetal growth restriction has long been associated with increased neonatal morbidity (Sharma et al., 2004, Garite et al., 2004, Lal et al., 2003, Bernstein et al., 2000). There is however a reduced incidence of some morbidities such as respiratory distress syndrome (Sharma et al., 2004) and cerebral haemorrhage (Amato et al., 1993) but an increased incidence of chronic lung disease (Sharma et al., 2004, Garite et al., 2004, Lal et al., 2003) and cerebral palsy, although the latter seems to be less marked in the growth restricted infants born preterm (Jarvis et al., 2003).

In the past, it has been suggested that "stress" of the intrauterine condition in IUGR may enhance fetal maturation and be protective against the effects of prematurity compared with appropriately grown preterm infants so that mortality and some neonatal morbidities may be reduced; however, the evidence for this is lacking and severe IUGR has clearly been shown to be harmful (Bernstein et al., 2000) (Baschat and Hecher, 2004, Ley et al., 1997). As preterm infants are often also growth restricted, centiles for birth weights in premature infants are distorted (skewed to the left, as healthy better grown infants are more likely to progress to term) and may

conceal the degree of growth restriction in a given infant. Hence using fetal growth (estimated fetal weight standards by ultrasound measurements), rather than birth weight standards, gives a better indication of the incidence and role of IUGR in neonatal mortality and disease such as necrotising enterocolitis (increased risk) and periventricular haemorrhage (protective) (Cooke, 2007). Similar conclusions have been made by other authors (Lackman et al., 2001) (Gardosi, 2006). In addition, compared with AGA infants, SGA infants are more susceptible to TPN-associated cholestasis (Baserga and Sola, 2004) which can undermine or delay delivery of optimum nutrition in these infants.

As neonates, babies born SGA have problems maintaining body temperature and normoglycaemia. Brown fat is reduced or absent, severely impairing non-shivering thermogenesis. In a study of perinatal correlates and neonatal outcomes of infants born SGA at term, Doctor et al defined SGA as birthweight < 10th centile for gestational age but found that the only significant difference between infants with birth weights between the 5th and 10th centile for gestation and their matched AGA controls was the development of neonatal hypothermia, with significant differences for all other variables occurring in infants with birthweights <5th centile. The differences in rates of hypothermia and symptomatic hypoglycaemia between SGA infants and controls remained significant even after controlling for identified medical or pathological causes of IUGR, leading the authors to suggest that neonatal morbidities are related to growth failure per se rather than its cause (Doctor et al., 2001).

Newborns with intrauterine growth retardation (IUGR) have multiple risk factors for developing hypoglycaemia. Hyperinsulinism, both transient and prolonged, is one of

the major risk factors responsible for the hypoglycaemia observed in some newborns with IUGR. Once the child has progressed beyond infancy, ketotic hypoglycaemia is the most common cause of hypoglycaemia and observations by Kochar et al suggest that ketotic hypoglycaemia may be more common in children with a history of IUGR (Kochar and Hussain, 2006). In contrast, premature very low birth weight infants can experience varying degrees of hyperglycaemia in the neonatal period due to factors such as stress, sepsis, administration of postnatal steroids and complications of parenteral nutrition. In a study of hyperglycaemia in extremely low birth weight infants, studies have shown that IGF-I and IGF-II are not related to hyperglycemia and that hyperglycemic infants do not have baseline insulin deficiency; most having a normal insulin response to hyperglycemia (Meetze et al., 1998).

1.5.3 Infancy and Childhood

1.5.3.1 Catch-up Growth

A general definition of catch-up growth is a growth velocity (cm/year) greater than the median for chronological age and gender (height velocity SDS > 0). It is typically an early postnatal process that in most infants is completed by the age of 2 years and results in attainment of height within the normal range (i.e. height > - 2SDS) (Albertsson-Wikland and Karlberg, 1997, Karlberg and Albertsson-Wikland, 1995). Studies have shown that most SGA infants approach the length of their AGA peers by the age of 2 years (Hokken-Koelega et al., 1995, Ong et al., 2000, Albertsson-Wikland and Karlberg, 1997), with catch-up occurring in > 80% of SGA infants within the first 6 months, although it can be longer in premature infants (Albertsson-Wikland and Karlberg, 1997). In fact, most of the increase in height SDS in these

children has been found to occur by 2 months of age (Albertsson-Wikland and Karlberg, 1997). For this reason regular growth monitoring during the early postnatal period is recommended (Clayton et al., 2007) and different growth patterns may emerge in infants as young as 3 months of age (Saenger et al., 2007). Perinatal factors associated with failure of catch-up by 6 months in SGA infants (<10th centile) were analysed by McCowan et al. in a cohort of over 200 infants. The authors found that shortness at 6 months was associated with shortness at birth and male gender. In addition, low head circumference was associated with small head at birth and low weight at 6 months was associated with antenatal detection of SGA (McCowan et al., 1999). Furthermore, overall smallness (low weight and length) was associated with prematurity, and z-score birth length (McCowan et al., 1999). Those who have failure of catch-up growth by 2 years, and whose height and/or weight remain ≤ 2SDS below the mean, have been shown to be at increased risk of short stature (Karlberg and Albertsson-Wikland, 1995, Hokken-Koelega et al., 1995, Luo et al., 1998). In a large Swedish birth cohort study (n= 3656), birth length was found to be the most powerful risk factor for short final adult height (Albertsson-Wikland and Karlberg, 1997). The investigators found that lack of postnatal catch-up in SGA children by age 2 years gave a relative risk of short stature at 18 years of 5.2 if born light and 7.1 if born short. In this context, 20% of short adults are estimated to have been born SGA (Karlberg and Albertsson-Wikland, 1995). In a smaller French study by Leger et al, approximately 13% of children born SGA (BW < 3rd centile) had a final height ≥ 2 SDS below the mean, compared to 1.7% of children born AGA (Leger et al., 1998b).

In the studies by Ong et al analysing longitudinal growth data in a total of 1335 normal infants up to five years of age (as part of The Avon Longitudinal Study of

Pregnancy and Childhood (ALSPAC)) complete catch-up growth by 12 months was demonstrated in children of maternal smokers who were symmetrically small at birth. In contrast, infants of primiparous pregnancies were thin at birth, showed dramatic catch-up growth and were heavier and taller than infants of non-primiparous pregnancies from 12 months onwards. Of the infants who caught up, males caught up more rapidly than females (Ong et al., 2002b).

The literature can be confusing when definitions of catch-up growth in the postnatal period are considered. Although the classic definition refers to linear catch-up (length or height) (Karlberg and Albertsson-Wikland, 1995, Hokken-Koelega et al., 1995) some studies referring to catch-up have concentrated on postnatal weight gain (Monteiro and Victora, 2005). (Monteiro et al., 2003, Ong et al., 2000, Cameron et al., 2003), especially given the association of rapid postnatal weight gain with later risk for obesity.

Early postnatal growth rates are strongly influenced by a drive to compensate for antenatal restraint or enhancement of fetal growth by maternal-uterine factors (Ong et al., 2002b). Mechanisms that signal and regulate early catch-up growth in the postnatal period may influence associations between small size at birth and risks for disease in later life (Ong et al., 2000). The development of insulin resistance during childhood or adult life underpins the associations between birth weight and risk of cardiovascular disease and type 2 diabetes. This has led to an early hypothesis that determinants of size at birth could also be determinants of later risk of adult disease (Hattersley and Tooke, 1999). The pathway from size at birth to adult disease however, is complex and early or later rapid postnatal weight gain may be the more

important determinant of disease outcome (Cianfarani Arch Dis Child Fetal Neonatal Ed 1999). Studies reported in the literature appear to concur that there are two distinct types of child with a history of SGA (i) those that catch up and (ii) those who fail to catch up.

(i) In those who catch up height and weight come within the normal range but rate of postnatal catch-up may determine future risks for overweight or obesity. A 2005 systematic review of growth in infancy and childhood identified 13 papers showing an association with rapid weight gain from birth with risk of overweight or obesity at 3-17 years (Monteiro and Victora, 2005). However, there are various differences used in these publications to define rapid catch-up. The most consistent interval between measurements for rapid growth calculation was 0-2 years, used in three studies which also used the same definition for clinically significant catch-up growth (variations greater than +0.67 weight-for-age z-scores between two separate evaluations) (Ong et al., 2000), (Monteiro et al., 2003, Cameron et al., 2003). This value is based on the difference between percentiles 25, 50 and 75 in a growth chart. Ong found children who showed catch-up growth between 0-2 years to be heavier, taller, and fatter (BMI, percentage body fat, and waist circumference) at five years than other children (Ong et al., 2000). Another study of 588 children by Tanaka et al. found a positive correlation between weight gain during the first month of life and BMI at 3 years of age (Tanaka et al., 2001). In addition, associations have been made between linear growth and later BMI. A follow-up study of infants born in 1958 studied at age 33 years (72.8% of original cohort of 10,683) showed percentage of eventual final height attained at age 7 years in boys was associated with birth weight, and their mother's weight or BMI (Parsons et al., 2001). The percentage of eventual adult height at age 7 was used as the criterion for rapid growth. In a large Swedish follow up growth study

of men born SGA (<-2 SDS for birth weight or length), Lundgren et al. showed that men born SGA for length (SGA_L) and achieving a final height >-2SDS had a 61% increased risk of being overweight (Lundgren et al., 2001). However, there was no increased risk of high blood pressure, which was the primary outcome being assessed. There was no difference in association between SGA_W (weight) and SGA_{WL} (weight&length). The analyses however, were not adjusted for major confounders.

(ii) In contrast, the child who is born SGA but fails to show catch-up and remains short during childhood displays a defect in prenatal and postnatal growth, although the risks for later health problems are less clear especially in those who remain short and are treated with growth hormone (Saenger et al., 2007). SGA children who fail to catch up could reflect the severe degree of IUGR and the development of irreversible changes in fetal metabolism that impair the possibility of postnatal catch-up growth; for example, children born SGA who fail to catch up often have early loss of appetite and reduced food intake (Boonstra et al., 2006) (Dunger et al., 2006). Alternatively, candidate genes could not only affect fetal but also postnatal growth (genes included IGF-1, IGF-2, IGF1R and genes encoding the insulin receptors and their respective post-receptor signalling cascade). It is also more likely that as yet unidentified isolated gene defects play a role in the severity of postnatal growth failure in children born SGA who do not catch up (Dunger et al., 2006). Whatever the underlying mechanism, it is clear that SGA children who exhibit lack of catch-up growth constitute a high risk group for persistent short stature (Leger et al., 1998b, Karlberg and Albertsson-Wikland, 1995, Hokken-Koelega et al., 1995).

1.5.3.2 Insulin resistance and metabolic syndrome – The "catch-up growth hypothesis"

Decreased insulin sensitivity has been demonstrated not only in adults born SGA, but also in children born SGA (Soto et al., 2003, Veening et al., 2002, Hofman et al., 1997, Arends et al., 2005). For this reason it has been speculated that the rapid increase in height velocity experienced shortly after birth, involving over-activation of the IGF system which was quiescent during intrauterine life, induces metabolic adaptations with long-term consequences (Cianfarani et al., 1999).

Growth-restricted infants are characterised by fetal hypoglycaemia, which acts to maintain the maternal/fetal glucose concentration gradient and transport of glucose across the placenta to the fetus (Hay et al., 1997). The hypoglycaemia also limits insulin secretion, initially potentiating fetal glucose production, but subsequently resulting in increased protein breakdown and decreased protein accretion, limiting the growth of lean body mass (Hediger et al., 1998a). Children born after IUGR have low insulin, IGF-1, IGFBP-3 and high GH, IGFBP-1 and IGFBP-2 which normalises in the first few months of postnatal life (Cianfarani et al., 1998, Leger et al., 1996). Tissues chronically depleted of insulin and IGF-1 in utero which are suddenly exposed to increased concentrations of the two hormones shortly after birth, may counteract their additive insulin-like actions by developing insulin resistance as a metabolic defense mechanism to protect the organism from hypoglycaemia (Cianfarani et al., 1999). Therefore the crucial time for development of long term consequences may be in early postnatal life when catch-up growth occurs in the majority of SGA children (Karlberg and Albertsson-Wikland, 1995, Hokken-Koelega et al., 1995). The glucose induced insulin response in infants with catch-up growth is higher than that in children without significant catch-up growth, therefore infants with

IUGR who show early and complete recovery from IUGR may be at higher risk for the occurrence of metabolic disturbances like insulin resistance and NIDDM in adulthood (Colle et al., 1976) (Cianfarani et al., 1999). Early "adiposity rebound", the point of maximal leanness which is usually achieved at 5 to 6 years of age, may be a marker for growth acceleration and cell hyperplasia which are exaggerated during catch-up growth in infants born following IUGR (Whitaker et al., 1998). Therefore these infants may also have an additional risk of developing insulin resistance in adulthood.

These hypotheses are strengthened by the observations of various studies. In a study by Soto et al., insulin resistance was found only in the infants born SGA who achieved catch-up growth and not in infants born SGA who did not catch up or who were born AGA (Soto et al., 2003). Veening et al. found no differences in glucose tolerance and beta-cell function between SGA and AGA groups of children, however reduced insulin sensitivity was found in SGA children using hyperinsulinaemic euglycaemic clamp studies, especially in those with catch-up growth and a high BMI (Veening et al., 2002).

A large prospective case-control study by Leger et al. of 1,500 young adults born between 1971 and 1985 in France, compared those born SGA (birth weight < 10th centile) with those born AGA (birth weight 25th -75th centile) between 1971 to 1985, and reported that insulin resistance was more prominent in the SGA group (Leger et al., 1997).

Although catch-up growth has been associated with insulin resistance, in addition short (<5th percentile for height) prepubertal children born SGA have been shown to

have abnormal insulin sensitivity, tending towards insulin resistance, when compared with short children born AGA (Hofman et al., 1997). Using intravenous glucose tolerance test, Hofman et al. compared 15 short prepubertal children who had been born following IUGR (with birth weight < 10th centile) with 12 children of normal birth weight, and found the insulin sensitivity index to be significantly decreased in the former. In addition the acute insulin response revealed higher insulin levels in the IUGR group, but there was no difference in glucose effectiveness between the two groups (Hofman et al., 1997). Similarly Arends et al. showed that mean insulin sensitivity levels in short SGA children was significantly reduced compared to short AGA controls. Mean acute insulin response (AIR) was also significantly higher in the SGA children and these differences between the two groups remained significant after adjusting for age and BMI (Arends et al., 2005).

Furthermore, with the increasing adiposity of puberty, such children could develop significant insulin resistance. Similar to term infants born SGA, preterm infants born SGA have also been shown to have an isolated reduction in insulin sensitivity (Hofman et al., 2004). In contrast however, in a case-control study by Cianfarani et al., 26 children born SGA did not have altered insulin sensitivity when compared with 26 auxologically identical AGA subjects, but did show significantly lower glucose levels (Cianfarani et al., 2003). In addition, Cianfarani et al. found higher thyroid stimulating hormone (TSH) concentrations in SGA children who had failure of catch-up growth, leading the authors to propose that intrauterine reprogramming may involve thyroid function, affecting postnatal growth and cholesterol metabolism, thereby increasing the risk of later cardiovascular disease (Cianfarani et al., 2003).

1.5.3.3 Influence of gestational age – growth in premature infants

Poor growth, regardless of whether it occurs during antenatal or early postnatal life, is associated with increased risk to long-term health. It is known that fetuses destined to deliver preterm do not reach their individual growth potential in utero (Bukowski et al., 2001) and that variation in birth weight may be determined, at least in part, by fetal growth in the first 12 weeks after conception through effects on timing of delivery and fetal growth velocity (Bukowski et al., 2007). However, very preterm infants are exposed to extra-uterine life during a period that is normally characterised by rapid intrauterine growth. Welberg and Seckl, who reviewed the studies by Barker, suggested that the Barker hypothesis could be mediated by fetal brain programming or imprinting from high levels of glucocorticoids in utero (Welberg and Seckl, 2001). Both antenatal (used in the management of anticipated preterm delivery) and postnatal steroid administration (used in the management of chronic lung disease) may also have a role in growth outcomes. As infants who are born very small or very early are more likely to have a range of morbidities, particularly neurological, respiratory and gastrointestinal (Bernstein et al., 2000, Murphy et al., 1995) and have a greater risk of dying during the first year of life (Law, 2002), antenatal steroids are now recommended in any IUGR fetuses in whom delivery is anticipated prior to 34 weeks gestation (Baschat and Hecher, 2004). A meta-analysis Crowley in 1995 has concluded that overall antenatal corticosteroids reduce the odds of developing respiratory distress syndrome by approximately 50%, and this also has consequences for both neonatal morbidity and mortality rates (Crowley, 1995). Therefore use of corticosteroids either antenatally or postnatally may further alter growth in infants born prematurely, along with the effects of various perinatal complications and morbidities recognised in these infants.

Antenatal corticosteroid administration may be associated with a reduction in birth weight and head circumference which are independent of other predictive factors (Thorp et al., 2002). In addition, it has been associated with a reduction in head circumference even after controlling for birth weight; and the effect on birth weight and head circumference increases with advancing gestational age (Thorp et al., 2002). Many studies have looked at follow-up growth in children born prematurely. Comparing children born prematurely (< 32 weeks) with standardised Dutch growth charts at two years corrected age, Rijken found significantly shorter length, lighter weight and smaller weight-for-length. Head circumference was comparable with the reference group. Lower birth weight SDS was associated with significantly lower growth in all parameters. Postnatal use of dexamethasone to prevent chronic lung disease in this cohort was negatively associated with all growth parameters especially head circumference; however no associations were found between the cumulative dose, duration of treatment or age at start of dexamethasone and growth (Rijken et al., 2006). Rijken's findings are backed up by studies by Yeh who found impaired growth (length and head circumference) at two and eight years of age after dexamethasone use (Yeh et al., 2004). In contrast Romagnoli et al. have reported no differences at 3-years corrected age in premature infants with or without dexamethasone (Romagnoli et al., 2002b, Romagnoli et al., 2002a). Rijken's group however, note that cumulative dose of dexamethasone was high at the time the children were treated (1996/1997) in comparison with the cumulative dosage in presently used short courses. MRI findings at term-corrected gestational age show a 35% reduction of cortical grey matter in infants who received postnatal dexamethasone compared to those who did not (Murphy et al., 2001).

Despite slow growth in infancy, the majority of preterm infants catch up into the normal range for height as well as weight over several years (Bracewell, Arch Dis Child Fetal Neonatal Ed 2007). However, the acceleration that follows the period of suboptimal growth in utero or infancy also increases risk. What is not known is the optimal growth velocity during recovery (Vasu and Modi, 2007). There is also increasing evidence that accelerated growth increases the risks of adverse metabolic and cardiovascular outcomes in adult life. Reports include increased risk of obesity (Ong et al., 2000), visceral adiposity (Ekelund et al., 2006), metabolic risk scores (Ekelund et al., 2007), insulin resistance (Singhal et al., 2003), dyslipidaemia (Singhal et al., 2004), hypertension (Singhal et al., 2007) and coronary heart disease (Eriksson et al., 1999).

When it comes to management of the preterm infant born AGA, other issues, such as extrauterine growth restriction, may come to light. Extra-uterine growth retardation (EUGR) often results in these infants who shift energy expenditure from growth-promoting activities in order to cope with increased requirements. Regardless of whether a premature child is born SGA or not, as a result of EUGR very preterm infants tend to end up "small at term" (SAT) corrected-gestational-age. A considerable proportion (25%) could even be classified as SGA at this stage. Estimated fetal weight standards may be a more appropriate goal for preterm infants than postnatal growth curves. However, since many extremely low birth weight infants are discharged from the NICU below the median body weight of a fetus of the same postmenstrual age plotted on a body-weight-based growth chart, they would be even further below the median if plotted on an EFW-based growth chart. However, as there are inherent errors associated with derivation of EFW-based growth charts,

reference curves based on birth weight which are in current clinical practice are probably preferable for use at present (Ehrenkranz, 2007). Approximately 10% of very preterm (< 32 weeks gestation) children have a height <-2 SDS at 4-5 years of age. This is which is similar to the proportion of term SGA infants who do not show postnatal catch-up (Niklasson et al., 2003, Knops et al., 2005). Hence, it has been suggested that GH should be offered to ex-preterm children, who were small at term and who have persistent short stature at age 4-5 years, in spite of the exclusion of this indication from the current GH licence (Wit et al., 2006).

1.5.4 Infant Nutrition

Attention has recently turned to the importance of nutrition in the first year of life on early childhood growth. This is emphasised by the marked difference in growth rates between breast-fed and bottle fed infants. In the ALSPAC study there was no difference in size at birth in breast-fed infants compared to bottle-fed infants but the former grew more slowly during infancy (Ong et al., 2002b). Current WHO recommendations are to encourage exclusive breastfeeding until the age of 6 months. This also has added immunological advantages (World Health Organization, 2007a). In term born infants the growth performance of those breast-fed is now considered the gold-standard, although growth velocity is slower than that of formula-fed infants (Vasu and Modi, 2007). A number of studies also report effects of early diet on cognition (Lucas et al., 1992) (Hurtado et al., 1999). A recent meta-analysis by Anderson et al. has indicated that, after adjustment for appropriate key cofactors such as socioeconomic status or maternal education, breast-feeding was associated with significantly higher scores for cognitive development than was formula feeding (Anderson et al., 1999). Of particular note was the fact that low birth weight infants

showed larger differences, suggesting that premature infants derive more benefits in cognitive development from breast milk than do full-term infants. In addition, the cognitive developmental benefits of breast-feeding increased with duration (Anderson et al., 1999). The ALSPAC Group and others have described the protective effects of breastfeeding in avoiding excess infant weight gain, childhood obesity and higher blood pressure (Ong et al., 2002b, Martin et al., 2004) (Reilly et al., 2005).

Dietary energy intake in bottle-fed infants at the age of 4 months has been reported to predict infant weight gain and childhood BMI (Ong, 2006, Ong et al., 2002b). Similarly, a systematic review by Huxley et al. concluded that accelerated postnatal growth is also associated with raised blood pressure (Huxley et al., 2000).

Animal studies have shown that postnatal dietary interventions that attenuate catch-up growth not only increase longevity but also protect against the added risks posed by a high carbohydrate, high fat diet later in life (Vasu and Modi, 2007). Guidelines as to how, when or whether to safely intervene to avoid over-rapid weight gain during the first months of life are, as yet, very unclear (Ong, 2006), and inappropriate weight restriction may in fact be harmful for short-term health (Victora et al., 2001). In addition, the optimum pattern of postnatal growth after extremely preterm birth is unknown, and both growth restraint and growth acceleration are associated with beneficial as well as adverse outcomes (Vasu and Modi, 2007).

Long-term follow-up of two randomized trials of nasogastric tube-feeding of premature infants report an association between higher caloric content and adverse effects on body size and risk of metabolic syndrome in later life (Singhal et al., 2001,

Singhal et al., 2003). In the first paper, consumption of formula instead of human milk in infancy was shown to increase diastolic and mean arterial blood pressure in later life (Singhal et al., 2001). Singhal's second study looked at fasting 32-33 split pro-insulin (a marker of insulin resistance) levels. It found lower concentrations in preterm infants fed a lower-nutrient diet who gained weight slower in the first two weeks of life versus those babies fed a nutrient-enriched diet (Singhal et al., 2001, Singhal et al., 2003).

1.5.5 Body Composition, Size at Birth and Size in Later Life

Recent studies show continuing secular trends in increasing rates of obesity in adults and young children in Ireland and in the UK (Department of Health, 2005). Data from recent surveys indicate that one in five Irish boys and girls is overweight and one in twenty is obese (Irish Health Promotion Unit, 2007). Worryingly, the age of onset of obesity in children across the world is falling and a child is twice as likely to be an obese adult if obese in childhood (World Health Organization, 1997). The International Obesity Taskforce (IOTF) has reported that one in 10 children is overweight, a total of 155 million worldwide. Around 30-45 million within that figure are classified as obese - accounting for 2-3% of the world's children aged 5-17. A further 22 million younger children are also affected according to previous IOTF global estimates based on WHO data for under fives (International Obesity Task Force, 2007).

Overall, higher birth weight, adjusted for gender and gestational age, weakly predicts larger childhood and adult body size and BMI (Ong, 2006). However, when body

composition and distribution of body fat are examined, these emerge as more important determinants of obesity-related disease than body weight or BMI. These abnormalities in body composition are greatly enhanced when low birth weight (LBW) is followed by rapid postnatal weight gain. Total body fat was also shown to be highest in individuals with LBW and high current weight. Barker also showed a relationship between LBW and increased subscapular-to-triceps skinfold thickness ratio in adolescent girls (Barker et al., 1997) and among men born in Hertfordshire and Preston, England, after adjustment for current BMI, mean waist-to-hip ratio increased with decreasing birth weight (Law et al., 1992). Affluence may also have a role. In Pune, India, fetal growth restriction is associated with increased central fat at age 8 years in affluent urban children, but not in poor rural children (Yajnik, 2000). In the developing world rates of obesity are increasing faster in urban than in rural areas. Assessing children born SGA for skinfold thickness and arm circumference measurements, Hediger found a higher percentage of body fat in these children from ages 2 to 47 months, due to reduced lean tissue mass in children born SGA compared with children born AGA and LGA (Hediger et al., 1998a). There was a persistent overall deficit in muscularity (mid-upper arm circumference and mid-upper arm muscle area) of approximately -0.50 SDS in the children born SGA (defined as BW $<10^{th}$ percentile for gender and gestation). At all ages, compared with children and infants born AGA, infants and children born SGA showed no significant differences in subcutaneous fatness. In fact, there was a tendency in the first year for SGA infants to have significantly higher arm-fat index compared with AGA infants. The children born LGA ($\geq 90^{th}$ percentile) were shown to have persistent increased muscularity, as well as less of an excess of fat mass compared to AGA children (Hediger et al., 1998a). Using mid-upper arm anthropometry and indices, Yau and Chang followed 38

preterm infants born SGA from birth to a corrected gestational age (CGA) of 37 to 40 weeks and compared the SGA infants with 193 infants at similar postmenstrual ages. At birth the SGA infants were smaller in all dimensions (mid-upper arm circumference, mid-upper arm muscle and fat areas). However, at 37 to 40 weeks CGA, the SGA infants still weighed less, were shorter, had smaller head circumference and had less muscle mass (smaller mid-upper arm circumference), but had skinfold thickness (fat mass) that was comparable (Yau and Chang, 1993). Growth in less mature (31-33 weeks gestation) infants born SGA or those preterm SGA infants with an eventful clinical course, was sub-optimal compared with other SGA infants in the same subgroup. Differences between postnatal enteral and placental nutrition or in energy utilization in preterm infants born SGA are hypothesized to account for these observations (Yau and Chang, 1993). Thus preterm infants born SGA appear to disproportionately retain excess calories as fat, while protein reserves in the form of muscle remain low. The same pattern most likely applies to growth restricted infants born at term (Hediger et al., 1998a).

1.5.6 Insulin –like Growth Factor-1 (IGF-1)

The insulin-like growth factor-1 (IGF-1) is a peptide, structurally related to the insulin and proinsulin molecules, which binds to specific receptors (type 1 IGF receptor) and, with lower affinity, to insulin receptors, thereby acting as an insulin sensitiser. It is produced and secreted in the liver, as well as in many other organs, and regulation of its production and release from the liver is mediated by GH (Delemarre et al., 2007). IGF-1 circulates in the blood bound to carrier proteins (the IGFBPs family) that regulate the bioavailability and bioactivity of IGF-1, also exerting IGF-independent

actions. Levels of IGFBP-1 and IGFBP-3 are regulated by insulin and GH respectively (Hwa et al., 1999). In contrast to the insulin-antagonist effects of GH, IGF-1 induces hypoglycaemia by suppression of hepatic production of glucose and stimulation of peripheral glucose uptake (Delemarre et al., 2007). During fetal life, serum IGF-1 levels are relatively low, increasing with gestational age (Leger et al., 1996). In newborns, serum IGF-1 levels correlate with birth weight and length; with lower IGF-1 concentrations in SGA compared to AGA infants (Leger et al., 1996, Ogilvy-Stuart et al., 1998). However, recent reports have shown an inverse relationship between serum IGF-1 levels in childhood and birth weight (Ong et al., 2002a, Cutfield et al., 2002, Garnett et al., 1999). In a study of 317 children, Leger et al. showed a positive correlation between IGF-I increment and weight gain during the first 3 months of life (Leger et al., 1996). None of the biologic parameters at birth, however, were predictive of either later growth or of short stature at 2 years of age. The authors concluded that low serum IGF-I and IGFBP3 levels at birth were related to fetal malnutrition and were not predictive parameters for later growth. A large study of 1030 subjects by Juul et al., has shown a slow increase in serum IGF-1 and IGFBP-3 concentrations in early childhood, with a steep increase in puberty and thereafter, a decrease, while serum IGF-2 levels remain constant after the first 2 weeks of life (Juul et al., 1994, Juul et al., 1995).

Children born following intrauterine growth retardation (IUGR)/SGA who do not catch up have however been found to have lower than average IGF-1 levels in some studies (de Waal et al., 1994, Boguszewski et al., 1996, Leger et al., 1996). However, higher (Cutfield et al., 2002) or normal (Woods et al., 2002) IGF-1 and IGFPB-3 concentrations compared to short AGA controls (at mean age 7-8 years) have also

been reported. In addition, it has been proposed that short children born SGA may have a degree of IGF-1 resistance as higher basal and GH-induced IGF-1 levels are required to achieve a normal growth velocity (Chatelain et al., 1998). This hypothesis could explain why supra-physiological doses of GH are required to significantly improve growth velocity and final height in children born SGA who fail to catch up spontaneously (de Zegher et al., 1997b, de Zegher et al., 1999, Stanhope et al., 1991, Van Pareren et al., 2003a). Recent reports suggest that mutations in the *IGF-IR* gene are uncommon but potential causes of intrauterine and postnatal growth failure (Abuzzahab et al., 2003). Growth problems due to IGF-1 gene polymorphisms and single copy of IGF-1 receptor gene have also been identified (Johnston et al., 2003, Okubo et al., 2003).

1.5.7 Dual-energy x-ray absorptiometry (DXA)

DXA is a tool increasingly being used to assess body composition and bone mineral density with ever expanding applications in the area of Paediatrics. From studies using dual-energy X-ray absorptiometry (DXA) in 70-75 year old men and women, Gale et al. have shown that low birth weight (LBW) is specifically associated with reduced lean tissue mass (Gale et al., 2001). Crabtree et al. performed a study of over 600 school children and showed that the relationship between height and lean body mass, and lean body mass and bone mineral content can be a useful method for diagnosing osteoporosis in children. These relationships can be used to identify if the primary abnormality is in muscle or bone (Crabtree et al., 2004). However, no specific relationship between muscle or bone abnormalities and LBW/SGA was explored. As observed by Hediger et al., SGA infants remain smaller and LGA infants larger in size through early childhood. However the discrepancies in weight are primarily

attributable to differences in lean body mass (muscularity) (Hediger et al., 1998a). In addition, de Zegher has reported that children born SGA who completed catch-up growth at the age of 2 years continue to accumulate excess central fat, as assessed by DXA, over the following 2 years, despite lack of further catch-up in overall height or weight (de Zegher et al., 2006).

Bone mineral content (BMC) in adults has positively correlated with weight at one year of age in several studies (Cooper et al., 1995, Cooper et al., 1997, Dennison et al., 2005, Weiler et al., 2002). Other studies have shown a positive correlation between birth weight and BMC (Dennison et al., 2005, Gale et al., 2001, Antoniades et al., 2003, Yarbrough et al., 2000).

1.5.8 Neuro-developmental and Psychosocial issues in SGA

Birthweight and postnatal growth are independently associated with cognition (Richards et al., 2002). SGA was one of the factors associated with a reduction in neuro-developmental impairment at 18-24 months corrected age in former extremely low birth weight infants reported by The NICHD Neonatal Research Network (Vohr et al., 2004). In the short term, reduced muscularity in infancy and early childhood could be associated with delays in motor development (upright locomotion and exploratory behaviour). For example, preterm infants born SGA are more likely to show deviant walking quality when compared to AGA preterm infants and term infants (de Groot et al., 1997).

Cognitive impairment is independently associated with low birth weight, short birth length and small head circumference for gestational age. The effect is moderate but significant. Lack of catch-up in height and/or head circumference is associated with

worst outcome (Sommerfelt et al., 1998, Lundgren et al., 2001). There have been conflicting results on the psychosocial impact of short stature on children's wellbeing (van der Reijden-Lakeman et al., 1996, Sandberg et al., 2004); however children born SGA have shown increase in head circumference and significant improvement in IQ scores, behaviour and self-perception over time in a GH-treated cohort compared with untreated controls (van Pareren et al., 2004, Arends et al., 2004). Comparing self-concept measures of short children born SGA with a non-SGA Dutch school sample showed significant improvement in "social acceptance" and "general self-worth" scores following two years of GH treatment (van der Reijden-Lakeman et al., 1996). Quality of life in adolescents born SGA with GH-induced improvement in height has also been shown to be better in many aspects when compared to untreated adolescents born SGA (Bannink et al., 2005).

1.5.9 Puberty

There is increasing evidence to suggest a link between puberty and prenatal growth. An earlier and shorter period of puberty could contribute to the decreased final height in SGA children (Ibanez et al., 2000). The prominence of a history of SGA and prematurity among children presenting with precocious pubarche suggests that the prenatal and/or postnatal stress to which these infants are subjected may induce permanent reprogramming of the endocrine and metabolic pathways (Neville and Walker, 2005).

Girls born SGA have smaller uterine and ovarian volumes (Ibanez et al., 2000). Large epidemiological studies of girls born SGA compared with AGA girls have shown an earlier start of puberty as assessed by age of menarche. However, it was still within

the normal range (Adair, 2001, dos Santos Silva, 2002, Lazar et al., 2003) and rate of postnatal catch-up growth associated with hyperlipidaemia and excess adiposity appears to play an important role in age of menarche (Adair, 2001, Sloboda et al., 2007). In one study the association between birth weight and age at menarche disappeared after controlling for growth in infancy (dos Santos Silva, 2002). A more rapid progression of puberty among SGA girls compared to AGA girls has also been described (Ibanez et al., 2000, Veening et al., 2004). Premature adrenarche (increased early androgen secretion before puberty) may predict later ovarian hyperandrogenism which is linked to insulin resistance. This is proposed as a possible link between birth weight and later adult health problems. A number of case-control studies have shown an inverse relationship between birth weight and dehydroepiandrosterone sulphate (DHEAS) levels in prepubertal girls (Francois and de Zegher, 1997, Dahlgren et al., 1998, Ibanez et al., 1999, Ghirri et al., 2001), and particularly in those who were born small and had rapid childhood weight gain had increased androgen levels compared to those with normal birth weights (Ong et al., 2004b). In contrast, comparing short prepubertal SGA children with AGA children of normal stature in a large case-control study showed no relationship between size of birth and DHEAS levels (Boonstra et al., 2004).

Current evidence suggests that insulin resistance is a key mechanism linking a post-SGA state to early menarche; hence, insulin sensitization may become a valid approach to prevent early menarche and early growth arrest in girls born SGA (Ibanez and de Zegher, 2006).

Only a few studies address the timing of puberty in boys and in those studies no difference between SGA and AGA boys was reported (Lazar et al., 2003, Persson et al., 1999, Potau et al., 1999). However the studies are limited and lack longitudinal

clinical data This makes onset of puberty difficult to determine in boys. One study has shown boys born SGA to be at risk of high levels of follicle-stimulating hormone (FSH) and low levels of inhibin B and a small testicular volume during adolescence (Ibanez and de Zegher, 2006). In contrast however, another study has shown no association between smallness at birth and adolescent male pituitary-testicular function (Jensen et al., 2007b).

1.6 GROWTH HORMONE TREATMENT IN SGA

Treatment is now available and licensed in the European Union for children born SGA who have failure of catch-up growth and persistent short stature. The 2007 recommendations of the joint committee of The Societies of Paediatric Endocrinology and the Growth Hormone Research Society are that for children born SGA (birth weight ± length ≤ -2SD) with severe growth retardation, defined as height ≤ -2.5SDS at age 2-4 years, early intervention with growth hormone should be considered at a dose of 35-70μg/kg/day (Clayton et al., 2007). The difference between this consensus statement and the 2001 international consensus statement was that, in the latter, short stature was defined as height < -2SD (Lee et al., 2003). In addition the age limit was ≥ 4yrs old. Height velocity should also be < 0 SDS and other causes of short stature should have been excluded before GH treatment should be considered (Ibanez and de Zegher, 2006, de Zegher et al., 2006).

In some European countries short children born SGA comprise a large group of GH-treated children, accounting for 30% of new cases (Dutch Growth Foundation, Rotterdam, The Netherlands) (van Dijk et al., 2007).

GH treatment has been licensed to commence from the age of 4 years (to allow time for any catch-up to occur), however the appropriate time to commence GH is controversial and few studies have examined the use of GH in young children. A Spanish study looked at 76 children born SGA without catch-up, aged 2 to 5 years, who were randomized to receive GH at a dosage of 0.06mg/kg/day for 2 years, or no treatment for 12 months followed by GH treatment for 12 months (Argente et al.,

2007). Growth velocity SD score increased from -2.2 at baseline to 4.7 at 12 months in the GH group, whereas in the control group there was no change until year 2, reaching a mean value of 5.2 at month 24. Children younger than 4 years in both groups had the greatest gain in growth velocity. Children younger than 4 years had a significantly greater effect of GH versus those 4 years or older, not only for SD score but also in absolute increase in centimeters. There were no changes in insulin sensitivity associated with GH treatment.

1.6.1 Growth Hormone Status

Compared to controls, increased serum GH and decreased serum IGF-1 and IGFBP-3 levels have been found among IUGR neonates. However none of these 3 markers at birth has been found to be predictive of later growth or persistent short stature at age 2 years (Leger et al., 1996). Reports on the use of GH in SGA have demonstrated a satisfactory growth response irrespective of the aetiology of IUGR. However, a supra-physiological dose of GH is required to produce a satisfactory anthropometric response in children born SGA. Disturbances of the GH/IGF axis have been described in previous studies (de Waal et al., 1994, Albertsson-Wikland, 1989, Stanhope et al., 1989, Boguszewski et al., 1995). But a large proportion of short children born SGA exhibit normal GH secretion on testing, and response to GH treatment appears unrelated to maximum GH levels following stimulation testing (Sas et al., 1999, Azcona et al., 1998). In addition, there is no clear relationship between GH, IGF-1 or IGFBP-3 status and spontaneous catch-up growth (Boguszewski et al., 1996).

1.6.2 Growth Hormone Dosage/Growth Response

Studies to date have shown that the size of the final height gain is dependent on the GH dose, and in general high supra-physiological GH doses (2 or 3 times higher compared to the doses used in GH deficient children) are needed to overcome the IGF-I resistant state of children born SGA (Ranke et al., 2003, Coutant et al., 1998). The recommended dose of GH varies between 35 and 67μg/kg/day. However, in some countries the lower dose is suggested as the initial dose, whereas other European countries suggest starting on the higher dose. Data from recent long-term studies indicate that children born SGA can benefit from treatment with relatively high-dose GH (up to 67μg/kg/day) which if given from 4-6 years can reduce height deficit by 7-11cm (de Zegher and Hokken-Koelega, 2005).

1.6.3 The d3-Growth Hormone (GH) Receptor Polymorphism

A protein polymorphism of the GH receptor (GHR) due to the genomic deletion of exon 3 (d3-GHR) has recently been linked to the degree of growth response to high-dose GH treatment of short children without GH deficiency including children born SGA and Turner syndrome. Several studies have found conflicting results in terms of responsiveness to high-dose GH (0.058-0.066mg/kg/day) in association with the d3-GHR genotype (Binder et al., 2006) (Carrascosa et al., 2006); however, the latter study had significantly larger numbers and found no increased responsiveness with the d3-GHR genotype. Interestingly, a recent Danish follow-up study by Jensen et al. found decreased third trimester fetal growth velocity in children born SGA who were carriers of the d3-GHR allele. In contrast however, overall in the whole cohort of children born SGA and AGA the carriers of the d3-GHR allele showed increased

height and an increased spontaneous postnatal growth velocity compared with carriers of the full-length GHR allele (Jensen et al., 2007a).

1.6.4 Safety of Growth Hormone Treatment in SGA

Overall GH treatment has been shown to have a good safety profile following over 14 years' experience (Sas et al., 2001, Cutfield et al., 2006). Recent comprehensive reviews on the use of GH to final height internationally have concluded that GH therapy appears to be a safe and effective therapy in children born SGA who have failed to catch-up (Johnston and Savage, 2004) (Saenger et al., 2007). However due to the short history of its use in such children, there are limited international studies of long term safety of GH treatment in children born SGA, and as its use is likely to increase in the coming years, there is a need to ascertain the efficacy, optimum dosage and safety of this treatment. Concern has been voiced regarding the late consequences of GH treatment on risk factors for type 2 diabetes and associated co-morbidities, especially given that SGA children may be predisposed to these conditions even without treatment (Hofman et al., 1997, Jaquet et al., 2000, Veening et al., 2002, Arends et al., 2005, Phillips et al., 1994a). Hence the effect of GH treatment on glucose metabolism in children born SGA is the main area of potential concern (Saenger et al., 2007). However there is increasing evidence that long-term GH treatment does not increase the risk for type 2 diabetes mellitus and metabolic syndrome in young adults (van Dijk et al., 2007).

Since growth hormone (GH) increases IGF-I levels, concern has been raised regarding its potential role as a cancer initiation factor. However, the epidemiological studies,

which indicate an association between serum IGF-I levels and cancer risk, have not established causality (Cohen et al., 2000).

Methods used to assess Glucose Homeostasis

A reduction in insulin sensitivity has been shown to be an early defect in the development of type 2 diabetes (Martin et al., 1992). Children with reduced insulin sensitivity who may be at risk of type 2 diabetes later in life are unlikely to have impaired glucose tolerance on routine testing (Cutfield et al., 2003b). In 1979, Turner et al. proposed that concentrations of both basal plasma glucose and insulin are regulated by a negative feedback loop between the liver and pancreatic beta cells (Turner et al., 1979). This hypothesis led to the development of the homeostatic model assessment (HOMA) to provide an index of insulin sensitivity (Matthews et al., 1985, Hosker et al., 1985). HOMA assessment of insulin sensitivity takes into account the effect of variation in fasting blood glucose levels on insulin levels, and is now available in a structural computer model (Matthews et al., 1985). The HOMA model has been found to compare favourably with the other models to assess insulin sensitivity and resistance, and has the advantage of requiring only a single plasma sample assayed for insulin and glucose (Wallace et al., 2004), however it relies on robust primary input data and careful interpretation.

Growth hormone and insulin resistance

GH has an insulin-antagonistic effect, and reduces peripheral glucose uptake. Rizza et al. studied the insulin dose-response characteristics for suppression of glucose production and stimulation of glucose utilisation and their relationship to monocyte insulin binding in six normal volunteers after a 12-hour infusion of growth hormone

and 12-hour infusion of saline (Rizza et al., 1982). The authors then proposed that increases in plasma GH within the physiologic range can cause insulin resistance, which is due to decreases in both hepatic and extra-hepatic effects of insulin (Rizza et al., 1982). Those SGA children who have not caught up in growth in the early years may be expected to have less insulin resistance, as the glucose induced insulin response as a metabolic defense mechanism to protect the organism from hypoglycaemia in infants with catch-up growth is higher than in children without significant catch-up growth (Colle et al., 1976) (Cianfarani et al., 1999, Cianfarani et al., 1998).

Some studies have shown that short children born SGA have reduced insulin sensitivity even before receiving GH (Hofman et al., 1997, Arends et al., 2005, Veening et al., 2002). Children born SGA are characterized by reduced insulin sensitivity related to elevated levels of overnight GH secretion (Veening et al., 2002, Hofman et al., 1997, Woods et al., 2002). It is thus hypothesized that resistance to the somatotropic actions of GH and IGF-I in short SGA children may contribute directly to reduced insulin sensitivity. Reduced insulin sensitivity has been reported to be further reduced during GH treatment, but appears to be reversible following discontinuation of treatment (van Pareren et al., 2003b, Hokken-Koelega et al., 2004), de Zegher et al., 2002). However this means that insulin sensitivity (in addition to height velocity) should be monitored closely when treating children born SGA with GH.

Other effects of Growth hormone

There are over 30 published studies showing an association between lower birthweight and higher blood pressure. Children born SGA have a higher systolic

blood pressure and are more often hypercholesterolaemic (Sas et al., 2000, Tenhola et al., 2000). GH has also shown beneficial effects on blood pressure, lipid profiles (van Dijk et al., 2007, Hokken-Koelega et al., 2004), body composition, bone mineral density and head growth (Hokken-Koelega et al., 2004). No negative influences on pubertal age of onset, progression, duration or pubertal height gain have been reported. The discontinuation of GH does not affect blood pressure, body composition or atherogenic index, suggesting that GH therapy might have a positive effect on these parameters which might last even after discontinuation of therapy (Hokken-Koelega et al., 2004). Of note, in van Dijk's cohort, 32% of untreated young adult controls versus none of the GH-treated subjects had an increased blood pressure.

1.6.5 Bone Age

Although radiological assessment of skeletal maturation is routinely performed in children with short stature, predictors of adult height based on estimates of bone age are unreliable in children born SGA with short stature (de Zegher et al., 2000, Coutant et al., 1998). However, bone age has been shown to be normal or delayed in children born SGA. GH treatment is associated with an advancement of bone age. Some reports in the literature show that acceleration of bone maturation depends on GH dose (de Zegher et al., 1997a), whilst other studies have shown acceleration of bone maturation regardless of the GH dose given (Arends et al., 2003, Sas et al., 1999). In an open-labelled, controlled multicentre study of 87 short prepubertal SGA children by Arends et al., a 1-year delay in bone age was found at baseline, which persisted after 3 years in the untreated children. The GH treated (0.033mg/kg/day) children showed an initial advancement in bone age, but after 3 years this advancement decelerated such that no significant difference in bone age was found when compared

with the untreated control group. During the entire 3-year period, bone age advanced by 3.2 years in the untreated group and by 4.3 years in the GH-treated group (Arends et al., 2003). In a retrospective analysis of GH-treated short SGA children, mean progression of bone age was 1 year during 1 year of GH treatment although there was large inter-individual variation (Arends et al., 2004).

1.6.6 Silver Russell Syndrome

Silver Russell syndrome (SRS) is associated with IUGR and being born SGA. Clear diagnostic criteria for SRS have not been established. SRS is a spectrum of phenotypes and it is relatively straightforward to recognise the classic case. Short stature following IUGR/SGA with subtle dysmorphic features however, can be more challenging to classify. Lai diagnosed SRS with the presence of three of the following features: low birth weight ($\geq$ 2 SD below the mean adjusted for maternal stature, gestation, ordinal position of the child, and gender), short stature, a characteristic craniofacial appearance as described by Russell, (Ahmed et al., 2005), limb, body, or facial asymmetry, and clinodactyly (Lai et al., 1994). Price reevaluated 57 patients in whom the diagnosis of SRS had been considered definite or likely, and in 50 patients the clinical findings complied with a very broad definition of SRS (Price et al., 1999).

By contrast to the approximately 86% of children born SGA who catch up during the first two years of life (Albertsson-Wikland and Karlberg, 1994, Albertsson-Wikland and Karlberg, 1997), children with SRS have a marked deceleration in postnatal growth and remain small during childhood, growing at a slower rate than normal and having an earlier pubertal growth spurt of smaller magnitude than in normal children (Tanner et al., 1975, Davies et al., 1988). Overall these factors result in a lower final

height than genetic potential with a mean final height of -3.6SDS (Tanner et al., 1975, Davies et al., 1988). Bone age is usually delayed in early childhood, but it approaches normality as it increases faster than chronological age and the result is a progressive decrease in height for bone age SDS. Hence bone age delay does not translate into increased final stature in children with SRS (Tanner et al., 1975). A number of clinical complications of SRS can further contribute to poor growth in infancy and childhood: (i) Hypoglycaemia in early life may be related to poor appetite, feeding problems as a consequence of high arched palate, gastrointestinal dysmotility or GH insufficiency (Christoforidis, 2005). (ii) Nocturnal sweating is common in children with SRS predominantly during the first year of life, and although this may be part of the clinical syndrome, it may also be related to nocturnal hypoglycaemia (Azcona and Stanhope, 2005). Recurrent nocturnal hypoglycaemia may also be related to impaired educational progress that often occurs with SRS (Stanhope et al., 1998). (iii) There is also a reported incidence of gastrointestinal problems in children with SRS of 77%; including gastro-oesophageal reflux, food aversion and oesophagitis (Anderson et al., 2002). (iv) Asymmetry, which varies in extent and severity, occurs in approximately 60% of cases of SRS and compensatory spinal scoliosis often results (Silver et al., 1953).

Many studies have analysed GH secretion in children born SGA, and all have demonstrated a higher incidence of GH insufficiency in this group (Rochiccioli et al., 1989). In children with SRS however, a characteristic abnormality of only a single nocturnal GH pulse was found in many children with SRS, in comparison with non-dysmorphic growth retarded children (Ackland et al., 1988). It is still to be determined whether hypoglycaemia and extensive nocturnal sweating which is reported in children with SRS is due to this nocturnal GH pulse abnormality.

Children with SRS have been shown to have a short-term response to GH, independently of whether there is GH insufficiency or sufficiency, which suggests that the observed abnormalities in growth hormone secretion may have little relevance to the aetiology of the growth failure (Stanhope et al., 1998). A problem in the literature is that many authors have included SRS patients as part of a general group of SGA patients, extracting results which are not so representative of this unique group of SRS children (Christoforidis, 2005). In contrast to non-dysmorphic children born SGA treated with GH, there is some case report data to suggest that children with SRS may sustain an increased growth rate, even after GH treatment is stopped (Azcona and Stanhope, 1999). It may thus be that continued GH treatment until final height is unnecessary in contrast to those with non-dysmorphic IUGR/SGA and that short term GH treatment may be an option in SRS patients (Stanhope et al., 1998). Predictors of response to GH after three years in children with SRS are low birth weight SDS, low height SDS for chronological age and presence of catch-up growth (Rakover et al., 1996). However data on final height is limited in this group. Rapid growth acceleration with GH treatment has not been associated with accentuation of any skeletal malformation and does not alter lower limb asymmetry in children with SRS (Rizzo et al., 2001).

1.7 THE IRISH PERSPECTIVE

To date there have been no large studies on risk factors for IUGR/SGA using the definition agreed by international consensus (Clayton et al., 2007, Lee et al., 2003), nor have there been studies of outcomes in children born SGA in Ireland. In addition

there have not been any studies conducted to identify those children born SGA who may be at particular risk of problems into adulthood. The recent recommendations of the joint committee of The Societies of Paediatric Endocrinology and the Growth Hormone Research Society are that children born SGA should have length, weight and head circumference measured every 3 months in the first year, and every 6 months thereafter, and that those who remain short by 2 years of age should be investigated for conditions that limit growth (Clayton et al., 2007). To date this has not been routinely implemented in Ireland, with most children being discharged by neonatologists by 2 years of age (personal communication). From other follow up studies we know there is up to 10-15% chance that the child born SGA will not catch up in growth (as defined by height SDS < -2) (Karlberg and Albertsson-Wikland, 1995, Hokken-Koelega et al., 1995, Albertsson-Wikland and Karlberg, 1997), however clearly many of these children are not represented at Paediatric Endocrinology clinics. Equally, as survival rates of preterm infants improve and in many without significant morbidity early growth problems, although not in themselves life-threatening, may become a concern addressed by nutritional supplementation leading to inappropriate rapid catch-up growth which puts the child at future adult health risks but is masked by the fact they have reached "normal centiles". However, no data exists on the prevalence of these problems and on the clinical aspects of SGA in Ireland. There is also very little data available on the efficacy and safety of growth hormone which is a new treatment for children born SGA with persistent short stature.

1.7.1 The North European Small for Gestational Age Study (NESGAS)

The North European SGA Study is a multicentre, multi-national clinical trial to evaluate the safety and efficacy of Growth Hormone treatment at varying doses in short children born SGA. Centres in Denmark, Ireland, Sweden and the UK are involved in the clinical trial. This will allow pooling of data during the course of the study. Specialised laboratories in Copenhagen, Denmark and Cambridge, UK are used for central analysis of IGF-1 and insulin samples respectively. The Department of Endocrinology at the National Children's Hospital, Tallaght, Dublin is the centre co-ordinating the study in Ireland.

1.8 AIMS OF THE STUDY

This study was conducted in order to assess children born small for gestational age (SGA) in Ireland who are at risk of two major life-long problems: short stature and metabolic syndrome.

The main aims of the study were to:

(i) Identify the population of children born SGA in a large Dublin maternity hospital and evaluate possible contributory risk factors.

(ii) Evaluate growth and clinical data on a cohort of Irish children born SGA at ages 4-6 years and identify those at risk of short stature, obesity and metabolic syndrome.

(iii) Identify children born SGA with persistent short stature in the community.

(iv) To assess the efficacy and safety of Growth Hormone treatment of children born SGA who have persistent short stature.

The results of this study will provide important information on Irish children born SGA in relation to pregnancy, perinatal and clinical outcomes including auxological data at 4 to 6 years of age. This study will also provide new important data on the use of GH in children born SGA in relation to efficacy and safety.

CHAPTER 2 PATIENTS AND METHODS

In order to identify the population of children born SGA, a two year birth cohort database for the period 1st July 1999 – 30th June 2001 was accessed at the Coombe Women's Hospital, Dublin. In addition, children born SGA with short stature requiring treatment with growth hormone were identified through liaison with Consultant Paediatricians nationally.

2.1 CASE DEFINITION

Small for gestational age (SGA) was defined as a Birth Weight (BW) of 2 SDS or more below the mean (≤- 2 SDS) for age and gestation. BW SDS was calculated using the cross sectional height and weight reference curves for the UK 1990 as the reference population (Freeman et al., 1995) as standardised birth weight references are not available for the Irish population. All SGA infants with gestation ≥ 28 weeks fulfilled the case definition. In order to achieve the objectives of this study the populations were divided into two main components:

(1.) Coombe Women's Hospital Cohort - SGA Group

(2.) Patients born SGA treated with Growth Hormone

2.1.1 Calculation of Gestational Age

Calculation of gestational age is made on the basis of date of last menstrual period (LMP) given by the mother at the time of antenatal booking. This is also consistent with the procedure used in the CWH. In some cases, women may not have booked their pregnancy at the hospital ('late' or 'unbooked' pregnancies) or may have been unsure of the date of LMP and gestation. For this reason infants with a biologically implausible gestation documented on the computer database ($\geq$ 44 weeks) were excluded due to insufficient data.

2.2 POPULATION (1) – COOMBE WOMEN'S HOSPITAL COHORT (1/7/99-30/6/01)

The patient group to study was those children born small for gestational age (SGA) at the Coombe Women's Hospital (CWH) during the two year period 1st July 1999 to 30th June 2001, with a gestation of greater than or equal to 28 weeks. At the time of the follow up review these children were aged 4-6 years.

2.2.1 Identifying Patient Population – Methods in Data Extraction

In order to identify the population of interest, the mother and infant patient database from the CWH was accessed and examined, following approval by the Coombe Women's Hospital Ethics Committee. Data pertaining to gestational age, gender and birth weight was used to select those infants fulfilling the case definition who could

be contacted for follow up. The following infants were identified and excluded as follows:

- Infants documented as intrauterine deaths or stillbirths.
- Neonatal deaths - ≥ 28 weeks gestation.
- Infants born < 28 weeks gestation. These infants were excluded as it was believed that such premature infants would have had a complicated neonatal course, leading to compounding variables possibly contributing to poor growth. In addition, data to calculate birth weight standard deviation scores is not available for gestations < 28 weeks. On consultation with a Consultant Neonatologist (Dr M Sheridan-Pereira), it was also agreed that these children would be adequately followed up from a medical, growth and developmental perspective until the age of 2-4 years by virtue of their background history of prematurity and admission to Neonatal Intensive Care (NICU).
- Infants with insufficient data. This group was comprised of infants with unrecorded birth weights or gestation in whom BW SDS could not be calculated and infants with Apgar scores of 0 at 1 minute and 5 minutes without documentation of whether infant was born alive or not. The latter infants were excluded as Apgar score of 0 at 5 minutes would be inconsistent with a healthy live infant.
- Infants documented as having a fetal abnormality (diagnosed on antenatal ultrasound) or congenital malformations and syndromes.

2.2.2 SGA Group

From the remaining infants, those with BW SDS ≤ -2 SDS were selected out using the LMS methodology of Cole (1990) (Freeman et al., 1995) UK references, determined for age and gender. This group was called "SGA Group".

A number of approaches were then taken to exclude from this SGA Group infants not yet identified from the CWH database who may have died or had major congenital anomalies or syndromes. These children were then excluded from the cohort to be contacted. These children were identified as follows:

- Contact was made with the Irish office of Eurocat (European Concerted Action on Congenital Anomalies and Twins), a European network of population-based registries for the epidemiologic surveillance of congenital anomalies. The SGA Group was crossed referenced, by hospital number and date of birth, with the list of infants born at CWH during the time period in question with congenital anomalies and/or who had died infancy. The type of congenital anomaly as given by Eurocat was documented.
- Contact was then made with the Child Health Systems to identify any infants who may have died from any cause in the 4-6 years period since birth; these deaths may not have been reported to Eurocat. The list of infants was crossed referenced by name and date of birth with the list of deceased children for the time period in question.
- The National Sudden Infant Death Register (of the Irish Sudden Infant Death Association, the Children's University Hospital, Temple Street, Dublin) was consulted in order to exclude any possible cases of SIDS that may have occurred within the group.

- A chart review was undertaken to establish the appropriateness or otherwise of contacting the parents of infants who had been admitted to the Neonatal Intensive Care (NICU) with complicated neonatal courses. The Consultant Neonatologist, Dr Margaret Sheridan-Pereira, was consulted for her opinion and a decision made whether to contact the mother or not. In each case, the reason for not contacting the mother was documented.

2.2.3 Patient Recruitment

Using the address on the database the mother of each infant within the cohort was written to in May 2005 and invited to attend with her child for auxological assessment at the Department of Paediatric Endocrinology, The National Children's Hospital, Tallaght (Appendix I). Attached to each letter was a questionnaire (Appendix II) pertaining to height, weight and developmental milestones of the child. The parents were requested to complete the questionnaire and return it to us in a stamped addressed envelope. Contact details were also requested. The purpose of this was to establish whether parents were interested in attending for auxological assessment and to provide us with up-to-date contact details in order to make appointments. It also gave an opportunity for parents not interested in attending to provide us with current heights and weights on the child. To ensure maximum response, mothers who did not reply to the letter sent in May 2005, were contacted again in October 2005. In the case of letters returned to us unopened and marked "not at this address", attempts were made to obtain current addresses by consulting the Regional Health Authorities and Medical Card holders list and cross-referencing with our list of patients in question.

2.2.4 Parent Interviews

On attendance the mother/father was interviewed in detail by the investigator (SO'C) for antenatal and delivery history, neonatal course, childhood development and health to date using a study sheet designed specifically for the study (Appendix III). Particular attention was paid to confirm gestational age and birth weight to ensure that it agreed with the database records. Attention was also given to possible factors contributing to the SGA, such as smoking in pregnancy, history of pre-eclampsia and whether IUGR was diagnosed during the pregnancy.

2.2.5 Patient Assessments

Each child was measured and assessed by the investigator (SO'C) who had received training in Auxology (Certified Auxology Course at the Royal Hospital London). The child was measured for standing height, sitting height, weight, and head circumference (see section 2.4 Auxological Methods). Parental heights were also measured. If only one parent was in attendance, a reported height was accepted and documented as "reported".

The child was then examined clinically for signs of poor nutrition or any medical conditions which would lead to poor growth. Incidental findings were dealt with by referral to the appropriate specialist where indicated (e.g. cardiac murmur, undescended testes). Where a child was found to have low weight or height, appropriate investigations were undertaken depending on the clinical findings in each patient (e.g. full blood count, coeliac screen, thyroid function tests, renal liver bone profile, growth hormone stimulation testing). Follow up assessment was arranged for any child who required further growth monitoring or referral to a dietician. In the

cases of blood analysis being performed and revealing no abnormality, the parents and General Practitioner were informed. Following each child assessment, the parents were informed of the child's progress and a letter was sent to the General Practitioner informing him/her of the child's attendance and auxological measurements with a comment on any follow-up plans (Appendix IV).

2.2.6 Classification of Ethnic Origin

In order to determine ethnic groupings, the classification developed by the Perinatal Institute in the UK was used. This classification uses Geographical Ethnic Origin (GEO) and was used because the up-to-date census groupings were not available at the time of analysis and do not meet requirements for medical data. In the perinatal field, this includes detailing maternal ethnic origin when assessing fetal growth, as is now also recommended by the Royal College of Obstetricians and Gynaecologists in the UK. It is used in the West Midlands UK customised growth chart software (Gestation Network, 2007) and the agree dataset of MANNERS, the Maternal and Neonatal Electronic Recording System (NHS UK, 2003). This classification is not by race or ethnic group but by ethnic *origin* (Appendix V).

2.2.7 Classification of Socio-economic Group

Socio-economic group was defined according to the "Socio-economic groups - list of constituent occupations" provided by the Central Statistics Office and used for the national census. This is a classification of each occupation to one of ten specific socio-economic groups (introduced in 1996). In addition, a residual group entitled "All others gainfully employed and unknown" is included where sufficient details are

not provided. The classification aims to group together persons with similar social and economic statuses on the basis of level of skill or educational attainment required (Appendix VI).

CHAPTER TWO

METHODS

2.3 POPULATION (2.) PATIENTS BORN SGA TREATED WITH GROWTH HORMONE

2.3.1 Patient recruitment

As GH is a relatively new treatment for children born SGA, focus was first turned on raising awareness of the condition and importance of follow up and referral of children born SGA with failure of catch-up growth. A letter was written to all Consultant Paediatricians in Ireland (list obtained from Royal College of Physicians of Ireland) informing them of the study and requesting that they refer any children with growth concerns (Appendix VII). Attached to the letter were two scientific papers pertaining to the indications for treatment with GH in children born SGA (Johnston and Savage, 2004, Lee et al., 2003). Any letters received with queries from Paediatricians were promptly dealt with by return of post and, where necessary, further information provided.

A presentation was made at the Faculty of Paediatrics Scientific meeting on 4th March 2005 to inform Consultant Paediatricians of the study and queries were addressed. A Study Day on Small for Gestational Age was organised in October 2005 with a number of expert speakers in the field of Neonatology and Paediatric Endocrinology. All Consultant Paediatricians and Paediatric Trainees in Ireland were invited to the Study Day.

A letter was also sent to the President of the Irish College of General Practitioners (ICGP) informing him of the study should there be any queries from members of the ICGP.

A search was done on the Paediatric Endocrinology department database looking for children listed under a diagnosis of IUGR, SGA and Silver Russell Syndrome. All consultant paediatricians and non-consultant hospital doctors at the National Children's Hospital were informed of the study.

Patients referred to the clinic with a history of being born small for gestational age were seen by the investigator (SO'C). Calculations of birth weight SDS, current height SDS and height velocity SDS were made. Children were deemed eligible for high dose (0.067mg/kg/day) growth hormone (GH) treatment as participants in the North European Small for Gestational Age Study (NESGAS) if the following criteria were fulfilled:

2.3.1.1 Inclusion criteria for GH treatment within NESGAS:

- Small for gestational age (BW $\leq$ - 2SD)
- Gestational age at birth more than 28 weeks
- Short at 4 years of age (height SDS $\leq$ -2.5)
- Short for parental height (height SDS > 1 SD below MPH SDS)
- Age 4-8 years (girls) and 4-9 years (boys)
- Prepubertal at start of treatment (Tanner stage 1)
- Height velocity SDS < 0 during last 6 months
- No previous GH therapy

2.3.1.2 Exclusion criteria for GH treatment within NESGAS:

- Known or suspected allergy to GH
- Previous participation in GH study
- Severe learning disability as judged by the investigator
- Previous or active malignancy
- Benign intracranial hypertension (past or present)
- Diabetes or hypertension
- Psychological problems likely to lead to significant non-compliance
- Growth retardation secondary to chronic diseases, syndromes (like fetal alcohol syndrome) and chromosomal anomalies (except for Silver Russell syndrome).

2.3.1.3 Consent

Parents and child were given written information and documentation on the study prior to reaching a decision to have their child enrolled in the study (Appendix VIII and IX). A consent form was then signed by the parents once any questions had been addressed and the parents had at least 24 hours to consider the information (Appendix X).

2.3.1.4 Patients ineligible for inclusion in NESGAS

Patients, who were ineligible for inclusion in the NESGAS study due to the strict age limits were considered for treatment using the standard dose of GH (0.035mg/kg/day) if they fulfilled the other criteria and were expected to benefit from treatment.

2.3.2 Investigations

Prior to commencing GH treatment, height velocity based on two height measurements at the Department of Paediatric Endocrinology at least six months apart, were required. If a child had been referred from the Department of Paediatric Endocrinology of another hospital (e.g. Our Lady's Hospital for Sick Children, Crumlin) the prior height measurements could be used (as the same auxological methods are employed). Otherwise the child would be seen again six months after the initial assessment to have auxology repeated and height velocity calculated.

Baseline

Each child underwent the following investigations prior to GH treatment (Table 2.1).

- Oral glucose tolerance testing (OGTT)
- Intravenous tolerance testing (IVGTT) – *NESGAS study patients only
- Growth hormone stimulation testing [ARG (1 patient), CLO (1 patient), GLU (1 patient), ITT (5 patients) or L-DOPA (7 patients)]
- Full blood count, renal, liver, bone profile, thyroid function
- Bone age x-ray
- Dual Energy X-ray Absorptiometry (DXA)

Every 3 months

Height, sitting height, weight, head circumference, clinical examination including blood pressure measurement and pubertal staging. Blood samples (IGF-I, IGFBP-3, HbA1c) (Table 2.1).

Table 2.1 Schedule of investigations for patients treated with GH			
	Baseline	**Year 1**	**Year 2**
DNA	X		
GH stimulation test	X		
Auxology	X	X (4)	X (4)
Clinical exam	X	X (4)	X (4)
IGF-I* & HbA1c	X	X (4)	X (4)
Bone age x-ray	X	X	X
OGTT	X		X
IVGTT	X	X	
DXA	X	X	

*** IGF-I assessed every 3 months. Numbers in parentheses refer to number of annual assessments if different from 1**

One year following commencement of GH treatment

As for 3 monthly assessment plus IVGTT, DXA scanning, bone age x-ray (Table 2.1).

Two years following commencement of GH treatment

As for 3 monthly assessment plus OGTT, bone age x-ray (Table 2.1).

2.3.3 Growth Hormone Dosage

If a child did not qualify for the study on the basis of age (2 patients over age 10), the standard dose of 0.035mg/kg/day GH was used. All other patients commenced GH at a dose of 0.067mg/kg/day for the first year of treatment. Dosing was adjusted every 3 months according to weight. The background for this dosing regimen is based on the present indication and the existing literature and to easily detect non-responders.

2.4 AUXOLOGICAL METHODS

All growth measurements followed the methodology recommended by Cameron (Cameron, 1978) and were performed by the investigator (SO'C) with the assistance of research nurse Ms Elaine O'Mullane.

- Height was measured using the Harpenden stadiometer at the Paediatric Endocrinology clinic and recorded to the last completed millimetre. The stadiometer was checked and re-calibrated regularly. Each child was measured standing straight in bare feet, held in the Frankfurt plane with gentle upward pressure applied under the mastoid process by the measurer.
- Weight was measured using a Seca electronic self-calibrating scales which was checked regularly. Children were weighed to the last completed 0.1kg in bare feet and wearing only light clothing.
- Birth weight SDS, birth length SDS, height SDS, weight SDS, BMI SDS and head circumference SDS were calculated using the LMS method of Cole (Cole, 1990).
- Mid-parental height (MPH) was calculated by the formula:

$$\text{MPH} = \frac{\text{Father's Height SDS} + \text{Mother's Height SDS}}{2}$$

- Height corrected for MPH was determined as (Height SDS) – (MPH Height SDS)
- Body Mass Index (BMI) was calculated using the formula:

$$\frac{\text{Weight (kg)}}{\text{Height}^2\text{ (m)}}$$

- Pubertal development was recorded by the investigator (SO'C) using the methodology described by Tanner (1976) (Tanner and Whitehouse, 1976).

2.5 LABORATORY METHODS

2.5.1 GH Stimulation Testing

Children who required GH stimulation testing, who had not been tested previously, had an Insulin Tolerance Test (ITT) or L-Dopa/Propranolol stimulation test at the National Children's Hospital to assess peak growth hormone secretion. Some children referred from other institutions (eg Our Lady's Hospital for Sick Children, Crumlin) had already had GH stimulation testing performed by different stimulation tests; Glucagon (N = 1), L-Dopa/Propranolol (N = 1), Arginine (N = 1), Clonidine (N = 1), and analysis was done locally. If these tests were normal they were not repeated. In any case where the peak growth hormone was low (<15mU/L) an ITT was performed or repeated to confirm the finding.

Samples from each individual were analysed in a single run. Each single run was done on separate occasions so that possible variability between assays must be considered. Results generated were expressed relative to WHO MIBSC 2nd International Standard 98/574 for r-DNA Growth Hormone. The analyzer used for GH assays was the Immulite 2500 Analyzer for quantitative measurement of human growth hormone in serum. Immulite 2500 Growth Hormone is a solid phase, two site chemiluminescent

immunometric assay. The reference range values were generated on the Immulite 2000 analyser. Based on its relationship to Immulite 2500 Growth Hormone, the assay can be expected to have essentially the same reference ranges. The Immulite 2500 assay employs the same reagent and bead formulation as Immulite 2000. All performance characteristics are equivalent between the 2 platforms. (Immulite 2500 Growth Hormone was compared to DPC's Immulite 2000 Growth Hormone on 75 samples: concentration range approx 0.01 to 38ng/ml): Means (Immulite 2500 12.9ng/ml, Immulite 2000 12.2ng/ml).

Insulin Tolerance Test

The ITT was performed in the Department of Paediatric Endocrinology by the endocrine nurse specialist and the investigator (SOC).

- Patients were asked to fast from midnight the previous night. An iv cannula was inserted and baseline blood samples taken for growth hormone, cortisol and glucose assays.
- An insulin solution of 20 units of Actrapid added to 19.8mls of 0.9% NaCl was given intravenously at a dose of 0.1units/kg (0.1mls/kg). If baseline blood glucose was less than 3.5mmols, the insulin solution was given at a dose of 0.05mls/kg.
- Patients were closely observed for signs of hypoglycaemia (drowsiness, faintness, sweating, tachycardia and decreasing levels of consciousness). Blood samples were reserved for growth hormone, cortisol and glucose at t = 15 minutes, t = 30 minutes, t = 45 minutes, t = 60 minutes, t = 90 minutes and t = 120 minutes for assay in the laboratory.

- Blood glucose was expected to fall to 50% of baseline or <2.2mmols. If sufficient hypoglycaemia did not result, a further 0.05mls/kg of insulin solution was infused.
- The cannula was flushed with 1ml of 0.9% NaCl after each sampling and 0.5mls of blood withdrawn and discarded prior to drawing samples. Patients were asked to remain supine during the test, and were not permitted to sleep.
- Hypoglycaemia was treated with oral dextrose or if severe with iv dextrose. With adequate hypoglycaemia, peak GH levels <15mU/L indicated growth hormone insufficiency.

L-Dopa/Propranolol test

The L-Dopa/Propranolol test was performed in the Department of Paediatric Endocrinology by the endocrine nurse specialist and the investigator (SOC). In one patient the test was performed at the Department of Paediatric Endocrinology, Our Lady's Hospital for Sick Children, Crumlin.

- Patients were asked to fast from midnight the previous night. An iv cannula was inserted and baseline blood samples taken for growth hormone, cortisol and glucose assays.
- L-Dopa 0.5g/1.73m^2 and Propranolol 0.75mg/kg (to a maximum of 40mg) were given orally.
- Blood samples were reserved for growth hormone, cortisol and glucose at t = 15 minutes, t = 30 minutes, t = 45 minutes, t = 60 minutes, t = 90 minutes and t = 120 minutes for assay in the laboratory.
- Patients were observed for possible side effects such as nausea, vomiting and hypotension.

Arginine and Glucagon Growth Hormone stimulation tests were performed in the Department of Paediatric Endocrinology Our Lady's Hospital for Sick Children by the endocrine nurse specialist. Another patient had a Clonidine Growth Hormone stimulation test performed at the Department of Paediatrics, Sligo General Hospital.

2.5.2 Insulin-like Growth Factor-1 (IGF-1)

For patients not included in the NESGAS study, IGF-1 samples were analysed at the Guildford Peptide Hormone Laboratory, Royal Surrey County Hospital, Guildford, UK. IGF-1 was measured using the Nicholls Advantage automated immunoassay analyser. Specific age-related references were provided with each result (nmol/L) (Appendix XI).

All patients included in the NESGAS study had IGF-1 samples analysed by radioimmunoassay as described by Juul et al, at the Department of Growth and Reproduction, Rigshospitalet, Copenhagen, Denmark (Juul et al., 1994). Results were age-related, given in ng/ml and the IGF-1 SDS plotted on a graph and SD scores calculated using the references of Juul et al. (Juul et al., 1994).

For the purposes of analysis, IGF-1 levels were converted from nmol/L to ng/ml using the appropriate conversion factor (mmol/L ÷ 0.13 = ng/ml) as per the conversion factor quoted by DPC Immulite 1 based on the molar size of IGF-1 and confirmed by both analysing laboratories.

2.5.3 Glucose Homeostasis

2.5.3.1 Glucose and Glycosylated Haemoglobin A1c (HbA1c)

Plasma glucose samples were processed in the Biochemistry Laboratory at the National Children's Hospital, Tallaght using the glucose hexokinase method on the Roche Modulars IPPE analyser. Results were given in mmol/L.

HbA1c samples were processed in the Haematology Laboratory at the National Children's Hospital, Tallaght using the TOSOH HbA1c 2.2 analyzer which uses HP Liquid Chromatography. Results were given as a percentage (normal reference range 4.6-5.8%).

2.5.3.2 Oral Glucose Tolerance Test (OGTT)

- Patients were told to fast from midnight the previous night after prior normal carbohydrate intake.
- An iv cannula was inserted and baseline fasting blood glucose and insulin was taken.
- Oral glucose at a dose of 1.75g/kg body weight was given over approximately 3-5 minutes (maximum 75g).
- Blood glucose and insulin sampling was repeated at t = +60 minutes and t = +120 minutes and sent for assay to the laboratory.
- Following the procedure, the cannula was removed and the patient was given something to eat and drink.

- Results were analysed using values from Consensus Guidelines 2000, ISPAD Consensus Guidelines for the Management of Type 1 Diabetes Mellitus in Children and Adolescents (ISPAD, 2000) and the WHO 1985 definition of impaired glucose tolerance (Table 2.2).

Table 2.2 Values for diagnosis of diabetes & impaired glucose tolerance

	Impaired fasting glycaemia (IFG)	**Impaired glucose tolerance (IGT)**	**Diabetes**
Fasting Plasma Glucose (mmol/L)	≥ 6.1 to < 7.0	N/A	≥ 7.0
2-Hour Plasma Glucose (mmol/L)	N/A	7.8 – 11.1	≥ 11.1

***In asymptomatic patients the diagnosis must only be made on the basis of at least two separate abnormal measurements of significant hyperglycaemia; N/A = not applicable**

2.5.3.3 Intravenous Glucose Tolerance Test (IVGTT)

The short IVGTT as described by Davis (Davis et al., 1992) was used in all patients who were included in the NESGAS study at both baseline and one year following GH treatment (Table 2.3). The 3-minute-insulin concentration and the incremental area under the insulin secretion curve (AUC) (0-10 minutes) IVGTT have been shown to be valid estimates of insulin secretion. From the 10 minute IVGTT, the following parameters were estimated:

(1.) Insulin sensitivity from fasting glucose and insulin, Homeostasis Model Assessment (HOMA) – see section 2.5.3.5

(2.) Insulin secretion from the acute insulin response (AUC above baseline)

(3.) Disposition index, calculated as insulin sensitivity X insulin secretion (degree of beta-cell decompensation for insulin sensitivity) – product of (1) and (2).

Table 2.3 Procedure for Intravenous glucose tolerance test (IVGTT)

	Timing (minutes)	Glucose	Insulin	C-peptide Pro- and Prepro-insulin	IGFs IGFBPs
Glucose 0.5g/kg → over 3 mins max	-10	X	X		
	-5	X	X		
	0	X	X	X	X
	1	X	X		
	3	X	X		
	5	X	X		
	10	X	X		

- Patients were told to fast from midnight the previous night after prior normal carbohydrate intake.
- Two iv cannulae were inserted and baseline (t = -10 minute) fasting blood glucose and samples for insulin assay were taken.
- Blood glucose and insulin samples were obtained at t = -5 and t = 0 minutes. At 0 minutes, samples were also taken for IGF-1, C-peptide, pro-insulin and pre-proinsulin assay.
- An infusion of dextrose 20% at a dose of 0.5g/kg was given over a maximum 3 minute duration following sampling at 0 minutes.
- Samples for blood glucose and insulin assay were taken at t = +1, t = +3, t = +5, t = +10 minutes after completion of the dextrose infusion.

- At all sample times glucometer readings were also taken and the patient was monitored for possible side-effects such as nausea, weakness, decreased level of consciousness.
- Following the procedure, the cannulae were removed and the patient was given something to eat and drink.

2.5.3.4 Insulin, C-Peptide, Proinsulin, Pre-Proinsulin

Insulin, C-peptide, proinsulin and pre-proinsulin samples from both the OGTT and IVGTT were sent to University of Cambridge, Department of Paediatrics, Addenbrooke's Hospital, Cambridge, UK for analysis. Patient weights and glucose results were sent with the samples. Results were interpreted using the method described by Davis et al (Davis et al., 1992) and using the Homeostasis Model Assessment (HOMA2) as outlined below.

2.5.3.5 Homeostasis Model Assessment (HOMA)

Homa was calculated using the HOMA2 calculator (HOMA2 calculator, 2007) from fasting glucose and insulin values obtained during the IVGTT (Matthews et al., 1985). This provides an index of tissue sensitivity to insulin (IS) and relies on the product of fasting plasma glucose and insulin concentrations.

2.5.4 Thyroid Function

Free T4 and TSH immunoassay were performed in the Endocrinology Laboratory at the National Children's Hospital, Tallaght using Immulite 2500.

2.5.5 Full blood count and renal, liver, bone profile

Full blood count samples, including 5 part differential, were processed in the Haematology Laboratory at the National Children's Hospital, Tallaght using the Sysmex XE 2100 automated high throughput analyser. Renal, liver and bone profiles were processed in the Biochemistry Laboratory using the Roche Modular IPPE system.

2.5.6 Tissue Transglutamase test (tTG)

Samples for tTG were processed in the Immunology Laboratory at St James Hospital, Dublin, using the Dynex 2000 analyser.

2.6 RADIOLOGICAL METHODS

2.6.1 Bone Age X-ray

This was done by performing a plain film x-ray of the left fingers, hand and wrist and were interpreted using the methodology of Greulich and Pyle (Greulich, 1959).

2.6.2 Magnetic Resonance Imaging (MRI)

MRI was performed in the National Children's Hospital, Department of Radiology on two patients who had low growth hormone levels in order to assess the anatomical structure of the pituitary stalk.

2.6.3 Dual Energy X-ray Absorptiometry (DXA)

DXA scans were performed on each patient at the Department of Radiology National Children's Hospital Tallaght using the Prodigy DXA System (software version: 8.80) manufactured by GE Medical Systems LUNAR with a Narrow Fan beam. Baseline scans in three patients were performed at Blackrock Clinic using the LUNAR DFXIQ machine.

Prior to scanning, the child was measured and weighed and any metal objects were removed (to avoid artefacts). The child was informed of what was happening at all times. The aim was to minimise the child from moving to optimise reproducibility and avoid the need for repeat scanning. Following the scan the child was shown the images on the computer to assist in understanding the procedure. The scan took approximately 10 minutes.

The fundamental principle of DXA is to measure the transmission of x-rays through the body at high and low energies. The use of two energies is to allow discrimination between soft tissue and bone. X-ray attenuation values are converted to a pixel-by-pixel measurement of 'areal' bone mineral density (aBMD in g/cm^2). Software algorithms detect the bone edges, and bone area (BA in cm^2) is calculated by summing the pixels within the bone edges. The reported value of the aBMD is the mean bone density over all the pixels within the bone area, and the bone mineral content (BMC in g) is calculated by multiplying the mean aBMD by BA. In prepubertal children the lumbar spine is the most useful site to scan in clinical practice. Whole body DXA remains a research tool at present. The patient is subjected to a low effective radiation dose which gives DXA a major advantage. Radiation

doses at all sites is appreciably less than that to which one is exposed from the natural environment (background radiation) (National Osteoporosis Society, 2004).

2.7 DATA MANAGEMENT

2.7.1 Data entry and calculations

The data was analysed using a personal computer, DELL Latitude D610. The CWH database was received on an Excel file and the Excel Lookup tool and Microsoft Access programs were used to tidy up and code the data. Decimal ages were calculated throughout the study using an Excel spreadsheet and a formula for deciage calculation = [(date of measurement) – (date of birth)/ 365.25]. All SDS calculations were made using the LMS method of Cole (Cole, 1990) by inputting the formulas into the Excel spreadsheet. Random patients were intermittently rechecked to ensure accuracy of data entry. The data was then transferred into the SPSS (Statistical Package for Social Science version 14.0) for statistical analysis.

2.7.2 Data Protection

Data confidentiality was maintained by filing of all paper case records in a locked filing cabinet to which only the investigator (SO'C) and research assistant (EO'M) had access. Data entered in the computer was password protected (Data Protection Act 1988).

2.8 Statistical Analysis

(1) Coombe Women's Hospital Cohort

The patient population of interest (SGA group) was identified from the CWH database and numerous maternal, perinatal and infant characteristics were compared with the non-SGA group using the chi-squared test. Where the assumptions of the chi-squared test were not met (due to small expected values), a Monte Carlo approximation to an Exact test was used. Comparisons were also made between the SGA group which was seen versus the group which was not seen, using the chi-squared test.

Birth measurements were recorded and parameters such as height, weight, head circumference and BMI were measured for each child at 4-6 years. Data was summarised using summary statistics such as means, standard deviation scores (SDS), maximum and minimum values. The reference standard used was the LMS methodology of Cole (1990) (Freeman et al., 1995) UK references, determined for age and gender. Using current SDS measurements of height, weight, BMI and head circumference, univariate analysis was employed using the chi-squared test and independent t test, to determine if any subgroups differed in growth outcome (eg children born preterm, children of mothers who smoked or who had pre-eclampsia in pregnancy). The outcome of interest was whether or not these children born SGA had caught up in terms of growth (height > -2 SDS). In the case of twin pairs, comparisons were made in terms of initial birth weight versus current height and weight differences.

(2) Patients born SGA treated with Growth Hormone

The outcome of interest was the effect of GH in children born SGA without catch-up growth on height gain and height velocity (Δ Height SDS, Δ Height velocity), insulin resistance, IGF-1 levels and changes in bone age, body composition and bone mineral density (BMD) (Table 2.4). Safety endpoints were insulin resistance (IVGTT), (OGTT), HbA1c levels, changes in physical exam (such as development of precocious puberty) and occurrence of adverse events (Table 2.5). Means and standard deviation scores (SDS), standard error of the mean, scatter plots, maximum and minimum values were determined for measurements at birth and height SDS, weight SDS, head circumference SDS, body mass index (BMI) and BMI SDS in each child prior to treatment. Growth increments (Δ Height SDS) were assessed by 3-monthly measurements. The reference standards used were the LMS methodology of Cole (Cole 1990) (Cole et al., 1995) UK references, determined for age and gender. In order to assess metabolic and safety aspects of GH, baseline insulin sensitivity (HOMA), insulin secretion values and disposition indices were compared with those following one year of GH treatment (see section 2.5.3). Non-treated patients who fulfilled criteria for GH were used as a comparison group for growth outcome in terms of Δ Height SDS and Δ Height velocity.

Table 2.4 Efficacy Endpoints
Primary:
Δ Height SDS from point of commencing treatment with GH or not
Δ Height velocity from point of commencing treatment with GH or not
Secondary:
Insulin resistance (IVGTT & OGTT)
Δ IGF-1 levels
Changes in bone age, body composition and bone mineral density (DXA)

Δ = change

Table 2.5 Safety Endpoints
Insulin resistance (IVGTT), (OGTT), HbA1c levels
Changes in physical exam
Adverse events

2.9 Ethical Approval

Ethical Approval was sought and obtained for the study from both: (i) The Coombe Women's Hospital Ethics Committee and (ii) St James Hospital and Federated Dublin Voluntary Hospitals, Joint Research Ethics Committee, AMNCH.

2.10 Irish Medicines Board

The Irish Medicines Board was informed about the study and permission was granted.

CHAPTER THREE

RESULTS

CHAPTER 3 RESULTS

The patient populations for this study were identified and recruited from the Coombe Women's Hospital (CWH) (N = 284) and from referrals from Paediatricians nationally (N = 20).

3.1 POPULATION (1) – COOMBE WOMEN'S HOSPITAL COHORT (1/7/99-30/6/01)

3.1.1 Patient Recruitment

The Coombe Women's Hospital (CWH) database with a total of 14,840 births recorded for the period 1st July 1999 – 30th June 2001 was analysed. Following exclusions, data from a total of 14,366 infants were analysed. These infants were divided into two groups; non-SGA infants (N=14,082) and SGA infants (N=284) and the groups were compared for the variables as described in sections 3.1.3-3.1.12. The infants born SGA were identified by extracting data in two steps:

3.1.1.1 Step 1- Excluded Infants

From the CWH database of 14,840 births, 449 (3%) infants were excluded due to intrauterine death/stillbirth, neonatal death, gestation < 28 weeks, congenital anomalies or insufficient data as outlined in Table 3.1.

Table 3.1 Infants excluded from CWH database - Step 1

Indication for exclusion	**N = 449 (3%)**
Intrauterine Death/Stillbirth	101 (23%)
Neonatal Death ≥ 28 weeks gestation*	10 (2%)
Gestation < 28 weeks	57 (13%)
Congenital Anomalies/Syndromes	144 (32%)
Insufficient Data**	137 (31%)

***Includes 6 early & 1 late neonatal death **Includes missing Apgar scores n=47, missing birth weight or gestation n=90**

3.1.1.2 Step 2 - SGA Group recruited from Coombe Women's Hospital

From the remaining infants (N=14,391), those with BW SDS ≤ -2 SDS were identified based on birth weight for gestational age (LMS methodology of Cole, 1990). This group was called "SGA Group", which included a total of 309 (2.2%) such infants.

From this group a further 25 infants were excluded because of death, congenital anomalies and complicated medical histories, using the data sources of Eurocat

Register, Child Health Systems Register, medical charts and National SIDS Register (Table 3.2).

Table 3.2 Infants excluded from SGA Group - Step 2	
Source of Data	**N = 25 (8%)**
Eurocat Register	11 (4%)
Child Health Systems Register	5 (2%)
Chart review	9 (4%)
National SIDS Register	0 (0%)
Total Exclusions	25
Remaining SGA Group	**284**

Number in parenthesis refers to % of the 309 identified SGA infants excluded

Eurocat

By cross-referencing the SGA Group with the Irish office of Eurocat, 11/25 infants were identified. These infants had not been so identified in the CWH database:

- Deaths secondary to major congenital anomalies (N = 7)
- Major congenital anomalies – death not recorded (N = 4)

Child Health Systems Register

On cross referencing the SGA Group with the Child Health Systems (CHS) register of deceased children, 5 children were identified: there were 2 neonatal deaths; 1 early (cause not recorded), and 1 late (by pulmonary haemorrhage), 2 infants had died at less than 6 months of age (cause not recorded), and 1 infant had age and cause of death unrecorded (Table 3.3).

Table 3.3 Exclusions following CHS Cross Referencing				
Gestation	**Gender**	**BW SDS**	**Cause of Death**	**Age of Death (months)**
28^{+2}	Girl	-2.6	-	Day 1
31^{+1}	Boy	-3.9	PH	2
39^{+2}	Boy	-2.6	-	3
41^{+3}	Girl	-2.1	-	4
36^{+0}	Girl	-2.3	-	-

- Unknown
PH = Pulmonary Haemorrhage

Chart review

Following review of charts and consultation with Consultant Neonatologist (Dr Margaret Sheridan-Pereira) 9 infants with complicated neonatal courses who had been admitted to the Neonatal Intensive Care (NICU) were excluded from the SGA Group as follows: 1 case of Sudden Infant Death Syndrome (SIDS), 2 infants had complicated history secondary to maternal HIV/Hepatitis C, there were 2 cases of maternal intravenous drug abuse, and 4 infants with severe complications of prematurity.

National Sudden Infant Death Register

It was not possible to reliably cross reference the National Sudden Infant Death Register with the SGA Group, as no identifying information is held on the cases of sudden infant death syndrome (SIDS) on the register. Hence no cases of SIDS were identified in this manner.

3.1.2 Congenital Anomalies & Syndromes

In this study 24 SGA infants in total were excluded because of congenital anomalies and syndromes. These were identified from both the CWH database as described in Step 1 (section 3.1.1.1) and the Eurocat Register as described in Step 2 (section 3.1.1.2) (Table 3.4).

Table 3.4 Infants born SGA with congenital anomalies & syndromes

Infant No.	Source	Gestation (wks + days)	BW SDS	Congenital Anomaly/Syndrome
1	CWH	40 + 1	-2.4	AVSD
2	CWH	37 + 1	-2.3	Coarctation of Aorta
3	CWH	32 + 4	-3.6	PDA,ASD,PS
4	CWH	35 + 3	-2.3	PDA & VSD*
5	CWH	40 + 3	-2.8	Tetralogy of Fallot
6	CWH	36 + 5	-2.7	Congenital Nephrotic Syndrome
7	CWH	36 + 1	-3.3	Multicystic Dysplastic Kidney
8	CWH	39 + 4	-2.7	Imperforate anus & Dysmorphic features
9	CWH	40 + 1	-2.4	Microcephaly
10	CWH	39 + 2	-3.9	Dandy-Walker Malformation
11	CWH	36 + 5	-3.5	Cornelia de Lange
12	CWH	37 + 0	-2.1	Trisomy 21
13	CWH	35 + 5	-2.3	Duodenal Atresia
14	Eurocat	36 + 5	-3.9	Microcephaly & agenesis of corpus callosum
15	Eurocat	41 + 1	-2.8	Cystic Adenomatoid Malformation of Lung
16	Eurocat	39 + 3	-2.0	Gastroschisis
17	Eurocat	39 + 4	-2.8	Hypospadias & dysmorphic features
18	Eurocat	40 + 0	-2.2	ASD/VSD/PDA*
19	Eurocat	40 + 5	-2.1	CHD - unknown*
20	Eurocat	41 + 0	-2.5	Trisomy 13*
21	Eurocat	40 + 5	-2.0	Trisomy 13*
22	Eurocat	37 + 0	-4.7	Trisomy 18*
23	Eurocat	39 + 5	-2.9	Potter's Sequence*
24	Eurocat	38 + 1	-2.3	Diaphragmatic Hernia – deletion chrom.11*

AVSD = Atrioventricular Septal Defect; PDA = Patent Ductus Arteriosus; PS = Pulmonary Stenosis; ASD = Atrial Septal Defect; VSD = Ventricular Septal Defect
*** = Death as a result of congenital anomaly/syndrome**

3.1.2.1 CWH Database:

Data extraction identified 144 infants with congenital anomalies and syndromes of which 13 were born SGA (Table 3.5 – Infants 1-13). Congenital Heart Defects (CHDs) were documented in 5, renal anomalies in 2, congenital central nervous system disorders in 2, 1 had imperforate anus with dysmorphic features and 1 had non-syndromic duodenal atresia. Recognisable syndromes (Cornelia de Lange syndrome and Down syndrome) were documented in 2 infants.

3.1.2.2 Eurocat Register:

Cross referencing the SGA Group (n = 309) with Eurocat identified 11 patients with congenital anomalies and syndromes. Death secondary to the congenital anomaly was recorded in 7 (Table 3.4 – Infants 18-24).

3.1.3 Maternal Socio-Economic Characteristics

3.1.3.1 Marital status (SGA versus non-SGA)

There was a significant difference in the marital status between the SGA and non-SGA groups ($\chi^2 = 48.4$, df = 3, $p < 0.001$). A higher percentage of single mothers was seen in the SGA group compared with the non-SGA group (51% versus 32%) (Table 3.5).

Table 3.5 Marital status of Mothers

Marital Status	SGA Group N (%)	Non-SGA Group N (%)	Total N (%)
Married	129 (45)	9132 (65)	9261 (65)
Single	146 (51)	4517 (32)	4663 (33)
Separated/Divorced/Widowed	6 (2)	278 (2)	284 (2)
Unknown	3 (1)	155 (1)	158 (1)
Total	284	14082	14366

3.1.3.2 Mother's Occupation & Socio-Economic Group (SGA versus non-SGA)

There was a significant difference between the two groups in terms of occupation/socio-economic group ($\chi^2 = 35.0$, df = 10, $p < 0.001$). A higher percentage of mothers of SGA infants belonged to the lowest socio-economic group compared with the mothers of the non-SGA infants (53% versus 41%) and a lower percentage belonged to the higher socio-economic groups (Table 3.6).

Table 3.6 Mother's Occupation

Occupation	SEG	SGA Group N (%)	Non-SGA Group N (%)	Total N (%)
Employers & Managers	1	8 (3)	615 (4)	623 (4)
Higher Professional	2	2 (0.7)	483 (3)	485 (3)
Lower Professional	3	24 (9)	1658 (12)	1682 (12)
Non-Manual	4	75 (26)	4547 (32)	4622 (32)
Manual Skilled	5	14 (5)	367 (3)	381 (3)
Semi Skilled	6	4 (1)	388 (3)	392 (3)
Unskilled	7	6 (2)	123 (0.9)	129 (0.9)
Own Account Workers	8	2 (0.7)	79 (0.6)	81 (0.6)
Farmers	9	0	8 (0.1)	8 (0.1)
Agricultural Workers	10	0	24 (0.2)	24 (0.2)
Others gainfully occupied & unknown	11	149 (53)	5790 (41)	5939 (41)
Total		284	14082	14366

SEG = Socio-economic Group

3.1.3.3 Partner's Occupation & Socio-Economic Group (SGA versus non-SGA)

There was a significant difference between the SGA and non-SGA groups in terms of partners' occupations ($\chi^2 = 60.8$ df = 10 $p < 0.001$). The results showed that partners were more likely to belong to lower socio-economic groups and less likely to belong to higher socio-economic group in SGA infants than non-SGA infants (Table 3.7).

Table 3.7 Partner's Occupation by Groups

Occupation	SEG	SGA N (%)	Non-SGA N (%)	Total N (%)
Employers & Managers	1	14 (5)	1243 (9)	1257 (9)
Higher Professional	2	7 (3)	1176 (8)	1183 (8)
Lower Professional	3	12 (4)	848 (6)	860 (6)
Non-Manual	4	16 (6)	1425 (10)	1441 (10)
Manual Skilled	5	33 (12)	2093 (15)	2126 (15)
Semi Skilled	6	12 (4)	573 (4)	585 (4)
Unskilled	7	0	18 (0.1)	18 (0.1)
Own Account Workers	8	4 (1)	338 (2)	342 (2)
Farmers	9	1 (0.4)	260 (2)	261 (2)
Agricultural Workers	10	2 (0.7)	55 (0.4)	57 (0.4)
Others gainfully occupied & unknown	11	183 (64)	6053 (43)	6236 (43)
Total		284	14082	14366

SEG = Socio-economic Group

3.1.3.4 Geographical Distribution (SGA versus non-SGA)

There was a significant difference in the geographical distribution of the mothers of SGA infants compared with mothers of non-SGA infants ($\chi^2 = 8.5$ df = 1 p = 0.004). It was observed that a higher proportion of mothers of infants born SGA were living in the Dublin area (city and county) compared with those in non-SGA group (76% versus 68%) (Table 3.8).

Table 3.8 Geographical Distribution of Patients by Groups

Place of residence	SGA N (%)	Non-SGA N (%)	Total N (%)
Dublin City/County	215 (76)	9512 (68)	9727 (68)
Outside Dublin	69 (24)	4570 (33)	4639 (32)
Total	284	14082	14366

3.1.4 Ethnic Origin

Information was available on mothers' place of birth and ethnicity. Information was only available for partners' ethnicity. Data on ethnicity did not distinguish between Irish and European origin.

3.1.4.1 Place of Birth of Mother (SGA versus non-SGA)

There was no significant difference in the place of birth of the mothers between the two groups ($\chi^2 = 1.0$ df = 3 p = 0.81) (Table 3.9).

Table 3.9 Mother's Place of Birth by Groups

Country of Birth	SGA N (%)	Non-SGA N (%)	Total N (%)
Ireland	171 (60)	8703 (62)	8874 (62)
Europe	18 (6)	944 (7)	962 (7)
Africa/Asia/Middle East/Caribbean	18 (6)	728 (5)	746 (5)
Other/Unknown	77 (27)	3797 (26)	3784 (26)
Total	284	14082	14366

3.1.4.2 Mother's Ethnic Group (SGA versus non-SGA)

There was no significant difference in the ethnic grouping of the mothers observed between the two groups ($\chi^2 = 1.5$ df = 2 p = 0.48) (Table 3.10).

Table 3.10 Mothers' Ethnic Group

Ethnicity	SGA N (%)	Non-SGA N (%)	Total N (%)
European	261 (92)	13188 (94)	13449 (94)
African/Asian/MiddleEastern/Caribbean/ African-American	21 (7)	825 (6)	846 (6)
Other/Mixed Race/Unknown	2 (0.7)	69 (0.5)	71 (0.5)
Total	284	14082	14366

3.1.4.3 Partners' Ethnic Group (SGA versus non-SGA)

There was a significant difference in the ethnic grouping of the partners between the two groups (χ^2=15.5 df = 2 p value < 0.001). A higher percentage (9 %) of the SGA group belonged to the non-European group compared with the non-SGA group (6%) (Table 3.11).

Table 3.11 Partners' Ethnic Group

Ethnicity	SGA N (%)	Non-SGA N (%)	Total N (%)
European	247 (87)	12987 (92)	13234 (92)
African/Asian/Middle-Eastern/ Caribbean/African-American	26 (9)	893 (6)	919 (6)
Other/Mixed Race/Unknown	11 (4)	202 (1)	213 (2)
Total	284	14082	14366

3.1.5 Lifestyle factors

3.1.5.1 Smoking (SGA versus non-SGA)

There was a significant difference in the percentage of mothers of SGA infants who smoked during pregnancy compared with mothers in the non-SGA group ($\chi^2 = 173.6$, $df = 7$, $p < 0.001$) (Table 3.12).

Table 3.12 Mother's Smoking History by Groups

Cigarettes per day	SGA N (%)	Non-SGA N (%)	Total N (%)
Never	79 (28)	7969 (57)	8048 (56)
Stopped since booking	10 (4)	719 (5)	729 (5)
Occasional	4 (1)	237 (2)	241 (2)
1-5	31 (11)	841 (6)	872 (6)
6-10	57 (20)	1339 (10)	1396 (10)
11-20	54 (19)	957 (7)	1011 (7)
> 20	10 (4)	100 (0.7%)	110 (0.8%)
Not stated/ Not known	39 (14)	1920 (14)	1959 (14)
Total	284	14082	14366

3.1.5.2 Alcohol Consumption (SGA versus non-SGA)

There was no significant difference between the mothers of SGA infants versus non-SGA infants in their reports of alcohol consumption during pregnancy ($\chi^2 = 5.8$ df = 7 p = 0.57) (Table 3.13).

Table 3.13 Mothers' Alcohol History by Groups

Units of Alcohol per week	SGA N (%)	Non-SGA N (%)	Total N (%)
Occasional	69 (24)	3243 (23)	3312 (23)
1-5	30 (11)	1646 (12)	1676 (12)
6-9	9 (3)	305 (2)	314 (2)
10-14	2 (0.7)	103 (0.7)	105 (0.7)
15-20	1 (0.4)	39 (0.3)	40 (0.3)
> 20	0	27 (0.2)	27 (0.2)
None	103 (36)	5775 (41)	5878 (41)
Not known	70 (25)	2944 (21)	3014 (21)
Total	284	14082	14366

3.1.6 Maternal Auxology

3.1.6.1 Maternal height (SGA versus non-SGA)

Self-reported maternal heights were available for 67.6% of mothers of SGA infants and in 72.8% of mothers in the non-SGA group. There was a significant difference in maternal height SDS between the two groups ($\chi^2 = 33.4$, df = 4, $p < 0.001$). There were more tall mothers found in the non-SGA group (2.2% versus 1.8%) and more short mothers found in the SGA group (3.2% versus 1.2%) (Table 3.14).

Table 3.14 Mothers' Heights by Groups

Mothers' Height SDS	SGA N (%)	Non-SGA N (%)	Total N (%)
Missing data	92 (32.4)	3834 (27.2)	3926 (27.3)
-4.99 to -2	9 (3.2)	168 (1.2)	177 (1.2)
-1.99 to 0	126 (44.4)	5192 (36.9)	5318 (37)
+0.01 to +1.99	52 (18.3)	4572 (32.5)	4624 (32.2)
+2 to +4.99	5 (1.8)	316 (2.2)	321 (2.2)
Total	284	14082	14366

3.1.6.2 Maternal Weight at Booking (SGA versus non-SGA)

The weight of the mother at booking was only recorded in 15.5% of mothers of SGA infants and in 21.9% of mothers in the non-SGA group.

3.1.6.3 Mothers' Body Mass Index (SGA versus non-SGA)

As Body Mass Index (BMI) is a function of weight and height (weight(kg)/height^2(m)), it was only possible to calculate BMI for those in whom both values were available (14.8% of SGA group and 21.3% of non-SGA group). In those in whom mother's BMI was available, there was no significant difference between the two groups (χ^2 (Exact) = 6.4, df = 3, p = 0.09) (Table 3.15).

Table 3.15 Mother's BMI by Groups

BMI	SGA N (%)	Non-SGA N (%)	Total N (%)
< 18.5 (underweight)	2 (5)	91(3)	93 (3)
18.5 – 24.9 (normal)	32 (76)	1768 (59)	1800 (59)
25.0 – 29.9 (overweight)	6 (14)	803 (27)	809 (27)
> 30 (obese)	2 (5)	331 (11)	333 (11)
Total	42	2993	3035

3.1.7 Medical Disorders in Pregnancy (SGA versus non-SGA)

3.1.7.1 Medical Problems in Pregnancy (SGA versus non-SGA)

There was no significant difference between the two groups in terms of medical problems experienced during pregnancy by the mothers of SGA infants compared with non-SGA infants ($\chi^2 = 5.3$ df = 4 p = 0.26) (Table 3.16).

Table 3.16 Medical Problems in Pregnancy by Groups

Medical Problem	SGA N (%)	Non-SGA N (%)	Total N (%)
None	247 (87)	12285 (87)	12532 (87)
Chronic condition(s)	7 (3)	281 (2)	288 (2)
Diabetes (IDDM & Gestational)	1 (0.4)	166 (1)	167 (1)
Infections*	7 (3)	542 (4)	549 (4)
Other†	22 (8)	808 (6)	830 (6)
Total	42	2993	3035

† Uterine abnormalities/fibroids/hyperemesis gravidarum, anaemia, cholecystitis, thrombophilia, congenital heart defect, psychiatric problems, surgery, cervical suture insertion, symphysis pubis problems

*** Urinary Tract Infections requiring antibiotics, HIV, Hepatitis, TB, Malaria**

IDDM = Insulin Dependent Diabetes Mellitus

3.1.7.2 Maternal Hypertension (SGA versus non-SGA)

There was a significant difference in the percentage of mothers experiencing hypertension overall between the two groups ($\chi^2 = 32.2$, df = 2, $p < 0.001$). A higher proportion of mothers of SGA infants experienced pre-eclampsia (13% versus 5%) (Table 3.17).

Table 3.17 Hypertension in Pregnancy by Groups

Type of Hypertension	SGA N (%)	Non-SGA N (%)	Total N (%)
Pre-eclampsia (treated or untreated)	36 (13)	748 (5)	784 (6)
None/Unknown	229 (81)	12648 (90)	12877 (90)
Hypertension (no proteinuria)	19 (7)	686 (5)	705 (5)
Total	284	14082	14366

3.1.8 Fetal Problems in utero (SGA versus non-SGA)

There was a significant difference in the rate of documented fetal problems in the SGA group versus non-SGA group ($\chi^2 = 1007.2$, df = 4, $p < 0.001$). The most common documented fetal problem was intrauterine growth retardation (IUGR)/Small for dates (SFD) documented in 40% of SGA infants versus only 3% of non-SGA infants (Table 3.18).

Table 3.18 Fetal Problems in utero by Groups

Fetal Problem	SGA N (%)	Non-SGA N (%)	Total N (%)
None	150 (53)	12899 (92)	13049 (91)
IUGR/SFD	116 (40)	474 (3)	590 (4)
Fetal distress/abnormal blood flow/oligohydramnios	12 (4)	308 (2)	320 (2)
Pre-term labour, pre-term rupture of membranes	5 (2)	166 (1)	171 (1)
Rhesus, Malpresentation, Amnionitis, PROM, Polyhydramnios, Macrosomia	1 (0.3)	235 (2)	236 (2)
Total	284	14082	14366

IUGR = Intrauterine Growth Retardation; SFD = Small for Dates
Rhesus = Rhesus incompatibility; PROM = Prolonged rupture of membranes

3.1.9 Labour and Delivery

3.1.9.1 Onset of Labour (SGA versus non-SGA)

There was a significant difference in the trend of labour onset in SGA infants versus non-SGA infants ($\chi^2 = 161.1$, df = 4, $p < 0.001$). There were higher rates of emergency (12% versus 2%) and elective caesarean section (CS) without labour (10% versus 6%) in the SGA group (Table 3.19).

Table 3.19 Labour Onset by Groups

Type of Labour onset	SGA N (%)	Non-SGA N (%)	Total N (%)
No Labour – Elective CS*	28 (10)	879 (6)	907 (6)
Induced/Accelerated	92 (32)	3585 (26)	3677 (26)
No Labour – Emergency CS*	33 (12)	261 (2)	294 (2)
Spontaneous	128 (45)	9289 (66)	9417 (66)
Failed Induction – CS*	3 (1)	68 (0.5)	71 (0.5)
Total	284	14082	14366

***CS = Caesarean Section**

3.1.9.2 Type of Delivery (SGA versus non-SGA)

There was a significant difference in the type of delivery experienced in the two groups ($\chi^2 = 84.8$, df = 4, $p < 0.001$). There was a higher rate of emergency CS in the SGA group (19% v 7%) (Table 3.20).

Table 3.20 Type of Delivery by Groups

Delivery Method	SGA N (%)	Non-SGA N (%)	Total N (%)
Elective CS*	28 (10)	896 (6)	924 (6)
Assisted instrumental delivery	31 (11)	1953 (14)	1984 (14)
Emergency CS*	55 (19)	1036 (7)	1091 (8)
Normal Vaginal Delivery	148 (52)	9697 (69)	9845 (69)
Failed Induction – CS*	22 (8)	500 (4)	522 (4)
Total	284	14082	14366

3.1.9.3 Type of Delivery in relation to Parity (SGA versus non-SGA)

When the data was analysed for primiparous mothers only, again there was a significant difference in the type of delivery between the two groups ($\chi^2 = 52.536$, df = 4, $p < 0.001$). There was a higher rate of emergency CS in the SGA group (23% v 8%) (Table 3.21).

Table 3.21 Type of Delivery Primiparous Mothers by Groups			
Delivery Method	**SGA N (%)**	**Non-SGA N (%)**	**Total N (%)**
Elective CS*	10 (7)	193 (4)	203 (4)
Assisted instrumental delivery	21 (15)	1386 (25)	1407 (25)
Emergency CS*	32 (23)	444 (8)	476 (8)
Normal Vaginal Delivery	64 (46)	3232 (58)	3296 (58)
Failed Induction – CS*	12 (9)	332 (6)	344 (6)
Total	139	5587	5726

A similar trend was seen in multiparous mothers with a significant difference in the type of delivery between the two groups ($\chi^2 = 44.2$, df = 4, $p < 0.001$). The rate of emergency CS was 15% in the SGA group compared with 6% in the non SGA group (Table 3.22).

Table 3.22 Type of Delivery Multiparous Mothers by Groups			
Delivery Method	**SGA N (%)**	**Non-SGA N (%)**	**Total N (%)**
Elective CS*	12 (9)	650 (8)	662 (8)
Assisted instrumental delivery	9 (7)	502 (6)	511 (6)
Emergency CS*	20 (15)	503 (6)	523 (6)
Normal Vaginal Delivery	84 (63)	6301 (78)	6385 (78)
Failed Induction – CS*	9 (7)	115 (1)	124 (2)
Total	134	8071	8205

3.1.9.4 Indication for Caesarean/Instrumental Delivery (SGA versus non-SGA)

The most common indication for Caesarean section or instrumental delivery was fetal distress in both groups, but there was no significant difference between the two groups ($\chi^2 = 3.4$, df =1, p = 0.06) (Table 3.23).

Table 3.23 Indication for Caesarean Section or Instrumental by Groups

Indication	SGA N (%)	Non-SGA N (%)	Total N (%)
Fetal distress	51 (71)	1901 (60)	1952 (60)
Other (maternal, multiples, IUGR)	21 (29)	1265 (40)	1286 (40)
Total	72	3166	3238

IUGR = Intrauterine Growth Retardation

3.1.9.5 Intrapartum Problems (SGA versus non-SGA)

Compared with non-SGA infants, there was a significant difference between the two groups in the rate of intrapartum problems in the fetus ($\chi^2 = 18.5$, df = 2, $p < 0.001$). There was a higher incidence of signs of fetal distress (abnormal cardiotocography (CTG), fetal acidosis, meconium-stained liquor) in the infants born SGA compared with the non-SGA group (29% v 19%) (Table 3.24).

Table 3.24 Intrapartum Problems by Groups

Problem	SGA N (%)	Non-SGA N (%)	Total N (%)
None	200 (70)	11323 (80)	11523 (80)
Fetal distress	81 (29)	2604 (19)	2685 (19)
Other*	3 (1)	154 (1)	157 (1)
Total	284	14081	14365

***haemorrhage, prolonged rupture of membranes, maternal pyrexia, cord prolapse, polyhydramnios or absent liquor, malpresentation.**

However, when the data was analysed separately for rate of intrapartum problems in term infants and preterm infants, there was only a significant difference between the SGA group compared with non-SGA group in the term infants ($\chi^2 = 29.6$, df = 2, $p < 0.001$). The rate of fetal distress was 33% in the SGA group versus 19% (Table 3.25).

Table 3.25 Intrapartum Problems in Term Infants by Groups

Indication	SGA N (%)	Non-SGA N (%)	Total N (%)
None	154 (66)	10706 (80)	10860 (80)
Fetal distress	77 (33)	2548 (19)	2625 (19)
Other*	1 (0.4)	127 (1)	128 (1)
Total	232	13381	13613

***maternal, multiples, IUGR**

There was no significant difference in the rate of intrapartum problems between the two groups in the premature infants ($\chi^2 = 0.006$, df = 2, p = 1.0) (Table 3.26).

Table 3.26 Intrapartum Problems in Preterm Infants by Groups

Indication	SGA N (%)	Non-SGA N (%)	Total N (%)
None	46 (89)	617 (88)	663 (88)
Fetal distress	4 (8)	56 (8)	60 (8)
Other*	2 (4)	27 (4)	29 (4)
Total	52	700	752

***maternal, multiples, IUGR**

3.1.10 Parity, Multiple Pregnancy and Birth Order

3.1.10.1 Parity (SGA versus non-SGA)

There was a significant difference in parity overall between the SGA and the non-SGA groups (χ^2=14.8 df = 6 p = 0.03). A higher percentage of mothers in the SGA group were primiparous (Table 3.27).

Table 3.27 Parity by Groups

Previous births	SGA N (%)	Non-SGA N (%)	Total N (%)
0	139 (49)	5587 (40)	5726 (40)
1	69 (24)	4229 (30)	4298 (30)
2	35 (12)	2347 (17)	2382 (17)
3	15 (5)	904 (6)	919 (6)
4-10	15 (5)	574 (4)	589 (4)
11-19	0	17 (0.1)	17 (0.1)
Unknown	11 (4)	424 (3)	435 (3)
Total	284	14081	14366

3.1.10.2 Multiple Pregnancy (SGA versus non-SGA)

There was a significant difference in the rate of multiple pregnancies between the two groups. A higher rate of twin pregnancy was seen in the SGA Group ($\chi^2 = 116.1$, df = 2, $p < 0.001$) (Table 3.28).

Table 3.28 Multiple Pregnancy by Group

Type of Pregnancy	SGA N (%)	Non-SGA N (%)	Total N (%)
Singleton	248 (87)	13735 (98)	13983 (97)
Twins	36 (13)	338 (2)	374 (3)
Triplets	0	9 (0.1)	9 (0.1)
Total	284	14082	14366

3.1.10.3 Birth Order (SGA versus non-SGA Twins)

There was no difference between the SGA twins and non SGA twins in terms of birth order ($\chi^2 = 0.2$, df = 1, $p = 0.7$) (Table 3.29).

Table 3.29 Birth Order for Twin Pregnancies by Groups

Birth Order	SGA N (%)	Non-SGA N (%)	Total N (%)
1	17 (47)	171 (51)	188 (50)
2	19 (53)	167 (49)	186 (50)
Total	36	338	374

3.1.11 Infant Characteristics

3.1.11.1 Gender (SGA versus non-SGA)

There was no significant difference in the gender distribution between the SGA and non-SGA groups (χ^2= 0.1, df = 1, p = 0.72) (Table 3.30).

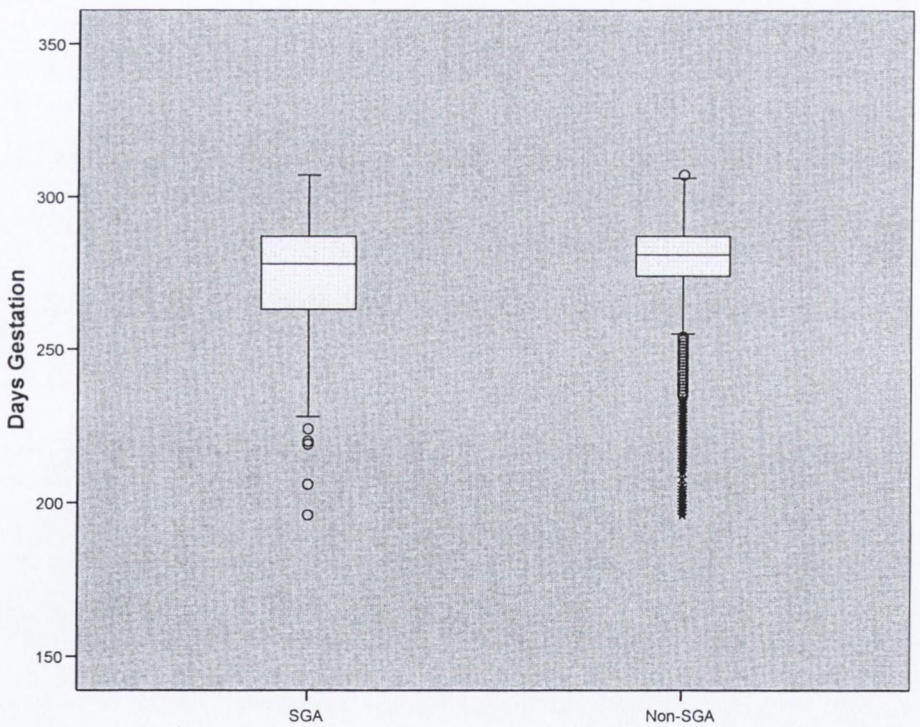
Table 3.30 Infant Gender

Gender	SGA Group N (%)	Non-SGA Group N (%)	Total N (%)
Male	142 (50)	7190 (51)	7332 (51)
Female	142 (50)	6892 (49)	7034 (49)
Total	284	14082	14366

3.1.11.2 Gestational Age (SGA versus non-SGA)

There was a significant difference (4.7 days) between the mean number of days gestation between the SGA Group (274.2 days = 39^{+1}) and non-SGA group (279 days = 39^{+5}) in terms of gestational age by independent samples t test, (equal variance is not assumed, t = 4.3, df = 288, $p < 0.001$) (95% CI for difference in the population means = 2.6 to 6.9) (Figure 3.1).

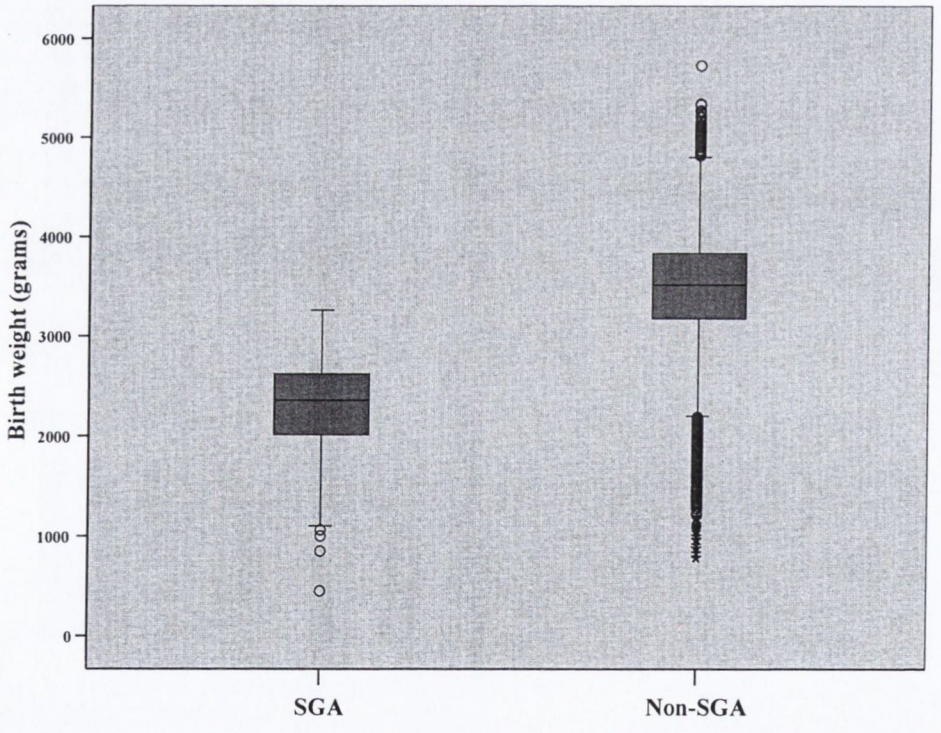
Figure 3.1 Gestational Age of SGA and non-SGA infants



3.1.11.3 Birth weight and Birth Weight SDS (SGA versus non-SGA)

The mean birth weight in the SGA group was 2278g (range 450-3260g) and in the non-SGA group it was 3488g (range 780-5726g). There was a significant difference between the two groups in terms of mean birth weight by independent t test (equal variance not assumed $t = 42.4$, $df = 298$, $p < 0.001$) (95% CI for difference in the population means = 1266g to 1154g). Mean birth weight SDS in the SGA group was -2.38. Mean birth weight SDS in the non-SGA group was 0.08 (Figure 3.2).

Figure 3.2 Birth Weight of SGA and non-SGA infants



3.1.11.4 Method of Infant Feeding (SGA versus non-SGA)

There was a significant difference in the method of feeding of infants between the two groups ($\chi^2 = 37.1$, df = 3, $p < 0.001$). There was a lower rate of breast feeding amongst mothers of SGA infants versus non-SGA infants (19% versus 32%). There was also a higher rate of combined breast and bottle feeding in the SGA group (3% versus 2%) (Table 3.31).

Table 3.31 Method of infant feeding by Groups

Feeding method	SGA N (%)	Non-SGA N (%)	Total N (%)
Breast	53 (19)	4509 (32)	4562 (32)
Bottle	198 (70)	8798 (63)	8996 (63)
Combined breast & bottle	9 (3)	245 (2)	254 (2)
Not stated	24 (9)	530 (4)	554 (4)
Total	284	14081	14366

3.1.12 Infants admitted to the Special Care Baby Unit (SCBU)

From the total group of 14,366 infants analysed, 2507 infants were admitted to the SCBU. Of the SGA group, 173 (61%) were admitted to SCBU compared with 2334 (17%) of the non-SGA group. There was a significant difference in the indication for admission to the SCBU between the SGA and non-SGA group ($\chi^2 = 162.8$, df = 11, $p < 0.001$). There was a higher rate of low birth weight/IUGR or prematurity as the indication for admission in the SGA Group (41.1% v 9.6%) and a higher rate of hypoglycaemia and hypothermia (14.1% v 12.7%) (Table 3.32).

Table 3.32 Reason for admission to SCBU by Groups

Reason for admission	SGA N (%)	Non-SGA N (%)	Total N (%)
LBW/IUGR/Prematurity	67 (41)	191 (10)	258 (12)
Grunting/Perinatal Asphyxia/Low Apgars	38 (23)	579 (29)	617 (29)
Hypoglycaemia/Hypothermia	23 (14)	254 (13)	277 (13)
Suspected Sepsis	20 (12)	266 (13)	286 (13)
Infant of IVDA	6 (4)	71 (4)	77 (4)
Jaundice/Haematological	4 (3)	266 (13)	270 (13)
Non-specific	3 (2)	176 (9)	179 (8)
Gastrointestinal reason	1 (0.6)	35 (2)	36 (2)
Feeding problems/FTT	1 (0.6)	41 (2)	42 (2)
Infant of Diabetic Mother	0	76 (4)	76 (4)
Abnormal neurological	0	17 (1)	17 (1)
Investigations	0	23 (1)	23 (1)
Total	163	1995	2158

LBW = Low birth weight; IUGR = Intrauterine Growth Retardation; FTT = Failure to Thrive

3.1.12.1 Respiratory Problems (SGA versus non-SGA)

There was no significant difference in the rate of respiratory problems between the SGA infants and non-SGA infants ($\chi^2 = 6.6$, df = 2, p = 0.04) (Table 3.33).

Table 3.33 SCBU Infants – Respiratory problems by Groups

Respiratory Problem	SGA N (%)	Non-SGA N (%)	Total N (%)
None/Apnoea/Periodic Breathing/Stridor	158 (91)	1963 (84)	2121 (85)
RDS/TTN/Pneumothorax/MAS/Aspiration/ Atelectasis/BPD/CLD	14 (8)	332 (14)	346 (14)
Bronchiolitis/Viral LRTI/URTI	1 (1)	39 (2)	40 (2)
Total	173	2334	2507

RDS = Respiratory Distress Syndrome; TTN = Transient Tachypnoea of Newborn; MAS = Meconium Aspiration Syndrome; BPD = Bronchopulmonary Dysplasia; CLD = Chronic Lung Disease; LRTI/URTI = Lower/Upper Respiratory Tract Infection

3.1.12.2 Ventilation Procedures (SGA versus non-SGA)

There was no significant difference between the SGA Group and non-SGA Group in terms of rate and type of ventilation procedures required ($\chi^2 = 5.5$, df = 4, p = 0.24) (Table 3.34).

Table 3.34 SCBU Infants - Ventilation procedures by Groups

Type of ventilation	SGA N (%)	Non-SGA N (%)	Total N (%)
Mechanical	6 (4)	134 (6)	140 (6)
Nasal CPAP*	6 (4)	86 (4)	92 (4)
Supplemental O_2 only	3 (2)	85 (4)	88 (4)
Initial ventilation only	1 (1)	3 (0.1)	4 (0.2)
None	157 (91)	2026 (87)	2183 (87)
Total	173	2334	2507

***Continuous Positive Airway Pressure; O_2 = oxygen**

3.1.12.3 Central Nervous System complications (SGA versus non-SGA)

There was no significant difference between the two groups in terms of documented neurological complications ($\chi^2 = 5.8$, df = 2, p = 0.06). Of note there was only one case of hypoxic ischaemic encephalopathy (HIE) and neonatal seizures in the SGA group compared with 100 (0.4%) cases documented in the non-SGA group (Table 3.35).

Table 3.35 SCBU Infants – Central Nervous System problems by Groups

CNS Problem	SGA N (%)	Non-SGA N (%)	Total N (%)
None	166 (96)	2150 (92)	2316 (92)
HIE/Neonatal Seizures	1 (0.6)	100 (4)	101 (4)
Other*	6 (4)	84 (4)	90 (4)
Total	173	2334	2507

HIE = Hypoxic Ischaemic Encephalopathy * Other = Neonatal Abstinence Syndrome, Intraventricular Haemorrhage, Abnormal tone/behaviour

3.1.12.4 Gastrointestinal complications (SGA versus non-SGA)

There was a significant difference between the SGA group and non-SGA group in the incidence of gastrointestinal problems ($\chi^2 = 6.0$, df = 2, p = 0.05) (Table 3.36). Only one case of suspected necrotizing enterocolitis (NEC) was recorded in the SGA group compared with 100 cases (4.3%) in the non-SGA group.

Table 3.36 SCBU Infants – Gastrointestinal Problems by Groups

GI Problem	SGA N (%)	Non-SGA N (%)	Total N (%)
None	166 (97)	2150 (92)	2316 (93)
Suspected NEC*	1 (0.6)	100 (4)	101 (4)
Other	5 (3)	82 (4)	87 (4)
Total	172	2332	2504

***Necrotising Enterocolitis**
Other = distended abdomen/obstruction/bilious vomits/congenital/ Feeding Problems/GOR/FTT/ Meconium Ileus/ Pyloric Stenosis
Other – non-acute: colic, constipation, gastritis/ conjugated Jaundice

3.1.13 SGA Group - Response to Invitation to participate in study

Letters were sent to mothers of the 284 SGA infants (2% of total 14,366 infants analysed) inviting them to attend with their child for auxological assessment at the Department of Paediatric Endocrinology, The National Children's Hospital, Tallaght in May 2005. 79 mothers responded. A total of 57 children were seen for auxological assessment. Of these children, 4 were the SGA twin of a non-SGA/SGA twin pair. In 22 cases the mother responded but indicated that she did not wish to attend with her child for assessment. A second letter was sent in October 2005 to the 200 mothers from whom no response had been received by this date. By December 2005 in total 47 envelopes had been returned unopened, with indication that the address was no longer valid. No response was received from 157 mothers. One mother telephoned to inform us that her infant had died in the early neonatal period. This had not been documented on the CWH database (Table 3.37).

Table 3.37 SGA Group - Response to Letters

Total Letters sent	**284**
Children seen	57 (19.9%)
Responded but not seen	22 (7.7%)
Not at the address	47 (16%)
No response	157 (55.3%)
Early neonatal death not identified on database	1 (0.3%)

3.1.13.1 SGA Group Socio-Economic Characteristics

This study collected demographic information on all mothers identified (n = 284). This information included socio-economic characteristics of mothers, ethnicity, pregnancy history, maternal auxology, maternal wellbeing in pregnancy, fetal problems in utero, labour and delivery, multiple pregnancies, infant characteristics and Special Care Baby Unit admissions. Comparisons were made between the children seen (N = 57) and not seen (N = 227) for each of the factors listed above.

SGA Group – Mother's Marital Status (seen versus not seen)

There was a statistically significant difference in marital status between the SGA patients who were seen and those who were not (χ^2 (Exact) = 7.75 df = 3 p = 0.05). A higher proportion of married mothers were found in the SGA patients who were seen compared with those who were not seen (61% v 41%) (Table 3.38).

Table 3.38 SGA Group – Marital status of Mothers

Marital Status	Seen N (%)	Not seen N (%)	Total N (%)
Married	35 (61)	94 (41)	129 (45)
Single	21 (37)	125 (55)	146 (51)
Separated/Divorced/Widowed	1 (2)	5 (2)	6 (2)
Unknown	0	3 (1)	3 (1)
Total	57	227	284

SGA Group – Mother's Occupation (seen versus not seen)

There was a difference in the occupations of the mothers in the group of SGA infants who were seen when compared with those who were not seen ($\chi^2 = 18.1$, df = 2, $p < 0.001$). 61% of mothers of those seen were in non-manual employment versus 33% of those not seen (Table 3.39).

Table 3.39 SGA Group – Mother's Occupation

Occupation	Seen N (%)	Not seen N (%)	Total N (%)
Non-Manual	35 (61)	74 (33)	109 (38)
Manual	6 (11)	20 (9)	26 (9)
Others gainfully occupied & unknown	16 (28)	133 (59)	149 (53)
Total	57	227	284

SGA Group – Partner's Occupation (seen versus not seen)

There was a difference in the occupations of the partners in the group of SGA infants who were seen when compared with those who were not seen ($\chi^2 = 12.0$, df = 2, $p = 0.003$). 29.8% of partners of those seen were in non-manual employment versus 14.1% of those not seen (Table 3.40).

Table 3.40 SGA Group – Partner's Occupation

Occupation	Seen N (%)	Not seen N (%)	Total N (%)
Non-Manual	17 (30)	32 (14)	49 (17)
Manual	14 (25)	38 (17)	52 (18)
Others gainfully occupied & unknown	26 (46)	157 (69)	183 (64)
Total	57	227	284

SGA Group – Geographical Distribution (seen versus not seen)

There was no difference between the group of SGA patients who were seen and those who were not seen whether the mothers were living in the Dublin area or not at the time of delivery ($\chi^2 = 2.1$, df = 1, p = 0.15) (Table 3.41).

Table 3.41 SGA Group – Geographical Distribution of Patients

Place of residence	Seen N (%)	Not seen N (%)	Total N (%)
Dublin City/County	39 (68)	176 (78)	215 (76)
Outside Dublin	18 (32)	51 (23)	69 (24)
Total	57	227	284

3.1.13.2 SGA Group – Ethnic Origin (seen versus not seen)

There was no difference in mothers' and partners' ethnic origin between the SGA patients who were seen and those who were not (χ^2 (Exact) = 4.8, df = 2, p = 0.08) (Table 3.42) and ($\chi^2 = 1.4$, df = 2, p = 0.51) (Table 3.43) respectively.

Table 3.42 SGA Group – Mother's Ethnic Origin

Ethnic Origin	Seen N (%)	Not seen N (%)	Total N (%)
European	55 (97)	206 (91)	261 (92)
African/Asian/Middle-Eastern/ Caribbean/African-American	1 (2)	20 (9)	21 (7)
Other/Mixed Race/Unknown	1 (2)	1 (0.4)	2 (0.7)
Total	57	227	284

Table 3.43 SGA Group – Partner's Ethnic Origin			
Ethnic Origin	**Seen N (%)**	**Not seen N (%)**	**Total N (%)**
European	52 (91)	195 (86)	247 (87)
African/Asian/Middle-Eastern/ Caribbean/African-American	3 (5)	23 (10)	26 (9)
Other/Mixed Race/Unknown	2 (4)	9 (4)	11 (4)
Total	57	227	284

3.1.13.3 SGA Group - Lifestyle Factors (seen versus not seen)

SGA Group Maternal Smoking (seen versus not seen)

Comparing smoking history in those seen from the SGA Group with those not seen, there was no significant difference between the two groups ($\chi^2 = 5.2$, df = 2, p = 0.08) (Table 3.44).

Table 3.44 SGA Group – Mother's Smoking History			
Smoking	**Seen N (%)**	**Not seen N (%)**	**Total N (%)**
Any smoking	29 (51)	127 (56)	156 (55)
None/Stopped since booking	24 (42)	65 (29)	89 (31)
Unknown	4 (7)	35 (15)	39 (14)
Total	57	227	284

SGA Group Alcohol consumption (seen versus not seen)

There was also no significant difference between the mothers of SGA infants seen versus not seen in report of alcohol consumption during pregnancy ($\chi^2 = 1.8$, df = 2, p = 0.41) (Table 3.45).

Table 3.45 SGA Group – Alcohol taken during pregnancy

Alcohol	Seen N (%)	Not seen N (%)	Total N (%)
Any alcohol	20 (35)	91 (40)	111 (39)
None	25 (44)	78 (34)	103 (36)
Unknown	12 (21)	58 (26)	70 (25)
Total	57	227	284

3.1.13.4 SGA Group – Maternal Auxology (seen versus not seen)

It was not possible to compare the group of SGA patients who were seen with the group that was not seen due to lack of complete data pertaining to maternal heights and weights.

3.1.13.5 SGA Group – Medical Problems in Pregnancy (seen versus not seen)

There was no difference in the proportion of mothers experiencing medical problems during the pregnancy when comparing the SGA group of infants seen with those not seen ($\chi^2 = 3.8$, df = 1, p = 0.51) (Table 3.46).

Table 3.46 SGA Group – Medical Problems in Pregnancy

Medical Problem	Seen N (%)	Not seen N (%)	Total N (%)
No	54 (95)	193 (85)	247 (87)
Yes	3 (5)	34 (15)	37 (13)
Total	57	227	284

SGA Group – Maternal Hypertension (seen versus not seen)

There was no difference between the group of SGA patients seen compared with those who were not seen in terms of incidence of hypertension experienced by the mothers during the pregnancy ($\chi^2 = 1.7$, df = 2, p = 0.43) (Table 3.47).

Table 3.47 SGA Group – Maternal Hypertension in Pregnancy

Type of Hypertension	Seen N (%)	Not seen N (%)	Total N (%)
Pre-eclampsia (treated/untreated)	7 (12)	29 (13)	36 (13)
No/unknown	44 (77)	185 (82)	229 (81)
Hypertension (no proteinuria)	6 (11)	13 (6)	19 (7)
Total	57	227	284

3.1.13.6 SGA Group – Labour and Delivery (seen versus not seen)

There was no difference between the group of SGA infants who were seen and those not seen with respect to labour onset ($\chi^2 = 7.5$, df = 4, p = 0.11), type of delivery ($\chi^2 = 8.9$, df = 4, p = 0.06) (Tables 3.48 and 3.49).

Table 3.48 SGA Group – Labour Onset (seen versus not seen)

Type of Labour onset	Seen N (%)	Not seen N (%)	Total N (%)
No Labour – Elective CS*	4 (7)	24 (11)	28 (10)
Induced/Accelerated	19 (33)	73 (32)	92 (32)
No Labour – Emergency CS*	12 (21)	21 (9)	33 (12)
Spontaneous	21 (37)	107 (47)	128 (45)
Failed Induction – CS*	1 (2)	2 (1)	3 (1)
Total	57	227	284

Table 3.49 SGA Group – Type of Delivery (seen versus not seen)

Delivery Method	Seen N (%)	Not seen N (%)	Total N (%)
Elective CS*	4 (7)	24 (11)	28 (10)
Assisted instrumental delivery	4 (7)	27 (12)	31 (11)
Emergency CS*	16 (28)	39 (17)	55 (19)
Normal Vaginal Delivery	25 (44)	123 (54)	148 (52)
Failed Induction – CS*	8 (14)	14 (6)	22 (8)
Total	57	227	284

SGA Group – Indication for Caesarean /Instrumental Delivery (seen v. not seen)

There was no difference between the group of SGA patients seen and those who were not seen in terms of indication for operative or instrumental delivery (Table 3.50).

Table 3.50 SGA Group – Indication for Caesarean /Instrumental Delivery

Indication	Seen N (%)	Not seen N (%)	Total N (%)
Fetal distress	10 (71)	41 (71)	51 (71)
Other (maternal, multiples, IUGR)	4 (29)	17 (29)	21 (29)
Total	14	58	72

IUGR = Intrauterine Growth Retardation

SGA Group – Intrapartum Problems (seen versus not seen)

There was no difference between the two groups in the rate of intrapartum problems experienced (χ^2 (Exact) = 0.8, df = 2, p = 0.66) (Table 3.51).

Table 3.51 SGA Group – Intrapartum Problems (seen versus not seen)

Problem	Seen N (%)	Not seen N (%)	Total N (%)
None	42 (74)	158 (70)	200 (71)
Fetal distress	14 (25)	67 (30)	81 (29)
Other*	1 (2)	2 (1)	3 (1)
Total	57	227	284

***haemorrhage, prolonged rupture of membranes, maternal pyrexia, cord prolapse, polyhydramnios or absent liquor, malpresentation.**

3.1.13.7 SGA Group – Parity and Multiple Pregnancy

SGA Group – Parity (seen versus not seen)

There was no difference in the proportion of primiparous versus multiparous mothers represented in the group of SGA infants seen when compared with those not seen (χ^2 = 5.1, df = 2, p = 0.08) (Table 3.52).

Table 3.52 SGA Group – Parity (seen versus not seen)

Mother's Parity	Seen N (%)	Not seen N (%)	Total N (%)
Primiparous	34 (60)	105 (46)	139 (49)
Multiparous	23 (40)	111 (49)	134 (47)
Unknown	0	11 (5)	11 (4)
Total	57	227	284

Multiple Pregnancies (seen versus not seen)

There was no difference in rate of twins in the SGA Group who were seen compared with those not seen (χ^2 = 2.1, df = 1, p = 0.15) (Table 3.53).

Table 3.53 SGA Group – Multiple Pregnancy (seen versus not seen)

Type of Pregnancy	Seen N (%)	Not seen N (%)	Total N (%)
Singleton	53 (93)	195 (86)	248 (87)
Twins	4 (7)	32 (14)	36 (13)
Total	57	227	284

3.1.13.8 SGA Group – Infant Characteristics

SGA Group – Gender (seen versus not seen)

There was no significant difference in the gender distribution between the SGA and non-SGA groups or between those SGA infants seen and not seen (χ^2= 0.2, df = 1, p = 0.66) (Table 3.54).

Table 3.54 SGA Group – Infant's Gender (seen versus not seen)

Gender	Seen N (%)	Not seen N (%)	Total N (%)
Male	30 (53)	112 (49)	142 (50)
Female	27 (47)	115 (51)	142 (50)
Total	57	227	284

SGA Group – Gestation (seen versus not seen)

There was a difference of several days in mean length of gestation between the group of children born SGA who were seen (38^{+5} weeks) when compared to those who were not seen (39^{+2} weeks). However this difference was not statistically significant as assessed by independent t test (t = - 1.38, p = 0.17).

SGA Group – Birth Weight SDS (seen versus not seen)

There was no significant difference in mean birth weight SDS between the two groups (t = 1.42, p = 0.2); mean BW SDS in the SGA group seen was -2.3 compared with a mean BW SDS of -2.4 in the group not seen.

3.1.13.9 SGA Group - Special Care Baby Unit Infants

Of the 57 infants seen 41 infants (72%) had been admitted to the Special Care Baby Unit compared with 132 of the 230 infants (58%) who were not seen.

3.1.14 SGA Group – Clinical and Auxological Assessment at 4-6 years (N=56)

Full clinical assessments on 57 patients born SGA between the ages of 4 and 6 years were performed at the Department of Paediatric Endocrinology, The National Children's Hospital, Tallaght. One case was excluded from the statistical analysis of auxological outcome because of uncertainty relating to his birth weight.

The outcome of SGA boys (n = 29) compared to girls (n = 27) in relation to auxological data were analysed separately. The independent t test showed no statistical difference between the two groups (p value > 0.05 for all variables) (Table 3.55).

3.1.14.1 Age of assessment

The mean age of assessment was 5.3 years (range 4.1 to 6.5). Mean age of assessment of the boys was 5.4 years (range 4.3 to 6.5) and for the girls was 5.2 years (range 4.1 to 6.1) (Table 3.55).

Table 3.55 Birth & auxological data of SGA children assessed at age 4-6 yrs

	Total (N = 56)	Boys (N = 29)	Girls (N = 27)
Age	5.3 (4.1 – 6.5)	5.4 (4.3 – 6.5)	5.2 (4.1 – 6.1)
BW (kg)	2.27 (0.9 – 3.2)	2.25 (1.0 – 3.2)	2.20 (0.9 – 2.8)
BW SDS	-2.3 (-3.5 to -2.0)	-2.3 (-3.0 to -2.0)	-2.3 (-3.5 to -2.0)
Gestation	38^{+5} (29^{+3} – 43^{+6})	38^{+4} (31^{+2} – 43^{+6})	38^{+6} (29^{+3} – 43^{+1})
Ht SDS	-0.7 (-3.1 – 1.2)	-0.8 (-3.1 – 1.2)	-0.7 (-1.8 – 0.4)
Wt SDS	-0.9 (-3.7 – 2.6)	-1.0 (-3.7 – 2.6)	-0.8 (-2.6 – 0.6)
BMI	14.9 (12.2 – 20.4)	15.0 (12.2 – 20.4)	14.9 (12.4 – 17.8)
BMI SDS	-0.6 (-3.5 – 2.7)	-0.6 (-3.5 – 2.7)	-0.6 (-2.6 – 1.4)
HC SDS	-0.9 (-3.6 – 1.2)	-0.9 (-3.6 – 1.2)	-0.9 (-3.5 – 1.2)

***Median given in the case of Birth Weight (BW); Gest = Gestational age; Ht = Height; Wt = Weight; BMI = Body Mass Index; HC = Head circumference; SDS = Standard Deviation Score**

3.1.14.2 Birth Data

Median birth weight in the SGA patients seen was 2.27kg (range 0.9 to 3.2kg). Mean birth weight SDS (BW SDS) was -2.3 SDS (range -3.5 to -2.0). Mean gestational age was 271 days (38^{+5} weeks) (range 206 to 307 days = 29^{+3} to 43^{+6}) (Table 3.55).

3.1.14.3 Auxological Assessment at 4-6 years

Height at 4-6 years

Mean height SDS was -0.74 SDS (range -3.1 to +1.2) (Table 3.55).

Mean height SDS for the boys was -0.8 SDS (range -3.1 to +1.2) slightly lower than for the girls (mean height -0.7 SDS) (range -1.8 to +0.4) which was not a significant difference ($p = 0.87$).

Weight at 4-6 years

Mean weight SDS was -0.9 SDS (range -3.7 to +2.6) (Table 3.55).

Mean weight SDS for the boys was -1.0 SDS (range -3.7 to +2.6) and for the girls mean was slightly higher at -0.8 SDS (range -2.6 to +0.6) which was not a significant difference ($p = 0.7$).

Body mass index (BMI) at 4-6 years

Mean BMI was 14.9 (range 12.2 to 20.4) (Table 3.55). Mean BMI SDS was -0.6 (range -3.5 to +2.7). Mean BMI for the boys was 15.0 (range 12.2 to 20.4) and for the girls was similar at 14.9 (range 12.4 to 17.8). Mean BMI SDS for the boys was -0.6 (range -3.5 to +2.7) and for the girls was also -0.6 (range -2.6 to +1.4).

Head circumference at 4-6 years

Mean head circumference SDS was -0.9 SDS (range -3.6 to +1.2). Mean head circumference SDS for the boys was -0.9 SDS (range -3.6 to +1.2) and for the girls was also -0.9 SDS (range -3.5 to +1.2) (Table 3.55).

Preterm versus term children born SGA – birth Data and auxology at 4-6 years

Comparing the SGA children born preterm (<37/40) (N=12) with those born at term (≥37/40) (N=44), there were significant differences observed in height and weight at 4-6 years, with those born preterm being shorter (mean Ht SDS -1.4 v -0.6) and lighter (mean Wt SDS -1.7 v -0.7). However, although BMI and BMI SDS were slightly lower for the preterm group, there was no statistically significant difference observed. This would indicate that the children born preterm had not experienced inappropriate postnatal weight gain. There was no significant difference observed in birth weight SDS, indicating that the expected lower birth weights observed in the children who were born preterm was accounted for by lower gestational age. There was also no significant difference in head circumference at 4-6 years between the children born preterm compared with those born at term (Table 3.56).

Table 3.56 Comparing Auxological Data for Preterm versus Term Infants

	†Total (N = 56)	*Term (N = 44)	*Preterm (N = 12)	95% CI	p value
BW (kg)	2.27 (0.9 – 3.2)	2.47 (0.4)	1.35 (0.3)	-1.3 to -0.9	< 0.001
BW SDS	-2.3 (-3.5 to -2.0)	-2.3 (0.3)	-2.4 (0.5)	-0.3 to 0.1	0.48
Gestation	38^{+5} (29^{+3} – 43^{+6})	40^{+1}	33^{+3}	-56 to -39 days	< 0.001
Auxology 4-6 yrs					
Ht SDS	-0.7 (-3.1 – 1.2)	-0.6 (0.9)	-1.4 (0.9)	1.4 to -0.2	0.006
Wt SDS	-0.9 (-3.7 – 2.6)	-0.7 (1.1)	-1.7 (1.1)	1.7 to 0.3	0.008
BMI	14.9 (12.2 – 20.4)	15.1 (1.6)	14.4 (1.1)	1.7 to -0.3	0.16
BMI SDS	-0.6 (-3.5 – 2.7)	-0.5 (1.2)	-1.0 (1.0)	1.3 to 0.3	0.18
HC SDS	-0.9 (-3.6 – 1.2)	-1.0 (1.0)	-0.6 (1.2)	0.3 to -1.1	0.31

†Mean (Range) *Mean (SD); CI = Confidence Interval of the Difference

3.1.14.4 Mid-Parental Height

Parents' Heights

Maternal height was measured at the Department of Paediatric Endocrinology, The National Children's Hospital, Tallaght in 52 cases. Reported heights were used in 4 additional cases; in 3 cases the father attended instead of the mother and in 1 case the mother had died (road traffic accident). These reported heights agreed closely with those recorded on the CWH database. There was no evidence of a difference between the mother's reported height SDS and the actual measured mother's height SDS as analysed for 35 mothers (mean difference -0.08) ($t = 1.24$, p value = 0.2). Mean maternal height was -0.5 SDS. In addition paternal height was measured in 20 cases and reported heights were available for 34 fathers. In 3 cases father's height was not available due to social circumstances. Mean paternal height was -0.3 SDS.

Child's Height at 4-6 years with respect to Parental Height

Mean mid-parental height (MPH) was -0.3 SDS. Using paired t test, there was a significant difference between the means of height SDS (-0.7) measured in each child and mean heights corrected for MPH (-0.5), mean difference -0.26 SDS ($t = 3.46$, $df = 52$, p value < 0.001). Hence there is some influence of shorter parental heights (genetic potential) on the shorter mean heights in the children at 4 to 6 years.

3.1.14.5 Questionnaire on Children's Height & Weight

Questionnaires requesting information from parents about their child's growth were completed for height in 33 cases, and for weight in 43 cases.

Parents tended to report shorter height measurements done at home when compared with those measured in the clinic (difference between the means = 0.13 SDS), however this was not significant by paired t test (t = 0.7, p value = 0.5). In contrast, children were reported by parents to be heavier than found by weight measurement in the clinic (mean difference in weight SDS = 0.65), which was significant (t = -3.5, 2-tailed sig $p < 0.001$).

3.1.14.6 Smoking in Pregnancy - Birth Weight & Auxology at 4-6 years

There was general agreement between mother's recall (when interviewed at time of child's assessment) of smoking during the pregnancy compared with that which had been stated by the mother around the time of delivery of the infant. The children were divided into two groups – those whose mothers had smoked and those whose mothers had not smoked during pregnancy. There was no evidence of a statistically significant difference found between the two groups in any of the variables (BW SDS, height SDS, weight SDS, BMI, BMI SDS, head circumference SDS) by independent samples t test comparing the means (Table 3.57). However it was noted that the children of mothers who smoked had slightly lower mean birth weights and at 4-6 years were heavier than the children of non-smokers (weight SDS -0.7 versus -1.2), with higher BMIs (15.3 versus 14.6) that almost reached statistical significance (p = 0.07). This would indicate that children of mothers who smoked had more postnatal catch-up growth.

Table 3.57 Children of smokers v non-smokers

	Total (N = 56)	Smokers (N = 28)	Non-Smokers (N = 28)	95% CI	p value
BW (kg)	2.27 (0.9 – 3.2)	2.2 (0.5)	2.26 (0.6)	-0.4 to 0.3	0.69
BW SDS	-2.3 (-3.5 to -2.0)	-2.4 (0.3)	-2.3 (0.4)	-0.3 to 0.1	0.24
Gestation	38^{+5} (29^{+3} – 43^{+6})	38^{+4}	38^{+5}	-14 to 12 days	0.89
Auxology 4-6 yrs					
Ht SDS	-0.7 (-3.1 – 1.2)	-0.7 (0.9)	-0.8 (0.9)	-0.5 to 0.6	0.85
Wt SDS	-0.9 (-3.7 – 2.6)	-0.7 (1.3)	-1.2 (1.0)	-0.3 to 1.0	0.23
BMI	14.9 (12.2 – 20.4)	15.3	14.6	-0.1 to 1.5	0.07
BMI SDS	-0.6 (-3.5 – 2.7)	-0.3 (1.3)	-0.9 (0.9)	-0.1 to 1.1	0.12
HC SDS	-0.9 (-3.6 – 1.2)	-0.8 (1.0)	-1.0 (1.2)	-0.4 to 0.8	0.44

†Mean (Range) *Mean (SD); CI = Confidence Interval of the difference between the means

3.1.14.7 Maternal Hypertension and Auxology at 4-6 years

There was a statistically significant difference found in terms of mean birth weight and length of gestation between the groups of children born to mothers who had hypertension or pre-eclampsia during pregnancy compared to those who did not. The children of mothers who had hypertension or pre-eclampsia overall were born several weeks earlier and with a lower birth weight. However adjusting for the prematurity the mean birth weight SDS was not statistically different between the two groups by independent samples t test. Although the mean height SDS at 4-6 years was lower in the group of children born to mothers who had hypertension or pre-eclampsia this was not statistically significant. In addition there was no significant difference in mean weight SDS, BMI SDS or head circumference SDS (Table 3.57). This would indicate that children of mothers who had hypertension or pre-eclampsia during pregnancy compared with the group of children whose mothers did not, although born more prematurely, had similar birth weight SDS and postnatal catch-up growth

Table 3.58 Hypertension/Pre-eclampsia – BW SDS & Auxology at 4-6 yrs

	Total (N = 56)	HT/PET (N = 13)	HT/PET (N = 43)	95% CI	p value
BW (kg)	2.27 (0.9 – 3.2)	1.59 (0.5)	2.42 (0.4)	1.1 to 0.5	< 0.001
BW SDS	-2.3 (-3.5 to -2.0)	-2.5 (0.5)	-2.3 (0.2)	0.4 to 0.0	0.16
Gestation	38^{+5} (29^{+3} to 43^{+6})	35^{+1}	39^{+5}	-48 to -17 days	< 0.001
Auxology 4-6 yrs					
Ht SDS	-0.7 (-3.1 – 1.2)	-1.2 (1.0)	-0.6 (0.9)	-1.1 to 0.0	0.06
Wt SDS	-0.9 (-3.7 – 2.6)	-1.4 (1.3)	-0.8 (1.1)	-1.4 to 0.1	0.08
BMI	14.9 (12.2 – 20.4)	14.7 (1.4)	15.0 (1.6)	-1.3 to 0.6	0.49
BMI SDS	-0.6 (-3.5 – 2.7)	-0.8 (1.1)	-0.5 (1.2)	-1.1 to 0.5	0.42
HC SDS	-0.9 (-3.6 – 1.2)	-1.0 (0.9)	-0.9 (1.1)	-0.8 to 0.6	0.76

†Mean (Range) *Mean (SD); CI = Confidence Interval of the difference between the means

3.1.14.8 History of IUGR and Auxology at 4-6 yrs

Comparing the group of children born SGA who had a documented history of IUGR with those with no such history, there was a significant difference in birth weight, weight SDS and BMI SDS, with the former being smaller for each variable (Table 3.59). However, no significant differences were seen with height or head circumference.

Table 3.59 History of IUGR – BW SDS & Auxology at 4-6 years

	Total (N = 56)	IUGR (N = 22)†	No IUGR (N = 34)†	95% CI	p value
BW (kg)	2.27 (0.9 – 3.2)	2.0 (0.5)	2.4 (0.6)	-0.7 to -0.1	0.02
BW SDS	-2.3 (-3.5 to -2.0)	-2.4 (0.4)	-2.3 (0.3)	-0.2 to 0.1	0.52
Gestation	38^{+5} (29^{+3} to 43^{+6})	262 (20)	277 (25)	-28 to -3 days	0.02
Auxology 4-6 yrs					
Ht SDS	-0.7 (-3.1 – 1.2)	-0.9 (0.9)	-0.6 (1.0)	-0.8 to 0.2	0.29
Wt SDS	-0.9 (-3.7 – 2.6)	-1.3 (1.1)	-0.6 (1.2)	-1.3 to -0.0	0.05
BMI	14.9 (12.2 – 20.4)	14.5 (1.5)	15.2 (1.5)	-1.6 to 0.0	0.06
BMI SDS	-0.6 (-3.5 – 2.7)	-1.0 (1.2)	-0.3 (1.1)	-1.3 to -0.0	0.04
HC SDS	-0.9 (-3.6 – 1.2)	-1.1 (1.3)	-0.7 (0.9)	-1.0 to 0.2	0.2

†Mean (Range) *Mean (SD); CI = Confidence Interval of the difference between the means

3.1.14.9 Patients identified with growth problems at 4-6 years

In total 5 patients were identified with short stature (Ht SDS < -2) (Table 3.60), of whom 3 had severe short stature (Ht SDS ≤ -2.5). These 3 patients (patients 1-3), who were eligible for treatment with Growth Hormone, are described in the next section, 3.2 on Growth Hormone treatment. Height corrected for mid-parental height was below the mean in all 5 patients (corrected height SDS range -3.7 to -1.0) indicating that the short stature was not attributable to short parental height.

All 5 patients also had weight well below the mean (weight SDS range -3.7 to -1.0). BMI was also low and BMI SDS and head circumference were below the mean in 4 of the 5 patients (patients 1-4).

Table 3.60 Patients with short stature (N=5)					
Patient	**1***	**2***	**3***	**4**	**5**
Gender	Male	Male	Male	Male	Male
Age (years)	4.9	5.3	6.2	5.4	5.9
BW (kg)	1.4	1.0	1.9	3.2	2.7
BW SDS	-2.1	-2.7	-2.5	-2.1	-2.1
Gestation	33^{+1}	31^{+3}	37^{+1}	43+6	40+6
Auxology 4-6 years					
Ht SDS	-3.1	-2.9	-2.6	-2.2	-2.2
Corr Ht SDS	-2.9	-2.9	-1.0	-1.9	-1.3
Wt SDS	-2.9	-3.7	-3.7	-2.9	-1.0
BMI	14.9	13.5	13.0	13.6	16.7
BMI SDS	-0.6	-2.0	-2.4	-1.8	0.8
HC SDS	-1.1	-1.5	-3.6	-1.9	0.1

*** eligible for treatment with Growth Hormone; Gest =Gestational age; Ht=Height; CorrHt=Height corrected for mid-parental height; Wt=Weight; BMI=Body Mass Index; HC=Head circumference**

GH stimulation tests were performed on four of the children identified with short stature. GH insufficiency (peak GH 12.4mU/L) was found in one child (patient 2) (Table 3.61) who was subsequently treated with GH (see section 3.2).

Table 3.61 Peak Growth Hormone values in children with short stature

Patient	**1**	**2**	**3**	**4**
Type of Test	ITT	ITT	ITT	L-Dopa/ Propranolol
Peak GH mU/L	47.8	12.4	59.2	25.9
Time of Peak (mins)	45	45	30	60

ITT = insulin tolerance test

3.1.14.10 Patients identified with medical problems

Blood tests were performed in 8 children due to low weight or height. One child had a positive tissue transglutamase test (tTG = 33.5 U/ml – normal <1.9U/ml) and was subsequently diagnosed on small bowel biopsy with coeliac disease. Clinically she was asymptomatic and her height was -1.6 SDS and weight -1.9 SDS, with low BMI 13.9 and BMI SDS -1.1 SDS. Two years following diagnosis and treatment her weight and height have improved (height -1.4 SDS and weight -1.0 SDS, BMI 15.6, BMI SDS -0.2 SDS). Low ferritin levels (< 20ug/L) were found in two children with low weight and these children were commenced on iron supplementation. One child with low height (height SDS -1.7) and weight (weight -1.8 SDS) with severe atopic dermatitis was referred to the dermatology service for further management.

3.1.14.11 Patients identified at risk of metabolic syndrome

Only one patient (male) was identified as being at risk of the metabolic syndrome on the basis of BMI. His characteristics are outlined in Table 3.62. The boy's BMI was 20.4 (+2.7SDS) which is in the obesity range. He had achieved good catch-up in height at 6 years (Ht SDS = +1.2). Blood pressure was normal. Unfortunately, as this child's mother did not wish to attend for further assessments, follow up data is therefore unavailable.

Table 3.62 Patient at risk of metabolic syndrome based on BMI at 6 years	
BW (kg)	2.24
BW SDS	-2.5
Gestation (weeks)	39
Auxology at age 6 years	
Ht SDS	1.2
Corr Ht SDS	1.3
Wt SDS	2.6
BMI	20.4
BMI SDS	+2.7
HC SDS	-1.1

Ht =Height; CorrHt = Height corrected for mid-parental height;
Wt =Weight; BMI = Body Mass Index; HC=Head circumference

3.1.14.12 Twin Pairs Birth Data and Auxology at 4-6 years

There were four twin pairs assessed and in each pair only one twin had been born SGA. Both twins in each pair were assessed (Table 3.63). The child born SGA had height SDS greater than that of its non-SGA twin in two of the twin pairs (B and C). In the two other twin pairs (A and D) height SDS was considerably less in the child born SGA. Of note, BMI SDS was less in the child born SGA than in the non-SGA twin in all 4 cases which is reassuring. Head circumference at 4-6 years was similar within each twin pair. Due to the small numbers involved, it was not possible to perform any statistical analysis of auxological outcome at 4-6 years in these twin pairs.

Table 3.63 SGA: Non-SGA Twins – Birth Data & Auxology at 4-6 years

Twin Pair	Sex	Age	Gest	BW SDS	BO	Ht SDS	Corr Ht SDS	Wt SDS	BMI	BMI SDS	HC SDS
A*	**M**	**5.4**	**37^{+1}**	**-2.1**	**1**	**-0.9**	**-1.6**	**-1.6**	**13.8**	**-1.6**	**-0.6**
A	F			-0.8	2	1.7	1.0	1.0	15.4	0.0	-0.7
B*	**M**	**5.5**	**37^{+4}**	**-2.8**	**2**	**-0.9**	**0.0**	**-1.2**	**14.5**	**-0.9**	**0.2**
B	M			-1.0	1	-1.1	-0.2	-0.8	15.5	0.0	0.5
C*	**F**	**5.5**	**36^{+5}**	**-2.2**	**2**	**-0.1**	**0.1**	**-0.1**	**15.4**	**-0.1**	**+0.8**
C	M			-0.9	1	-0.6	-0.3	-0.4	15.5	0.0	N/A
D*	**F**	**4.7**	**39^{+5}**	**-2.5**	**1**	**-0.5**	**-1.0**	**-0.2**	**16.0**	**0.3**	**0.5**
D	M			-1.9	2	0.5	0.0	1.3	17.5	1.4	-0.3

***SGA twin**
Gest = gestation; BW SDS = birth weight SDS; BO = birth order; Ht = height; Corr Ht =corrected height; Wt = weight; HC = head circumference

3.1.14.13 Admissions to Special Care Baby Unit

71% (40) of the SGA infants seen had been admitted to the SCBU. The commonest reason for admission was in the category "low birth weight/IUGR/prematurity" (18%) with 10% being admitted due to clinical signs of perinatal asphyxia or low Apgar scores, and 7% having hypoglycaemia or hypothermia. Reason for admission was not documented in 17%. Reported median length of stay in SCBU was 1.3 weeks (range 1 day to 14 weeks).

3.1.14.14 Follow up in Infancy

Parents reported that 46% (26) of the infants had been followed up in terms of growth and/or development at the Coombe Women's Hospital. In 12 cases the mother reported that there had been some concern regarding the child's weight gain at some point in time, 9 of whom had attended the CWH until discharge or referral to a specialist by age 2 years. Of the other 3 cases the mother had not been followed up at CWH but had later sought medical advice from a Paediatrician due to concerns regarding her child's growth.

3.1.14.15 Developmental progress at 4-6 years

Developmental concerns were reported by the mother in 30% (17) of the children seen. Hearing problems secondary to glue ear had been a transient concern in 4 children. The concern in the remaining 13 children was in the area of delayed speech and language acquisition (11 had been referred to speech and language therapy). In

addition other developmental problems were reported in 3 children of these children (one with autistic spectrum disorder, the other two had been investigated for global developmental delay with a white matter abnormality being detected in one child).

Schooling

The majority of the children assessed were in mainstream education. Remedial teaching was required by 2 children in the mainstream setting. Special schooling was required by 2 children: 1 child had autistic spectrum disorder and the other had global developmental delay of unknown cause (despite multiple investigations) (Table 3.64).

Table 3.64 Children with learning disabilities requiring special schooling

Diagnosis	Autistic Spectrum Disorder	Global Delay
Gender	Male	Female
Age (years)	5.7	5.2
BW SDS	-2.1	-2.2
Gestation	42^{+5}	36^{+1}
IUGR	No	Yes
SCBU	No	Yes
Auxology at 4-6 years		
Ht SDS	-0.8	-0.8
Wt SDS	-2.7	-1.1
BMI SDS	-0.6	-2.0
HC SDS	0	-1.9

Ht =Height; CorrHt = Height corrected for mid-parental height;
Wt =Weight; BMI = Body Mass Index; HC=Head circumference

3.2 POPULATION (2) - PATIENTS BORN SGA TREATED WITH GH

3.2.1 Patient Population

In this study, 20 prepubertal children born SGA with persistent short stature were identified who might benefit from treatment with Growth Hormone (GH). With parental consent 13 of these children were included in the North European Study of Small for Gestational Age (NESGAS study) and treated with high dose (0.067mg/kg/day) GH. A further 2 children were treated outside the NESGAS study using the standard licensed dose (0.035mg/kg/day) GH as they were above the age limit for inclusion. One of these patients has Silver Russell syndrome. Data for over one year of treatment is available for 12 patients, 9 of whom have had two years of treatment. In addition 3 other patients have been treated with GH: one for 6 months and two for 3 months (Table 3.65).

Table 3.65 Short children born SGA identified for GH treatment

	NESGAS Study	Non-NESGAS Study	Comparison group of patients untreated to date
GH Dose	0.067mg/kg/d	0.035mg/kg/d	N/A
Total Patients	13	2	5
GH ≥ 1yr	10	2	N/A
GH ≥ 2 yrs	6	2	N/A

N/A = not applicable

A further 5 patients have been identified with severe short stature, eligible for GH treatment, however to date their parents have declined treatment, and their data has been analysed for comparison with the GH treated group (see section 3.2.5).

3.2.2 Source of recruitment

There were various sources of referral of the patients with short stature. The birth history and birthweight of patients with short stature attending the Growth clinic at AMNCH were reviewed and 4 were identified with a history of SGA and eligible for GH treatment. A further 3 patients were identified during the CWH follow-up study (see Results section 2). The remaining 13 patients were referred by Neonatologists (3), Paediatricians (7) and other Paediatric Endocrinologists (3) (Table 3.66).

Table 3.66 Source of referral for GH treatment

	Number
Already attending AMNCH Growth clinic	4
CWH follow up study	3
Neonatologist	3
Paediatrician	7
Other Paediatric Endocrinologist	3

3.2.3 Growth Hormone Stimulation Tests

Peak Growth Hormone (GH) levels were assessed in all 20 patients by GH stimulation testing to establish the presence or absence of GH insufficiency. A normal peak GH value was found in 15 patients. In total 5 patients had peak GH values below 20 mU/L, of whom 2 patients had a value < 15 mU/L (Table 3.67). This information did not affect whether the child would be treated with GH or not, and did not influence the dosing schedule during treatment.

Table 3.67 Results of Growth Hormone Stimulation Tests

Patient	Type of Test	Peak GH mU/L
1	Clonidine	60.0
2	L-Dopa/Propranolol	34.6
3	ITT	16.2
4	ITT	12.4
5	L-Dopa/Propranolol	58.8
6	Glucagon	24.2
7	ITT	35.1
8	Arginine	15.3
9	ITT	34.7
10	L-Dopa/Propranolol	48.2
11	L-Dopa/Propranolol	59.4
12	L-Dopa/Propranolol	81.4
13	ITT	13.2
14	ITT	59.2
15	ITT	47.8
16	L-Dopa/Propranolol	78.2
17	L-Dopa/Propranolol	102
18	ITT	17.5
19	ITT	36.2
20	L-Dopa/Propranolol	38.6

3.2.4 Growth Hormone Treated Patients

3.2.4.1 Growth Hormone Treated Patients - Birth data and auxology

In total 15 patients received GH treatment: 12 boys and 3 girls. Mean BW SDS was -2.5 (-3.5 to -1.8). Detailed birth history and auxological measurements were obtained prior to commencing treatment. Mean gestational age was 34^{+2} weeks. Only 4 of the patients were born at term (≥ 37/40). Median age to start GH treatment was 7.3 years (range 4 to 11.8 years). All patients had persistent severe short stature with mean height SDS at start of treatment –3.2 (-4.8 to -2.02). They were also short for parental height, with mean height corrected for mid-parental height (MPH) -2.7 SDS (-3.6 to -1.5). Height velocity was poor with mean height velocity SDS –1.7 SDS (-6.2 to -0.4) (mean height velocity 4.5cm/year: range 0.73 to 6.2cm/yr). Median weight was –3.6 SDS (-6.5 to -0.8), Mean BMI was low at 14.3 (11.8 to 20.2) and mean BMI SDS -1.7 (-3.9 to +1.6). Mean head circumference was -2.6 SDS (-6.3 to +0.4) (Table 3.68).

Table 3.68 Summary of birth data & auxology pre GH treatment

Measurement	Mean	SD
BW SDS	-2.5	0.5
Gestation (weeks^{+days})	34^{+2}	4 days
Age (years)	7.3	2.5
Ht SDS	-3.2	0.8
Corrected Ht SDS*	-2.7	0.7
HV SDS	-1.7	1.5
Wt SDS	-3.6	1.5
BMI	14.3	2.4
BMI SDS	-1.7	1.6
HC SDS	-2.6	1.7

***Height SDS corrected for MPH mid-parental height**

The birth data characteristics of each individual patient are outlined in Table 3.69 and individual baseline auxology prior to starting GH treatment is detailed in Table 3.70.

Table 3.69 Birth data of individual patients treated with GH (N = 15)

Pt	Sex	Gestation	BW (kg)	BW SDS	HC (cm)	HC SDS	BL (cm)	BL SDS
1	M	40+5	2.78	-2.0	N/A	N/A	47.0	-2.3
2	M	38+4	2.41	-2.0	N/A	N/A	-	-
3	F	34+0	1.08	-3.4	27.8	-2.4	36.0	-5.3
4	M	30+1	1.00	-2.1	30.0	1.1	30.0	-
5	M	32+1	1.19	-2.3	29.0	-0.8	30.0	-
6	M	29+6	0.78	-2.9	24.5	-3.0	33.5	-
7	M	38+2	1.67	-3.6	32.5	-1.3	39.0	-5.4
8*	M	32+0	1.00	-2.9	26.0	-3.0	36.0	-
9	M	35+4	1.58	-2.7	29.5	-2.3	42.0	-2.8
10	M	32+5	1.36	-2.0	N/A	N/A	37.8	-
11	F	33+0	1.22	-2.5	N/A	N/A	N/A	N/A
12	M	28+2	0.69	-2.6	N/A	N/A	N/A	N/A
13	F	38+4	1.90	-3.0	N/A	N/A	45.0	-2.2
16**	M	36	2.00	-2.0	N/A	N/A	N/A	N/A
17†	M	34	1.34	-2.7	27.4	-3.1	N/A	N/A

BW = Birth Weight; HC = Head circumference; BL = Birth Length
- Not possible to calculate by Cole methodology due to prematurity
N/A = not available
***Twin 2 of MZ twin pair **Twin 1 of DZ twin pair**
† Silver Russell Syndrome

Table 3.70 Pre treatment auxology of individual patients treated with GH

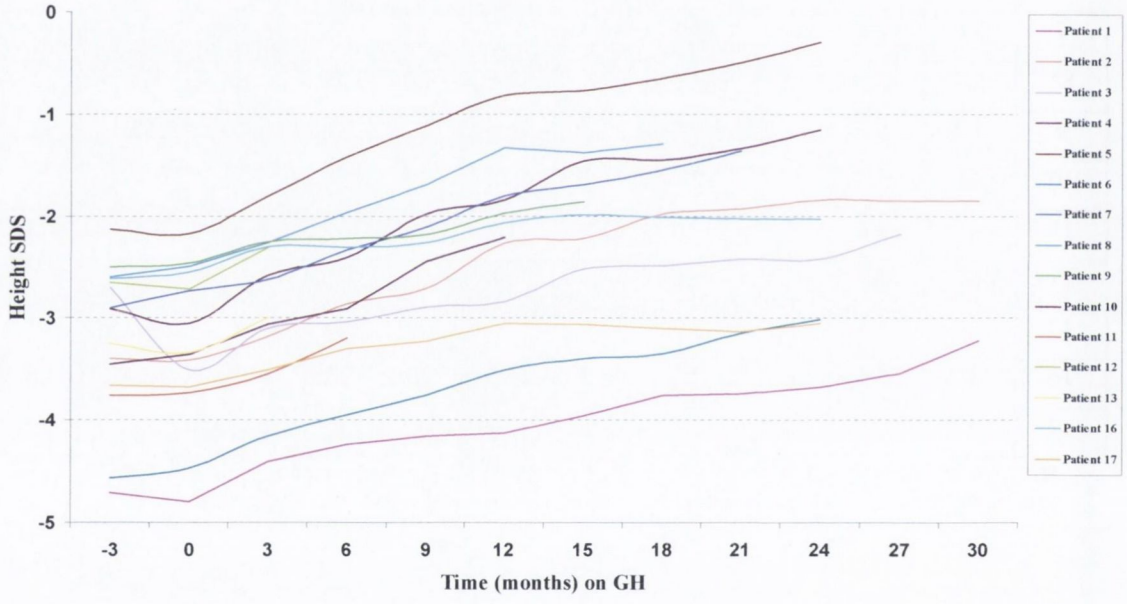
Pt	Age Start GH	Ht SDS	MPH SDS	Ht Corr MPH	Wt SDS	BMI	BMI SDS	HC	HC SDS	HV	HV SDS
1	9.9	-4.8	-3.1	-1.7	-4.4	15.6	-0.5	50.0	-2.8	0.7	-6.2
2	9.9	-3.4	-0.9	-2.5	-0.8	20.2	1.6	53.0	-0.9	3.4	-2.5
3	6.6	-3.5	0.0	-3.5	-4.3	12.7	-2.2	48.0	-3.7	5.1	-1.0
4	5.5	-3.1	-0.1	-3.0	-3.7	13.6	-1.8	50.9	-1.4	4.0	-2.3
5	7.9	-2.0	0.3	-2.3	-1.4	15.6	-0.1	54.4	0.4	4.8	-1.0
6	4.7	-4.5	-0.9	-3.6	-6.5	12.2	-3.8	48.3	-2.9	6.4	-0.4
7	7.0	-2.8	0.8	-3.6	-4.5	12.2	-3.4	52.3	-0.8	5.5	-0.5
8*	5.7	-2.5	-0.4	-2.2	-3.9	12.6	-3.0	48.0	-3.3	6.0	-0.4
9	7.2	-2.5	-1.0	-1.5	-3.1	13.6	-1.7	48.9	-3.0	5.0	-0.9
10	7.0	-3.4	-0.7	-2.7	-4.1	13.4	-1.9	50.0	-2.3	5.5	-0.4
11	4.0	-3.8	-0.2	-3.6	-5.9	11.8	-3.9	43.5	-6.3	5.7	-1.2
12	4.9	-2.7	-0.1	-2.6	-3.9	13.0	-2.7	48.4	-2.9	4.8	-1.7
13	5.6	-3.4	-0.5	-2.9	-3.9	13.1	-1.9	48.0	-3.3	4.5	-1.8
16	11.6	-2.6	-0.5	-2.1	-1.9	16.7	-0.3	N/A	N/A	2.9	-3.0
17	12.0	-3.7	-0.9	-2.8	-2.3	17.9	0.3	N/A	N/A	3.8	-2.0

Ht = height; MPH = mid-parental height; Ht Corr MPH = height corrected for mid-parental height; Wt = weight BMI = body mass index; HC = head circumference; HV = height velocity

3.2.4.2 Growth Response following Growth Hormone treatment

All patients had a significant increase in growth following GH treatment (Figure 3.3). This figure illustrates the change in height SDS in all patients from pre-treatment (-3 months), baseline (0 months) and while on GH treatment (0 to up to 30 months).

Figure 3.3 Change in Height SDS while on GH treatment (N = 15)



Mean increase in height SDS was +1.1 SDS after one year of treatment as calculated for 12 patients. Mean increase in height velocity was +6.3 SDS. Mean increase in weight was +1.2 SDS, mean increase in BMI SDS was +0.5, and mean increase in head circumference was +0.5 SDS (Table 3.71).

Table 3.71 Growth Response following one year of GH treatment (N = 12)			
Measurement	**Baseline***	**1 Year***	**p**
Height SDS	-3.2 (0.2)	-2.3 (0.3)	< 0.001
HV SDS	-1.7 (0.5)	4.6 (0.6)	< 0.001
Weight SDS	-3.4 (0.5)	-2.2 (0.4)	< 0.001
BMI SDS	-1.4 (0.5)	-0.9 (0.3)	0.021
Head Circ SDS †	-2.1 (0.4)	-1.6 (0.4)	0.007

***Mean (SE); † calculated for 10 patients**

These results were similar to those found in the interim results of the NESGAS study which included the Irish patients (Table 3.72).

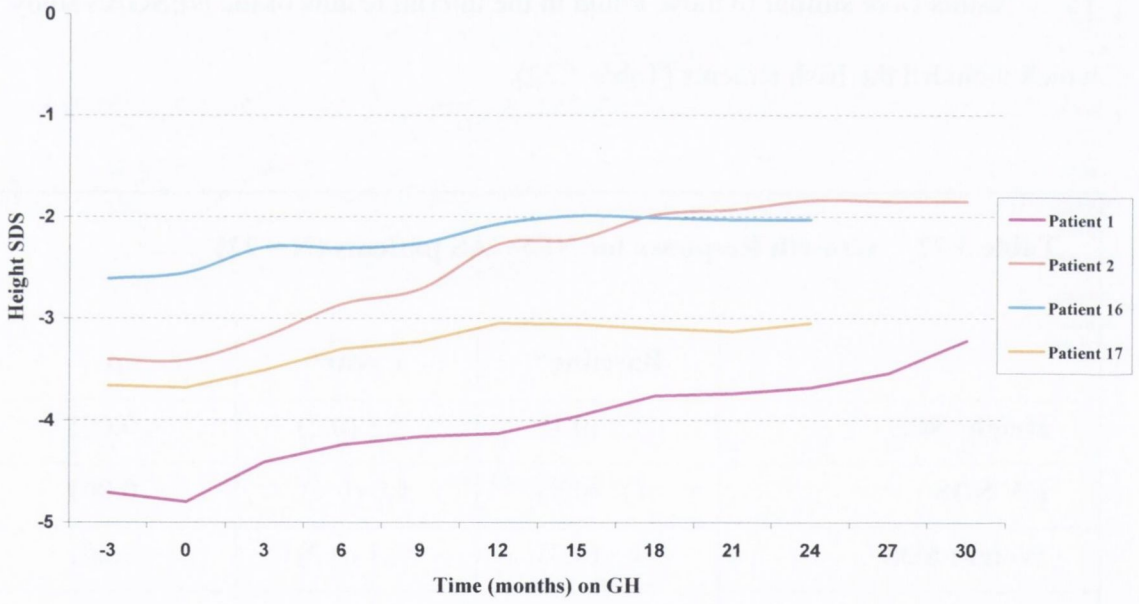
Table 3.72 Growth Response for NESGAS patients (N = 22)			
	Baseline*	**1 year***	**p**
Height SDS	-3.2 (0.1)	-2.1 (0.2)	< 0.001
HV SDS	-1.1 (0.3)	4.0 (0.4)	< 0.001
Weight SDS	-3.3 (0.3)	-2.1 (0.2)	< 0.001
BMI SDS	-1.7 (0.4)	-1.2 (0.3)	0.008

***Mean (SE)**

3.2.4.3 Growth response in older children starting GH (age > 9.9 years)

The growth response in the children who started GH later (at age 9.9 years or older) was generally less than that in those who started at a younger age (4-9 years). Two of these patients (patients 2 and 17) have been treated with lutenising hormone releasing hormone (LHRH) analogue in an attempt to arrest the progression of puberty and allow more growing time and benefit from GH treatment (Figure 3.4).

Figure 3.4 Change in Height SDS in older children starting GH (age > 9.9 yrs)



3.2.5 Comparison Group – Children born SGA eligible for GH but not yet treated

Untreated comparison group - birth data and auxology

Data on 5 children born SGA followed for at least 12 months but not yet treated with GH are presented in order to provide a comparison with the GH treated group in terms of height velocity. Birth data were similar to the GH treated group with mean birth weight SDS -2.5 (-3.2 to -2.1) and mean gestational age of 34 weeks (Table 3.73). All patients were short with mean height SDS -2.8 (-3.4 to -2.2). They were also short for parental height; mean height corrected for mid-parental height was -1.9 SDS (-2.6 to -1.0). Mean weight SDS was -3.0 (-3.9 to -2.0), mean BMI SDS was -1.7 (-2.7 to -0.7) and mean head circumference SDS was -1.4 (-1.5 to -1.3).

Table 3.73 Baseline data in untreated SGA patients (N = 5)

Measurement	Mean	SD
BW SDS	-2.5	0.4
Age (years)	5.6	1.1
Ht SDS	-2.8	0.5
Corrected Ht SDS	-1.9	0.8
HV SDS	-0.4	0.8
Wt SDS	-3.0	0.8
BMI	13.8	0.7
BMI SDS	-1.7	0.9
HC SDS	-1.4	0.1

*** Height SDS corrected for MPH mid-parental height**

The characteristics of each individual patient are outlined in the tables on birth data and baseline auxology (Tables 3.74 & 3.75). In all cases the parents have not yet consented to GH treatment for their child.

Table 3.74 Birth data individual untreated SGA patients - comparison group

Patient	Sex	Gestation	BW (kg)	BW SDS	HC (cm)	HC SDS	BL (cm)	BL SDS
18	F	40+3	2.10	-3.2	N/A	N/A	N/A	N/A
19	M	28+0	0.66	-2.4	N/A	N/A	N/A	N/A
20	M	36+4	1.90	-2.3	N/A	N/A	N/A	N/A
14	M	37+1	1.93	-2.5	N/A	N/A	44	-2.4
15	M	33+1	1.40	-2.1	N/A	N/A	39	-3.3

N/A = not available

Table 3.75 Baseline auxology individual untreated SGA patients – comparison group

Patient	Age	Ht SDS	MPH SDS	HtCorr MPH	Wt SDS	BMI	BMI SDS	HC SDS	HV SDS
18	7.0	-3.1	-1.0	-2.1	-2.7	14.6	-0.7	-1.3	-0.3
19	4.6	-3.4	-1.5	-1.8	-3.9	13.8	-1.7	-1.6	-0.7
20	4.2	-2.2	-1.4	-0.8	-2.0	13.1	-2.7	-0.9	1.0
14	6.2	-2.6	-1.6	-1.0	-3.7	13.0	-2.4	-3.6	-1.0
15	6.2	-2.9	-0.3	-2.6	-2.9	14.4	-0.9	-1.5	-0.8

Ht = height; MPH = mid-parental height; Ht Corr MPH = height corrected for mid-parental height; Wt = weight BMI = body mass index; HC = head circumference; HV = height velocity

Untreated comparison group - height velocity in children born SGA

Poor height velocity was documented in 4 patients 6 after intial presentation (mean HV SDS was -0.4 (-1.0 to +1.0)). In one case height velocity was above the mean (+1.0 SDS) following 6 months of growth monitoring, but subsequently decreased to -1.6 SDS after one year of further monitoring (Table 3.76). Height velocity deteriorated in all patients after one year of growth monitoring (mean HV SDS of -1.5 (-2.4 to -0.7)). The height velocity of this untreated comparison group was similar to the pre-treatment height velocity of the GH treated group (by independent t test $t = 1.8$, $p < 0.08$). Height velocity following one year of GH treatment in the GH treated group ($N = 12$) increased significantly in contrast to this untreated comparison group ($t = 9.74$, $p < 0.001$).

Table 3.76 Individual height velocity – untreated comparison group

Patient	Ht SDS	HV SDS	Ht SDS after 1 year	HV SDS after 1 year	Δ HV SDS
18	-3.1	-0.3	-3.3	-2.4	-2.1
19	-3.4	-0.7	-4.1	-1.4	-0.7
20	-2.2	1.0	-2.5	-1.6	-2.6
14	-2.6	-1.0	-2.6	-1.2	-0.2
15	-2.9	-0.8	-2.9	-0.7	+0.1

Ht = height; HV = height velocity; Δ HV SDS = change in HV SDS

3.2.6 Glucose Homeostasis

3.2.6.1 Oral Glucose Tolerance Test at baseline

All patients had a baseline OGTT performed prior to commencing GH treatment to out rule impaired glucose intolerance or diabetes mellitus. The OGTT was normal in all patients at baseline thereby excluding glucose intolerance in these patients (Table 3.77). Mean fasting glucose was 4.3mmol/L, at 60 minutes mean glucose was 5.8mmol/L and at 120 minutes it was 4.8mmol/L.

Table 3.77 OGTTs – Pre GH treatment

	Glucose mmol/L		
Patient	**0mins**	**60mins**	**120mins**
1	4.4	6.1	4.9
2	4.6	4.5	5.3
3	4.3	4.2	5.5
4	4.2	5.4	4.8
5	4.0	5.5	4.9
6	3.9	5.1	5.2
7	5.1	7.4	3.4
8	4.5	6.6	5.1
9	4.0	4.3	5.3
10	4.6	7.2	3.0
11	4.0	4.8	3.8
12	4.0	6.1	4.5
13	3.8	5.9	4.9
16	4.7	5.7	4.6
17	4.7	8.3	6.5

3.2.6.2 Insulin sensitivity at baseline and following 1 year of GH treatment

The 13 children enrolled in the NESGAS study, prior to commencing high dose GH (0.067mg/kg/day) were also tested by an Intravenous Glucose Tolerance Test (IVGTT) to determine insulin sensitivity. Homeostasis Model Assessment-S (HOMA2-S%) as a marker for insulin sensitivity was calculated using the fasting glucose and C-peptide values obtained during the IVGTT (Table 3.78). At baseline in 13 patients mean HOMA2-S% was 252% (SD = 110). These results are normal, considering the normal healthy individual would have a HOMA-S ~ 100%, however no specific reference values are available for children.

Table 3.78 IVGTTs – Pre GH treatment (N = 13)

Patient	Fasting Glucose	C-peptide nmol/L	HOMA2-S%
1	3.9	0.21	240.4
2	5.3	0.28	160.8
3	4.3	0.26	182.6
4	4.2	0.15	331.3
5	4.1	0.10	498.6
6	4.4	0.20	231.5
7	4.2	0.18	262.5
8	4.2	0.21	230.6
9	4.6	0.37	125.8
10	4.3	0.17	278.6
11	4.8	0.19	239.1
12	4.2	0.13	365.9
13	4.7	0.36	130.4

At one year following GH treatment in 9 patients, mean HOMA2-S% was 155% (SD = 107) as assessed by IVGTT which suggests a decrease in insulin sensitivity. However, there was no significant difference between HOMA-S at baseline and at one year by paired t test ($t = 2.12$, $df = 8$, $p = 0.07$) (Table 3.79).

Table 3.79 IVGTTs – Following one year of GH treatment (N = 10)

Patient	Fasting Glucose	C-peptide nmol/L	HOMA2-S%
1	5.2	0.80	56.6
2	4.8	0.57	80.8
3	4.5	0.38	124.0
4	3.8	0.14	353.6
5	4.8	0.51	89.7
6	3.7	0.17	301.4
7	4.4	0.25	187.3
8	4.7	0.33	140.9
9	5.4	0.74	59.4
10	5.0	pending	pending

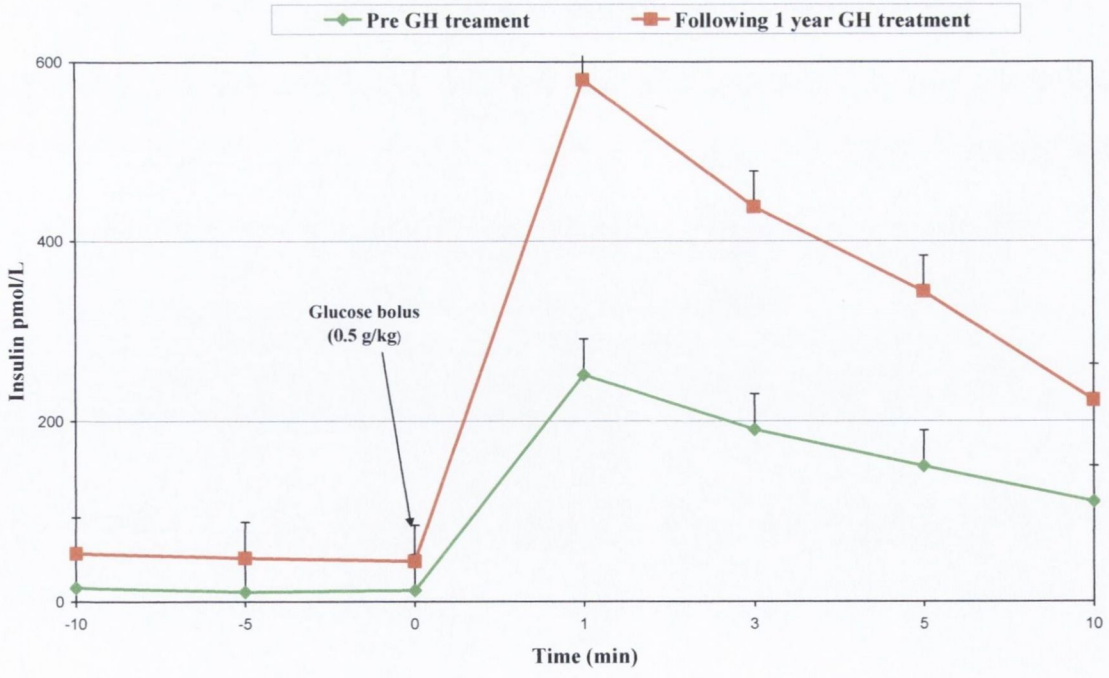
N/A = not applicable

Individual patient insulin and glucose values for each time point in the IVGTTs at baseline and one year following one year of GH treatment can be seen in Appendices XII and XIII respectively.

3.2.6.3 Insulin secretion at baseline and following one year of GH treatment

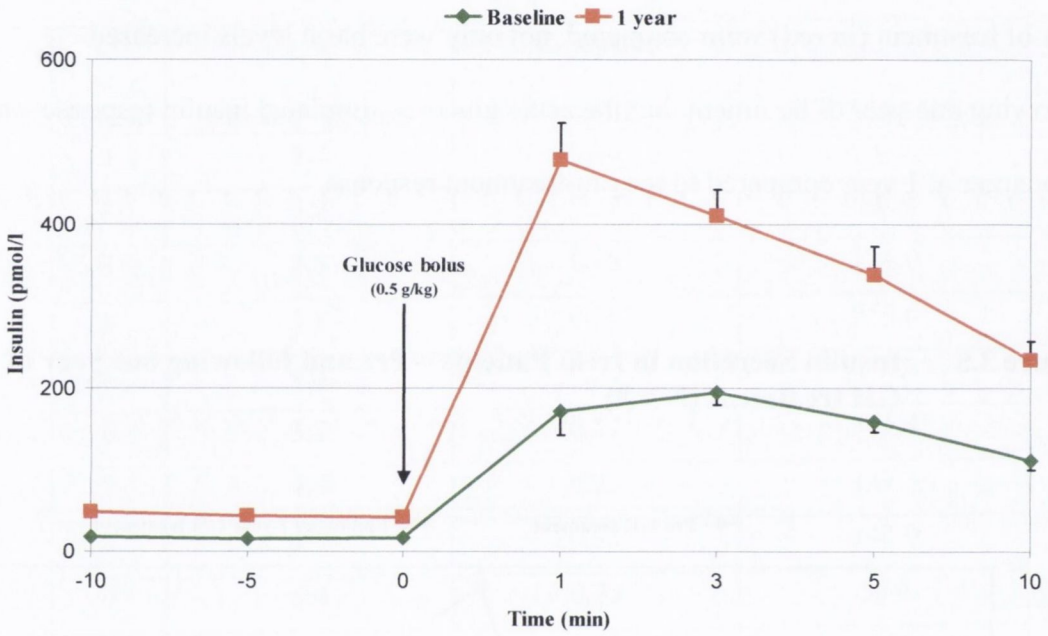
Insulin secretion was assessed by IVGTT measuring insulin levels at 3 time points prior to and 4 time points following an infusion of glucose (Figure 3.5). Data on 9 patients were available from IVGTT at both baseline and following a full year of GH treatment. When basal insulin levels before treatment (in green), and following one year of treatment (in red) were compared, not only were basal levels increased following one year of treatment, but the acute glucose-stimulated insulin response was also larger at 1 year compared to the pre-treatment response.

Figure 3.5 Insulin Secretion in Irish Patients – Pre and following one year of GH treatment (N = 9)



Similar results were seen with the interim results of the NESGAS group of 22 patients, which includes the Irish cohort (Figure3.6).

Figure 3.6 Insulin Secretion NESGAS Patients N = 22



3.2.6.4 Insulin & C-peptide values before & following 1 year of GH treatment

Insulin and C-peptide values were assessed during IVGTT. Pre GH treatment insulin values were lower than when repeated following one year of GH treatment. Fasting basal insulin levels had quadrupled and C-peptide levels had doubled, which was statistically significant ($p = 0.01$ and $p = 0.02$ respectively) indicating that insulin secretion had increased (Table 3.80).

Table 3.80 Insulin & C-peptide pre and following one year of GH (N = 9)

Measurement	Baseline*	1 year*	p
Insulin (pmol/l)	12.9 (1.6)	56.9 (9.7)	0.01
C-peptide (pmol/l)	217 (26)	433 (80)†	0.02

***Mean (SE)**

These were similar to findings in the NESGAS study interim results of 22 patients which includes the Irish patients (Table 3.81).

Table 3.81 Insulin & C-peptide pre and following one year of GH (N = 22)

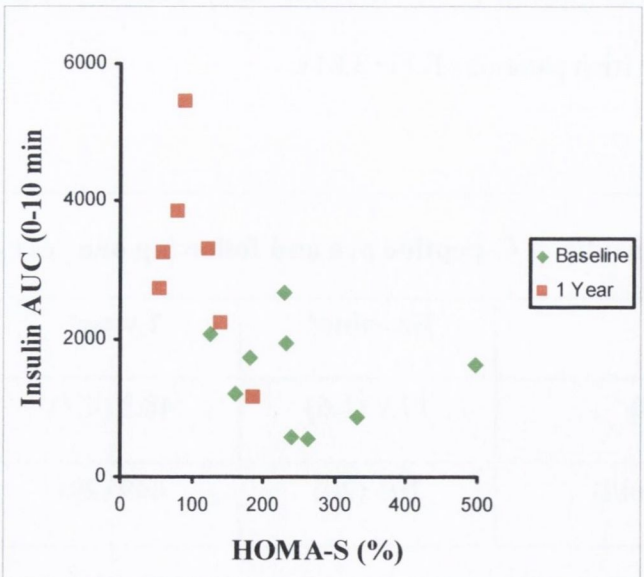
Measurement	Baseline*	1 year*	p
Insulin (pmol/l)	17.0 (1.6)	48.3 (4.7)	< 0.001
C-peptide (pmol/l)	191 (20)	449 (29)	< 0.001

***Mean (SE)**

3.2.6.5 Insulin Disposition Index

The insulin disposition index is the product of insulin secretion and insulin sensitivity. Insulin secretion as assessed by the area under the insulin curve (AUC) from 0-10 minutes during the IVGTT. The area under the curve (AUC), calculated according to the trapezoid rule, is an accurate measure of insulin secretion over a time period. Insulin sensitivity was determined by using HOMA-S% (using fasting insulin C-peptide levels). In this figure insulin secretion is plotted against insulin sensitivity before (in green) and after 1 year of treatment (in red). There was no significant change ($p = 0.5$) in disposition index (DI) (insulin secretion x insulin sensitivity) following one year of GH treatment, therefore as insulin sensitivity decreases, insulin secretion increases to compensate (Figure 3.7).

Figure 3.7 Disposition Index for patients pre GH treatment (N = 9) & following 1 year of GH treatment (N = 7)



3.2.6.6 Oral Glucose Tolerance Test - following 2 Years of GH Treatment

(a.) High dose (0.067mg/kg/day) GH treated group (N=7)

All 7 Irish patients within the NESGAS study had oral glucose tolerance tests (OGTT) performed following two years of GH. The blood glucose results were reassuringly normal. Mean glucose values at 0, 60 and 120 minutes on OGTT were normal pre GH treatment and following two years of GH treatment (Table 3.82). However there was a statistically significant increase in mean glucose value at 0 minutes following one year of GH treatment (mean 4.4mmol/L pre treatment to a mean of 5.0mmol/L at 2 years: $t = 2.7$, $df = 6$, $p = 0.04$). There was also an increase at 60 and 120 minutes but these were not statistically significant (5.4 versus 5.8 @ 60 minutes and 4.9 and 5.5 @ 120 minutes; $t = 0.7$, $df = 6$, $p = 0.5$ and $t = 1.8$, $df = 6$, $p = 0.1$ respectively). Insulin results for these patients are pending.

Table 3.82 NESGAS patients OGTTs – following 2 years of GH

	Glucose (mmol/L)		
Patient	**0mins**	**60mins**	**120mins**
1	4.7	5.4	5.3
2	5.3	6.9	5.5
3	4.6	4.9	4.4
4	5.3	7.4	6.6
5	5.1	4.2	5.9
6	5.4	5.9	5.9
7	4.7	6.1	4.7

(b.) Low dose (0.035mg/kg/day) GH treated group (N = 2)

The 2 children who received standard dose GH (0.035mg/kg/day) had only an oral glucose tolerance test (OGTT) performed at baseline, 1 year and 2 years following GH treatment. The OGTTs were normal at all 3 time points, with no significant change in the mean glucose values observed at 0, 60 and 120 minutes between baseline and one year, and baseline and 2 years (Table 3.83).

Table 3.83 Non-NESGAS patients OGTTs: pre treatment, at 1 year & 2 yrs

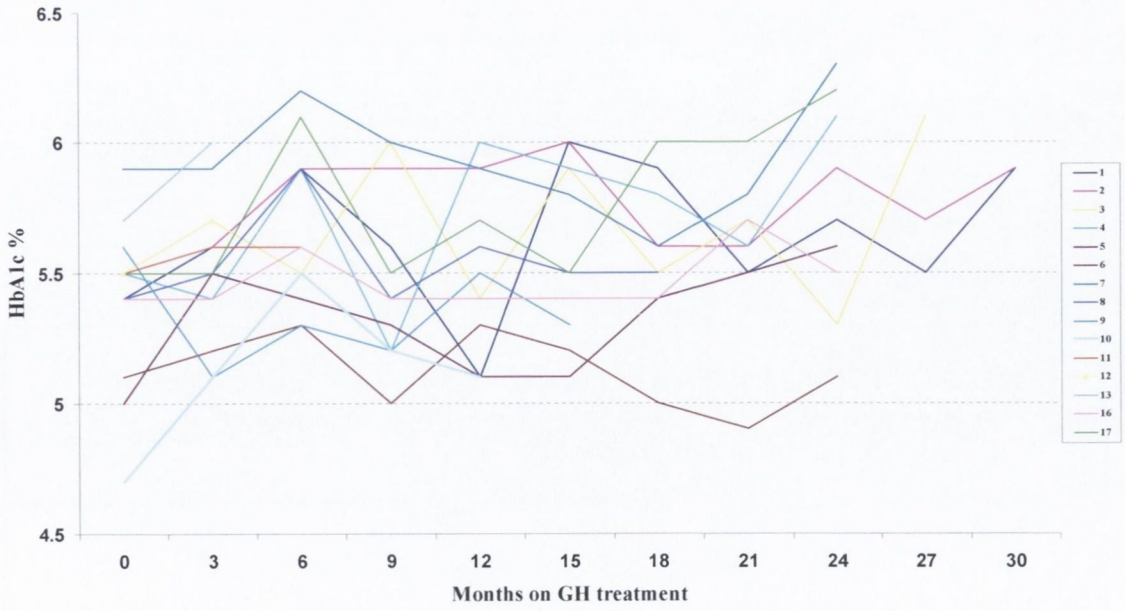
	Baseline			Year 1			Year 2		
Patient	**0***	**60**	**120**	**0**	**60**	**120**	**0**	**60**	**120**
16	4.7**	5.7	4.6	4.8	5.4	4.8	4.9	4.6	5.5
17	4.7	8.3	6.5	5.0	5.7	4.9	5.3	5.5	4.8

***Time expressed in minutes**
****Glucose values in mmol/L**

3.2.6.7 Glycosylated Haemoglobin A1c levels (HbA1cs)

Mean HbA1c at baseline was 5.4% (4.7-5.9%). There was a small increase in HbA1c following 6 months of GH treatment (mean = 5.7%, 5.3-6.2%) which was statistically significant (p = 0.002), however these levels returned towards pre-treatment values by 9 months (Figure 3.8) and at one year mean HbA1c was 5.5%. Throughout treatment HbA1c levels on all patients remained within or very slightly above the normal range (4.6-5.8%). The maximum HbA1c was 6.3% observed in one patient, and two patients had values of 6.2%. The values for individual patients can be seen in Appendix XIV.

Figure 3.8 Profile of HbA1c (%) levels pre and during course of GH treatment



3.2.7 Insulin like Growth Factors (IGF-1)

IGF-1 levels were performed on 18 patients, 15 of whom received GH treatment and 3 of whom were not treated with GH. Mean IGF-1 in the 18 patients was -0.9 SDS (-2.6 to 0.5 SDS). In addition, data is available at baseline and following one year of GH treatment in 11 patients which showed an increase in mean IGF-1 SDS from -0.8 SDS at baseline to +1.2). In 8 patients following two years of GH treatment showed similar IGF-1 SDS values; +1.1 and +1.0 SDS at one year and two years respectively (Table 3.84).

Table 3.84 IGF-1 SDS levels at baseline & following one year of GH

Number	Baseline*	1 Year*	p	2 Year*	p
11	-0.8 (0.3)	1.2 (0.2)	<0.000	N/A	N/A
8	-1.0 (0.3)	1.1 (0.2)	<0.000	1.0 (0.5)	0.008

***Mean (SE)**

These IGF-1 SDS results were similar at one year in the Irish cohort and in the full NESGAS group which included the Irish patients (Table 3.85).

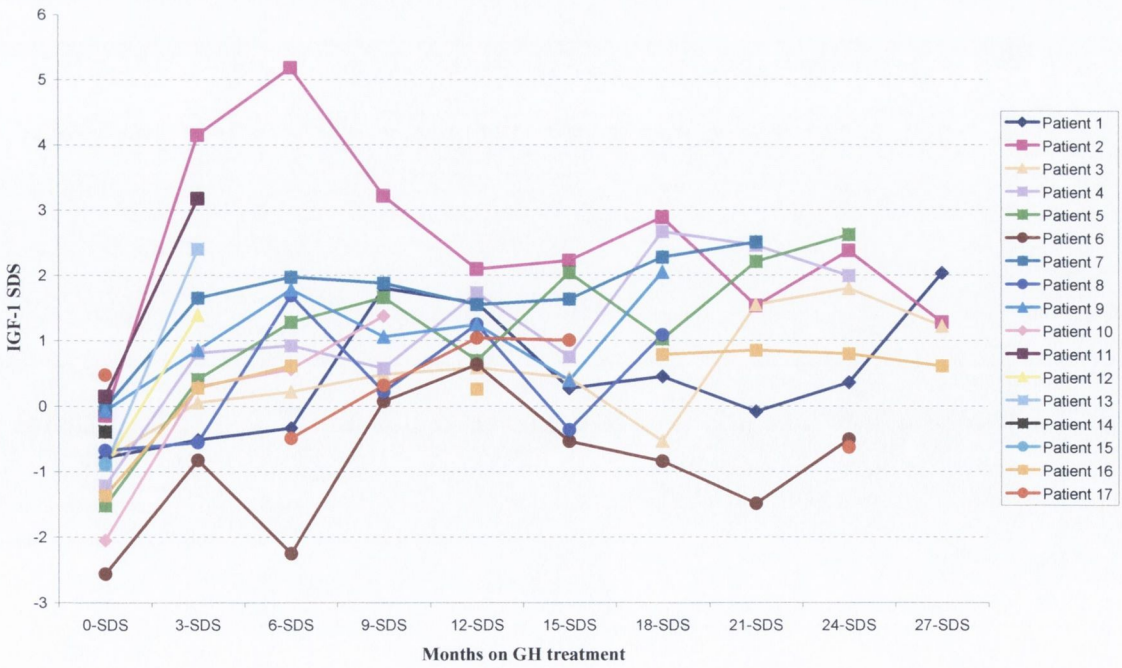
Table 3.85 IGF-1 SDS levels at baseline & following one year of GH NESGAS patients (N = 22)

No. of Patients	Baseline*	1 Year*	p
22	-1.1 (0.2)	1.2 (0.2)	< 0.001

***Mean (SE)**

A profile of 3 monthly IGF-1 levels which were assessed as part of ongoing patient monitoring are shown in Figure 3.9. It shows the IGF-1 SDS profile for all patients from baseline and during GH treatment. It illustrates the normalisation of IGF-1 SDS levels towards the mean. In all but 3 patients baseline IGF-1 SDS levels were below the mean and within 3 months of GH treatment they had begun to rise (to varying degrees). In two patients minor adjustments of GH were made: patient 2 high IGF-1 levels resulted in some concern, and the dose of GH was reduced until IGF-1 levels had normalised. In patient 6 fluctuations in IGF-1 SDS levels were seen, this patient had developed mild periorbital oedema which was thought to be related to the high dose of GH, thus it was several months before he achieved full dose of GH. Individual IGF-1 levels at baseline, and following 1 and 2 years of GH treatment can be seen in Appendix XV.

Figure 3.9 Baseline IGF-1 SDS and change over course of GH treatment



3.2.8 Associations with growth velocity – baseline & following 1 year of GH treatment

Association of IGF-1 levels & insulin secretion with growth velocity at baseline

The strongest relationship of baseline height velocity (HV) was with acute insulin secretion although this association was not statistically significant (r = 0.44, p = 0.15). There was no association between IGF-I levels and baseline height velocity (Table 3.86).

Table 3.86 Associations of IGF-1 levels & insulin secretion with baseline HV

	Height velocity SDS	p
IGF-I SDS*	r = -0.17	p = 0.5
Insulin AUC (0 - 10 min)**	r = 0.44	p = 0.15

* N = 18 ** N = 12

These were similar to findings of the NESGAS study, in 22 patients, which includes the Irish patients (Table 3.87).

Table 3.87 Associations of IGF-1 levels & insulin secretion with baseline HV NESGAS patients (N = 22)

	Height velocity SDS	p
IGF-I SDS*	r = -0.16	p = 0.5
Insulin AUC (0 - 10 min)*	r = 0.39	p = 0.04

* N = 22

Association of insulin secretion with improvements in growth velocity following 1 year of GH treatment

The increase in acute insulin secretion showed the closest association with the improvements in height velocity following one year of GH treatment although this was not statistically significant (r = 0.6, p = 0.15). Again the change in IGF-I levels was not strongly related to changes in height velocity (Table 3.88).

Table 3.88 Associations of Δ IGF-1 SDS & Δ insulin secretion with improvements in HV following 1 year of GH

	Δ Height velocity SDS	p
Δ IGF-I SDS†	r = 0.28	p = 0.4
Δ Insulin AUC (0 - 10 min)*	r = 0.60	p = 0.15

* N = 7 † N =11

These results were similar to those found in the NESGAS study of 22 patients which includes the Irish patients (Table 3.89).

Table 3.89 Associations of Δ IGF-1 SDS & Δ insulin secretion with improvements in HV following 1 year of GH [NESGAS (N = 22)]

	Δ Height velocity SDS	p
Δ IGF-I SDS	r = 0.15	p = 0.3
Δ Insulin AUC (0 - 10 min)	r = 0.44	p = 0.04

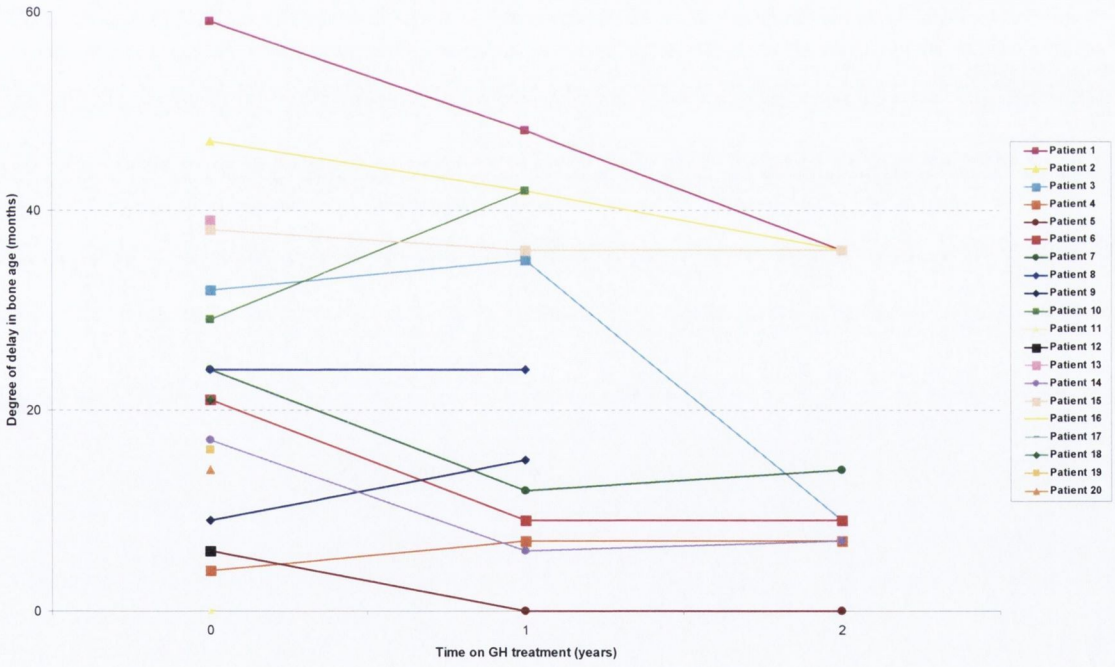
N = 22

3.2.9 Bone Age

Bone age was assessed by x-ray of the left wrist and hand using the methodology of Greulich and Pyle. At baseline, bone age was appropriate or delayed in all 20 patients. Mean delay when compared to chronological age was 21.4 months (range 0 to 59 months). Following one year of GH treatment in 12 patients, there was no change in mean bone age delay which was 23 months (range 0 to 48), and following 2 years of GH in 8 patients mean delay in bone age was 17.1 months (range 0 to 36). There was no inappropriate advancement in bone age in any patient at baseline or following GH treatment (See Figure 3.10 and Appendix XVI).

This figure illustrates the degree of delay in bone age in each patient (chronological age minus bone age) and the improvement in the degree of bone age delay while on GH treatment. All patients had delayed (N = 18) or normal bone age (N = 2) at baseline. Most patients had some small decrease in the degree of bone age delay while on GH treatment, however only one patient reached a bone age appropriate for chronological age, and no patient developed advanced bone age (Figure 3.10).

Figure 3.10 Delay in bone age as assessed at baseline (N = 20), after one year of GH (N = 12) and after 2 years (N = 9)



3.2.10 Dual Energy X-ray Absorptiometry (DXA)

DXA scans were performed at baseline and repeated at one year following initiation of GH treatment. Full body data at baseline was analysed on 13 patients, whereas in 4 patients data was available at one year but not at baseline due to technical difficulties. At baseline, mean total lean body mass was 11.9kg, mean bone mineral content was 0.49kg and mean bone mineral density was 0.80g/cm^2 (Table 3.90).

Table 3.90 Pre GH treatment DXA findings (N = 13)

Lean Body Mass (kg)*	Bone Mineral Content (kg)*	Bone Mineral Density (g/cm^2)*
11.9 (3.3)	0.49 (0.2)	0.8 (0.05)

*Mean (SD)

Comparing DXA scan results at baseline with those at one year following GH treatment in 8 patients by paired t test, statistically significant improvements in total lean body mass and total bone mineral content ($t = 7.8$, $df = 7$, $p < 0.001$ and $t = 4.4$, $df = 7$, $p = 0.003$ respectively) were found. A marginal improvement in bone mineral density was also observed but this was not statistically significant ($t = 1.3$, $df = 7$, $p = 0.2$) (Table 3.91). Values for individual patients can be seen in Appendix XVII.

Table 3.91 DXA findings at baseline and 1 year following GH (N = 8)

Lean Body Mass (kg)*	Bone Mineral Content (kg)*	Bone Mineral Density (g/cm^2)*
12.7 (3.5)	0.51 (0.2)	0.81 (0.05)
17.2 (4.7)	0.77 (0.2)	0.82 (0.05)
$p < 0.001$	$p = 0.003$	$p = 0.2$

*Mean (SD)

CHAPTER FOUR

DISCUSSION

CHAPTER 4 DISCUSSION

4.1 INTRODUCTION

Children born small for gestational age (SGA) are at risk of perinatal complications (Figueras et al., 2007, Doctor et al., 2001) (Cnattingius et al., 1998), short final adult height (Karlberg and Albertsson-Wikland, 1995, Luo et al., 1998) and health problems in adult life including the metabolic syndrome (Gluckman and Hanson, 2006, Barker, 2004a). Birth weight, the strongest determinant of perinatal survival, is a simple inexpensive measurement performed at the threshold between intrauterine and extrauterine life, and when assessed with respect to gestational age and gender, provides important information on pre-natal development and may indicate risk markers for health problems in later life. Detection of SGA should occur as early as possible, ideally by detection of fetal growth restriction, or at least at birth, so that appropriate follow up can be arranged beyond the neonatal period and into childhood.

4.2 POPULATION (1) – COOMBE WOMEN'S HOSPITAL COHORT

4.2.1 Identifying Patient Population

A two year birth cohort of 14,840 births recorded for the period 1st July 1999 – 30th June 2001 was studied. Following exclusions for congenital anomalies and syndromes, 284 SGA infants were identified which was 2% of the total infants (14,366) analysed. This is consistent with the definition of SGA used which

approximates to those infants born with birth weights below the 2nd centile for gestational age.

Birth weight measurements are determined on all babies after birth. Infants are weighed in the delivery suite using digital weighing scales which are calibrated regularly. In all but one case, mother's recall of her infant's birth weight was inconsistent with that documented in the database. Possible overestimation of birth weight can occur in cases where an infant is oedematous due to an anomaly or use of equipment such as naso-tracheal tubes used in resuscitation; however those with known anomalies and extreme prematurity were excluded from this study.

4.2.2 Excluded Babies

A major challenge in the study was the process of extracting the data from the available database and excluding those who would not be eligible for analysis. In total, 449/14804 (3%) of the infants documented in the Coombe Women's hospital database were excluded from the onset; 111/449 (25%) of these exclusions were due to documented death of the infant (either antenatal or neonatal). Infants born at a gestational age less than 28 completed weeks accounted for 57/449 (13%) of the exclusions and were excluded for two reasons: (i) Due to lack of data, the cross sectional height and weight reference curves for the UK 1990 (Freeman et al., 1995) do not allow calculation of BW SDS below 28 weeks gestation. (ii) Infants born below 28 weeks gestation have a high rate of complications of prematurity such as chronic lung disease, intra-ventricular haemorrhage (IVH), periventricular leucomalacia (PVL) and sepsis – all factors which can interfere with postnatal growth

and act as confounding variables. It may however be argued that these are the infants who are most vulnerable for post natal growth failure and thus most in need of follow-up care. Indeed, much of the literature exploring perinatal outcomes and catch-up growth pertains to very low birth weight or extremely premature infants with or without a history of fetal growth restriction. However, due to their history of prematurity, such infants are always closely followed for two years at the Coombe Women's Hospital for growth and developmental assessment, and thus the danger of growth problems in such infants not being identified is negligible. This is clearly a small proportion of infants, born extremely prematurely, which requires further study in relation to small for gestational age and outcomes in this complex group.

4.2.3 Congenital Anomalies & Syndromes

Congenital anomalies and syndromes were identified in two steps. Step one found 144/449 (32%) who were excluded from the onset due to a major congenital anomaly or syndrome; and of these, 13/144 infants (9%) were born SGA. This is not surprising as infants with certain congenital and chromosomal anomalies and syndromes are more likely to suffer intrauterine growth retardation which results in small size at birth (Baschat and Hecher, 2004, Khoury et al., 1988), (Snijders et al., 1993). As the risk of a major defect being diagnosed in the first year of life has been reported to increase from 3.3% for infants without IUGR, to 8% for infants with IUGR, the detection of IUGR may also help in the prenatal and neonatal detection of congenital anomalies (Khoury et al., 1988). The question remains as to how many infants had overestimation of birth weight due congenital anomalies such as Potter's sequence or hydrops fetalis causing severe oedema at birth.

Step two looked at 309/14,391 (2.2%) infants who were born SGA. Consultation with the Eurocat register identified a further 11/309 infants with a congenital anomaly or syndrome. Unfortunately Eurocat was not cross-referenced for the non-SGA infants hence the number of additional infants with a major congenital anomaly or syndrome in this group was not determined. For this reason it is not possible to comment on what percentage of infants overall born with congenital anomalies or syndromes were born SGA. However as low birth weight/IUGR is associated with a higher incidence of congenital anomalies one would expect more anomalies in the SGA group than the non-SGA group. The total reported prevalence rate of major congenital anomalies, based on 16 selected European centres is 23.6 per 1,000 births (2.36%) (EUROCAT Central Registry Service of Epidemiology, 1997).

Following consultation with the Child Health Systems (CHS) register, five children who were born SGA were found to have died. Unfortunately cause of death was only recorded in one case (pulmonary haemorrhage in a premature infant) so it is not possible to draw conclusions on the role of SGA in these infants' deaths, although only 2 infants were born at term so prematurity is a likely factor. Again it was beyond the scope of this study to use the CHS to identify non-SGA infants who may have died; hence the overall proportion of SGA versus non-SGA infants who died cannot be calculated.

When insufficient data on birth weight or gestation was available (90 infants), it was impossible to calculate BW SDS and hence such babies were excluded. In other cases where Apgar scores were recorded as 0 at 5 mins (47 infants) the infants were excluded as it was not possible to reliably determine if the infant had been born alive.

Review of 50 infant medical charts was undertaken to identify any infants who had been admitted to SCBU and who had a complicated medical history which may interfere with follow up. As a result, 9 infants were excluded from the SGA group for follow up. One case of Sudden Infant Death Syndrome (SIDS) at 3 months of age was identified in the SGA twin of a SGA/non-SGA twin pair. Preterm and/or low birth weight have been consistently identified across studies as one of the independent risk factors for SIDS (American Academy of Pediatrics Task Force on Sudden Infant Death Syndrome, 2005) and being born small for gestational age is thought to cause greater hypoxic-related vulnerability for SIDS (Malloy, 2007). This case highlights the vulnerability of preterm, SGA infants following discharge from hospital. A history of maternal methadone maintenance during pregnancy and neonatal abstinence syndrome in this case also increased this infant's risk of SIDS. It was not possible to establish any further cases of SIDS on consultation with the National SIDS Register due to the lack of identifying information hence it is not possible to draw conclusions on the incidence of SIDS in SGA infants in Ireland. This is in important area which warrants further research.

4.2.4 Calculation of Gestational Age

Gestational age is defined as the completed number of weeks plus days since the first day of the last menstrual period (LMP). The LMP is documented by the CWH to calculate gestational age when a mother is booking her pregnancy at the hospital. Although this method has been widely used (Thompson et al., 2001, Cnattingius et al., 1998, Thorp et al., 2002, McIntire et al., 1999), a limitation of the definition is that estimated date of delivery (EDD) is calculated assuming a regular menstrual cycle

length of 28 days. This does not take into account variations between menstrual cycle durations. Studies have reported that it is more accurate to calculate gestational age is by ultrasound scan performed in the first trimester (≤ 12 weeks). However at the time of the study this is not performed in all pregnancies (personal communication) and the reliability of the dating ultrasound scan depends on the time at which it is performed, the operator and is also subject to limitations (Degani, 2001). Other studies suggest that the most accurate method for estimating gestational age includes use of ultrasonography and the date of the LMP which correlate well with eachother and with paediatricians' assessments of gestational age in neonates (McIntire et al., 1999).

Data on first trimester ultrasound scans was not available for this cohort and in order to overcome possible limitations of using LMP to calculate gestational age, all infants with a potentially invalid gestation (> 44 weeks) were identified from the SGA Group. Review of their charts identified inconsistencies in records of gestational age and these infants were excluded from the analysis due to insufficient data. Such cases were attributable to 'late' or 'unbooked' pregnancies which may have prevented accurate calculation of gestational age. A recent Irish study (Murrin et al., 2007) excluded 10.8% of infants due to gestational ages that were not biologically credible and a previous study in the USA, using a large database reported an exclusion rate of approximately 8% for missing or unreliable information on LMP (Khoury et al., 1988). Therefore the exclusion rate for this study of 0.6% for insufficient data compares favourably. This may reflect the high standard of detailed computerised data based on patients attending the CWH.

Since July 2006 all women who now book their pregnancy at the CWH have a dating scan (personal communication). This should improve accuracy of calculation of gestational age for future studies (Taipale and Hiilesmaa, 2001, Morin et al., 2005).

4.2.5 Maternal socio-economic characteristics

The main mediating variables of IUGR include; maternal nutritional factors (maternal stature, pre-pregnancy BMI, gestational weight gain); cigarette smoking; alcohol consumption and other illicit drug exposure; all of which are also known to be risk factors for low birth weight. Given the data available, this study explored the influence of marital status, parents' occupations/socio-economic grouping and the place of residence of the mother and rates of SGA births. As with previous studies of lower birth weight (Spencer et al., 1999, Elmén, 1996, David and Collins, 1997), a general trend to markers of social disadvantage was seen in this study, with higher rates of SGA births to single mothers, to mothers from lower socio-economic groups and to mothers living in the Dublin area (city and county) when compared to non-SGA infants. This compared with Elmén et al's study of a population of 22,085 live births in Sweden which found a strong relationship with birth weight SDS and socio-economic index (Elmén, 1996) and to Spencer et al's study of 19,359 births in the UK who found that a substantial proportion of births < 2500g and < 1500g were statistically "attributable" to social inequality (Spencer et al., 1999). However, variations in the definitions of SGA used in the different studies, the settings in which they were undertaken and the outcomes explored, mean that not all observations necessarily apply to the Irish situation. Undoubtedly the socio-economic profile in Ireland is changing, and was undergoing a period of unprecedented and rapid change

around the time of the start of the new millennium (2000) when the infants studied were born.

Maternal age was not analysed in this study, however, analysis of infants born in the CWH in the year 2000, weighing 1500g or less at birth, showed that those born SGA were more likely to be born to slightly older mothers (maternal age range 20-40) compared with the AGA infants (maternal age range 17-35) (Coombe Women's Hospital, 2000). Some studies have shown that for unknown reasons, extremes of maternal age increase the risk of fetal growth restriction (Johnstone and Inglis, 1974) and low birth weight (David and Collins, 1997). However in other studies, after controlling for other confounders, maternal age did not show any significant effect (Thompson et al., 2001).

Marital Status

In this study there was a significant difference in marital status found between the SGA and non-SGA groups. In the SGA group 51% of the mothers were single, whilst in the non-SGA group only 32% of the mothers were single. This is one observation, which may reflect the impact of lower socioeconomic status on fetal growth which has been observed in other studies (Kramer, 1998) (Thompson et al., 2001, Murrin et al., 2007) even with SGA infants born at term (Doctor et al., 2001). A recent Irish study by Murrin et al, has reported a direct, graduated relationship between marital status and birth weight. However, the role of marital status as a risk factor for adverse outcomes such as infant mortality and low birth weight is complex as it has interactions with ethnicity, maternal age and education (David and Collins, 1997) (Bennett et al., 1994). Hence, a limitation of the observations from this study is that maternal age and education were not analysed in conjunction with marital status. For

example, unmarried status alone is not a good predictor of infant mortality, as has been shown by Bennett et al in her study of 10.3 million mothers. Bennett reported risk factors indicating high rates of infant mortality among unmarried Black women; women with over 3 children; women < 18 and > 34 years old; women with fewer than 12 years of education, and women with later or no prenatal care. This is due to the fact that in general unmarried women, regardless of race, tend to have higher poverty rates (Bennett et al., 1994). Similarly, Sung et al who studied over 200,000 births in the USA, reported that unmarried status appears to increase the risk of LBW much more among adult women than among teenage women, although ethnicity also plays a role (Sung et al., 1993). There is also evidence to suggest that unmarried women are more likely than married women to smoke during pregnancy (Kleinman and Kessel, 1987). The risk of mothers in de facto relationships (i.e. co-habiting) giving birth to an SGA infant was not assessed in this study however in a similar study in New Zealand of 1714 mothers, the risk was found to fall between those for married and single mothers (Thompson et al., 2001). As over 30% of infants in Ireland are now born to unmarried parents (Central Statistics Office, 2001), a trend which appears to be rising (Central Statistics Office, 2004), clearly there is a spectrum ranging from co-habiting two-parent families to unmarried supported or unsupported mothers. However, data in this respect were not available for this study and is an area which deserves further research.

Parents' Occupation and Socio-Economic Group

A difference between the SGA group and non-SGA group was found for both mothers' & partners' occupations. Occupations were used as a marker for socio-

economic group (SEG) based on the classification system provided by the Central Statistics Office Ireland (Appendix VI). The unemployment rate quoted in the national census report for the year 2002 was 8.8% and for 1996 was 14.8%, hence the finding of this study of 41% of the total mothers and 43% of the total partners belonging to SEG 11 ("others gainfully occupied and unknown") suggests that there was incomplete data for this variable. It is possible that the occupations of a large proportion of this group were "unknown" instead of unemployed but this was not possible to quantify with the data available. However, the general trend to lower socio-economic groups for mothers of SGA infants and their partners compared to those of non-SGA infants, and that they were less likely to be in the higher socio-economic groups again suggests that socio-economic factors may very well have a role in the incidence of SGA births. These observations are consistent with previous studies where Lieberman found maternal education level and being in receipt of welfare support to be risk factors for premature birth in a study of over 8,000 women in the USA (Lieberman et al., 1987). In addition, David and Collins found > 12 years of maternal education to be a protective factor for low birth weight in her offspring (David and Collins, 1997). However as borne out by these studies, level of education of the mothers and their partners may be a more suitable measure of economic status, especially if used in conjunction with data on occupation; however such information was not available on the database studied. The mechanism by which poorer socioeconomic status and lower educational levels may play a role in fetal growth may be linked to the quality of women's diets before and during pregnancy. As reported by Robinson et al, educational attainment was the most important factor related to diet found in a study of 6125 non-pregnant 20-34 year old women of reproductive age in the UK (Robinson et al., 2004). Murrin et al also reported

educational level of the mothers' parents to be independently associated with maternal BMI; those with higher educated parents having a lower self-reported pre-pregnancy BMI in a recent Irish study (Murrin et al., 2007). An alternative crude measure of socioeconomic status in Ireland to use is means-tested General Medical Services (GMS) eligibility which was not explored in this study. In addition some of these factors may influence the level of uptake of antenatal care, and prevention of risk factors for SGA such as maternal smoking and poverty.

Geographical Distribution

There was a significant difference in the geographical distribution of the mothers of SGA infants compared with mothers of non-SGA infants. A higher proportion of mothers of infants born SGA were living in the Dublin area (city and county) compared with those in non-SGA group (76% versus 68%). As the Coombe Women's Hospital (CWH) is an urban hospital largely serving the Dublin South West area, it is difficult to draw any definite conclusions from this observation without closer examining the reasons why women outside the Dublin area attended the Coombe Women's Hospital (CWH) for delivery of their infant. In addition, many of the addresses given by mothers at booking may have been temporary addresses especially in the unbooked or late bookers and in the immigrant population, who may have moved out of Dublin following their infant's birth. This is also reflected by the fact that 16% of addresses were no longer valid (with no forwarding address) when mothers were written to for the follow-up study 4-6 years after the birth of their child. As outlined by Zimmer et al, variation by place of residence can be a function of differences in characteristics of individuals, differences in urban and rural

communities, or a combination of individual and community factors (Zimmer, 2006). However, the higher urban distribution of mothers of SGA infants compared to non-SGA infants may point to a general socio-economic trend which has been observed in the other results of this study. Although urban poverty has been identified as a risk factor for low birth weight in a study of over 100,000 births in the USA (Collins and David, 1990), the literature on SGA and IUGR does not specifically refer to urban versus rural place of residence as a risk factor, but rather to socioeconomic disadvantage (Kramer, 1998). According the Central Statistics Office, rates of consistent poverty and those at-risk of poverty, are higher in urban compared to rural areas (Central Statistics Office, 2007b), as are rates of smoking (Central Statistics Office, 2007c).

Social determinants of health are important, generally, yet can have different effects in different settings from urban to rural, between countries, between cities, and within cities (Ompad et al., 2007) however, the results of the many studies looking at urban and rural differences in socio-economic status, education levels and health may not be applicable to the Irish setting. Perhaps more important issues to examine rather than urban or rural place of residence as markers for social deprivation would be social determinants of health such as membership of the travelling community, refugee status or type of housing and exposure to consistent poverty (Central Statistics Office, 2007a), factors which were not possible to assess with the data available for this study. However the changing demographic profile of Irish urban and rural settings with overall improvements in affluence, employment rates and infrastructure over the past decade and including the study period, would suggest that place of residence has only a minor role in rates of SGA/IUGR and that factors such as maternal age,

socioeconomic status, education level and maternal smoking during pregnancy are more important.

4.2.6 Ethnic Origin

No difference was found between the SGA group and non-SGA group with respect to mothers' place of birth or mother ethnic origin in this study. Although the literature suggests that ethnicity may have a role in birth weight (Sung et al., 1993, Thompson et al., 2001, David and Collins, 1997, Fang et al., 1999), the findings of this study would suggest that the non-national immigrant population was not over-represented in the SGA group. This may be related to a variety of reasons. Many infants of "unbooked" pregnancies (mothers who receive no antenatal care) or "late bookers" (those attending 2 to 28 days before delivery) may not have had accurate estimation of gestational age. As mothers often booked late it was also not possible to reliably estimate gestational age by ultrasound scan. Hence it was not possible to reliably calculate birth weight SDS and infants were excluded from this study due to gestations which were not valid (> 44 weeks gestation) calculated on the basis of mother's reported LMP. It is hence conceivable that some cases of SGA in non-national minority ethnic groups were not detected. However, a recent Irish study of 1,954 deliveries to immigrant women, in another Dublin maternity hospital, the Rotunda Hospital, has identified 'late booker' immigrants (20% of the deliveries) as a high-risk group. The 'late bookers' infants were more likely to be preterm, low birth weight and had a higher rate of neonatal ICU (NICU) admissions ($p < 0.01$) (Treacy et al., 2006).

The classification system chosen to analyse ethnic groups was that developed by the Perinatal Institute in the UK (Gestation Network, 2007) (Appendix V) is the classification recommended by the Royal College of Obstetricians and Gynaecologists in the UK. Although this was the most suitable system available, it is noted that the ethnicity profile of the UK differs greatly to that of Ireland. Due to small numbers, the subgroups of minor ethnic groups were not examined individually. For example, no distinction was made between infants of Black African mothers and infants of Asian mothers in the study. Looking at international studies, we would expect African-born black mothers to have bigger infants (similar to Irish mothers) than Asian mothers (David and Collins, 1997) (Fang et al., 1999) (Thompson et al., 2001, Gould et al., 2003). Hence pooling of such infants in the same group may mask the influence of such ethnicities on birth weight.

In contrast to these mothers, there was a statistically significant slightly higher number of partners in the SGA group compared to non-SGA group who were of non-European origin (13% versus 8%). However the influence of paternal ethnicity on birth weight is thought to be much less than that of maternal ethnicity due to the factors involved in maternal constraint (Barker, 2004a).

It is therefore not possible to draw conclusions on the precise role of ethnic origin in this study.

4.2.7 Lifestyle Factors

Smoking

Overall there was a 25.8% rate of maternal smoking in pregnancy in the cohort studied. This compares with rates of smoking found in similar studies (26.2%) (Horta et al., 1997) (30%) (Kramer, 1998), however a lower rate (11%) has recently been reported in the USA (Martin et al., 2005). Overall rates of smoking for women (irrespective of pregnancy status) in the 18-34 year age group reported by the Central Statistics Office were 40% and 33% for 1998 and 2002 respectively (Central Statistics Office, 2003). There was a significant difference found in this study in the percentage of mothers of SGA infants who smoked during pregnancy compared with mothers in the non-SGA group. Overall 55% of mothers of infants born SGA smoked in pregnancy versus 25.7% of the mothers in the non-SGA group (number of cigarettes ranged from occasional to > 20 cigarettes per day). Similarly, a recent Irish study has shown a clear gradient in relation to maternal smoking, from 38% of mothers of infants in the lowest quintile for birth weight having smoked, versus 11.4% of mothers of infants in the highest (Murrin et al., 2007). These findings while concerning are not surprising as cigarette smoking during pregnancy is the single most common cause of impaired fetal growth (Kramer, 1998) and is also one of the most important avoidable factors associated with low birth weight (Horta et al., 1997). In comparison with a specific study of rates of maternal smoking in groups of SGA infants compared with AGA infants (25% versus 17%) (Doctor et al., 2001) the rate of maternal smoking in the SGA group in this study appears very high. However, in Doctor et al's study, SGA was defined as birth weight < 10th centile. The number of cigarettes smoked also appears to be important. For example, McDonald et al found

that smoking more than 20 cigarettes per day was associated with a more than threefold increased risk of delivering an infant with a birth weight <5th centile (McDonald et al., 1992). Similar results have been found in this study with 4% of mothers of SGA infants smoking more than 20 cigarettes per day versus 0.7% in the non-SGA group. The economic costs of smoking in relation to low birth weights are substantial and as it is one of the most preventable factors associated with SGA births, it raises clear public health issues in this country. With intensive anti-smoking assistance to pregnant women, some studies have shown that some fetal growth retardation can be overcome (Sexton and Hebel, 1984). Even women who stop smoking in the first trimester of pregnancy may have a risk of IUGR similar to that of non-smokers (Horta et al., 1997). However, other risk factors interact with smoking during pregnancy; it has been shown only to have half the impact on fetal growth in obese versus thin mothers, and in black versus white mothers (Cliver et al., 1995), and this is clearly just one of the contributory risk factors for SGA, which interacts with social deprivation, maternal education and diet during pregnancy. In addition, implementation of best practice to promote prenatal smoking cessation is shown to be limited due to resource and organisational issues (Hartmann et al., 2007). Although Ireland has led the way in Europe with the introduction of the law banning tobacco use in the workplace in March 2004 (McElvaney, 2004), (The Lancet, 2005, Spinney, 2007) smoking rates in young people remain high (16% of 12-17 year olds) (Office for Tobacco Control, 2006). The vast majority of smokers start smoking by age 17, but young women are more likely to start smoking later than young men, but are also more likely to continue smoking later in life. A study by the Office of Tobacco Control has reported that 25% of women who commence smoking do so after age 17 years (Office for Tobacco Control, 2003). Hence advertising campaigns to

deglamourise smoking, targeted specifically at teenage girls, such as the 'NICO' campaign, developed in 2000 (Institute of Advertising Practitioners in Ireland, 2004), are well founded. However interestingly, the effects of maternal smoking during pregnancy are not highlighted to this younger age group and this is an area that requires further development of specific campaigns.

Alcohol consumption

There was no difference found in the rates of reported alcohol consumption in pregnancy between the group of mothers of SGA infants and those of non-SGA infants. However, quantification of alcohol consumption can be difficult as people's perception of a unit of alcohol and reliability of self-report of alcohol consumption vary (Sanchez-Craig and Annis, 1982),(Chang et al., 1999) (Robles and Day, 1990). Pregnant women may under-report prenatal alcohol consumption due to feelings of guilt or fears of social or medical disapproval, which has led some researchers to suggest that women reporting more than 1.3 drinks per week antenatally may be drinking at levels which risk alcohol-related birth defects (Jacobson et al., 1991). The effects of prenatal exposure to alcohol have been found to have an influence not only on growth of the fetus but also that of the infant and child (Day et al., 1990, Jones and Smith, 1973, Day et al., 1994, Carter et al., 2007). Therefore, obtaining accurate information about prenatal alcohol consumption is important, as the risk for negative neonatal outcomes ranging from subtle developmental problems to fetal alcohol syndrome may occur with as little as one drink per day (Jacobson, 1994). Risk-drinking during pregnancy has been defined as a level of maternal drinking associated with adverse pregnancy outcome, including developmental deficits in the offspring and has been quantified as 1 ounce or more of alcohol per day (Sokol et al., 1989). A questionnaire (T-ACE) for health care workers designed specifically to detect risk

drinking during pregnancy has been developed (Sokol et al., 1989), however its application would undoubtedly increase workload for those involved. The observations of follow-up studies in children (Carter et al., 2007, Day et al., 1990), are particularly concerning given that Ireland has one of the highest rates of alcohol consumption in the European Union (Department of Health and Children, 2004), and that one recent Irish study has highlighted increased rates of alcohol-related pancreatitis especially in women in the 20-29 year age group which parallels increased rates of binge-drinking in Ireland (O'Farrell et al., 2007).

Fetal alcohol syndrome (FAS) is characterised by specific growth, mental and physical birth defects associated with the mother's high levels of alcohol consumption in pregnancy (Jones and Smith, 1973). Fetal alcohol spectrum disorder (FASD) is a term used to describe the range of effects caused by alcohol consumption during pregnancy which is also associated with low birth weight for gestational age. Interestingly, there were no cases of FAS or FASD detected during the analysis of the infants with congenital anomalies and syndromes conducted during this study. There are no official statistics available for the prevalence of FASD in Ireland. However, applying the rates of FAS reported by the Substance Abuse and Mental Health Services Agency, Center for Disease Control in the United States (Ryan and Ni Chionnaith, 2005) to the 2002 Irish birth rates, we can estimate that 1% could have FASD. The incidence may even be higher due to the high rate of binge drinking among young women in Ireland (Ryan and Ni Chionnaith, 2005). Clearly according to the above statistics we should expect an incidence of approximately 140 infants to have been born with FASD in the two year cohort studied, although it is possible that

certain minor anomalies consistent with the features of FAS were not indicated on the database.

A diagnosis of fetal alcohol spectrum disorder had been queried (but not confirmed) by health professionals in one child at age 3 with a history of developmental delay and poor social circumstances. The mother reported consuming 1-2 units of alcohol during her pregnancy which was consistent with that documented on the CWH database. Of note, when seen for auxological assessment at age 6 years, this child had failure of catch-up growth with short stature (height SDS = -2.6, weight SDS = -3.7). Of particular concern was his head size (-3.6 SDS). He is currently in mainstream education but requires additional remedial teaching. In addition, as he fulfils the criteria for treatment with GH, he is being worked up for future inclusion in the NESGAS study. This again highlights the importance of follow-up of children born with low weight for gestational age so that FASD can be detected early and appropriate interventions made. Although many paediatricians may lack expertise in recognition of the characteristic features of the disorder, short training sessions by dysmorphologists have been reported to help improve this situation (Jones et al., 2006) and clearly identification of this condition in Irish children is an area warranting attention.

4.2.8 Maternal auxology

Maternal Height

Mother's reported heights were not available in many cases (~30%). In addition, as women's heights were not routinely measured using standard auxological methods,

the accuracy of self-reported heights comes into question. However with the available data, a significant difference in reported maternal height SDS was seen between the two groups with taller mothers found in the non-SGA group. These results are not surprising as smaller women tend to deliver smaller babies (Gluckman and Hanson, 2004, Bernstein and Divon, 1997, Thompson et al., 2001). Some of the infants born to smaller mothers therefore may be constitutionally rather than pathologically small. This is ideally assessed using ultrasonography and customised fetal growth charts which adjust for physiological variation in order to identify those babies who are pathologically small (Gardosi, 2006).

Maternal Body Mass Index

There was no significant difference in mothers' BMI found between the two groups, but a higher number of overweight (27% versus 14%) and obese (11% versus 5%) mothers were seen in non-SGA group compared with the SGA group. The findings of this study may not be truly representative of the whole cohort, as it was only possible to calculate BMI in 15.5% of mothers of SGA infants and in 21.9% of mothers in the non-SGA group, due to lack of data on booking weight and height. It does however highlight the importance of accurate measurement of maternal height and weight at booking due to its role in the individual adjustments required in determining normal or pathological fetal growth (Gardosi, 2006). In addition, consistent with increased rates of obesity in the general population, there appears to have been an increase in maternal weight at booking (Kanagalingam et al., 2005) (Murrin et al., 2007) which has had a significant impact on increased birth weight and other pregnancy outcomes (May, 2007, Jensen et al., 2003). A Scottish study reported an 1.37 unit increase in adjusted mean booking BMI over the period 1990 to 2002/2004 (Kanagalingam et al., 2005). A recent Irish study by Murrin et al of self-reported pre-pregnancy maternal

BMI and infant birth weights has shown mean BMI of the mothers at first booking visit to be 23.74kg/m^2 (range 14.9-44.95). The study reported an association between lower birth weight, regular smoking and BMI <25. In addition, the rate of maternal overweight or obesity tended to increase in higher birth-weight groups (Murrin et al., 2007). The BMI of the expectant mothers was also positively associated with a participating sub-group of their own mother's BMI, another example of the possible intergenerational effects of fetal growth and the role of maternal education.

The literature would suggest however, that maternal weight gain in pregnancy may be one of the most important predictors of infant birth weight, with lower and higher than recommended weight gain predicting low infant birth weight (May, 2007, Lawton et al., 1988, Stotland et al., 2006). In the study of 233 mother-infant pairs by May et al in the USA, lower (162g) and higher (153g) than recommended maternal weight gain predicted lower infant birth weight (May, 2007). In particular, Lawton et al, in a study of 158 low-risk pregnant women in Manchester reported that poor maternal weight gain between 28 and 32 weeks gestation was associated with a higher rate of birth weights below the 10th centile (Lawton et al., 1988). Another study in the USA looking at 10,418 pregnant women found that maternal height, hypertension, caesarean delivery and fetal size positively correlated with rate of maternal weight gain in each trimester (Abrams et al., 1995). Stotland et al's retrospective cohort study of 20,465 non-diabetic, term, singleton births showed increased odds of small for gestational age (OR 1.66) with gestational weight gain below guidelines of the Institute of Medicine (Institute of Medicine, 1990) (Stotland et al., 2006). It was not possible in this study to assess any possible association between maternal weight gain in pregnancy with SGA births due to the limitations of the data available. However, this area has profound implications for obstetric management during antenatal care

and education of mothers regarding diet, especially given the current trends of adult obesity. This is clearly an area warranting further research in relation to SGA, and consideration should be given to include such information in the database so that high risk pregnancies based on maternal weight gain can be identified and audited.

4.2.9 Medical Disorders in Pregnancy

Medical Problems in Pregnancy

There was no significant difference overall in the rate and type of medical problems observed in the SGA group compared with the non-SGA group. Although numbers were small, the rate of diabetes in pregnancy (gestational or pre-existing) was higher in the non-SGA group although this was not statistically significant. As hyperinsulinaemia of diabetic pregnancies is known to contribute to higher birth weight (Lindsay et al., 2000) the lower rate of diabetes in pregnancy for SGA infants is not surprising. Despite changes in diabetic management and obstetric practice over the past 40 years which have resulted in enormous improvements in the outlook for offspring of mothers with diabetes, this has not been associated with a reduction in overgrowth of the fetus (Johnstone et al., 2006) or diminishing risk of diabetes and obesity experienced by offspring (Lindsay et al., 2000). Due to the large numbers in the study it was not possible to examine individual medical conditions more closely and for this reason it is conceivable that small effects on fetal growth relating to specific medical problems may have been masked due to the pooling of different conditions together in the analysis. However, in the future it would be interesting to explore any possible effect of severe or prolonged hyperemesis gravidarum on birth weight due to the known associations of maternal nutrition and pregnancy weight gain with fetal growth.

Maternal Hypertension

As expected, there was a significant difference in the percentage of mothers experiencing hypertension overall between the two groups. There was a higher

proportion of mothers of SGA infants experiencing pre-eclampsia compared with the non-SGA group (13% versus 5%). Rates of hypertension without proteinuria were similar (7% versus 5%). These results are not surprising as the fetal growth restriction has been clearly associated with hypertension of pregnancy in various studies (Heard et al., 2004, Martikainen et al., 1989, Scott, 1981). This study did not distinguish between pre-existing hypertension and pregnancy induced hypertension as in other studies (Thompson et al., 2001), however a clear link with SGA and pre-eclampsia has been demonstrated.

4.2.10 Fetal Problems in utero

As expected there was a significant difference between the two groups in the rate of detection of fetal problems in utero, with higher rates IUGR (40% v 3%) and markers of fetal distress and factors associated with fetal distress (abnormal fetal blood flow and oligohydramnios). The rate of detection of IUGR depends on the rate of fetal ultrasonography; therefore those in whom there is clinical suspicion of growth retardation are more likely to have serial scans. However, in numerous studies clinical examination has not been shown to correlate well with detection of IUGR (Tejani and Mann, 1977, Hall et al., 1980, Rosenberg et al., 1982, Persson et al., 1986), although use of a customised fundal height chart does improves clinical accuracy in prediction of SGA fetuses and thereby a reduction in unnecessary investigations for fetal growth (Gardosi and Francis, 1999). In theory the rate of diagnosed IUGR (40%) by ultrasonography in the SGA group suggests both a high standard of clinical assessment leading to appropriate scanning and also a high standard of scanning itself which is also supported by the relatively low rate of IUGR (3%) detected in the non-

SGA group. However, this also depends on the percentage of scans being performed which do not detect IUGR or in which an SGA infant is missed, as analysis of fetal growth velocity depends on at least two separate ultrasound scans. It was not possible to explore rates of fetal ultrasonography with the data available however it would be useful in the future to determine what percentage of mothers in each group had serial antenatal scans. Of note, over the past year the Coombe Women's Hospital has changed its policy and only those where a fetus is found on ultrasound to be $\leq 5^{th}$ centile for weight will have further fetal growth scans (personal communication). What are truly of interest are those fetuses in which IUGR goes undetected, either due to a lack of scanning due to lack of clinical suspicion, or problems inherent with the scanning process itself. As the accuracy of both ultrasound and gestational age dating are subject to limitations (Degani, 2001) (as discussed in section 4.2.4), errors would be expected to occur in the more marginally growth-restricted infants. On the other hand, a fetus with growth restriction may not be SGA as defined by the cut-off definition used (Chard et al., 1992). This has also been highlighted by a study of 29,916 preterm infants (23-34 weeks) by Garite et al where 37% of those who had been antenatally diagnosed with IUGR had a birth weight > 10th centile (Garite et al., 2004). Similarly an Irish study by Stratton et al in 1995, also from the Coombe Women's hospital, demonstrated that 38% of term infants with a birth weight between the 10th and 90th centiles had third trimester ultrasound evidence of reduced growth, but that it was not associated with increased perinatal moribidity (Stratton et al., 1995). In this study, although such observations may explain the 3% rate of IUGR fetuses detected in the non-SGA group, the results however do not reveal the percentage of SGA infants who were constitutionally small, which is another argument for the case to use customised fetal growth curves (Gardosi, 2006).

4.2.11 Labour and Delivery

Onset of labour

There was a significant difference in the type of labour onset (or lack thereof) in the mothers of the group of SGA infants compared with non-SGA infants. Mothers in the former group were less likely to go into spontaneous labour (45% versus 66%) due to the higher rates of obstetric intervention (induction of labour, elective and emergency Caesarean section) before onset of labour. These results are not surprising as the detection of fetal growth problems will inevitably lead to closer obstetric monitoring and detection of signs of fetal distress leading to a lower threshold for operative delivery before term (Gardosi et al., 1997). IUGR is an indication for induction of labour especially among preterm pregnancies (Ananth et al., 2003). Other factors associated with IUGR such as multiple pregnancy and oligohydramnios are also more likely to lead to Caesarean section (Chauhan et al., 2007, McCarthy et al., 2007). Of note a study of antenatal ultrasound findings, birth weight and perinatal outcome in 285 term births at the Coombe Women's Hospital in 1995 by Statton et al, found that there was a increased incidence of Doppler abnormalities, induction of labour, meconium staining of liquor and intrapartum fetal blood sampling in infants whose birth weight fell below the 10th centile for gestational age (Stratton et al., 1995).

Type of delivery

Following on from differences in rates of spontaneous labour onset, there were also significant differences in the type of delivery between the SGA group compared with the non-SGA group, with higher rates of both elective and emergency Caesarean section being observed in the former. Of note, the discrepancy between the rates of emergency Caesarean section seen here (19%) when compared to the category "onset of labour" (12%) as discussed above can be explained by the fact that all types of emergency caesarean section (those with and without labour) are included under the former. This would suggest that an SGA fetus is more likely than a non-SGA fetus to experience intrapartum problems leading to indications for emergency caesarean section (see sections 3.1.9.4 "Indication for caesarean section or instrumental delivery" and 3.1.9.5 "Intrapartum problems"). Higher caesarean section rates reflect both the higher incidence of maternal conditions (pregnancy-induced hypertension) leading to IUGR, and concern regarding fetal compromise (Aucott et al., 2004). The very strong relationship between late fetal death (stillbirth at $\geq$ 28 weeks gestation) and SGA fetuses highlights the fact that an extremely SGA fetus must be closely monitored (Cnattingius et al., 1998). The known risks and increased monitoring in turn, increase the rate of elective caesarean section as obstetricians pre-empt the anticipated problems by delivering the fetus before such problems arise, although current data is not sufficient to justify a policy of elective caesarean section of all small for gestational age infants (Royal College of Obstetricians and Gynaecologists, 2002, Grant, 1997).

When data for type of delivery was analysed separately for nulliparous and multiparous women for the two groups (SGA v non-SGA), this study found a

significant difference in the type of delivery in both nulliparous and multiparous mothers of SGA infants compared with the SGA group, with higher rates of both emergency and elective caesarean. The reason for analysing nulliparous separately from multiparous pregnancies is that primigravid women are known to have different labours and their own pregnancy complications (Bai et al., 2002), also rates of delivery by caesarean section or instrumental assistance are higher in primigravidas than in multigravidas (Coombe Women's Hospital, 2000). However, the findings of this study would suggest that SGA rather than parity is a risk factor for operative delivery.

There was no significant difference between the two groups in the indication for caesarean section or instrumental delivery, although fetal distress as an indication was higher in the SGA group (71% v 60%). This is not surprising as due to closer monitoring of known SGA fetuses, fetal distress is more likely to be detected and to lead to operative delivery. Fetal growth restriction is also associated with intrapartum fetal distress and metabolic acidosis, which in turn, increase the risk of hypoxic encephalopathy and cerebral palsy (Figueras et al., 2007) (Jarvis et al., 2003). In addition, a four-fold risk for adverse perinatal outcome is associated with undiagnosed SGA fetuses (Lindqvist and Molin, 2005). A study by Doctor et al found that mothers of term SGA infants had similar rates of caesarean section compared to AGA infants. However in that study fetal distress was more commonly listed as an indication for caesarean section (45% of mothers compared with 20%), although numbers were smaller than in this study (Doctor et al., 2001).

There was a significantly higher rate of intrapartum problems in the group of SGA infants compared with the non-SGA group. Signs of fetal distress (abnormal CTG, fetal acidosis, meconium stained liquor) were more frequent in the SGA infants (29% v 19%). This most probably explains the increased rate of obstetric intervention (operative and instrumental delivery) as discussed above. However, analysing the data separately for term and preterm infants, this difference was only observed for the group of term SGA infants when compared to the non-SGA group. In the preterm SGA infants there were equal rates of fetal distress (8%) in preterm infants being seen in both the SGA and non-SGA groups. This could reflect different management of term compared to preterm infants during labour, or could be explained by the lower numbers in the preterm group.

4.2.12 Parity, Multiple Pregnancy and Birth Order

This study found a difference between two groups in terms of maternal parity with 49% of the mothers of SGA infants being nulliparous versus 40% in the non-SGA group. This is consistent with previous studies where increased risk of fetal growth restriction was shown with nulliparity or grand multiparity ($\geq$ 5 previous live births) (Vorherr, 1982). The effect of grand multiparity was not seen in this study, probably due to the small numbers involved, however gravida 2 or 3 has been identified in the women at lowest risk of giving birth to a low birth weight infant which was also found in this study (36% of mothers in SGA group were gravida 2 or 3 versus 47% in non-SGA group) (David and Collins, 1997). The incidence of delivery of a growth-retarded infant has been shown to increase if a woman has previously delivered a similarly affected infant (Bernstein and Divon, 1997). This is due to persistence of some of the factors which may have been responsible for the fetal growth restriction observed in the first pregnancy (Bernstein and Divon, 1997), however such analysis in this study was not possible with the available data.

There was a significant difference between the SGA and non-SGA groups in the multiple pregnancy rates. This was an expected observation as multiple pregnancy is associated with smaller birth weights (on average 900g lighter at birth than singleton infants of the same gestational age) (Phillips et al., 2001) (Hindmarsh et al., 2002). No triplet pregnancies were seen in the SGA group but there was higher rate of twins (13% v 2%). Interestingly, none of the infants in the three sets of triplets born during the study period, was born SGA. This could reflect the close obstetric monitoring likely to have occurred during the triplet pregnancies, leading to elective premature

delivery in the event of any growth problems being detected. However, given the (expected) very small number of triplet pregnancies, it is not possible to draw any concrete conclusions on the incidence of SGA/IUGR or lack thereof in such pregnancies, especially without ultrasonography data. Neither were monozygotic and dizygotic twins examined separately. Monozygotic are different to dizygotic twin pregnancies as birth weight discordance in monozygous twins is likely to be a result of differences in nutrient portioning and blood supply between twins, an extreme example of which is the Twin-Twin Transfusion syndrome (Phillips, 2004). In dizygotic twins there are genetic differences which may play a role in fetal growth, whereas in both cases discordance may reflect adaptive responses by twins in response to limitations in the fetal environment (Blickstein et al., 2000). However many studies would suggest that within-pair birth weight difference is the most important determinant of risks to adult health associated with low birth weight in twins, rather than absolute birth weight difference or zygosity, (Iliadou et al., 2004, Bo et al., 2000, Poulsen et al., 1997).

No significant difference in birth order was seen between the groups of SGA twins versus non-SGA twins. Although labour and delivery are associated with risks to the second twin at all gestations, and the second twin at term is at increased risk of perinatal morbidity and mortality (Smith et al., 2007, Thorngren-Jerneck and Herbst, 2001, Armson et al., 2006), it was beyond the scope of this study to further examine the relationship with birth order and obstetric outcome. Further analysis of the data may be warranted to establish the rate of high-level birth weight discordance (for example >25%), detection of IUGR in one or both twins, and how this influenced the

type and timing of delivery. However, the results of this study would indicate that the twin pregnancy itself rather than the birth order was the important variable in SGA.

4.2.13 Infant gender, gestational age, birth weight and method of feeding

Gender

No difference was seen in the gender of infants born SGA compared with non-SGA infants. This observation would be expected as there is no known influence of gender in fetal growth restriction. Although female infants are slightly smaller than male infants, the reference used for calculation of birth weight SDS takes gender into account (Freeman et al., 1995). Difference in birth weight between the two genders has been well described (Wilkin and Murphy, 2006, Alexander et al., 1999). Some animal studies suggest than female offspring may be more sensitive than males to fetal undernutrition, resulting in altered glucose tolerance in later life, which may offer some explanation for the intergenerational effects of IUGR, and which may include a possible genetic predisposition (Hay et al., 1997). In addition, Wilkin and Murphy have proposed that girls, who have been shown to have higher insulin concentrations at birth, are intrinsically more insulin resistant throughout life (Wilkin and Murphy, 2006). However, due the SDS calculations gender differences in absolute birth weight were not specifically explored in this study.

Gestational Age

A statistical difference in mean gestational age was observed in this study between the SGA and non-SGA groups with mean gestation in the group of non-SGA infants

being 4.7 days longer than that for the SGA group. However this finding can be somewhat explained by the discrepancy in numbers involved in each group (284 versus 14082). Secondly although the finding is statistically significant, the clinical significance of a mean difference of 4.7 days is less important than the fact that 18.3% of the SGA group versus 5% of the non-SGA group were born prematurely (< 37 weeks). Neither is this finding surprising, as the birth weights of the majority of the preterm infants fall below the mean-gestational age related estimated fetal weight (EFW), and the incidence of fetal growth restriction and SGA is more likely to be overrepresented at lower gestations (Marsal et al., 1996). In the USA one study showed that rates of term SGA births had declined but that rates of preterm SGA births increased between 1989 and 1998 regardless of ethnic group (Ananth et al., 2003). On a positive note, babies who are small for dates may be protected from adverse programming by early expulsion from the uterus (Barker, 1994). Notwithstanding, the small difference in mean gestational age between the SGA infants and non-SGA infants, highlights the fact that SGA infants are born at gestations ranging from the very preterm to the postmature. Again, the value of this observation depends on the accuracy of records of gestational age. However a limitation of this study is that infants born at gestations less than 28 weeks were excluded. Although the total number of such infants was only 57, it is likely that more than 2% of these infants were born SGA, as rates of IUGR/SGA are thought to be higher in the extremely premature (Lackman et al., 2001, Marsal et al., 1996, Ehrenkranz, 2007).

Birth weight & BW SDS

By definition there was a statistical difference between the two groups in the mean birth weight SDS. The fact that the non-SGA group of infants had a mean BW SDS

close to zero indicates that appropriate references were used for the Irish population such that it can be applied in future studies of SGA infants. Those infants with extremes of BW SDS (+4 SDS or -4 SDS) would suggest that there may have been a problem with accuracy of gestational age calculation and/or birth weight data, however given the similarity in the extremes observed in both groups they may well be true. What is more interesting is the significant difference in the mean and range of birth weights observed in the SGA group (2,278g) (range 450-3260g) compared with the non-SGA group (3,488g) (range 780-5726g). Mean infant birth weight in a recent Irish study of a smaller cohort of infants has very similar findings to this study with a mean overall birth weight of 3,493g (range 840g-5,360g) although BW SDS was not calculated (Murrin et al., 2007). The similar findings in both Irish studies would suggest that there has been no major change in birth weight in the 6-8 years since the birth of the infants analysed in this study.

Method of infant feeding

This study revealed a significant difference between the groups of SGA and non-SGA infants with respect to method of infant feeding. The poor rate of breastfeeding in the SGA group (19% versus 32%), although on the one hand not surprising, is alarming given that breastmilk, the optimum nutrition for all infants, should be particularly encouraged for vulnerable SGA infants. Possible explanations for this finding could be (i) the high perinatal morbidity in SGA infants and higher rate of admission to the special care baby unit (SCBU), which may impact on breastfeeding (ii) the data records may not reflect those in whom some breast milk is given by tube feeds while in the SCBU (iii) other factors associated with SGA which may also be associated with lower rates of breastfeeding such as socioeconomic group, maternal smoking and operative delivery. In addition there is some evidence that feeding with human milk

gives a lower risk of developing necrotising enterocolitis (NEC) (Lucas and Cole, 1990, McGuire and Anthony, 2003, Jayanthi et al., 1998). However, very few studies have randomly compared human milk with formula milk with NEC as a primary outcome (Puntis, 2006). A recent systematic review found only four such small trials suitable for meta-analysis (McGuire and Anthony, 2003). A large study by Lucas and Cole comparing formula feeds and banked breast milk with respect to growth and development suggested that NEC was 6-10 times more likely in preterm infants fed formula compared with those fed breast milk (Lucas and Cole, 1990).The goal of nutritional support of very low birth weight (VLBW < 1,500g) or growth retarded infants is the achievement of postnatal growth at a rate approximately that of the third trimester of intrauterine life. However this is rarely achieved. When Ehrenkranz et al prospectively assessed growth of 1666 VLBW infants, most of the infants had not achieve the median birth weight of term infants by the time of discharge from hospital (Ehrenkranz et al., 1999). In addition, the importance of infant nutrition on early childhood growth is emphasised by the marked differences in growth rates between breast and bottle-fed infants, which raises concerns for future obesity risks (Ong et al., 2002b) (Saenger et al., 2007). For example, the growth tracjectories of term-born infants who are breast-fed are now considered the gold-standard although growth velocity is slower than that of formula-fed infants (Vasu and Modi, 2007). The new World Health Organization growth charts (World Health Organization, 2007b) indicate that by one year of age, breast-fed infants are 500g lighter than the weight depicted in the UK 1990 Growth Reference (Freeman et al., 1995).

4.2.14 Infants admitted to the Special Care Baby Unit (SCBU)

There was a much higher rate of admission to the SCBU from the SGA compared with non-SGA group of infants (61% versus 17%). There was also a significant difference between the two groups in terms of the primary indications for admission to the SCBU. However, data was not available in this study on length of stay in the SCBU which may be better marker of morbidity and its economic implications. The most noticeable difference was that 41% of infants in the SGA group were admitted due to low birth weight, IUGR or prematurity whereas only 10% of those in the non-SGA group were admitted for these reasons. Due to the complexity and variety of problems in infants born SGA, it is possible that the data available did not accurately reflect the primary reason for admission to SCBU especially if there were several equally serious problems leading to admission (e.g. prematurity, hypoglycaemia and low Apgar scores). The increase rate of admission to SCBU is not surprising as low birth weight, prematurity and IUGR are all associated with increased neonatal morbidity (Sharma et al., 2004, Garite et al., 2004, Lal et al., 2003, Bernstein et al., 2000, Lackman et al., 2001). Some studies have shown SGA infants to be at greater risk of birth hypoxia and neonatal complications (McIntire et al., 1999), however there are conflicting studies looking at specific morbidities in preterm SGA infants such as respiratory distress syndrome (Sharma et al., 2004, Bernstein et al., 2000), necrotising enterocolitis (Bernstein et al., 2000) and periventricular haemorrhage (Cooke, 2007). In term infants IUGR has been identified as a risk factor for respiratory complications (Fleischer et al., 1992, Tyson et al., 1995). Lackman et al found that obstetric diagnosis of IUGR, based on fetal growth standards using ultrasound, correlates better with adverse outcome and with premature delivery than when neonatal growth standards were used and concluded that antenatal diagnosis of

IUGR may be more accurate than one that is based on neonatal assessment of gestational age and birth weight (Lackman et al., 2001). Zaw also demonstrated that fetal growth standards were more appropriate than currently used neonatal growth standards to identify preterm SGA neonates at risk of adverse neonatal outcome; particularly respiratory morbidity and intraventricular haemorrhage, even after correction for antenatal glucocorticoid administration (Zaw et al., 2003). Garite et al's study of perinatal outcomes in IUGR and prematurity highlighted the interplay of IUGR and SGA. The authors demonstrated that when antenatal diagnosis of IUGR is confirmed by a neonatal birth weight < 10th centile, only then was there a correlation with adverse outcome (Garite et al., 2004). During the period of the cohort studied, it was CWH hospital policy to administer antenatal steroids in cases of threatened preterm delivery before 34 weeks as is widely accepted management (Baschat and Hecher, 2004). This study did not explore rates of antenatal or postnatal steroid administration in the SGA versus non-SGA preterm infants, and one could argue that such interventions could have an effect on birth weight, perinatal outcome and on future childhood growth (Thorp et al., 2002) (Yeh et al., 2004). A clear limitation of this study when reporting results of neonatal complications is that the analysis did not include infants born extremely prematurely (< 28 weeks gestation), hence when referring to studies looking at prematurity and fetal growth restriction many of the conclusions may not apply in this study. Another limitation of the study is the lack of analysis of duration of stay in the SCBU which has significant staffing and economic implications and also impacts on rates of complications such as nosocomial infection. Length of stay for survivors of IUGR born prematurely has been shown to be similar to those of AGA infants with similar birth weights (Aucott et al., 2004). In the author's experience, many infants born with an antenatal diagnosis of IUGR or a birth

weight below 2.5kg were admitted to the SCBU regardless of clinical status and gestation, given the known risks of problems such as hypoglycaemia and hypothermia in the immediate neonatal period. In addition this study did not examine readmission rates to the SCBU which also may be more important in SGA infants if there are higher rates of feeding difficulties, failure to thrive, and other late neonatal complications which have been shown to be more common (Aucott et al., 2004).

Respiratory Problems and Ventilation Procedures

There was a significant difference in the rate of respiratory problems observed in the group of SGA infants compared with the group of non-SGA infants. SGA infants had a lower incidence of the group of conditions which included respiratory distress syndrome, transient tachypnoea of the newborn, pneumothorax, meconium aspiration syndrome, aspiration, atelectasis, and chronic lung disease, when compared to the non-SGA infants (8% versus 14%). These results would be consistent with studies showing that SGA infants are protected from respiratory distress syndrome (Sharma et al., 2004). However, the results of this study were not analysed specifically for preterm SGA infants versus non-SGA infants, and as discussed above, the analysis did not include infants born extremely prematurely (< 28 weeks gestation). The observations could be explained by detection of fetal growth problems which allow timely delivery with prenatal administration of steroids which accelerate lung development, compared with non-SGA infants born preterm who do not have time for prenatal steroid administration.

This study found no significant difference in rate and type of ventilation procedures required by SGA infants compared to non-SGA infants. This result would suggest that although SGA infants significantly impact on SCBU admissions, high intensity of

neonatal care in the form of mechanical ventilation is not more common in these infants when born ≥ 28 weeks gestation.

Central Nervous System complications

A lower incidence of neurological problems including hypoxic ischaemic encephalopathy (HIE) and neonatal seizures was found in the SGA group compared with the non-SGA group (0.6% versus 4.3%) however the difference between the two groups in terms of neurological complications was not statistically significant ($p = 0.06$). Although SGA infants had a higher rate of fetal distress than non-SGA infants, there was no consequent increased rate of abnormal neurological behaviour in the early neonatal period. One explanation could be the protective effect of early detection of fetal distress in known cases of IUGR leading to timely delivery and avoidance of severe hypoxia. However, the small numbers in this study make it difficult to draw firm conclusions in this area.

Gastrointestinal complications

Only one case of suspected necrotising enterocolitis (NEC) was found in the SGA group. For the purpose of the analysis only cases of NEC or "suspected NEC" were included in the "NEC" category, hence it is possible that other cases of NEC which were documented as surgical problems (with symptoms such as distended abdomen and vomiting) were not detected. NEC is primarily a disease of the premature infant with incidence inversely related to birth weight and gestational age (Cooke, 2007). Although specific numbers range from 4% to more than 40%, infants weighing < 1000g at birth have the highest incidence. This rate drops dramatically to 3.8 per 1000 live births for infants weighing 1501-2500 g at birth (Springer, 2007). Similarly, rates greatly decrease for infants born after 35-36 weeks gestation. Term infants who

develop NEC behave differently, with the average age of onset occurring within the first week of life or sometimes occurring within the first 1-2 days of life (Wiswell et al., 1988). Although the aetiology is multifactorial, ischaemia and/or reperfusion injury appears to play a significant role with predisposing conditions for NEC such as birth asphyxia, respiratory distress, congenital heart disease, metabolic abnormalities, hypoxia, umbilical catheterisation (Palmer et al., 1987). In addition a history of abnormal fetal growth pattern has been associated with risk for NEC (Garite et al., 2004), especially when intrauterine Doppler scans show signs of circulatory compromise, such as reversed diastolic flow in umbilical or fetal blood vessels (Hackett et al., 1987). In a recent study by Cooke et al the odd ratio for NEC was 3.44 in infants more than –3 SD below mean birth weight (Cooke, 2007). One of the main problems is that the fear of NEC can delay progressing with enteral feeding, which can result in significant nutrient deficients and postnatal growth retardation (Flidel-Rimon et al., 2006). Moreover, feeding with human milk appears to confer some protection (Puntis, 2006). However, due to the low numbers this study it is not possible to make conclusions on the specific risk of NEC in infants born SGA >28 weeks gestation.

4.2.15 SGA Group – Clinical & Auxological Assessment at age 4-6 years

Response to invitation to participate in study

Of the 284 mothers of children born SGA who were written to, 79 (27.6%) responded to the invitation to participate in the study. However, 22 (7.7%) of these mothers did not wish to attend with their child for auxological assessment and indicated that they did not have concerns regarding their child's growth. A major problem was the rate (16%) of envelopes returned to us unopened indicating that the address was no longer valid. In an attempt to find an alternative contact address for these mothers, the Regional Health Authorities and Medical Card holders list were consulted and cross-referenced with our patients. None of the mothers were on this register and hence no alternative addresses were available to us. The high proportion (32%) of non-nationals represented in this group is concerning – it could be that the most vulnerable SGA infants are those who are most difficult to follow up and those with growth problems may not be identified. The high rate (55%) of mothers who did not respond was disappointing. This may indicate a lack of understanding in these mothers of the significance of their child's growth and implications relating to future health in children born SGA. They may in fact have been falsely reassured by their child's weight gain, possibly inappropriately perceiving this as a positive sign. A recent systematic review by Lucas et al looked at publications since 1978 relating to lay views about infant size and growth (0-24 months) (Lucas et al., 2007). In relation to size and growth some parents had an optimistic feeling that children were simply going to be the size that they were going to be. Hence, provided that they were cared for, size was not something to worry about. Although Lucas et al's observations apply to attitudes of parents of younger children than in this study; many of the authors'

findings may explain why parents of children who appear to have normal growth by age 4-6 did not perceive a need to attend for assessment.

There could also be delay in referral of children with SGA by primary health care professionals. Recent market research conducted on behalf of Pfizer Endocrine Care (Psyma International, 2005) surveyed 396 paediatricians in the European Union (France, Spain, Italy, Germany, UK) and found that 25% of paediatricians do not measure height and weight of children systematically at each visit.

Comparison of children assessed versus not assessed

There was no statistically significant difference between the group of SGA children seen compared with those who were not seen in terms of geographical distribution, parents' ethnicity, rates of maternal smoking, alcohol consumption in pregnancy, medical disorders of pregnancy, labour onset or type of delivery, indication for operative or instrumental delivery, rate of intrapartum problems, parity, rates of twin pregnancy, gender, length of gestation or birth weight. The only statistically significant differences observed between the group of SGA children who presented for assessment and those who did not were in terms of the marital status of the mothers and type of mothers' and partners' occupations, factors which suggest a possible trend towards those of higher socio-economic grouping being more likely to attend for auxological assessment of their child than those of lower socio-economic groups. This is concerning as it implies that vulnerable children from lower socio-economic groups with growth problems, or risk of metabolic syndrome, are more difficult to trace and follow up.

4.2.16 SGA Group - Auxological Assessment at age 4-6 years

Data on 56 patients was suitable for analysis. The majority of children born SGA who were assessed in this study were found to be within the normal ranges for all parameters. However, when measured between 4-6 years mean height SDS (-0.7), weight SDS (-0.9), BMI SDS (-0.6) and head circumference SDS (-0.9) in this SGA group were below the mean for the age and gender. No gender differences were found in any of the variables assessed. The findings of this study are consistent with other studies looking at follow up growth in children born SGA which have shown that overall small for gestational age infants remain shorter and lighter and have smaller head circumferences (Hediger et al., 1998b).

Age of Assessment

Mean age of assessment was 5.3 years. As most children have caught up in growth by age 2 years, five years of age is therefore a good point at which to detect those who may have failed to catch up. As the children are at the age of school entry, parents will be more aware as to how their child compares to his/her peers. However, it could be argued that assessment at an earlier age (e.g. age 2-4) would be more appropriate, in order to allow appropriate investigations to be conducted on those with any growth concerns, and to allow maximum benefit from GH treatment by commencing at age 4 years. Difficulties with tracing children born SGA may also be minimised if follow up occurs earlier. A disadvantage of this approach would be that more children would require investigations due to the fact that a small minority of children may be small but will continue to catch up in height during childhood, beyond age 2 (Karlberg and Albertsson-Wikland, 1995). In addition, children born prematurely may take longer to

catch up (Hokken-Koelega et al., 1995, Albertsson-Wikland and Karlberg, 1997). Looking at detection of short stature in the general population, a study by Grote et al compared the referral patterns of children with poor growth using different referral guidelines in primary health care in the Netherlands and the UK (Grote et al., 2007). The authors concluded that by following the Dutch consensus guidelines (which includes current height or target height cut-off point for referral < -1.3 SDS) (de Muinck Keizer-Schrama, 1998) there would be too many referrals particularly before the age of 3 years. In contrast, the UK guidelines for referral (height < -2.67 SDS at age 5 years) (Hall, 2000) would lead to far less referrals but clinically relevant growth disorders such as Turner syndrome may be missed (Grote et al., 2007). Of note, children born SGA are not specifically mentioned in the UK guidelines (Hall, 2000). Therefore, it appears that for children born SGA, the International consensus guidelines, which recommend measurements of length, weight and head circumference every 3 months for the first year of life and every 6 months thereafter ideally up to age 2 for all children born SGA, are the most appropriate (Clayton et al., 2007).

Birth Data

The wide range of birth weight SDS (-2.0—3.0) and gestations ($29^{+3} - 43^{+6}$) of the children assessed reflects the heterogeneous nature of the group of children who was assessed. For this reason further subgroup analysis was conducted to detect any possible factors which may affect postnatal growth trajectories such as prematurity, maternal smoking, maternal hypertension and documented IUGR in these children.

Height at 4-6 years

Of the SGA group assessed the majority (91%) of children had achieved catch-up growth with a height > -2 SDS. In total 9%, 5 boys, had not caught up, with a height < -2 SDS, 3 of whom had severe short stature (height < -2.5). Although overall mean height was below the mean (-0.7 SDS) these findings are consistent with other studies of follow up growth in children born SGA (Luo et al., 1998) (Karlberg and Albertsson-Wikland, 1995) (Hokken-Koelega et al., 1995) and indicate a good prognosis in terms of final adult height for those who had achieved height > -2 SDS (Luo et al., 1998) (Albertsson-Wikland and Karlberg, 1994). However, the results of growth studies of children born SGA are difficult to compare due to a number of differences in methodology including: 1) definition of SGA used (e.g. based on birth weight, length or both), 2) various cut-off points for SGA (-2 SDS, 3rd, 5th or 10th centiles) as previously discussed, 3) inclusion of preterm and term, singleton or multiple births in the same or distinct groups and 4) outcome measures can be expressed as gender and age-independent SDS or as centiles with different cut-off definitions for catch-up and short stature.

Final height appears to be positively associated with catch-up growth during the first 6 months of life in term infants born SGA. The SGA group with final height < -2 SDS in Luo's study showed virtually no catch-up growth during the entire growth process monitored throughout childhood (Luo et al., 1998). However, data on growth in early infancy and childhood on the children assessed was not available for this study.

This study lacked data on other auxological variables at birth such as birth length and BMI due to lack of standardised measurements and inconsistent records. In some studies BMI at birth or weight for length SDS have shown no significant influence on

postnatal catch-up growth rates during any phase of growth in childhood (Luo et al., 1998) whereas in Karlberg and Albertsson-Wikland's large Swedish cohort, birth length and mid-parental height were found to be significantly related to the magnitude of catch-up growth from birth to 18 y of age (Karlberg and Albertsson-Wikland, 1995). In another study birth length SDS was more sensitive than birth weight SDS in predicting catch-up $\geq 3^{rd}$ centile in premature SGA infants by age 2, whereas birth weight SDS was the best predictor for catch-up $\geq 3^{rd}$ centile in full-term SGA infants by age 2 (Hokken-Koelega et al., 1995).

Weight and BMI at 4-6 years

Overall the children assessed had weights lower (-0.9 SDS) and BMI SDS (-0.6) than the mean expected for their age and gender which is reassuring. The paradoxical effect of lower birth weight and risk obesity may be partly explained by the observation that infants who have been growth restrained in utero tend to gain weight more rapidly, or 'catch up', during the early postnatal period, which leads to increased central fat deposition (Ong, 2006). However apart from one case of obesity detected, there was no overall trend for these children to be overweight. Although rates of postnatal catch-up growth from birth to 2 years were not specifically analysed, the findings for these children at age 4-6 years would indicate that Irish children born SGA are not fatter than their non-SGA peers, in contrast to a large British study which showed that children who showed rapid catch-up growth (gain in weight SDS > 0.67) between birth and 2 years had lower weight and length at birth and were fatter and had more central fat distribution at five years than other children (Ong et al., 2000). Of note Ong's study does not specifically examine SGA births. In contrast, Barker's Helsinki study associates adult coronary events with being small at birth and thin at

two years of age and rapid weight gain thereafter. This pattern of growth during childhood was also associated with insulin resistance in later life. The risk of coronary events was more strongly related to the tempo of childhood gain in BMI than to the BMI attained at any particular age (Barker et al., 2005). Due to the small numbers in this study it is conceivable however that an association with postnatal catch-up rates of children born SGA and overweight in childhood has not been detected.

Hediger et al's study of children born SGA found that lower birth weight was associated with a subsequent higher ratio of fat mass to lean mass, and greater central fat (Hediger et al., 1998a). Therefore infants born SGA who appear to be gaining weight appropriately may be found instead to have increasing fatness but poor growth in muscle. Thus, at any given weight for infants and children at 2 to 47 months of age, percent body fat appears to be relatively higher for children who were SGA at birth and lower in those who were LGA at birth (Hediger et al., 1998a). Such differences in body composition for children born SGA documented by Hediger et al may point to a link between disturbances in intrauterine growth and chronic disease associated with subsequent adiposity in adulthood (Hediger et al., 1998a). The clinical assessments performed in this study however were not sufficient to distinguish between lean and fat mass. Although BMI appears to be the best available tool for screening for obesity (Hall and Cole, 2006), the most appropriate tool used to assess lean and fat mass is dual-energy x-ray absorptiometry (DXA) which was not available for use as a screening tool in this study. Hence it is conceivable that despite attainment of weight and BMI within the normal range in the majority of the children assessed, they may have subtle differences in lean and fat mass which confers an increased risk of later adult disease such as insulin resistance. This would indicate that further follow up of these children later in childhood should be considered.

Head circumference at 4-6 years

Mean head growth in the children assessed was found to be in the normal range (-0.9 SDS) however six children had head circumference < -2 SDS. None of these children in required special schooling. From studies of postnatal growth, it appears that the significant disparity in head size from the normal-sized infant at birth is only partly reduced by the end of the first year in term infants born severely small for gestational age (Babson, 1970). However data on head circumference during infancy was not available for this study. Body proportions at birth also have a relationship with head circumference in childhood (Arends et al., 2004). Arends et al showed that in short SGA children mean head circumference SDS at the age of 5.9 years was significantly lower in children born SGA for both length and weight compared with those born SGA for length only. In those born SGA for length head circumference tends to be relatively large in many of these children (Arends et al., 2004). In addition, Huxley et al have reported that both birth weight and head circumference at birth are inversely related to systolic blood pressure and that accelerated postnatal growth is also associated with raised blood pressure(Huxley et al., 2000). In a large follow up Dutch study of premature infants, Rijken et al also found a relationship between smaller head circumference and an abnormal neurological examination and abnormal mental and psychomotor developmental index (Rijken et al., 2006). In addition, a follow up study by Hack et al of 249 children born with very low birth weight (<1.5kg), perinatal growth failure as evidenced by a subnormal head circumference at eight months of age, showed an association with poor cognitive function, academic achievement, and behaviour at eight years of age (Hack et al., 1991). Similarly, Forslund and Bjerre's study of Swedish children born ≤ 35 weeks gestation has shown

a neurological optimality score at 4 years of age to be related to head circumference but not to length or weight (Forslund and Bjerre, 1990). Another recent study demonstrated that small head circumference was strongly associated with learning problems in school-aged children (Stathis et al., 1999).

Although lack of accurate birth length and head circumference data make it impossible to determine any such relationship in this study, these studies highlight the importance of standardised measurements of head circumference at birth and throughout infancy.

Preterm versus Term Children born SGA – Birth Data & Auxology at 4-6 years

Comparing the children born preterm (<37/40) (N=12) with those born term (≥37/40) (N=44), there were significant differences observed in height and weight at 4-6 years, with those born preterm being shorter (-1.4 SDS versus -0.6 SDS) and lighter (-1.7 SDS versus -0.7 SDS). No significant differences were seen in birth weight SDS, or BMI, BMI SDS and head circumference at 4-6 years. Although catch-up growth may take longer in children born SGA and prematurely (Albertsson-Wikland and Karlberg, 1997), catch-up growth if it is to occur, should have occurred in the majority of children by age 2 years, hence this does not explain the auxological differences compared to term SGA infants observed in this study. However, despite evidence of catch-up growth during childhood, assessment in early adulthood has shown preterm infants to be at a disadvantage with respect to final height attainment, with this effect being more pronounced in males born SGA (Hack et al., 2003). Some evidence suggests that growth impairment is not restricted to the early postnatal period. Gibson et al investigated 200 preterm infants and 50 randomly selected healthy preterm term

infants from the same population and followed them from birth to age 7 years (Gibson et al., 2000). The investigators found early growth in all infants born preterm, but more rapid improvement in those born more mature. The Epicure Study of growth and blood pressure at 6 years of age following extremely preterm birth (< 26 weeks gestation) found the children to be 1.2 SDS lighter, 0.97 SDS shorter, BMI was 0.95 SDS lower and head circumference 1.3 SDS lower compared to their full term classmates (Bracewell et al., 2007). Birth weight for gestational age remained strongly associated with all growth outcomes at 6 years except BMI. However extreme prematurity was not examined in this study and therefore Bracewell's findings clearly represent a distinct entity of prematurity where infants are more vulnerable for neonatal complications which may affect growth. Another follow-up study by Gutbrod et al of children born < 32 weeks gestation has demonstrated similar findings to this study, with poor growth over the first 5 years of life. Being born underweight and with a short gestation (SGA and VLBW) was associated with poor weight gain and head growth in infancy but did not result in poorer growth than in infants of the same birth weight but shorter gestation (i.e. infants appropriate for gestational age but low birth weight) in the long term (Gutbrod et al., 2000). Some neonatal complications may explain differences in growth of infants born prematurely. SGA is related to early developmental delay and later language problems; however, neonatal complications may have a larger detrimental effect on long term cognitive development of VLBW infants than whether they are born SGA or AGA (Gutbrod et al., 2000).

For example, Rijken et al showed bronchopulmonary dysplasia (BPD) to be related to smaller length, weight and weight-for-length, possibly explained by higher energy expenditure in these infants. However others studies have not found a relationship

between BPD and growth at 3 and 2 years (Daily et al., 1994, Dusick et al., 2003). Due to the small number of children in this study who were born prematurely, and the fact that they were of gestation ≥ 28 weeks, such associations were not explored. Furthermore use of antenatal corticosteroids in this group was not explored but would be interesting to consider as antenatal corticosteroids administration has been associated with a reduction in head circumference even after controlling for birth weight, and the effect on birth weight and head circumference increases with advancing gestational age (Thorp et al., 2002). Of note, no statistical differences in head circumference SDS were found between those SGA infants born prematurely or those born at term. This is reassuring as small head circumference is significantly associated with low cognitive ability at 6 years in children born with extremely low birth weight (Stathis et al., 1999, Rijken et al., 2006). A study of 280 children born before 32 weeks gestation and 210 term infants found an association between prematurity and poor cognitive behaviour, with short stature and small head circumference being the strongest predictors of poor performance (Cooke and Foulder-Hughes, 2003).

The findings of this study would suggest that postnatal growth in infancy was appropriate in these children born SGA and preterm, resulting in attainment of height, weight and head circumference within the normal range, although mean height and weight were below that of the children born at term.

Child's Height at 4-6 years in relation to Parents' Height

Ideally both parents should have been measured by the investigator in order to accurately calculate mid-parental or target height for each child. However this was not

possible in all cases, although there appeared to be good agreement between reported heights and measured heights in the mothers. For those children in whom target height was calculated it was possible to deduce a corrected height SD score. The mean corrected height SDS was -0.5, which was significantly different to the original height SDS. This would indicate that some degree of the SGA children's height can be attributed to mid-parental or target heights being below the mean. Hence these children have almost reached their genetic potential. These observations have good prognostic implications for their final height as increased risk for adult shortness in children born SGA has been more evident in groups with higher target heights (Luo et al., 1998). In addition, in the Swedish cohort assessed by Karlberg and Albertsson-Wikland, mid-parental height was found to be significantly related to the magnitude of catch-up growth from birth to 18 y of age (Karlberg and Albertsson-Wikland, 1995). Of note however, definitions for catch-up growth are based on the normal height range for the population and do not allow for an estimation of the child's genetic potential in stature, i.e. expected adult or target height, based on mid-parental height corrected for gender. This is an important distinction, as for example target height is a strong predictor of response to GH treatment (Saenger et al., 2007).

As found by the questionnaire data received, parent reporting of their child's height and weight when measured at home was found to agree closely with the measurements taken in the clinic. This would indicate that parents are good at growth estimation and that the value of home measurements should not be dismissed.

Smoking in Pregnancy - Birth Weight & Auxology at 4-6 years

Although there were high rates (50%) of maternal smoking during pregnancy in the group of children born SGA who were assessed at 4-6 years, there was no evidence of a difference found between the two groups in any of the variables measured (BW SDS, HtSDS, WtSDS, BMI, BMISDS, OFCSDS). Interestingly, the children of mothers who had smoked were heavier (mean weight -0.7 SDS) than those who had not smoked (mean weight -1.1 SDS) although this was not statistically significant ($p = 0.23$). In addition there was a borderline statistically significant difference in BMI SDS ($p = 0.07$) between the two groups, with offspring of smokers having a higher BMI SDS (-0.4 versus -0.9). In previous studies infants of maternal smokers were found to be symmetrically small at birth compared with infants of non-smokers, and tended to show complete catch-up growth over the first year of life (Ong et al., 2002b). This indicates a drive by the body to compensate for antenatal growth restraint caused by maternal non-genetic factors which is present from early fetal development. The future health of children born SGA where maternal smoking contributed to or caused the low birth weight however may extend beyond growth issues, with possible deficits in bone mineral density and susceptibility to respiratory disease persisting (Jones et al., 1999) (Hofhuis et al., 2003). A study of 330 children by Jones et al found that maternal smoking during pregnancy was associated with deficits in growth and bone mass in children born at term, with documented lower height and a trend to lower weight at age 8 (Jones et al., 1999), although SGA births were not examined specifically. In addition von Mutius et al have found an association with prenatal maternal smoking and increased risk for symptomatic asthma (von Mutius, 2002). The findings of this study would suggest that children born SGA whose mothers smoked during pregnancy may be heavier at age 5 years

compared to those born SGA to non-smokers, however larger numbers would be required to reach more definite conclusions.

Maternal Hypertension & History of documented IUGR – Auxology at 4-6 years

In contrast to the offspring of mothers who smoked in pregnancy, both hypertension and a documented history of IUGR during pregnancy were associated with lower birth weight SDS than those infants with no history of maternal history or IUGR, although this did not reach statistical significance. Gestation however was significantly shorter in both those with a history of maternal hypertension or IUGR when compared to those with no such history. These findings indicate that those born small due to underlying pathology such as maternal hypertension or various causes of IUGR, are more likely to be born at earlier gestations. These observations are consistent with other studies, especially those where use of customised fetal growth charts adjust for maternal and fetal factors contributing to fetal size (Gardosi, 2006). It may also be an example whereby earlier delivery protects against adverse programming which would occur if the fetus were to stay in utero (Barker, 1994). In addition the children born SGA who had a documented history of IUGR were found to have significantly lower weight (weight SDS -1.3 versus -0.6) and lower BMI SDS (BMI SDS -1.0 versus -0.3) at 4-6 years when compared to those children who had no documented history of IUGR. No auxological differences at 4-6 years were seen in the group whose mothers had hypertension during pregnancy. It is conceivable that those children born with a history of IUGR are more susceptible to slower growth due to an inherent problem within the fetus rather than those with SGA attributable to maternal hypertension, however the two groups are not necessarily mutually exclusive and warrants further analysis. Studies of follow-up growth in children born SGA do not appear to

distinguish between those with or without IUGR, but are based on the various cut-off definitions for birth weight or length. In addition, it is probable that more than 23% of the children in this SGA group assessed had IUGR but that it was not detected on antenatal ultrasound. Therefore it is difficult to draw definite conclusions on the implications of antenatal growth restriction as distinct from being born SGA without a diagnosis of IUGR in association with follow up growth at age 4-6 years.

Medical problems identified, risk of metabolic syndrome & developmental progress

From the group of children assessed only one child was found to be obese (BMI = 20.4) when seen at age 6 years. Aside from short stature it has been shown that under-nutrition in utero increases the risk of obesity in adulthood (Stein et al., 1997, Barker et al., 1997). As shown in studies by Ong et al, those who develop the highest body mass index (BMI) early in life, have been found to be the most insulin-resistant, and at increased risk of developing type 2 diabetes (Ong, 2006, Ong and Dunger, 2004, Ong et al., 2002b). In a study of 29 SGA children (mean age 9.1 years) by Veening et al significant insulin resistance was only found in children with catch-up growth resulting in a current BMI $\geq$ 17 (Veening et al., 2002). As childhood obesity has been shown to have important consequences for morbidity and mortality in childhood and later life (Dietz, 2004) identification of risk factors that predict its very early development is required for obesity prevention (Ong, 2006).

Although this child was normotensive at the time of assessment, results of a study by Huxley would indicate that he is a risk of hypertension in later life, as accelerated postnatal growth is also associated with raised blood pressure (Huxley et al., 2000).

One girl seen at age 4 years with low weight was found to have a positive tissue transglutamase test leading to a subsequent diagnosis of coeliac disease. This highlights the importance of considering other causes of poor growth in children born SGA other than the perinatal history.

In any child born SGA, until other causes of growth problems are excluded, poor weight or height should not be attributed to the history of SGA alone. This is consistent with international consensus guidelines (Clayton et al., 2007).

Twin pairs – Birth data and Auxology at 4-6 years

In this study 4 twin pairs were assessed. In each pair only one infant was born SGA (2 boys, 2 girls). All 4 SGA infants had a height and weight within the normal range when assessed at 4-6 years. However, in two cases the twin born SGA was considerably smaller than its non-SGA twin (height difference 0.8 and 1 SDS, weight discrepancy 0.6 and 1.5 SDS). Of note, there are currently no standard data for multiple births, and as it is widely acknowledged that multiple gestations may in themselves be a cause of low birth weight/SGA. Therefore it may be argued that normal growth curves may not be the most appropriate reference model for twins (Saenger et al., 2007) and that SGA may be over diagnosed in twins where fetal growth potential is not taken into account (Gardosi, 2006). It is nevertheless recommended that normal standards for catch-up growth in height should be applied to individuals from multiple births (Saenger et al., 2007). In keeping with this in one study of catch-up growth in children born SGA, gestational age, multiple birth, and sex were not significantly associated with catch-up in height $\geq 3^{rd}$ centile by age 2 years (Hokken-Koelega et al., 1995).

Follow up in infancy

The low rates of follow up during infancy reported by the parents of the children assessed in this study suggest that international consensus on management of children born SGA (Clayton et al., 2007) were not being routinely implemented in 1999-2001. This highlights the importance of informing nursing and medical staff both of the risk of failure of catch-up growth and also the future health problems associated with rapid postnatal weight gain in these children, so that a service can be developed to monitor these children for the first 2-3 years of life.

4.3 Population (2.) Patients Born SGA Treated with Growth Hormone

4.3.1 Patient Population and Recruitment

Recruitment for the North Europe Small for Gestational Age Study (NESGAS) was slow but steady and improved once information on the study and its progress was disseminated. Interestingly boys represented a clear majority of patients treated with Growth Hormone (GH) which possibly reflects public perceptions of short stature being more of a problem for males and is consistent with studies of gender difference in referral rates for short stature (Lee et al., 2007, Grimberg et al., 2005). This has general implications for delayed diagnosis of conditions associated with short stature in girls, not just in girls born SGA but also conditions such as Turner's syndrome and GH deficiency. However, despite almost equal numbers of boys and girls presenting for the CWH follow-up study, all those detected with short stature were boys.

All Paediatricians (including Neonatologists) were informed by letter about the study and the importance of early referral of children born SGA with growth concerns. A review paper on the condition (Johnston and Savage, 2004), and the 2001 international consensus guidelines (Lee et al., 2003) were included with the letter in order to provide up to date and impartial information literature on the subject. A presentation was made at the Faculty of Paediatrics Scientific was aimed at informing Consultant Paediatricians of the study where a number of queries were addressed. In addition the information meeting on Small for Gestational Age with a number of expert speakers in the field of Neonatology and Paediatric Endocrinology highlighted the importance of recognising SGA and the new indications for treatment. Concern arises over the low numbers of referrals from other Paediatric Endocrinologists who are following children with short stature in their clinics, some of whom are likely to have been born SGA. This could be due to personal reservations on the part of some Paediatric Endocrinologists on the use of GH in children born SGA due to limited long-term safety data (personal communication). The positive results observed in this study however, may help to increase interest in the treatment and the study leading to further recruitment. The small number of referrals from Neonatologists would suggest that these children may be discharged to primary health care in early childhood. In SGA children who are being followed up for growth problems who have lack of catch-up and short stature, the International Consensus Statement on SGA, 2001 recommends referral to a Paediatric Endocrinologist by age 3 for investigation (Lee et al., 2003). The low number of young children in this study may indicate either lack of follow up or under-referral of children born SGA. In order to ensure maximum detection of failure of catch-up growth in children born SGA we would recommend

accurate measurements of length, weight and head circumference every 3 months for the first year of life and every 6 months thereafter ideally up to age 2 for all children born SGA at their hospital of birth. This is consistent with the recommendations of the 2007 Consensus Statement on Management of the Child Born Small for Gestational Age of the International Societies of Paediatric Endocrinology and the Growth Hormone Research Society (Clayton et al., 2007), and as most infants will have demonstrated catch-up by 6 months (Karlberg and Albertsson-Wikland, 1995) this should detect any child at risk of short stature for which timely appropriate referral to a Paediatric Endocrinologist could be arranged.

Potential side-effects including theoretical risks of neoplasia and diabetes were discussed with all parents. Hence some parents had reservations relating to potential side-effects of GH treatment which led to delays in commencement of treatment. Five children eligible for GH treatment were not treated during this study however one child has recently commenced treatment and two are currently being worked up for treatment. The International SGA Advisory Board (Lee et al., 2003) recommends that parents should be asked about a family history of type 2 diabetes, although any potential long-term risk as a consequence of elevated insulin levels is unknown. Although there is no evidence that the risk of malignancy is increased (Cutfield et al., 2006) the theoretical risks of potentiating a pre-existing neoplasm by stimulation of IGF growth factors was outlined to the parents before consent was given. These unknown potential risks and the number of investigations required prior to treatment with GH (OGTT/IVTT) may have an influence on parents' enthusiasm both for treatment and for inclusion of their child in a research study. In addition, as short stature is not a life-threatening condition *per se* they may be inclined to favour the

known risk of short final adult height versus the unknown long-term risks, despite the increasing number of studies now emerging with reassuring results.

4.3.2 Growth Hormone Status

Three patients were found to have GH insufficiency when tested by GH stimulation tests. Although 24 GH profiles were not performed in this study, the stimulation tests employed were consistent with hospital policy. In addition, as growth hormone status was not the main focus of the study it did not affect whether the child was treated or not, or the dosage used, which was consistent with other studies (Sas et al., 1999, Azcona et al., 1998). What complicates the matter is that GH is inconsistently defined and ranges from severe to borderline and there may be a transient character to GH insufficiency (Coutant et al., 1998). The accepted hospital definition for GH insufficiency is a peak level < 15 mU/L. The value of GH testing in SGA children is controversial due to the uncertainty of results and the risks and emotional effects incurred by the young patient and the fact that response to GH has been shown to be unrelated to spontaneous GH secretion and maximum GH levels following stimulation testing (Sas et al., 1999, Azcona et al., 1998). It is not surprising that some of the patients had low GH levels as disturbances of the GH/IGF axis have been described in previous studies of short children born SGA (de Waal et al., 1994, Ackland et al., 1988, Boguszewski et al., 1995). The proportion of short children born SGA with low GH levels appears to vary between studies. A study of 31 prepubertal short SGA children by Ackland et al found only 4 cases with a maximum overnight GH concentration of < 20mU/L (Ackland et al., 1988, Stanhope et al., 1989). In a study of 40 short prepubertal children born SGA (birth length < 3rd centile) by De

Waal et al, 50-60% had abnormal 24-hour profiles and/or irregular responses to GH stimulation testing (de Waal et al., 1994). Boguszewski et al's study of 106 children concluded that children born SGA and still short at ≥2 years of age spontaneously secrete less GH than healthy children with short stature born AGA, and that short prepubertal children born SGA secrete less GH than children of normal height (Boguszewski et al., 1995). Moreover, in the youngest SGA children (2-6 yr of age) there was another pattern of GH secretion, with a high basal GH level, low peak amplitude, and a high peak frequency. In contrast, Woods et al compared 13 short children born SGA with 15 normal stature prepubertal controls and found all parameters of overnight GH secretion to be higher in the short SGA children, and compared to those of other published studies (Woods et al., 2002).

Due to small numbers involved in this study, no analysis was performed to determine any association between growth outcomes and growth hormone levels prior to treatment, but previous large studies (56-79 patients) exploring this area have found that response to GH has been shown to be unrelated to spontaneous GH secretion and maximum GH levels following stimulation testing (Sas et al., 1999, Azcona et al., 1998). Specifically, Chernausek et al reported no significant correlation between peak stimulated GH levels and first-year growth velocity or first-year increment in growth velocity (Δ Height velocity SDS) (Chernausek et al., 1996). Furthermore GH levels at birth have not been found to correlate with short stature at age 2 years (Leger et al., 1996).

4.3.3 Growth Hormone Treated Patients

All but two patients were treated with double the standard EU dose of GH for the first year of treatment (0.067mg/kg/day). The other two patients were treated with standard dose of 0.035mg/kg/day. The reason for this was their lack of eligibility for the NESGAS study (due to age > 9.9 years) for which the higher dose had been approved. The rationale for using high dose for the first year of treatment was to detect any non-responders to GH – the reasoning being that if standard dose were used it may not be clear whether a poor response was due to an insufficient dose or for other reasons. At start of treatment all patients had severe short stature (< -2.5 SDS), mean -3.2 SDS, except for one patient with a height SDS of -2 who was included as he was very short for mid-parental height (-2.3SDS) and had poor height velocity (-1 SDS). However, it has not been unusual to treat patients with a height SDS of < -2 (Dahlgren and Wikland, 2005) (Coutant et al., 1998) or even < -1.88 (Sas et al., 1999) and indeed the International Consensus Statement on SGA, 2001 recommended treatment for height < -2 who have subnormal growth rates (Lee et al., 2003). In addition, as pointed out in a recent review of SGA by Saenger et al, definitions based on the normal height range do not incorporate the patient's expected adult height, based on parental stature or genetic potential (Saenger et al., 2007). For these reasons the patient was therefore included in the study. The auxological characteristics and mean age (mean 7.3 years; range 4-11.8) of starting treatment observed in these patients are similar (or slightly older) to those reported in other studies using GH for treatment of short SGA children; mean 5.2 years (de Zegher et al., 2000); mean 6.3-7.4 years (Chernausek et al., 1996); mean 8.1 years (Van Pareren et al., 2003a); 4.7 years (Boguszewski et al., 1998).

4.3.4.1 Growth Response following Growth Hormone Treatment

All patients in the study treated with GH responded significantly in all auxological parameters (height, weight, height velocity, BMI and head circumference SDS). There were no non-responders (defined as change in height velocity < +1 SDS). Importantly, although BMI SDS improved with treatment (mean -1.4 SDS at baseline to -0.9 SDS after one year of treatment), it remained below the mean, suggesting that body composition was not adversely affected.

Many parents reported that their child had a marked increase in appetite and food intake once treatment was commenced. This appeared to greatly contribute to overall patient well-being, parent satisfaction and compliance. A study by Boonstra et al reported that short SGA children have indeed a lower food intake than age-matched controls and found that it increased significantly during GH treatment (n = 62) compared to baseline in contrast to the randomized control group (Boonstra et al., 2006). This would be an interesting aspect of treatment response to explore further. No analysis was made in this study of the growth response in terms of the different dosages use. Such an analysis was beyond the scope of the study due to the small numbers and the short duration of treatment to date. However in the future any such effect will be explored when more data is available. The short-term growth response to GH in SGA children has been found to be dependent on GH dosage (evaluated doses are 33, 67 and 100 μg/kg/day) in most studies in a meta-analysis by de Zegher and Hokken Koelega (de Zegher and Hokken-Koelega, 2005). However final adult height after long-term GH treatment did not show significant difference between standard (0.033mg/kg/day) or high dose (0.067mg/kg/day) groups in a study by Van

Pareren et al (Van Pareren et al., 2003a). In addition, de Zegher and Hokken Koelega's study of 28 short children born SGA found that shorter stature at the start of GH treatment was associated with more long-term height gain (de Zegher and Hokken-Koelega, 2005).

Positive effects were also seen on weight gain following one year of GH treatment, with mean weight SDS increasing from -3.4 at baseline to -2.2 SDS. Overall BMI SDS increased from -1.4 at baseline to -0.9 SDS following one year of treatment which indicated appropriate weight gain for height gain. These observations are consistent with other studies where height and weight have both been shown to normalise with GH treatment (de Zegher et al., 1999, Dahlgren and Wikland, 2005). In a study by Ranke et al, analysis of data from 613 children born SGA and treated with GH led to the development of a clinical prediction model allowing GH treatment to be individualised in children born SGA. The GH dose was the most important predictor, accounting for 35% of the variability in response (Ranke et al., 2002, Ranke et al., 2003). Other predictors during the first year were in order of importance, age at the start of treatment (negative correlation), weight SDS at the start of treatment, and mid-parental height SDS (positive correlation) (Ranke et al., 2003). A model for the response to the second year of GH treatment showed that the most important predictor of subsequent growth was height velocity during the first year of treatment (Ranke et al., 2003). Two other studies have also found an association between weight and/or BMI at start of treatment and response to treatment (Coutant et al., 1998, Dahlgren and Wikland, 2005). Coutant et al reported an inverse relationship with BMI at start of treatment and final adult height attainment (Coutant et al., 1998). In addition,

Dahlgren and Wikland found that children with lower weight and/or BMI responded better to GH treatment (Dahlgren and Wikland, 2005).

In this study a positive effect on head circumference was also seen. Mean head circumference increased from -2.1 SDS at baseline to -1.6 SDS following one year of GH treatment. In a study of long-term GH treatment (mean duration of treatment 8 years) in 79 children born SGA (mean age at start of treatment 7.4 years) by Hokken-Koelega et al, head circumference SDS at the start of GH therapy and head growth during GH therapy were positively related to all IQ scores, whereas neither were related to height SDS at the start of, or to its improvement during, GH therapy. Head circumference increased in GH-treated children born SGA, but not in untreated SGA controls. In parallel to an improvement in height SDS, a significant improvement in intelligence quotient (IQ) was demonstrated. In addition, problem behaviour and self-perception improved significantly. Of note, IQ scores were positively related to head circumference, both at the start of, and during, GH therapy (Hokken-Koelega et al., 2005, van Pareren et al., 2004). Furthermore, an association between IQ and IGF-1 levels has been demonstrated (Gunnell et al., 2005) which suggests that there are important neuro-developmental processes in children born SGA which require further research (Saenger et al., 2007).

4.3.4.2 Growth in children starting GH over age 9.9 years

Signs of puberty were closely monitored in all patients while on treatment with GH. There were no cases of precocious puberty occurring while on GH treatment however two boys entered puberty at age 11.5 and 13 years respectively, both within two years of commencing treatment. The latter case has Silver Russell syndrome. Both boys were treated with an LHRH analogue in an attempt to arrest the progression of

puberty. Combination of treatment with GH and an LHRH agonist remains a controversial approach as no good final height data are available (Carel, 2006).In both cases the growth velocity appears to have slowed since completion of the first year of GH treatment. Although signs of puberty have not yet been observed in the two other boys who commenced GH treatment after the age of 9.9 years, in general however, these older children had less response overall than those who commenced GH at an earlier age. Clinical trials have shown that growth response to GH treatment is better when children commence treatment early in childhood and that age at initiation of treatment is a major determinant of the growth response (Sas et al., 1999, Albertsson-Wikland, 1989, Boguszewski et al., 1998). Two studies (Coutant et al., 1998, Zucchini et al., 2001) have looked at GH treatment in older children (10.9 and 10.7 years), and reported low mean final height SDS gain (+0.5 and 0.9 SDS). This may be explained by shorter duration of treatment and lower efficacy of GH treatment in pubertal children in comparison with other studies where GH commenced at a younger age (Van Pareren et al., 2003a, Hokken-Koelega et al., 2004). However it must be noted that a low mean dose of GH (0.4 +/- 0.1 IU/kg/week) used in the study by Coutant et al may explain the lower final height (Coutant et al., 1998). In addition, the study by Zucchini et al used different birth weight criteria (<10th centile) for treatment and only treated those with documented abnormal GH secretion (Zucchini et al., 2001).

The children born SGA in this study whose parents did not wish for their child to be treated with GH continued to grow poorly in comparison with those treated, and remained short.

These findings highlight the importance of early identification of children born SGA with persistent short stature who may benefit from GH treatment.

4.3.4 Glucose Homeostasis

The short intravenous tolerance test (IVGTT) was performed in 15 children commencing or due to commence high dose GH (0.067mg/kg/day). This was performed in order to examine insulin sensitivity and to out rule impaired glucose intolerance or diabetes mellitus prior to treatment. Consistent with hospital policy, OGTT was performed in all children prior to commencing treatment, including the 2 children who received standard dose GH (0.035mg/kg/day) and who had no IVGTT. No abnormal baseline IVGTTs or OGTTs were seen.

The method chosen to assess insulin secretion and sensitivity appears appropriate for the group studied. Davis et al. compared four methods for measuring insulin secretion in man: Hyperglycaemic clamp (Hy); Minimal model (MIN); shortened intravenous tolerance test (IVGTT) and continuous infusion of glucose with model assessment (C.I.G.M.A) (Davis et al., 1992). The authors found that the 3 minute insulin concentration and the incremental area under the insulin secretion curve from 0-10 minutes (IVGTT) were valid estimates of the insulin secretion and concluded that the shortened IVGTT is a practical, simple and reliable measure of insulin secretion in man which gives results similar to other more sophisticated methods. The homeostasis model assessment of insulin sensitivity (HOMA2-S%) takes into account the effect of variation in fasting blood glucose levels on insulin levels (Hosker et al., 1985, Matthews et al., 1985, Turner et al., 1979). Although this model has only been validated in adult populations (Phillips et al., 1994b, Haffner et al., 1996), it has been

used in similar studies of short children born SGA (Woods et al., 2002, Bozzola et al., 2005) and results have been consistent with Hofman et al's similar study in children using the modified minimal model assessment (Hofman et al., 1997). Using IVGTT, Hofman found a marked difference in the insulin sensitivity index between two groups of short children born following IUGR and those without a history of IUGR, with the IUGR group being less insulin sensitive. The acute insulin response was also significantly different between groups, with IUGR subjects having higher insulin levels (Hofman et al., 1997). However, the observation that hepatic and peripheral insulin sensitivity (IS) can differ considerably in the same individual raises concern about the use of HOMA as a measure of in vivo IS because an assumption of this model is that hepatic and peripheral IS are equivalent.

Insulin sensitivity, as assessed in 9 patients by the homeostasis model assessment (HOMA2-S%), showed a decrease in the mean HOMA2-S% after one year of GH treatment however this was not statistically significant. The homeostasis model assessment of insulin sensitivity (HOMA2-S%) provides an index of tissue sensitivity to insulin (IS) and relies on the product of fasting plasma glucose and insulin concentrations. The results are not valid if the glucose values are outside the range: 3.5-25mmol/L and if the insulin levels are outside the range 20-400pmol/L. Hence such cases were excluded from analysis.

Insulin secretion, as assessed by area under the curve (AUC) calculations from the insulin values obtained during the IVGTT was found to increase following one year of GH treatment, as assessed in 9 patients. Fasting basal insulin and C-peptide levels both significantly increased following one year of treatment, but in addition, the acute

glucose-stimulated insulin response was also larger compared to the pre-treatment response. Furthermore, the disposition index (insulin secretion x insulin sensitivity) was not found to have changed significantly, indicating that insulin secretion had adequately compensated for any change decrease in insulin sensitivity induced in these patients following one year of GH treatment.

The findings of this study are consistent with other studies of the effects of GH on insulin sensitivity and secretion. Despite no overall effect on glucose levels, in a study of 78 short children born SGA, Sas et al found that GH treatment induced higher fasting insulin levels and glucose-stimulated insulin levels, indicating relative insulin resistance (Sas et al., 2001). Although GH treatment was found to cause some insulin resistance in a study of 47 children born SGA as assessed by oral glucose tolerance test, van Pareren et al and Hokken-Koelega et al reported that the GH-induced insulin insensitivity had disappeared 6 months after discontinuation of GH, even after long-term GH treatment (van Pareren et al., 2003b, Hokken-Koelega et al., 2004). The degree of impaired glucose tolerance during GH therapy was found to be variable and unrelated to GH dosage (van Pareren et al., 2003b, Hokken-Koelega et al., 2004). Cutfield's study of 12 short children born SGA showed that with GH treatment insulin sensitivity fell 44% with a compensatory rise in the acute insulin response of 123%. In addition, reassessment of insulin sensitivity in 5 children 3 months after treatment was stopped did not demonstrate a recovery in this reduced insulin sensitivity (Cutfield et al., 2003a). In contrast, despite finding decreased insulin sensitivity during GH treatment of 13 short children born SGA, de Zegher et al, showed significant improvements in insulin sensitivity when they were tested 3 months after cessation of treatment and the slight increase in fasting insulin levels (5.2

mU/1, p = 0.04) was similar to that observed in non-GH treated children over the 2 yr study period (de Zegher et al., 2002). In a study by Bozzola et al, the homeostasis model assessment (HOMA) index was used to evaluate insulin sensitivity in 24 children treated with GH. After 2 years of GH therapy, glycosylated haemoglobin and basal glucose levels did not change significantly. Although insulin sensitivity fell, it still remained within the normal range. Moreover, the insulin sensitivity reduction did not correlate to the GH dose used (Bozzola et al., 2005). In a more long-term study van Dijk compared insulin sensitivity (SI) and disposition index (DI) in 37 previously GH-treated SGA subjects (mean 6.5 years after discontinuation of treatment) in young adulthood (mean 22.3 years old) with 25 untreated short SGA controls. No difference was demonstrated (van Dijk et al., 2007). Mean duration of treatment had been 7.3 years. Fasting levels of glucose and insulin increased during GH treatment but recovered after discontinuation. The positive family history rates were similar in both GH-treated patients and controls.

In some studies SGA children have been shown not to have altered insulin sensitivity when compared with auxologically identical AGA subjects but interestingly have shown significantly lower glucose levels (Cianfarani et al., 2003). In addition, the authors found higher TSH concentrations in SGA children who had failure of catch-up growth, suggesting that intrauterine reprogramming may involve thyroid function, which, as the authors suggest, in turn might affect postnatal growth and cholesterol metabolism, thereby increasing the risk of cardiovascular disease in later life. Those SGA children who have not caught up in growth in the early years, such as in this study, would be expected to have less insulin resistance as the glucose induced insulin response as a metabolic defense mechanism to protect the organism from

hypoglycaemia in infants with catch-up growth is higher than in children without significant catch-up growth (Colle et al., 1976, Cianfarani et al., 1999). Veening et al found no differences in glucose tolerance and beta-cell function between SGA and AGA groups of children, however reduced insulin sensitivity was found in SGA children using hyperinsulinaemic euglycaemic clamp studies, especially in those with catch-up growth and a high BMI (Veening et al., 2002).

The results from this study used to calculate disposition index indicate that as insulin sensitivity decreases, insulin secretion increases to compensate which is reassuring, although the numbers are too small to reach statistical significance. However, concern could be justified about the stress being placed on the already vulnerable beta cell in these SGA patients. Long term follow up of these children will be required in order to draw any concrete conclusions on the significance of these observations. The recent results of long term follow up studies on SGA patients previously treated with GH, however, are reassuring.

Glycosylated Haemoglobin A1c levels (HbA1cs)

Prior to commencing GH treatment, the mean glycosylated haemogloblin A1c (HbA1c) was 5.4% (normal range 4.6-5.8%). One patient had a value of 5.9%, just above the upper normal limit. There was a small initial increase in the mean HbA1c levels following six months of GH treatment but overall HbA1c levels remained essentially normal with little change from pre-treatment (mean 5.4%) values to those at one year (mean 5.5%). Although three patients experienced higher levels (6.2-6.3%) by two years of GH treatment the mean was still within the normal range (5.7%). There was no overall trend for levels to rise during the course of treatment, as

individual HbA1c levels appeared to fluctuate. A study of GH use for six years in 70 prepubertal children did not show any adverse effects on HbA1c levels (Sas et al., 2001). Doses were reported as a weekly dose of 0.24 or 0.48mg/kg/week which as daily doses equate to 0.034 mg/kg/day or 0.069 mg/kg/day, similar to the doses used in this study. In a study of safety of GH treatment in an American trial where GH doses ranged from 0.032 to 0.037 mg/kg/day, slightly increased levels of HbA1c from 5.2% at baseline to 5.4% were not clinically significant (Cutfield et al., 2006). Although numbers in this study are small, there does not appear to be a concerning effect of GH treatment on HbA1c levels however close monitoring of HBA1c is important.

4.3.5 Insulin like Growth Factors (IGF-1)

Mean IGF-1 levels in the 18 patients tested was -0.8 SDS. Baseline IGF-1 levels were around or below the mean in all patients and within 3 months of GH treatment they had begun to rise (to varying degrees). These result are consistent with other studies, reflecting low IGF-1 levels suggesting persisting dysfunction of the GH-IGF-1 axis in children born SGA (de Waal et al., 1994, Boguszewski et al., 1996, Leger et al., 1996, Sas et al., 1999, Van Pareren et al., 2003a). De Waal's study of 40 short prepubertal children born SGA found mean plasma IGF-1 and IGF-2 levels to be significantly reduced compared to controls. Similar to the results of study, Boguszewski et al's study of 72 short prepubertal children born SGA reported significantly lower levels of IGF-1 (mean -0.6 SDS) and IGFBP-3 compared to controls, although most individual IGF-1 and IGFBP-3 levels fell within the normal range (Boguszewski et al., 1996). In a study by Woods et al, IGF-1 levels in 16 short children born SGA were on average 1

SDS lower than the population reference used (Woods et al., 2002), however subjects were shorter and leaner than the control subjects and the comparison was not adjusted for current size. Of note Cutfield's study showed higher IGF-1 and IGFBP-3 concentrations in the SGA children (n = 15) compared to 12 AGA controls (mean age 7-8 years) but lower IGF-1 levels than in children with normal weight and stature (Cutfield et al., 2002). Tenhola et al's Finnish study of 55 children born SGA comparing with 55 AGA children aged 12 years (age and gender matched) found the BMI, sex, and puberty-adjusted mean serum IGF-1 concentrations to be significantly higher in SGA than in the AGA children (Tenhola et al., 2005). It is possible that pubertal changes expected around the age of 12, when IGF-1 levels rise (Juul et al., 1994), may explain some of the differences found in the Finnish study compared to this study. The advantage of the reference range chosen is that IGF-1 levels are expressed in standard deviation scores which adjust for age and gender (Juul et al., 1994) and reference ranges are based on a large Danish population study which appears to be the most appropriate reference standard currently available. However, the analysis in this study did not adjust for BMI or pubertal status as in the Finnish study. Further monitoring and analysis of the children in this study may further clarify these observations.

A statistically significant increase in IGF-1 levels was found between IGF-1 levels at baseline and following one year of GH treatment which is consistent with other studies. IGF-1 level increases with GH are to be expected as this is probably the main mechanism by which growth is induced (Chatelain et al., 1998). GH was associated with a marked and sustained increase in mean serum levels of IGF-1 from low to 1-2 SDS at GH doses of 0.033mg/kg/day and to 2 SDS with doses of 0.067mg/kg/day (Van Pareren et al., 2003a, Sas et al., 1999). In addition, discontinuation of GH has

been associated with a reduction in IGF-1 levels (Van Pareren et al., 2003a). Similar to the study by Sas et al, IGF-1 levels in this study after 2 years of GH treatment (IGF-1 SDS = 1.0) were similar to those following the first year of GH treatment (IGF-1 SDS = 1.1) when assessed in 8 patients. Higher IGF-1 SDS (1.9 v 1.2) in Sas et al's study was associated with higher dose (0.067mg/kg/day) compared to the lower dose (Sas et al., 1999) following one and two years of treatment. Associations between dose of GH and IGF-1 levels were not analysed in this study but will be considered in the future. In other studies positive correlations between fasting insulin and IGF-1 levels have been found (Cutfield et al., 2002, Tenhola et al., 2005). In addition, it has been suggested that circulating IGF-1 levels may have GH-independent actions in the regulation of insulin sensitivity and maintenance of insulin secretion (Dunger et al., 2003). However such a relationship between IGF-1 and insulin secretion has not been explored in this study and warrants further analysis in the future.

4.3.6 Associations with growth velocity at baseline & following 1 year of GH treatment

In relation to baseline growth velocity prior to GH treatment, no association was found in this study with IGF-1 levels. This is comparable to a study by Woods et al involving similar numbers (n = 16), and with patients of a slightly younger age (mean = 5.8 years) (Woods et al., 2002). However both studies involved small numbers. Higher acute insulin secretion in this study was found to be associated with greater baseline height velocity (r = 0.44) although this was not statistically significant, possibly due to the small numbers studied. However interestingly, Woods et al.

demonstrated similar associations in a group of short SGA children. In that study, greater C-peptide levels were associated with better baseline height velocity ($r = 0.75$; $p = 0.008$) (Woods et al., 2002). The authors postulate that compensatory hyperinsulinaemia in response to peripheral insulin resistance might lower IGFBP-1 levels (found to be lower in SGA subjects than controls) and thereby improve IGF-1 bioavailability (Woods et al., 2002). The authors also propose that the ability to increase insulin secretion in compensation for insulin resistance may be an important determinant of both glucose homeostasis and continuing growth in short children born SGA in the presence of a relative GH and IGF-1 resistant state. Furthermore, pre-treatment height velocity was reported to positively correlate with final adult height SDS in the study by Van Pareren et al of 54 GH treated short children born SGA (Van Pareren et al., 2003a) and hence this may be an important prognostic indicator.

Following one year of GH treatment increase in IGF-1 levels was not strongly associated with improvement in height velocity. However a clear correlation between increased IGF-1 levels and improved height has been reported in some studies involving larger numbers ($n = 54$-72) (Boguszewski et al., 1996, Van Pareren et al., 2003a). Boguszewski et al showed a negative correlation with change in height SDS and basal serum IGF-1 concentration, whereas positive correlation was found with one year growth response and the 10-day percentage increase in IGF-1 (Boguszewski et al., 1996). Using a multiple stepwise linear regression analysis, the model using chronological age at the start of GH therapy, the mother's height SDS, and the short term percent increase in IGF-I accounted for 42% of the variance in the 1-yr growth response. Overall, up to 59% of the variability in the 1-yr growth response to GH treatment could be explained by models using auxological and biochemical variables (Boguszewski et al., 1996). Van Pareren et al's study however did not find a

significant correlation between IGF-1 SDS at the start of GH treatment or increase in IGF-1 SDS with gain in height SDS from start of treatment until attainment of final adult height (Van Pareren et al., 2003a).

4.3.7 Bone Age

At baseline, bone age was appropriate or delayed in all 20 patients. There was no inappropriate advancement in bone age in any patient at baseline or following GH treatment. This is reassuring and inconsistent with reports from other studies showing acceleration of bone maturation (Arends et al., 2003, Sas et al., 1999, de Zegher et al., 1997a, Chernausek et al., 1996). Even in untreated patients born SGA, bone age may occasionally advance by more than one year in a single calendar year (Saenger et al., 2007). In theory inappropriate advancement in bone age could signal risk of early puberty or premature attainment of final adult height which could offset any height benefits of GH. De Zegher et al's study of over 100 children treated with various regimens of GH found that after 6 years bone age was still delayed by a few months in all treatment groups, even those on high dose (0.067mg/kg.day) GH (de Zegher et al., 2000). However, it is important to note that bone age-based height prediction tables based upon normally growing children may not be applicable to SGA children. Height at age 2 to 5 years appears to be a more reliable predictor of final height in short children born SGA (de Zegher et al., 2000). Inconsistencies in growth predictions may be due to an abnormal bone aging process in children with persistent short stature born SGA (Coutant et al., 1998). Although some studies have shown that acceleration of bone maturation is slower in younger than in prepubertal children (de Zegher et al., 1997a), due to the small numbers in this study, it was not possible to perform analysis of the effects on bone maturation according to age of the child.

4.3.8 Dual Energy X-ray Absorptiometry (DXA)

Despite small numbers in this study, significant improvements in total lean body mass and total bone mineral content were seen following one year of GH treatment compared to baseline. These results are encouraging. By using skinfold thickness measurements a study by Sas et al showed that normalisation of BMI was not accompanied by overall changes in percentage body fat but rather an increase in muscle mass (Sas et al., 2000). Similarly Leger et al has shown using MRI that after 2 years of GH treatment in 14 short prepubertal children born SGA that muscle mass significantly improved (Leger et al., 1998a). Obtaining a high peak bone mass early in life provides a larger bone reserve later in life (Saggese et al., 1996) which would be expected to reduce risk for osteoporosis and fractures (Goulding et al., 2000). The effects of improvements in bone mineral density (BMD) with GH is difficult to assess over the short term of the study in question, however previous studies suggest that BMD can significantly increase from subnormal baseline levels to lie within the normal range after 3 years of treatment (Arends et al., 2003) and these observations are similar to those observed in GH deficient children treated with GH (Boot et al., 1997, Saggese et al., 1996). The provisional positive findings of the effects of GH treatment demonstrated by DXA in this study suggest that DXA is an exciting new method by which to assess improvements in body composition in response to treatment. However further studies are required to further assess the usefulness of this tool in the assessment of children born SGA.

4.4 SUMMARY OF STUDY LIMITATIONS

This study identified the population of children born SGA in the Coombe Women's Hospital (CWH), one of Ireland's largest maternity hospitals, and evaluated possible contributory risk factors. A large cohort of over 14,000 babies born over a two year period at the CWH was examined. The incidence of SGA births was determined, and various characteristics of these infants and their mothers were compared with those of non-SGA infants born during the same period. Following exclusions for congenital anomalies and syndromes, 284 SGA infants were identified equal to 2% of the total infants (14,366) reviewed. The current standardised birth weight references curves for the UK (Freeman et al., 1995) were chosen as the most appropriate reference for this study cohort as no Irish references are yet available for the newborn period. This may have influenced under or over detection of SGA in the Irish context.

The data relating to the obstetric and neonatal variables on these infants were retrospective and obtained from a hospital database. There were difficulties with accurate determination of gestational age as this was based on last menstrual period (LMP) which is not always a precise measurement. Antenatal ultrasound assessment in addition to LMP would provide invaluable information in relation to gestational age; however this was beyond the scope of this study. In addition, data on ultrasound assessments of fetal growth velocity may distinguish between pathologically small versus constitutionally small for gestational age infants. Unfortunately data was not available to assess the possible influence of maternal age, previous history of SGA birth, maternal weight gain in pregnancy and complications such as antepartum haemorrhage and placenta praevia. In addition, information on use of illicit drugs

during pregnancy such as marijuana or cocaine which is also associated with IUGR (Hatch and Bracken 1986, Zuckerman 1989, Shiono 1995) was not available.

Although a higher rate of admission to the Special Care Baby Unit (SCBU) of SGA compared to non-SGA infants was highlighted, this study did not explore duration of stay in the SCBU, which may have important morbidity and economic implications. Moreover, infants born at gestations < 28 weeks were not included in the study due to the complex issues related to extreme prematurity and the lack of standardised methods for calculating birth weight SD scores for these infants.

This study undertook to evaluate growth and clinical data of this cohort of Irish children born SGA at ages 4-6 years and to identify those at risk of short stature, obesity and metabolic syndrome. The aim was to trace the 284 children identified from the CWH cohort who had been born SGA and determine their progress in terms of growth and development at ages 4-6 years. The difficulties in tracing these children at 4-6 years raised a number of issues regarding the assessment of the complete group, as only fifty six (20%) children who had been born SGA were traced and assessed. However no comparison of growth at 4-6 years was made with matched children born AGA at the same time which may have added more important information.

Studies have shown that children who were growth restricted in utero or who are relatively small at birth and show rapid weight gain in infancy are at greatest risk for the development of childhood obesity, increased visceral fat and insulin resistance, possible early markers of adult disease risk (Ong, 2006). As data was not available on

postnatal growth in the children assessed, it was not possible to explore any possible associations between rate of postnatal catch-up growth and auxology at 4-6 years.

The 15 children (of 20 eligible children identified) who received GH as part of this study had excellent growth responses and analysis of data on insulin sensitivity and secretion in these children both at baseline and following at least one year of treatment has been found to concur with those of other studies (Sas et al., 2001, Cutfield et al., 2006). Numbers however are small and further on-going monitoring and analysis is required in order to draw definite conclusions on the safety and efficacy of GH treatment in these children born SGA. Pooling of the Irish data from this study with that of the other centres involved in the multi-national NESGAS clinical trial should strengthen the observations made. Interesting data is pending on the possible role of the d3-growth hormone receptor polymorphism in the degree of response to GH treatment in this cohort of patients. In addition data on IGFBP-3 assays taken at the time of IGF-1 sampling will be analysed in these patients, the results of which may give more information on the role of these peptides in growth of children born SGA.

CHAPTER FIVE

CONCLUSIONS AND RECOMMENDATIONS

CHAPTER 5 CONCLUSIONS AND RECOMMENDATIONS

5.1 CONCLUSIONS

Small for gestational age is an entity which is difficult to determine due to limitations associated with accurate estimation of gestational age and the reference standards available. It is also difficult to compare outcomes due to the variety of definitions used in the numerous studies of outcome. However without doubt, it is an area which warrants research due to the numerous obstetric, perinatal, childhood and adult risk factors associated with being born small for gestational age. This is the first such study of Irish children born SGA, looking at maternal, obstetric and perinatal characteristics, follow-up growth at age 4-6 years, and use of growth hormone in those with severe short stature. The definition of SGA chosen for this study (birth weight < -2 SDS for gender and gestation), also agreed by international consensus, appears to be the most appropriate given that it represents those infants at the most severe end of the spectrum of fetal growth, and hence those at most risk of growth failure, short stature and metabolic syndrome. It is also the cut-off for birth weight at which growth hormone treatment is licensed.

This study of an Irish cohort of children born SGA identified numerous maternal and infant factors which would indicate that the cohort analysed had many similarities to those of other international studies (set in developed countries). As in other studies, this study has shown that both socioeconomic and lifestyle factors are associated with smaller weight infants. The social gradient in birth weight probably arises as a result of intergenerational effects, by the accumulation and addition of risk over time rather

than resulting entirely from exposure to risk within the current pregnancy (Spencer and Logan, 2002). In theory, some of these factors may be modifiable. Public health campaigns to decrease maternal smoking during, and ideally prior to pregnancy, would be expected to reduce SGA births, and improved nutritional status prior to conception may also have a beneficial effect (although this would be more difficult to quantify). Similarly, improvements in nutrition in childhood and adolescence, which optimise maternal height, may have small effects on future rates of SGA, however racial and genetic influences may persist. Although management of hypertension and/or pre-eclampsia is important, the degree to which treatment can modify fetal outcome is debated as good control of blood pressure during early pregnancy has not been shown to change the incidence of fetal growth restriction among hypertensive women (Redman, 1976). Other interventions such as low dose aspirin administration in patients with abnormal uterine artery blood flow have been studied and severity of IUGR may be decreased (Baschat and Hecher, 2004). However the detailed appraisal of other obstetric interventions to improve the fetal condition was beyond the scope of this thesis.

Of these modifiable factors, the strongest case can be made for endeavouring to decrease smoking amongst pregnant women, given the alarmingly high rates of women smoking both overall (26%) and in the SGA group (55%). Of equal importance will be efforts to improve the overall social environment in which children grow up so that protective factors such as maternal education are more evenly distributed across all social groups and risk factors are reduced in areas of disadvantage. Given the intergenerational effects of intrauterine growth retardation,

there is a sound rationale for emphasising the nutritional and health status of young children in general.

SGA is a descriptive term used to describe a baby who is born smaller than that expected for its gender and gestation. As borne out by this study, the major challenge in detection and management of this entity lies with the definition itself. The current consensus definition chosen for this study has some limitations; firstly as birth weight does not follow a normal distribution due to the biologically determined limited duration of pregnancy, and secondly because an absolute cut-off it does not take into account other factors such as maternal ethnicity, parity and size which play a role in the variations in fetal growth. Such factors greatly influence birth weight for gestation and create limitations for the cut-off definition of SGA currently in use. The known associations of parity, parental ethnicity, maternal height and weight with SGA infants highlights the limitations of the cut-off definition used, and why the management of fetal growth should not be based solely on estimated fetal size but rather growth velocity (Bernstein and Divon, 1997, Gardosi, 2005, Gardosi, 2006) (Degani, 2001). In addition correctly establishing whether an infant is 'true SGA' versus constitutionally small has profound implications for perinatal outcome and management due to higher rates of both preterm and operative delivery and perinatal complications (Zhang et al., 2007) (Figueras et al., 2007) (McCowan et al., 2005). The concern is to what "hidden" fetal growth restricted infants we may be missing, who are not born SGA according to the definition, but who may be at increased risk of the various neonatal problems associated with SGA, growth problems, and also later insulin resistance. Although there is consensus in much of the literature on the approaches to take, the practical application is another matter. Use of customized fetal

growth charts depends on a variety of variables many of which may be open to a variety of inaccuracies such as measurement of maternal height, maternal weight (depending on when in pregnancy it is measured) and racial assignment in cases of mixed race etc…Such discrepancies may expose the method to error and may nullify the potential benefits of its use. Appropriate training of staff would be required and a complete change in procedures already tried and tested in a country well-respected for its strong tradition of maternity services.

If part of the risk for adult health problems is determined during intrauterine life, how can postnatal growth modify or add to these established risks? Until recently, there were no formal management guidelines for the child born SGA following discharge from the neonatal unit. Often such children are followed for other reasons such as a history of prematurity but specific guidelines on the management of the infant born SGA in terms of optimising nutrition and growth especially in the first year have been lacking. There has been a tendency to supplement the low birth weight infant with high calorie feeds in order to achieve "normal" weight as quickly as possible. Various studies suggest that poor infant growth and excessive weight gain in childhood are associated with increased risk of childhood obesity, cardiovascular problems and insulin resistance (Vasu and Modi, 2007, Ong, 2006). Is it a question of "grow now, pay later"? This study identified extremely low rates of breastfeeding in children born SGA (on the background of a very low overall average rate) which raises immediate concerns as to the appropriateness of infant nutrition in this vulnerable population. It is important that parents are educated on the importance of infant nutrition (ideally breastfeeding) and whilst growth must be closely monitored, infants should not be over-fed due to the higher risk of metabolic syndrome in this group.

One of the objectives of this study was to assess growth and clinical status in a cohort of children born SGA, now aged 4-6 years, identified from a large database of over 14,000 births during a two period. Although the response rate from parents to the invitation to attend the Department of Paediatric Endocrinology at The National Children's Hospital was disappointing, 56 children born SGA were assessed, and the majority were found to have height, weight, and head circumference within the normal range, albeit slightly below average. These results were reassuring as they probably reflect appropriate postnatal weight gain and catch-up growth in the majority of children studied. In the course of this study, 5 (9%) children were identified with short stature (height SDS < -2), one was diagnosed with coeliac disease and one child was found to be overweight and at risk of metabolic syndrome. These are children who would not have otherwise been detected. In 3 cases with severe short stature, growth hormone treatment was indicated and has been commenced in 2 patients already, with the third patient due to commence shortly. However, due to poor response rates, we do not know if there are other children from the cohort identified who may have short stature requiring assessment or even treatment. It is conceivable that children most at risk of metabolic syndrome in adulthood are the least likely to present at this age as they may mistakenly appear to be healthy and thriving on a par with their peers. Without detailed clinical and auxological assessment of such children it is impossible to quantify their risk for future health problems. Therefore tracing these children remains a major issue.

International consensus now recommends that a child born SGA should have length, weight, and head circumference measured every 3 months in the first year, and every 6 months thereafter and that those who remain short by 2 years of age should be

investigated for conditions that limit growth (Clayton et al., 2007). This seems to be an appropriate screening tool for those children born SGA who may have growth problems, which should be evident by the age of 2 years and as it gives time for appropriate workup by a specialist and timely treatment with GH if indicated. Early close follow-up of children to age 2 years is preferable to later follow-up at school-entry age, as illustrated by this study where there were difficulties contacting parents.

Growth hormone therapy for short children born SGA has been shown to improve both short term and long-term height gain, is now licensed and is being increasingly used in such children. Although long-terms studies are limited, the data to date indicate positive effects in terms of linear growth, final height attainment and improvements in other parameters such as blood pressure, lipid profiles and bone density, without reports of permanent insulin resistance or development of type 2 diabetes in treated patients. This study which followed 15 children on growth hormone, confirms many of these observations, showing clear short-term and ongoing improvements in height and body composition, along with stability in disposition index as a result of compensatory increase in insulin secretion. All of these findings are reassuring for the health of these treated children, and for safety of GH treatment in similar children in the future. However, further research on the optimum dosage, efficacy and safety is required especially on the long-term risk factors for cardiovascular disease and type 2 diabetes mellitus.

Studies have shown that SGA is more common in preterm than term infants however this study did not include extremely premature infants born at < 28 weeks gestation. The important finding is that 40% of those born at a gestation ≥ 28 weeks had been

diagnosed with fetal growth restriction. This knowledge may have had a significant impact on their obstetric and neonatal management. In addition, given the risks for adverse neonatal outcome, future studies are required to improve accurate antenatal detection of fetal growth restriction and to examine the impact of IUGR on extremely premature deliveries and their postnatal course.

The major challenge is adequate detection of SGA, follow-up of such children and detection of those with persistent growth problems who may benefit from treatment with GH. To date in Ireland there are no formal guidelines for follow up of these children and referral to a Paediatric Endocrinologist may depend on their presentation to a Paediatrician for other reasons other than the parents' concerns about their child's growth. In addition, the small numbers of patients recruited to the GH study may reflect lack of awareness among both parents and physicians of the availability of treatment and the importance of early referral to specialist centres. It may also reflect reluctance for treatment given the relatively new indication and unknown possible long-term side effects.

The results of this study highlight the risks associated with SGA and the importance of follow up. The study provides important information on Irish children born SGA in relation to pregnancy, perinatal and clinical outcomes including auxological data at 4 to 6 years of age and shows that in most children normal growth ensues. In addition an effective treatment is available for those with poor growth and this study provides new important data on the use of GH in children born SGA in relation to efficacy and safety.

5.2 RECOMMENDATIONS

Close follow-up of any child born small for gestational age is vital to ensure early detection of growth failure, excessive postnatal weight gain and those at risk of metabolic syndrome. This should ideally begin prior to birth with early identification of fetal growth restriction to allow appropriate obstetric management and adequate preparation for neonatal complications regardless of gestation. Accurate calculation of gestational age should be established by use of date of last menstrual period combined with fetal ultrasonography and any maternal characteristics which may be risk factors for SGA should prompt close monitoring and where possible, specific charts for different communities should be employed. In addition the mother should be counselled on the risks posed to her baby by smoking, binge-drinking, illicit drug use, poor diet and inadequate or excessive weight gain. If there is a high chance that she will deliver an SGA infant, she should be informed about possible perinatal complications.

As current cut-off definitions for SGA amongst different medical specialities are heterogeneous, a clear consensus definition needs to be reached across all disciplines concerned with the management of these children both antenatally and after birth. This would ensure timely detection of those most at risk so that optimum management and follow-up can ensue. International consensus is required on the use of customised fetal growth curves given the known associations of parity, ethnicity, maternal height and weight with SGA. It may also facilitate more homogeneity across future studies of management and outcome.

Public health policy should include the provision of information to women of reproductive age (and their partners) about the importance of avoiding smoking and alcohol consumption, illicit drug use, a healthy balanced diet and appropriate weight gain during (and ideally prior to) pregnancy. In addition parents should be alerted to the consequences of fetal growth restriction, the impact it can have on perinatal outcomes and long-term health of their child, together with the importance of ongoing health surveillance.

When a child is born SGA, every attempt should be made to find out if there are any aetiological factors so that recurrence risks can be explored. If two or more severe cases of unexplained IUGR/SGA have occurred in the same family, referral to a medical geneticist should be considered. As growth outcomes may be different depending on whether an infant is short, light or both, accurate birth auxology should be performed on all infants regardless of birth weight or gestation by trained staff (nursing or medical) – this should include birth weight, birth length (by infant stadiometer) and head circumference. In addition breastfeeding should be encouraged as much as possible and emphasised as the ideal infant nutrition, ideally from the first day of life or as soon as enteral feeds are commenced. There has been a tendency to supplement the low birth weight infant with high calorie feeds in order to achieve "normal" weight as quickly as possible. This is thought to put the child at increased risk of childhood obesity and is no longer thought to be appropriate. However, as nutrition is vital for linear growth, brain growth and immune function, fear of inappropriate postnatal weight gain and its association with later adult health

problems needs to be balanced against the risks of suboptimal growth due to poor feeding and inadequate caloric intake.

Follow-up of any child born SGA should be initiated by the neonatal services and as per the international consensus we would recommend that any child born SGA should have length, weight, and head circumference measured every 3 months in the first year, and every 6 months thereafter and that those who remain short by 2 years of age should be investigated for conditions that limit growth. This is an appropriate screening tool for those children born SGA who may have growth problems, which should be evident by the age of 2 years and it gives time for appropriate workup by a specialist and timely treatment with GH if indicated. The importance of attending for follow-up should be stressed to all mothers at discharge to ensure maximum attendance, and attempts should be made to trace those who fail to attend any follow-up reviews so that the most vulnerable infants are not missed.

Any child born SGA in Ireland who has not caught up in growth by age 2 should be referred to a Paediatric Endocrinologist for further management. This should include detailed auxological assessment, monitoring of growth velocity, parental height assessment, growth hormone status (by stimulation testing), bone age and spinal x-rays and consideration for growth hormone if indicated. In addition, common causes of growth problems in the general paediatric population should be excluded, based on clinical suspicion, such as Silver Russell syndrome, Turner syndrome in girls, coeliac disease, cardiac anomalies, thyroid dysfunction, immunological deficiencies and scoliosis. Growth hormone should be considered in children with severe short stature as a means to improve not only growth, but also appetite, body composition, head

growth and bone mineral density and with potential benefits for blood pressure and lipid profiles. Appropriate investigation prior to commencing treatment should include IGF-1 and IGFBP-3 levels, oral glucose tolerance testing, HbA1c and thyroid function. Dual energy absorptiometry should be offered to assess body composition and bone mineral density both before and during treatment.

Prior to commencing the child on growth hormone treatment, parents should be informed that supra-physiological doses of growth hormone will be used, and of the theoretical and as yet unsubstantiated risks of potentiating a neoplasm, due to stimulation of the IGF system. In addition, they should be alerted to the uncertain risks of insulin resistance and type 2 diabetes in children treated with growth hormone. However, they should be reassured by the increasing body of evidence which points to favourable outcomes in such children, and that the benefits of treatment probably outweigh the risks. In addition, the consequences of not treating a child should be explored and follow-up monitoring of growth continued regardless of whether the child is on treatment or not. Large longitudinal collaborative studies are required to determine the long term safety and efficacy of GH treatment in this group.

Finally, as birth weight and length references corrected for gender and gestation are lacking for the modern Irish population, we recommend that funding be provided for a large study to develop national references. This will facilitate more accurate detection of infants born small for gestational age and study trends in birth weight over time.

CHAPTER SIX

REFERENCES

CHAPTER 6 REFERENCES

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APPENDICES

APPENDIX I

Mother's address

09/05/2005

Dear Ms ,

From our records your daughter, born on X/Y/2000 weighed XXXXgrams at birth, which is smaller than average. International studies show that although children who are born small are generally in the average range by two years and achieve a normal adult height, approximately 10% continue to be smaller than average for various reasons, and may have particular health issues in later life.

We are currently planning to study the progress growth of small babies born at the Coombe Women's Hospital, who are now aged between 4 and 6 years. We would like to invite you and your child to participate in this important study which is also being conducted in other European countries.

Assessment would include weighing and measuring your child. If possible we would also like to measure both parents. Following this we will be able to tell you how your child is progressing. If you wish to participate, we will arrange an appointment for you to meet Dr O'Connell at the growth clinic at the National Children's Hospital in Tallaght. If your child is not growing well we would discuss with you the possible causes and whether your child may benefit from treatment including growth hormone.

We hope that you will agree to have your child assessed and we would be grateful if you could complete the enclosed questionnaire and return it to us in the stamped addressed envelope. If you wish to make an appointment please contact us at **01-4142000** at the National Children's Hospital Tallaght and ask for **bleep 7352**. Alternatively, you can email susan.oconnell@tcd.ie.

Yours sincerely,

Dr Margaret Sheridan-Pereira

Dr M Sheridan-Pereira
Consultant Neonatologist

Hilary Hoey

Professor H Hoey,
Consultant Paediatric Endocrinologist

Susan O'Connell

Dr S O'Connell,
Paediatric Registrar

APPENDIX II

My Child's Growth

A few questions for parents

Dear Parent,

We are interested to know how your child is growing. This questionnaire should take 5-10mins to complete. Your co-operation is greatly appreciated. The information you provide will help us to decide the best way to follow-up babies who are born small in the future. All information will be dealt with in the strictest of confidence.

If you have any queries please contact Nurse Elaine O'Mullane or Dr Susan O'Connell at The National Children's Hospital 01-4142000 on Bleep 7352

1. Your child's details

I am the child's

Mother ☐ Father ☐ Other relationship ☐
Please specify_____

My child's first name:_____ Surname:_____

My child's date of birth is: ___/___ /_____

2. Here are some questions on your child's growth

Does your child seem smaller than:

your other children were at same age? Yes ☐ No ☐ N/A☐

school friends of the same age? Yes ☐ No ☐

What size clothes does your child wear? ____(e.g. age 3-4)

Have you any concerns about your child's growth? Yes ☐ No ☐

If yes, what are they? _____

What does your child now weigh? ___kgs/
___stone __ lbs

What date was your child weighed on? __/__ /____

What is your child's height now? _____cms/
_____inches

What date was your child measured? __/__/____

How was your child's height measured? By GP ☐
at school ☐
at home against wall ☐

3. Your child's development

Did your child	**Please choose one box**
Sit up without support by 7 months?	Yes ☐ No ☐
Crawl/bottom shuffle by 9 months?	Yes ☐ No ☐
Walk independently by 18 months?	Yes ☐ No ☐
Speak 2-3 single words by age 1 year?	Yes ☐ No ☐
Speak two word combinations by age 2?	Yes ☐ No ☐
Form recognisable sentences by age 3?	Yes ☐ No ☐

Can your child do the following?

Hop on one leg? Yes ☐ No ☐

Kick a ball? Yes ☐ No ☐

Skip? Yes ☐ No ☐

Use a knife and fork? Yes ☐ No ☐

Fasten buttons? Yes ☐ No ☐

Tie shoe laces? Yes ☐ No ☐

How is your child getting on at school?

Above average for class ☐

Average for class ☐

Below average for class ☐

Please choose one box

Does your child need remedial help in some subjects? Yes ☐ No ☐

Does your child attend a special school? Yes ☐ No ☐

How would you describe your child?

Is a good leader Yes ☐ No ☐

Prefers his/her own company Yes ☐ No ☐

Has trouble making friends Yes ☐ No ☐

Is very good at sports Yes ☐ No ☐

Looks younger than his/her age Yes ☐ No ☐

4. Your child's health

Does your child have any medical problems?

Asthma? Yes ☐ No ☐ Don't know ☐

Coeliac disease? Yes ☐ No ☐ Don't know ☐

A heart condition? Yes ☐ No ☐ Don't know ☐

Kidney problems? Yes ☐ No ☐ Don't know ☐

Diabetes? Yes ☐ No ☐ Don't know ☐

Other chronic disorder? Yes ☐ No ☐ Don't know ☐

Is your child attending a Consultant Paediatrician at the moment? Yes ☐ No ☐

If yes, what Consultant? _____

Would you like to add any further information on your child's medical history?_____

Did your child ever attend a dietician? Yes ☐ No ☐

If yes, where? _____

Did your child require speech and language therapy? Yes ☐ No ☐

Did your child have any problems with vision? Yes ☐ No ☐

Did your child have any problems with hearing? Yes ☐ No ☐

5. The family

Please list name, age, birth weight and duration of pregnancy for each of your children

If you need any more space please use back of page.

Name	Age	Birth Weight (lbs ozs)	How long was the pregnancy? (weeks)

6. Parent information

Mother's height ____cms / ___feet ___inches

Father's height ____cms / ___feet ___inches

Do both parents live at home? Yes ☐ No ☐

Is mother employed outside the home? Yes ☐ No ☐ N/A☐

Is father employed outside the home? Yes ☐ No ☐ N/A☐

7. Regarding the study described in the letter

I would like my child to participate Yes ☐ No ☐

My child will be unable to participate Yes ☐ No ☐

To help us arrange hospital visits please tick which times would be suitable for you

Mon am	Tues am	Wed am	Thur am	Fri am
☐	☐	☐	☐	☐
Mon pm	Tues pm	Wed pm	Thur pm	
☐	☐	☐	☐	

Please give us a phone number so that we can contact you _____

What is the best time of day for us to call you? _____

Signed:

_____

Please print name

_____

Date _____

Thank you for completing this form. Please return in the enclosed stamped addressed envelope to:

Dr Susan O'Connell, Department of Paediatrics, Trinity Centre for Health Sciences, National Children's Hospital, Tallaght, Dublin 24

If you have any queries please contact Nurse Elaine O'Mullane at The National Children's Hospital 01-4142000 on Bleep 7352 or extension 4111

APPENDIX III

S.G.A Growth Study(N.E.S.G.A.S)

Name: .....
Date of Birth: ___/___/___
Address.....
.....
Hospital No:.....

. **Number**

Source: **C.W.H**.....
N.M.H.....
A.M.N.C.H.....
OTHER-.....

Observations

DATE: .../.../...

Childs

Height-Standing: .....cms
Sitting:.....cms
Weight-.....kgs:
B/P:.....
Pulse:.....:
MAP:.....
Head Circumference:.....cms

Parents

Mum: **Height**-Standing:.....cms
Sitting:.....cms
Weight-.....kgs
Dad: **Height**-Standing:.....cms
Sitting:.....cms
Weight-.....kgs

Sibling

Name:.....
Date of Birth: ___/___/___
Height-Standing: .....cms
Sitting.....cms
Birth Weight.....kgs
Gestational Age:.....wks
Present Weight: .....kgs

Information/History

Birth History Pregnancy
(smoker/alcohol consumption/complications e.g. B/P, PET, DM etc):

Confirm gestation:.....wks
Confirm birth weight:.....kgs
Sure of dates?.....
.....
.....
.....
.....
.....

Delivery Method (why this method?).....
.....
.....

Neonatal Course (SCBU/PNW,prematurity,complications):
.....
.....
.....
.....

Follow up since discharge:.....
.....

Weight gain during infancy:.....
.....

Name: .....
Date of Birth: .....
Address: .....
Hospital No: .....

Childs History

DATE..../...../....

Past Medical/Surgical history:.....
.....
.....
.....
.....

Developmental history:

motor:.....
.....
speech:.....
.....
hearing: .....
.....
vision:.....
.....

Vaccination history.....
Social history:.....
.....
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.....
.....
.....
.....

Family history:.....
.....
.....
.....
.....
.....
.....
.....

Medications/Allergies:.....
.....

Diet and Activity:.....
.....
.....
.....

Name: .....
Date of Birth: .....
Address:.....
Hospital No:.....

Physical examination

DATE: .../.../....

Appearance: .....
.....
Dysmorphism:.....
.....
Nutritional Status: .....
.....
Teeth:.....
Skin:.....
Spine:.....
Chest Auscultation: .....
.....
C.V.S: .....
.....
Abdominal: .....
.....
Genitalia:
.....
.....
Neuro
Reflexes: .....
Hops:.....
Skips:.....
Heel-toe:.....
Finger nose:.....

Impression-

General:.....
.....
.....
.....
Eligibility to N.E.S.G.A.S:.....
Follow up plan:.....
.....
.....
.....
.....
G.P Letter Sent :Yes☐ To follow☐ Date Sent:__/__/__

Date:.....Signed..... Bleep No:.....

APPENDIX IV

Patient Sticker

Date __/__/__

Dear Doctor,

We are conducting a study of growth in children who were born small for gestational age (SGA) at the Coombe Women's Hospital between July 1999 and June 2001. About 10-15% of children born SGA will fail to catch up in growth by age 4, and will have short stature. Your patient above was assessed today as part of this study. I am happy to report that he/she has achieved good catch up growth and is within the target range for height. We have not made any follow-up plans, however should you have any concerns in the future, we would be happy to arrange a further appointment.

Patient's Height _____ Patient's Weight _____

Height Centile _____ Weight Centile _____

Head Circumference _____

Comment:

Yours sincerely,

Dr Susan O'Connell,
Specialist Registrar to Professor Hilary Hoey,
Consultant Paediatric Endocrinologist

APPENDIX V

Country of birth

Ethnic Origin (If mixed, tick more than one box)

	You	Baby's Father
Africa		
North Africa (eg Morocco, Algeria)	☐	☐
Sub-Sahara (eg Somalia, Kenya, Nigeria)	☐	☐
Other:		
Asia		
India	☐	☐
Pakistan	☐	☐
Bangladesh	☐	☐
China	☐	☐
Far East Asia - Other (eg Japan, Korea)	☐	☐
South East Asia (eg Malaysia, Thailand, Philippines)	☐	☐
Other:		
Caribbean (eg Barbados, Jamaica, Trinidad & Tobago)	☐	☐
Europe		
Britain (England, Scotland & Wales)	☐	☐
Ireland	☐	☐
Northern Europe (eg Denmark, Norway, Sweden)	☐	☐
Western Europe (eg France, Germany, Netherlands)	☐	☐
Eastern Europe (eg Balkans, Poland, Russia)	☐	☐
Southern Europe (eg Greece, Italy, Portugal, Spain, Turkey)	☐	☐
Other:		
Middle East (eg Egypt, Israel, Syria)	☐	☐
Other:		

APPENDIX VI

Code No.	Socio-economic group and occupation	Employment status
A	**Employers and managers (contd.)**	
490	Computer operators, data processing operators and other office machine operators	2
500	Bricklayers and masons	2
501	Roofers, slaters, tilers, sheeters and cladders	2
502	Plasterers	2
503	Glaziers	2
504	Builders and building contractors	2
506	Floorers, floor coverers, carpet fitters and planners, floor and wall tilers	2
507	Painters and decorators	2
509	Scaffolders, riggers, steeplejacks and other construction trades n.e.s.	2
515	Toolmakers	2
516	Metal working production and maintenance fitters	2
517	Precision instrument makers, goldsmiths, silversmiths and precious stone workers	2
519	Other machine tool setters and CNC setter-operators n.e.s.	2
521	Electricians and electrical maintenance fitters	2
523	Telephone fitters	2
524	Cable jointers and lines repairers	2
525	Radio, TV and video engineers	2
526	Computer engineers (installation and maintenance)	2
529	Other electrical and electronic trades n.e.s.	2
530	Smiths, forge/metal plate workers and shipwrights	2
532	Plumbers, heating and ventilating engineers and related trades	2
533	Sheet metal workers	2
537	Welders and steel erectors	2
540	Motor mechanics, auto electricians, tyre and exhaust fitters	2
541	Vehicle body repairers, panel beaters and spray painters	2
550	Weavers, knitters, warp preparers, bleachers, dyers and finishers	2
553	Sewing machinists, menders, darners and embroiderers	2
554	Coach trimmers, upholsterers and mattress makers	2
555	Shoe repairers and other leather makers	2
556	Tailors, dressmakers, clothing cutters, milliners and furriers	2
559	Other textiles, garments and related trades n.e.s.	2
561	Printers, originators and compositors	2
569	Bookbinders, print finishers and other printing trades n.e.s.	2
570	Carpenters and joiners	2
571	Cabinet makers	2
579	Other woodworking trades n.e.s	2
580	Bakers and flour confectioners	2
581	Butchers and meat cutters	2
582	Fishmongers and poultry dressers	2
590	Glass product and ceramics makers, finishers and other operatives	2
594	Gardeners and groundsmen/women	2
595	Horticultural trades	2
599	Other craft and related occupations	2
620	Chefs and cooks	2
650	Childminders, nursery nurses and playgroup leaders	2
652	Educational assistants	2
660	Hairdressers, barbers and beauticians	2
673	Launderers, dry cleaners and pressers	2
690	Undertakers, bookmakers and other personal service workers n.e.s.	2

Socio-economic groups - list of constituent occupations

Code No.	Socio-economic group and occupation	Employment status		
A	**Employers and managers**			
100	Senior managers in national government	2	3	1
101	General managers in large companies	2		1,
102	Local government officers	2	3	1,
103	General administrators in national government	2	3	1,
110	Production and works managers	2		1,
111	Building managers	2		1,
120	Company financial managers	2		1,
121	Marketing managers	2		1,
122	Purchasing managers	2		1,
124	Personnel managers	2		1,
126	Computer systems managers	2		1,
130	Credit controllers	2		1,
131	Bank and building society managers	2		1,
139	Other financial managers n.e.s.	2		1,
140	Transport managers	2		1,
141	Stores and warehousing managers	2		1,
150	Commissioned officers in armed forces			1
152	Senior police and prison officers			1
171	Garage managers and proprietors	2		1,
173	Hotel and accommodation managers	2		1,
174	Restaurant and catering managers	2		1,
175	Publicans, innkeepers and club managers	2		1,
176	Entertainment and sport managers	2		1,
177	Travel agency managers	2		1,
178	Managers and proprietors of butchers	2		1,
179	Managers and proprietors of shops	2		1,
191	Administrators of schools and colleges	2	3	1,
199	Other managers n.e.s.	2		1,
240	Judges	2	3	1,
270	Librarians, archivists and curators	2	3	1,
310	Draughtspersons	2		
331	Aircraft officers, traffic planners and controllers	2		
332	Ship and hovercraft officers	2		1,
361	Underwriters, claims assessors, brokers and investment analysts	2		
371	Matrons, houseparents, welfare, community and youth workers	2		
380	Authors, writers and journalists	2		
381	Artists, commercial/industrial artists, graphic and clothing designers	2		
384	Actors, musicians, entertainers, stage managers, producers and directors	2		
386	Photographers, camera, sound and video equipment operators	2		
387	Professional athletes and sport officials	2		
391	Vocational, industrial trainers and driving instructors	2		
410	Accounts and wages clerks, book-keepers and other financial clerks	2		
411	Cashiers, bank and counter clerks	2		
412	Debt, rent and other cash collectors	2		
430	Filing, computer, library and other clerks n.e.s.	2		
441	Storekeepers, warehousemen/women, despatch and production control clerks	2		
459	Secretaries, medical, legal; personal assistants, typists and word processor operators	2		

Code No.	Socio-economic group and occupation	Employment status
A	**Employers and managers (contd.)**	
702	Importers, exporters, commodity and shipping brokers	2
710	Technical and wholesale sales representatives	2
719	Auctioneers, estimators, valuers and other sales representatives n.e.s.	2
720	Sales assistants, check-out operators and petrol pump attendants	2
731	Roundsmen/women and van salespersons	2
732	Market/street traders and scrap dealers	2
790	Merchandisers, window dressers, floral arrangers and telephone salespersons	2
800	Bakery and confectionery process operatives	2
802	Tobacco process operatives	2
809	Other food and drink (incl. brewing) process operatives	2
810	Tannery production operatives	2
812	Spinners, doublers, twisters, winders and reelers	2
814	Other textiles processing operatives	2
820	Chemical, gas and petroleum process plant operatives	2
821	Paper, wood and related process plant operatives	2
824	Rubber process operatives, moulding machine operatives and tyre builders	2
825	Plastics process operatives, moulders and extruders	2
829	Synthetic fibre and other chemical, paper, plastics and related operatives	2
830	Moulders and furnace operatives (metal)	2
834	Electroplaters, galvanisers and colour coaters	2
839	Other metal making and treating process operatives n.e.s.	2
840	Machine tool operatives (incl. CNC machine tool operatives)	2
841	Other automatic machine workers, metal polishers and dressing operatives	2
850	Assemblers and lineworkers (electrical and electronic goods)	2
851	Assemblers and lineworkers (metal goods and other goods)	2
860	Inspectors, viewers and laboratory testers	2
862	Packers, bottlers, canners, fillers, weighers, graders and sorters	2
872	Drivers of road goods vehicles	2
873	Bus conductors and coach drivers	2
874	Taxi/cab drivers, chauffeurs and couriers	2
880	Seafarers (merchant navy), barge and boat operatives	2
885	Mechanical plant drivers/operatives and crane drivers	2
887	Fork lift truck drivers	2
889	Other transport and machinery operatives n.e.s.	2
895	Pipe layers/pipe jointers and related construction workers	2
897	Woodworking machine operatives	2
898	Mine (excluding coal) and quarry workers	2
899	Other plant, machine and process operatives n.e.s.	2
903	Fishing and related workers	2
923	Road construction workers, paviors and kerb layers	2
929	Other building and civil engineering labourers	2
930	Stevedores and dockers	2
931	Goods porters	2
933	Refuse and salvage collectors	2
955	Window cleaners and car park attendants	2
958	Cleaners and domestics	2
959	Other occupations in sales and services n.e.s.	2
990	All other labourers and related workers	2

Code No.	Socio-economic group and occupation	Employment status		
B	**Higher professional**			
200	Chemists	2	3	1,4
201	Biological scientists	2	3	1,4
202	Physicists	2	3	1,4
209	Other natural scientists n.e.s.	2	3	1,4
210	Civil and mining engineers	2	3	1,4
211	Mechanical engineers	2	3	1,4
212	Electrical and electronic engineers	2	3	1,4
214	Software engineers	2	3	1,4
215	Chemical, production, planning and quality control engineers	2	3	1,4
216	Design and development engineers	2	3	1,4
219	Other engineers and technologists n.e.s.	2	3	1,4
220	Medical practitioners	2	3	1,4
221	Pharmacists, pharmacologists, ophthalmic and dispensing opticians	2	3	1,4
223	Dental practitioners	2	3	1,4
224	Veterinarians	2	3	1,4
230	University, RTC and higher education teachers	2	3	1,4
242	Barristers and solicitors	2	3	1,4
250	Chartered and certified management accountants (incl. taxation experts)	2	3	1,4
252	Actuaries, economists, statisticians, management consultants and business analysts	2	3	1,4
260	Architects, town planners and surveyors	2	3	1,4
290	Psychologists and other social/behavioural scientists	2	3	1,4
292	Clergy	2	3	1,4
293	Social workers and probation officers	2	3	1,4
C	**Lower professional**			
121	Marketing managers		3	
132	Civil Service executive officers	2	3	1,4
233	Secondary and vocational education teachers	2	3	1,4
234	Primary and nursery education teachers	2	3	1,4
239	Other teaching professionals n.e.s.	2	3	1,4
300	Laboratory technicians	2	3	1,4
301	Engineering technicians	2	3	1,4
302	Electrical and electronic technicians	2	3	1,4
303	Architectural, town planning, building and civil engineering technicians	2	3	1,4
309	Other scientific technicians n.e.s.	2	3	1,4
312	Building inspectors and quantity surveyors	2	3	1,4
313	Marine, insurance and other surveyors	2	3	1,4
320	Computer analyst programmers	2	3	1,4
331	Aircraft officers, traffic planners and controllers			1,4
340	Nurses and midwives	2	3	1,4
342	Medical radiographers	2	3	1,4
343	Physiotherapists and chiropodists	2	3	1,4
346	Medical technicians, dental auxiliaries and dental nurses	2	3	1,4
347	Occupational and speech therapists, psychotherapists and other therapists n.e.s.	2	3	1,4
349	Other health associate professionals n.e.s.	2	3	1,4
350	Legal service and related occupations	2	3	1,4
361	Underwriters, claims assessors, brokers and investment analysts		3	1,4
363	Personnel, industrial relations and work study officers	2	3	1,4

Code No.	Socio-economic group and occupation	Employment status		
C	**Lower professional (contd.)**			
380	Authors, writers and journalists		3	1,4
381	Artists, commercial/industrial artists, graphic and clothing designers		3	1,4
384	Actors, musicians, entertainers, stage managers, producers and directors		3	1,4
390	Information officers, careers advisers and vocational guidance specialists	2	3	1,4
391	Vocational, industrial trainers and driving instructors			1,4
394	Inspectors of factories, trading standards and other statutory inspectors	2	3	1,4
396	Environmental health workers, occupational hygienists and safety officers	2	3	1,4
399	Other associate professional and technical occupations n.e.s.	2	3	1,4
640	Nurses' aids and ambulance staff	2	3	1,4
700	Buyers and purchasing officers	2	3	1,4
D	**Non-manual**			
310	Draughtspersons			1,4
371	Matrons, houseparents, welfare, community and youth workers			1,4
386	Photographers, camera, sound and video equipment operators			1,4
387	Professional athletes and sport officials			1,4
400	Civil Service administrative officers and assistants	2	3	1,4
401	Local government clerical officers and assistants	2	3	1,4
410	Accounts and wages clerks, book-keepers and other financial clerks			1,4
411	Cashiers, bank and counter clerks			1,4
412	Debt, rent and other cash collectors			1,4
430	Filing, computer, library and other clerks n.e.s.			1,4
459	Secretaries, medical, legal; personal assistants, typists and word processor operators			1,4
460	Receptionists and receptionist-telephonists	2	3	1,4
462	Telephone operators, telegraph operators and other office communication system operators	2	3	1,4
490	Computer operators, data processing operators and other office machine operators			1,4
600	Soldiers (sergeant and below)			1,4
610	Police officers (sergeant and below)			1,4
611	Fire service officers	2	3	1,4
612	Prison service officers			1,4
620	Chefs and cooks			1,4
621	Waiters and waitresses	2	3	1,4
622	Bar staff	2	3	1,4
630	Travel and flight attendants	2	3	1,4
650	Childminders, nursery nurses and playgroup leaders			1,4
652	Educational assistants			1,4
660	Hairdressers, barbers and beauticians			1,4
670	Housekeepers (domestic and non-domestic)	2	3	1,4
702	Importers, exporters, commodity and shipping brokers			1,4
710	Technical and wholesale sales representatives			1,4
719	Auctioneers, estimators, valuers and other sales representatives n.e.s.			1,4
720	Sales assistants, check-out operators and petrol pump attendants			1,4
732	Market/street traders and scrap dealers			1,4

Code No.	Socio-economic group and occupation	Employment status		
D	**Non-manual (contd.)**			
790	Merchandisers, window dressers, floral arrangers and telephone salespersons			1,4
881	Railway station workers, supervisors and guards	2	3	
953	Counterhands and catering assistants	2	3	1,4
E	**Manual skilled**			
500	Bricklayers and masons			1,4
502	Plasterers			1,4
504	Builders and building contractors			1,4
506	Floorers, floor coverers, carpet fitters and planners, floor and wall tilers			1,4
507	Painters and decorators			1,4
515	Toolmakers			1,4
516	Metal working production and maintenance fitters			1,4
517	Precision instrument makers, goldsmiths, silversmiths and precious stone workers			1,4
519	Other machine tool setters and CNC setter-operators n.e.s.			1,4
521	Electricians and electrical maintenance fitters			1,4
523	Telephone fitters			1,4
524	Cable jointers and lines repairers			1,4
525	Radio, TV and video engineers			1,4
526	Computer engineers (installation and maintenance)			1,4
529	Other electrical and electronic trades n.e.s.			1,4
530	Smiths, forge/metal plate workers and shipwrights			1,4
532	Plumbers, heating and ventilating engineers and related trades			1,4
533	Sheet metal workers			1,4
537	Welders and steel erectors			1,4
540	Motor mechanics, auto electricians, tyre and exhaust fitters			1,4
541	Vehicle body repairers, panel beaters and spray painters			1,4
550	Weavers, knitters, warp preparers, bleachers, dyers and finishers			1,4
554	Coach trimmers, upholsterers and mattress makers			1,4
555	Shoe repairers and other leather makers			1,4
556	Tailors, dressmakers, clothing cutters, milliners and furriers			1,4
559	Other textiles, garments and related trades n.e.s.			1,4
561	Printers, originators and compositors			1,4
569	Bookbinders, print finishers and other printing trades n.e.s.			1,4
570	Carpenters and joiners			1,4
571	Cabinet makers			1,4
579	Other woodworking trades n.e.s.			1,4
580	Bakers and flour confectioners			1,4
581	Butchers and meat cutters			1,4
582	Fishmongers and poultry dressers			1,4
590	Glass product and ceramics makers, finishers and other operatives			1,4
731	Roundsmen/women and van salespersons			1,4
800	Bakery and confectionery process operatives			1,4
810	Tannery production operatives			1,4
821	Paper, wood and related process plant operatives			1,4
824	Rubber process operatives, moulding machine operatives and tyre builders			1,4
830	Moulders and furnace operatives (metal)			1,4
834	Electroplaters, galvanisers and colour coaters			1,4
839	Other metal making and treating process operatives n.e.s.			1,4

Code No.	Socio-economic group and occupation	Employment status		
E	**Manual skilled (contd.)**			
871	Bus and road transport depot inspectors	2	3	1,4
872	Drivers of road goods vehicles			1,4
873	Bus conductors and coach drivers			1,4
874	Taxi/cab drivers, chauffeurs and couriers			1,4
881	Railway station workers, supervisors and guards			1,4
882	Rail engine drivers and other railway line operatives	2	3	1,4
885	Mechanical plant drivers/operatives and crane drivers			1,4
887	Fork lift truck drivers			1,4
889	Other transport and machinery operatives n.e.s.			1,4
897	Woodworking machine operatives			1,4
F	**Semi-skilled**			
441	Storekeepers, warehousemen/women, despatch and production control clerks			1,4
501	Roofers, slaters, tilers, sheeters and cladders			1,4
503	Glaziers			1,4
509	Scaffolders, riggers, steeplejacks and other construction trades n.e.s.			1,4
553	Sewing machinists, menders, darners and embroiderers			1,4
594	Gardeners and groundsmen/women			1,4
599	Other craft and related occupations			1,4
615	Security guards and related occupations	2	3	1,4
619	Other security and protective service occupations n.e.s.	2	3	1,4
644	Care assistants and attendants	2	3	1,4
672	Caretakers	2	3	1,4
673	Launderers, dry cleaners and pressers			1,4
690	Undertakers, bookmakers and other personal service workers n.e.s.			1,4
802	Tobacco process operatives			1,4
809	Other food and drink (incl. brewing) process operatives			1,4
812	Spinners, doublers, twisters, winders and reelers			1,4
814	Other textiles processing operatives			1,4
820	Chemical, gas and petroleum process plant operatives			1,4
825	Plastics process operatives, moulders and extruders			1,4
829	Synthetic fibre and other chemical, paper, plastics and related operatives			1,4
840	Machine tool operatives (incl. CNC machine tool operatives)			1,4
841	Other automatic machine workers, metal polishers and dressing operatives			1,4
850	Assemblers and lineworkers (electrical and electronic goods)			1,4
851	Assemblers and lineworkers (metal goods and other goods)			1,4
860	Inspectors, viewers and laboratory testers			1,4
862	Packers, bottlers, canners, fillers, weighers, graders and sorters			1,4
880	Seafarers (merchant navy), barge and boat operatives			1,4
893	Electrical, energy, boiler and related plant operatives and attendants	2	3	1,4
895	Pipe layers/pipe jointers and related construction workers			1,4
898	Mine (excluding coal) and quarry workers			1,4
899	Other plant, machine and process operatives n.e.s.			1,4
903	Fishing and related workers			1,4
913	Mates to metal, electrical and related fitters	2	3	1,4
922	Rail construction and maintenance workers	2	3	1,4
940	Postal workers and mail sorters	2	3	1,4
951	Hotel porters and kitchen porters	2	3	1,4
959	Other occupations in sales and services n.e.s.			1,4

Code No.	Socio-economic group and occupation	Employment status		
	G Unskilled			
892	Water and sewerage plant attendants	2	3	1,4
919	Labourers in engineering and other making/processing industries	2	3	1,4
923	Road construction workers, paviors and kerb layers			1,4
929	Other building and civil engineering labourers			1,4
930	Stevedores and dockers			1,4
931	Goods porters			1,4
933	Refuse and salvage collectors			1,4
934	Drivers' mates	2	3	1,4
955	Window cleaners and car park attendants			1,4
958	Cleaners and domestics			1,4
990	All other labourers and related workers			1,4
	H Own account workers			
101	General managers in large companies		3	
110	Production and works managers		3	
111	Building managers		3	
120	Company financial managers		3	
122	Purchasing managers		3	
124	Personnel managers		3	
126	Computer systems managers		3	
130	Credit controllers		3	
131	Bank and building society managers		3	
139	Other financial managers n.e.s.		3	
140	Transport managers		3	
141	Stores and warehousing managers		3	
171	Garage managers and proprietors		3	
173	Hotel and accommodation managers		3	
174	Restaurant and catering managers		3	
175	Publicans, innkeepers and club managers		3	
176	Entertainment and sport managers		3	
177	Travel agency managers		3	
178	Managers and proprietors of butchers		3	
179	Managers and proprietors of shops		3	
199	Other managers n.e.s.		3	
310	Draughtspersons		3	
331	Aircraft officers, traffic planners and controllers		3	
332	Ship and hovercraft officers		3	
371	Matrons, houseparents, welfare, community and youth workers		3	
386	Photographers, camera, sound and video equipment operators		3	
387	Professional athletes and sport officials		3	
391	Vocational, industrial trainers and driving instructors		3	
410	Accounts and wages clerks, book-keepers and other financial clerks		3	
411	Cashiers, bank and counter clerks		3	
412	Debt, rent and other cash collectors		3	
430	Filing, computer, library and other clerks n.e.s.		3	
441	Storekeepers, warehousemen/women, despatch and production control clerks		3	
459	Secretaries, medical, legal; personal assistants, typists and word processor operators		3	
490	Computer operators, data processing operators and other office machine operators		3	
500	Bricklayers and masons		3	

Code No.	Socio-economic group and occupation	Employment status
1	**Own account workers (contd.)**	
501	Roofers, slaters, tilers, sheeters and cladders	3
502	Plasterers	3
503	Glaziers	3
504	Builders and building contractors	3
506	Floorers, floor coverers, carpet fitters and planners, floor and wall tilers	3
507	Painters and decorators	3
509	Scaffolders, riggers, steeplejacks and other construction trades n.e.s.	3
515	Toolmakers	3
516	Metal working production and maintenance fitters	3
517	Precision instrument makers, goldsmiths, silversmiths and precious stone workers	3
519	Other machine tool setters and CNC setter-operators n.e.s.	3
521	Electricians and electrical maintenance fitters	3
523	Telephone fitters	3
524	Cable jointers and lines repairers	3
525	Radio, TV and video engineers	3
526	Computer engineers (installation and maintenance)	3
529	Other electrical and electronic trades n.e.s.	3
530	Smiths, forge/metal plate workers and shipwrights	3
532	Plumbers, heating and ventilating engineers and related trades	3
533	Sheet metal workers	3
537	Welders and steel erectors	3
540	Motor mechanics, auto electricians, tyre and exhaust fitters	3
541	Vehicle body repairers, panel beaters and spray painters	3
550	Weavers, knitters, warp preparers, bleachers, dyers and finishers	3
553	Sewing machinists, menders, darners and embroiderers	3
554	Coach trimmers, upholsterers and mattress makers	3
555	Shoe repairers and other leather makers	3
556	Tailors, dressmakers, clothing cutters, milliners and furriers	3
559	Other textiles, garments and related trades n.e.s.	3
561	Printers, originators and compositors	3
569	Bookbinders, print finishers and other printing trades n.e.s.	3
570	Carpenters and joiners	3
571	Cabinet makers	3
579	Other woodworking trades n.e.s.	3
580	Bakers and flour confectioners	3
581	Butchers and meat cutters	3
582	Fishmongers and poultry dressers	3
590	Glass product and ceramics makers, finishers and other operatives	3
594	Gardeners and groundsmen/women	3
595	Horticultural trades	3
599	Other craft and related occupations	3
620	Chefs and cooks	3
650	Childminders, nursery nurses and playgroup leaders	3
652	Educational assistants	3
660	Hairdressers, barbers and beauticians	3
673	Launderers, dry cleaners and pressers	3
690	Undertakers, bookmakers and other personal service workers n.e.s.	3
702	Importers, exporters, commodity and shipping brokers	3
710	Technical and wholesale sales representatives	3
719	Auctioneers, estimators, valuers and other sales representatives n.e.s.	3

Code No.	Socio-economic group and occupation	Employment status		
H	**Own account workers (contd.)**			
720	Sales assistants, check-out operators and petrol pump attendants		3	
731	Roundsmen/women and van salespersons		3	
732	Market/street traders and scrap dealers		3	
790	Merchandisers, window dressers, floral arrangers and telephone salespersons		3	
800	Bakery and confectionery process operatives		3	
802	Tobacco process operatives		3	
809	Other food and drink (incl. brewing) process operatives		3	
810	Tannery production operatives		3	
812	Spinners, doublers, twisters, winders and reelers		3	
814	Other textiles processing operatives		3	
820	Chemical, gas and petroleum process plant operatives		3	
821	Paper, wood and related process plant operatives		3	
824	Rubber process operatives, moulding machine operatives and tyre builders		3	
825	Plastics process operatives, moulders and extruders		3	
829	Synthetic fibre and other chemical, paper, plastics and related operatives		3	
830	Moulders and furnace operatives (metal)		3	
834	Electroplaters, galvanisers and colour coaters		3	
839	Other metal making and treating process operatives n.e.s.		3	
840	Machine tool operatives (incl. CNC machine tool operatives)		3	
841	Other automatic machine workers, metal polishers and dressing operatives		3	
850	Assemblers and lineworkers (electrical and electronic goods)		3	
851	Assemblers and lineworkers (metal goods and other goods)		3	
860	Inspectors, viewers and laboratory testers		3	
862	Packers, bottlers, canners, fillers, weighers, graders and sorters		3	
872	Drivers of road goods vehicles		3	
873	Bus conductors and coach drivers		3	
874	Taxi/cab drivers, chauffeurs and couriers		3	
880	Seafarers (merchant navy), barge and boat operatives		3	
885	Mechanical plant drivers/operatives and crane drivers		3	
887	Fork lift truck drivers		3	
889	Other transport and machinery operatives n.e.s.		3	
895	Pipe layers/pipe jointers and related construction workers		3	
897	Woodworking machine operatives		3	
898	Mine (excluding coal) and quarry workers		3	
899	Other plant, machine and process operatives n.e.s.		3	
903	Fishing and related workers		3	
923	Road construction workers, paviors and kerb layers		3	
929	Other building and civil engineering labourers		3	
930	Stevedores and dockers		3	
931	Goods porters		3	
933	Refuse and salvage collectors		3	
955	Window cleaners and car park attendants		3	
958	Cleaners and domestics		3	
959	Other occupations in sales and services n.e.s.		3	
990	All other labourers and related workers		3	
I	**Farmers**			
160	Farm owners and managers	2	3	1,4

Code No.	Socio-economic group and occupation	Employment status		
J	**Agricultural workers**			
595	Horticultural trades			1,4
900	Farm workers			1,4
901	Agricultural machinery drivers and other farming occupations			1,4
904	Forestry workers	2	3	1,4
Z	**All others gainfully occupied and unknown**			
000	Gainfully occupied but occupation not stated	2	3	1,4
999	All other gainful occupations n.e.s.	2	3	1,4

APPENDIX VII

07/01/2005

Re: Small for gestational age children and growth hormone therapy

Dear ,

Children born small for gestational age (SGA) have increased risk of very short adult stature. The risk of having short adult height (<-2SD) is 7 times higher for those with reduced birth length and 5 times higher for those born with low birth weight. The majority of SGA children catch up during the first two years of life, however approximately 15% fail to catch up and have a high risk of being short as adults. Growth hormone therapy for short children born IUGR/SGA has been shown to improve both short and long-term height gain.

We are conducting a study, which is part of a European multi-centre study looking at children born SGA (32 weeks gestation or more), at ages 4-8 years in girls, and 4-9 years in boys. For those children who have remained short for parental height with poor height velocity, we may offer growth hormone therapy.

We would be very happy to include children throughout the country in this study who have been born small for gestational age. We believe that the children who require growth hormone may greatly benefit from this therapy in terms of both long-term height and health. However there is a need for ongoing research and careful assessment in terms of efficacy, safety and long-term monitoring.
If you have any patients who:

whose birth weight is less than 3rd centile (≥28/40)
are now aged between 4-9 years
and whose current height less than 3rd centile

and you wish to refer them to us we would be very happy to assess them for consideration of growth hormone treatment.

We attach some literature on the subject for your information and if you require any further details on this study, please do not hesitate to contact us.
Thank you.

Yours sincerely,

Professor Hiliary Hoey,
Consultant Paediatric Endocrinologist

Dr Susan O'Connell,
Clinical Research Registrar

APPENDIX VIII

THIS NOTEPAPER MUST NOT BE USED FOR PRESCRIPTIONS OR INVOICING PURPOSES

THE ADELAIDE & MEATH HOSPITAL, DUBLIN
INCORPORATING
THE NATIONAL CHILDREN'S HOSPITAL

TALLAGHT, DUBLIN 24, IRELAND
TELEPHONE +353 1 4042000

PARENT INFORMATION LEAFLET

Treatment with recombinant Growth Hormone in Children born Small for Gestational Age (SGA) without Catch-Up Growth

A Randomised, multicenter, multinational trial to evaluate the safety and efficacy of Growth Hormone treatment at varying doses in short children born Small For Gestational Age (SGA).

Your child has been invited to take part in a research study. Before you decide whether or not you wish your child to take part, it is important for you to understand why the study is being carried out and what will be involved if you do decide to take part. Please read this leaflet carefully and discuss it with your child, friends, relatives, and your GP if you wish. Ask us if there is anything you don't understand or if you would like more information. You will be given as much time as you need to make your decision.

Thank you for thinking about your child taking part in this study.

What is the purpose of the study?

Children born short for gestational age who do not catch up during infancy have a high risk of being short as adults. Treatment with growth hormone significantly increases the speed at which they grow and the final height that they reach.
A relatively large dose of growth hormone is used in the first year as it ensures good 'catch up' growth in all but a few children. The dose that should be used in second or subsequent years is less clear and it is one of the aims of this study to find out the most appropriate dose.

Children born small for gestational age are 'insulin resistant': that is the body needs to make more of the hormone insulin to keep sugar levels normal in the blood. Growth hormone treatment may also cause insulin resistance. In previous trials of growth hormone, in children born small for gestational age, there have been very few problems with blood sugar, and where they have occurred they have gone away when treatment was stopped. Nevertheless we want to be sure of the safety of growth hormone treatment and a second aim of the study will be to carefully monitor the effects of treatment on sugar levels in the blood.

Why has your child been chosen?

Your child has been chosen to take part because he/she was born short at birth (Small for Gestational Age) and has not caught up during early life. It is expected that 300 children, who are between 4 and 9 years of age and who meet the criteria for treatment with growth hormone, will take part in this trial. The trial will be conducted in Denmark, UK, Sweden, and Ireland.

Does your child have to take part?

It is up to you to decide whether or not your child should take part in this study. If you would prefer them not to take part in this study, you do not have to give a reason. The study doctor will not be upset with your decision and their future treatment will not be affected in any way.

If you do decide to take part in this study, you may withdraw your child from the study at any time. Your decision to withdraw will not affect their future treatment. If you decide to withdraw your child from the study, and if your child is eligible, you may still request growth hormone treatment and continued follow up. In addition, we will destroy your child's blood samples if you request us to do so at withdrawal. Any samples not specifically asked to be destroyed will be kept for approximately 2 years beyond the 3 year treatment period.

What will happen if I do take part?

This study will require at least two visits to the clinic per year. Most children on growth hormone are seen routinely every 3-6 months.

The study will continue for 3 years and then a decision will be made about what is the best dose of growth hormone to use until your child reaches adult height.

Before your child takes part....

If you agree you will be asked to complete and sign a consent form before your child takes part.

The form must be signed and dated by the parent or legal representative of the child and also by the child themselves when they are old enough to make their own decision about taking part in the study. A separate information leaflet is provided for children.

You should also be aware that your childs participation in the study may be stopped at any time if the study doctor feels it is appropriate to do so e.g. if there are safety concerns.

During the first year of the study your child will receive a relatively high dose of growth hormone. This will tell us if treatment with growth hormone is suitable for your child and if it is appropriate for them to continue.

If your child responds to treatment with growth hormone in the first year they will have an equal chance of been given 1 of 3 doses of growth hormone during the second and third years of the study (a high dose, a low dose or a dose linked to the level of another hormone in the blood called IGF-I). Which of these three treatments your child receives will be decided by chance like tossing a coin. You and your study doctor will know what dose your child is taking during the study.

What does your child have to do at each visit?

This is a long-term study with four visits per year until treatment with growth hormone is stopped.

At your first visit, which will last no longer than a routine clinic appointment, you will be asked to fill in a form and answer a few simple questions about your child's birth weight and early growth. At each routine visit, your child's height, weight and growth will be measured. He/she will also undergo a routine clinical examination. At the end of each year, there will be a routine X-ray of one of your child's wrists.

What other procedures are involved?

A summary of procedures is provided below.

Visits	Appointment duration / time	Treatment	Tests
At Baseline	15 minutes	High Growth Hormone dose	• Blood sample and Glucose test • GH test (if not already done) • Wrist X-ray • DXA scan
+ 6 months	15 minutes		• Finger prick test
At 1 Year	Early morning	One of three growth hormone doses	• Blood sample and Glucose test • Wrist X-ray • DXA scan
+ 6 months	15 minutes		• Finger prick test
At 2 Years	Early morning		• Blood sample and Glucose test • Wrist X-ray

+ 6 months	15 minutes		• Finger prick test
At 3 Years	Early morning		• Blood sample and Glucose test • Wrist X-ray • DXA scan
Decision about what growth hormone dose to continue with until final height			

What procedures are additional to routine?

Procedure	Description	Time estimate for procedure
Glucose test (Baseline and annually) **and** DNA sample (Baseline only)	Glucose solution given as a sugary drink or injected into a vein and blood samples taken over a defined period. DNA extracted from blood sample	10 – 60 minutes
Measurement of IGF-I levels (2 times per year)	Finger prick test	5 minutes
DEXA scan (Baseline, every 2 years)	Whole body X-ray to determine bone density	40 minutes

DXA Scan

A DXA scan is a type of x-ray which can tell the difference between bone and soft tissue and which gives an accurate measure of the thickness of the bone. Your child will be asked to lie still on a padded table whilst they have the scan.

Glucose test

Your child will be asked to come to the clinic not having eaten or drunk anything other than water from 10 pm the previous evening. He/she will be asked to drink a glucose drink and blood samples will be taken at intervals over a set time period. These are simple tests of your child's insulin sensitivity. On alternate years (Year 1, 3) this will be changed to a short test where the glucose is given into a vein (IVGGT). At the end of each test a snack will be provided before you go home.

What happens after 3 years?

After 3 years we will be in a position to look at the responses to treatment and determine the 'best dose' for children born short for gestational age to be given, in order to achieve best growth. If your child has been given a dose during the first 3 years of the study which is different from that determined 'best', we will change the dose accordingly.

What happens to the blood samples?

The blood samples will be used to monitor hormones affected by growth hormone and check the normal biochemistry in the blood. A genetic sample will be taken at the beginning (this will be taken from the 15-20 ml blood sample). Genes are the building blocks that determine the colour of our hair, eyes etc and they may also determine how well a child responds to growth hormone. The sample will only be used to study genes related to growth and we will

not be doing any other 'genetic tests'. We are simply looking to see if there are any genes which might affect growth. The individual results will not be fed back to you, although we will try to keep you informed of the success of our studies. The genetic sample will be kept for 2 years beyond the end of the 3-year study period and will then be destroyed.

What else will your child have to do?

During the study you will be required to follow the study doctor's instructions. At every visit you will be asked if your child has taken any tablets or medicine since their last visit or if you have changed the dose of any medicine they are already taking.

What are the side effects of taking the treatment?

Side effects of growth hormone treatment are very rare during childhood. The most frequently occurring side effects of growth hormone are fluid retention, headaches and joint and muscle soreness, but these are very rare in childhood. Your child may also experience discomfort at the site of injection. Leukaemia has been reported in a very small number of growth hormone deficient patients some of whom were treated with growth hormone. However, based on current international data there is no increased risk of development of leukaemia or malignancy during growth hormone treatment. Your child will be carefully monitored at each visit and by undergoing the protocol assessment. Please let the study doctor know if you experience any problems.

What are the possible disadvantages and risks of taking part?

- Your child may be asked to visit the hospital more frequently for this study.

- Your child may feel some discomfort or bruising after the needle is removed when taking blood samples.

The DXA scans and X-Rays are painless. The X-Ray doses your child will be exposed to are extremely low and similar to that received on a long distance airplane flight.

If any new information becomes available during the trial i.e. information which could be important to you and/or affect your willingness for your child to continue in the study, it will be given to you as soon as possible.

What are the possible benefits of taking part?

It is likely that all but a very few of the children will grow well during the first year of treatment. Growth in subsequent years may well depend on which dose is being used. We should know the answer after all of the children have had 3 years of treatment and we will advise you then on the best dose to continue.

What are my child's alternatives?

If you did not want to participate in the study, and it was appropriate for your child to receive growth hormone treatment it would be given probably using a slightly lower dose in the first year and then continuing with a dose your consultant thought appropriate. Monitoring would depend on the consultant but national guidelines recommend some checks on blood sugar, bone age X-rays and regular follow up.

What if something goes wrong?

The growth hormone provided for this study is supplied by the pharmaceutical company also providing a research grant to support the study (Novo Nordisk A/S) and they carry product

liability for their products. This means that if products from Novo Nordisk cause bodily injury, legal liability will usually exist unless others have shown negligence. In addition, each investigator will carry their own insurance.

Who is organising and funding the research?

The study is being organised by the Department of Paediatrics, Trinity College, National Children's Hospital Tallaght, in collaboration with colleagues in Europe. A research grant has been given to the group by Novo Nordisk A/S to run the study but none of the investigators nor your local consultant will be paid. We will be able to reimburse carers for travel costs, but no other payments will be made.

Who has reviewed the study?

The study has been reviewed by the Local Research Ethics Committee of the hospital with which your study doctor is associated, who have decided that he/she is suitably qualified and has time to devote to conducting the study.

Will my childs taking part in this study be kept confidential?

If you participate in the study your child will be given a unique number which will be used on all the blood samples, results etc and will be the only identifier used by the laboratories and statisticians analysing the information.

Information about your child will be given the usual confidentiality that all patients can expect. When publishing the results from the trial the confidentiality of the children will be respected and the identity of any patient taking part in the study will not be given in any published report. If you are interested, the study doctor will be able to tell you the results of the study at a later stage. He can also give you details of where they may be published.

If you agree to take part, your GP will be informed, with your permission.

Other issues if my child takes part

If you decide to participate in this study, you will be asked to sign and date this Informed Consent Form indicating that you have been given information about the trial and you freely and voluntarily agree for your child to take part.

Contact for Further Information

For further information, or in case of emergency, your study doctor or nurse can be contacted as detailed below:

Doctor: Dr Susan O'Connell

Telephone number: 01-6083763/ 01-4142000

Nurse: Research Nurse Elaine

Telephone number: 01-6083763/ 01-4142000

APPENDIX IX

THIS NOTEPAPER MUST NOT BE USED FOR PRESCRIPTIONS OR INVOICING PURPOSES

THE ADELAIDE & MEATH HOSPITAL, DUBLIN
INCORPORATING
THE NATIONAL CHILDREN'S HOSPITAL

TALLAGHT, DUBLIN 24, IRELAND
TELEPHONE: +353 1 4142000

Child Information Leaflet (4-9 years)

A Study Of Growth Hormone Treatment

Why we need your help

You are about to start Growth hormone treatment and we hope this will improve your growth over the next year. You will probably stay on growth hormone until you stop growing and the doctors who are running the study want your help to answer two questions:

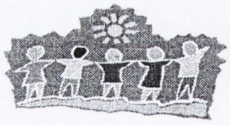
- How much growth hormone should be given to children like you after the first year of treatment?
- Will the growth hormone you take affect the levels of sugar in your blood?

How to answer these questions

Along with 300 other children, we are asking you to take part in a research study. This means we will see you a little more often in the clinic and each year ask you if you would agree to an extra blood test and X-ray.

What will happen if you take part?

At the end of 1 year's treatment with growth hormone we will put some children on big doses and others on lower doses of growth hormone to see which dose is best for growth. This will be decided by chance, like tossing a coin. You and your parents will know what dose you are taking. At the end of 3 years, everyone will be given the 'best' dose of growth hormone. This will be decided for you by looking at which children grew best on which dose.

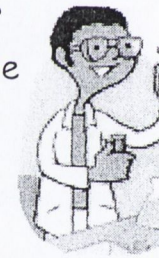


At the beginning, and every year during the study, we will ask you to give a blood sample (15-20 ml or 3-4 teaspoonfuls). It needs to be taken early in the morning before you have had your breakfast. The test will be taken after you have been given a sugary drink. Once the test is over we will give you something to eat.

The other extra thing is a special kind of X-ray, called a DEXA. This involves lying very still on a couch while your picture is taken. After the scan, you get to see a photograph of your skeleton.

What happens to the blood test?

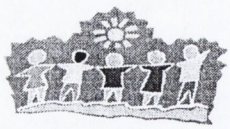
The blood you give will be used to check the levels of sugar in your blood. It will also be used to find out whether the way you grow is related to your parents, just the same way the colour of your hair or eyes can often come from your parents. At the end of the study, your blood sample will be destroyed.



Do I have to take part?

It is up to you and your parents to decide. If you decide not to take part that is OK, nobody will be upset with you and your treatment will not be affected. Your parents will then discuss with the study doctor in the clinic whether you still want to have growth hormone.

If you decide to help with the study and get fed up with it, you can stop at any time. If you decide to stop and want your blood sample to be destroyed, we will do this for you.



Are there any risks?

Growth hormone is very safe, but we will be watching things very carefully during the study. You must tell your parents and

the study doctor if you notice anything unusual or feel ill during treatment.

What if something goes wrong?

If anything happens to you which could be because of the growth hormone you are taking, the drug company who make growth hormone, Novo Nordisk, will provide compensation according to their guidelines. The study doctor will also have his/her own standard insurance cover in case something goes wrong. You should tell your parents straight away if there is a problem and they will contact the study doctor immediately.

Who can I contact for further information?

If you have any questions please contact the study doctor or nurse. They will be happy to help you.

Please contact: **Dr Susan O'Connell**
susan.oconnell@tcd.ie
Telephone:
01 6083763/ 4142000

Alternatively, you can contact the following address:

Adelaide and Meath Hospitals incorporating the National Children's Hospital, Tallaght, Dublin 24

Phone: 01-4142000, ask to speak with the research doctor or research nurse in the Department of Paediatrics

Thank you for taking the time to read this.

APPENDIX X

PARENT CONSENT FORM

Title of Project: Treatment with recombinant Growth Hormone in Children born Small for Gestational Age (SGA) without Catch-up Growth

Study Centre: National Children's Hospital, Tallaght, Dublin 24, Ireland

Patient Identification Number for this trial: _____

Name of Researcher: _____

	Please initial box Parent
1. I confirm that I have had at least 24 hours to read and understand the information sheet dated May 05 for the above study and have had the opportunity to ask questions and/ or have read the separate patient information leaflet.	☐
2. I understand that my child's taking part in the study is entirely my decision and that I am free to withdraw them at any time without giving any reason and without my child's medical care or legal rights being affected.	☐
3. I understand that some of my child's medical notes may be looked at by monitors, auditors and responsible individuals from regulatory authorities where it is relevant to my child's participation in research. I give permission for these individuals to have access to my child's medical records.	☐
4. I have had sufficient time to come to my decision and agree that my child may take part in the above study.	☐
5. I give consent that my child's GP may be contacted and access given to my medical notes held by this person.	☐
6. I agree to the additional blood tests required for this study.	☐
7. I agree to a blood sample being collected for the study of genes involved in the response to growth hormone.	☐
8. Please destroy my child's blood sample at the end of the study.	☐

9. I agree that data about my child relating to this study may be sent to countries that do not have the same data protection laws as those in Ireland, but understand that this information will be treated with the strictest confidence, and only accessible to study group members. ☐

_____

Name of Patient

_____ _____

Name of Consent Giver (Parent/ Legal Guardian) **Date**

_____

Signature of Consent Giver (Parent/ Legal Guardian)

_____ _____

Name of Person taking consent **Date**
(if different from researcher)

_____

Investigator Signature

1 copy for parent/legal guardian
1 copy to be kept with hospital notes
1 copy for case record file

APPENDIX XI

IGF-I Reference Ranges (Royal Surrey Hospital,Guildford 2001)

Age Group (years)	Reference Range (nmol/L)	
	New	Old
0-6	4 – 20	(2.5-20.0)
7 -9	7 – 40	(4.5-37.5)
10	12 - 50	(7.0-50.0)
11	17 – 60	(8.5-60.0)
12	20 – 85	(10.0-75.0)
13	23 – 90	(11.5-75.0)
14-16	30 – 90	(13.0-75.0)
17-20	23 – 70	(12.5-67-5)
21-40	13 – 50	(9.5-45.0)
41-60	9 – 40	(7.5-30.0)

APPENDIX XII

APPENDIX XIII IVGTT PRE GH TREATMENT

Intravenous Glucose Tolerance Tests – Pre GH Treatment (N = 13)														
	Insulin (pmol/L)							Glucose (mmol/L)						
Patient	-10	-5	0	+1	+3	+5	+10	-10	-5	0	+1	+3	+5	+10
1	9.5	H	11.0	82.0	73.0	74.9	54.6	4.1	3.8	3.9	17.0	16.4	14.8	13.2
2	36.6	14.7	H	154.0	44.0	150.0	164.0	4.8	4.9	6.3	20.9	18.7	17.0	15.3
3	15.0	15.9	13.4	380.0	237.0	191.0	64.6	4.2	4.2	4.5	18.1	14.9	14.0	10.7
4	14.9	6.6	11.6	150.0	125.0	102.0	60.0	4.2	4.0	4.3	16.7	14.4	13.2	11.2
5	7.0	13.4	7.5	294.0	201.0	172.0	108.0	3.8	4.2	4.2	17.6	15.1	13.1	11.5
6	13.1	9.0	16.4	413.0	248.0	178.0	129.7	4.2	4.5	4.6	17.6	14.9	13.1	11.0
7	19.2	13.2	14.7	121.0	78.5	66.2	53.9	4.4	4.1	4.1	13.4	13.1	12.7	11.0
8	7.1	9.9	13.0	379.0	339.0	199.0	196.0	4.3	4.1	4.3	15.8	14.9	13.1	10.4
9	H	3.2	10.3	286.9	267.0	215.5	164.0	4.6	4.7	4.6	17.3	15.3	13.8	11.8
10	H	H	14.8	253.0	144.0	102.0	52.5	4.3	4.3	4.4	15.1	12.9	11.6	9.3
11	H	H	15.1	H	H	H	116.0	4.7	4.6	5.2	16.1	14.9	14.1	11.6
12	12.6	9.6	20.8	107.0	62.2	57.0	60.8	4.1	4.2	4.2	18.8	14.3	12.7	11.4
13	40.5	38.3	31.6	435.0	297.0	251.0	165.0	4.9	4.8	4.3	16.3	15.1	14.4	12.0

H = Sample was haemolysed

APPENDIX XIII

APPENDIX XI IVGTT FOLLOWING ONE YEAR OF GH TREATMENT

Intravenous Glucose Tolerance Tests – Following 1 Year of GH (N = 9)														
	Insulin (pmol/L)							Glucose (mmol/L)						
Patient	**-10**	**-5**	**0**	**+1**	**+3**	**+5**	**+10**	**-10**	**-5**	**0**	**+1**	**+3**	**+5**	**+10**
1	92.7	74.3	77.8	484.0	403.0	334.0	324.0	5.2	5.2	5.1	18.3	16.7	15.5	13.4
2	59.7	H	H	758.0	544.0	455.0	245.0	4.8	4.7	4.8	16.4	15.4	13.7	10.1
3	42.1	46.1	43.8	665.0	518.0	371.0	154.0	4.5	4.5	4.6	13.6	12.8	11.6	7.5
4	H	13.0	9.8	H	H	131.0	74.2	3.8	3.8	3.8	16.7	14.1	12.9	10.8
5	60.2	58.6	79.7	909.0	707.0	665.0	389.0	4..8	4.8	4.9	19.7	16.3	13.7	10.6
6	16.0	H	7.5	H	H	H	H	3.9	3.7	3.6	18.2	16.7	15.1	12.5
7	26.9	22.8	24.4	252.0	151.0	134.0	98.9	4.5	4.4	4.4	17.1	15.0	14.0	12.1
8	31.0	24.5	30.0	419.0	265.0	237.0	158.0	4.7	4.7	4.6	16.7	15.5	13.7	11.5
9	99.3	98.0	84.0	570.0	475.0	423.0	342.0	5.5	5.5	5.3	15.9	14.6	14.5	11.9
10	P	P	P	P	P	P	P	5.0	4.9	4.7	12.0	11.0	10.3	9.7

H = Sample was haemolysed; P = Pending

APPENDIX XIV

HbA1c (%) levels over course of treatment (months)											
Patient	**0**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27**	**30**
1	5.4	5.6	5.9	5.6	5.1	6.0	5.9	5.5	5.7	5.5	5.9
2	5.5	5.6	5.9	5.9	5.9	6.0	5.6	5.6	5.9	5.7	5.9
3	5.5	5.7	5.5	6.0	5.4	5.9	5.5	5.7	5.3	6.1	
4	5.5	5.4	5.9	5.2	6.0	5.9	5.8	5.6	6.1		
5	5.0	5.5	5.4	5.3	5.1	5.1	5.4	5.5	5.6		
6	5.1	5.2	5.3	5.0	5.3	5.2	5.0	4.9	5.1		
7	5.9	5.9	6.2	6.0	5.9	5.8	5.6	5.8	6.3		
8*	5.4	5.5	5.9	5.4	5.6	5.5	5.5				
9	5.6	5.1	5.3	5.2	5.5	5.3					
10	4.7	5.1	5.5	5.2	5.1						
11	5.5	5.6	5.6								
12	5.5	5.7									
13	5.7	6.0									
16	5.4	5.4	5.6	5.4	5.4	5.4	5.4	5.7	5.5		
17	5.5	5.5	6.1	5.5	5.7	5.5	6.0	6.0	6.2		

APPENDIX XV

IGF-1 Levels at baseline, and following one and two years of GH treatment

Patient	Age Start GH	Ht SDS	Baseline IGF-1 (µg/l)	Baseline IGF-1 SDS	1-Yr IGF-1	1-Yr IGF-1 SDS	2-Yr IGF-1	2-Yr IGF-1 SDS
1	9.9	-4.8	163	-0.78	378	1.58	314	0.36
2	9.9	-3.4	208	-0.15	430	2.09	574	2.37
3	6.6	-3.5	152	-0.81	266	0.59	391	1.80
4	5.5	-3.1	80	-1.21	309	1.73	N/A	1.99
5	7.9	-2.0	92	-1.52	276	0.70	N/A	2.62
6	4.7	-4.5	23	-2.56	189	0.63	N/A	-0.51
7	7.0	-2.8	186	0.02	365	1.55	N/A	N/A
8	5.7	-2.5	107	-0.68	265	1.25	N/A	N/A
9	7.2	-2.5	182	-0.07	320	1.25	N/A	N/A
10	7.0	-3.4	90	-2.05	N/A	N/A	N/A	N/A
11	4.0	-3.8	111	0.15	N/A	N/A	N/A	N/A
12	4.9	-2.7	80	-0.90	N/A	N/A	N/A	N/A
13	5.6	-3.4	128	-0.90	N/A	N/A	N/A	N/A
14	N/A	-2.6	105	-0.39	N/A	N/A	N/A	N/A
15	7.1	-2.9	74	-0.88	N/A	N/A	N/A	N/A
16	11.6	-2.6	153	-1.36	366	0.26	531	0.29
17	12	-3.7	327	0.48	574	1.04	375	-0.63
18	N/A	-3.1	113	-1.78	N/A	N/A	N/A	N/A

APPENDIX XVI

Delay in bone age as assessed at baseline (N = 20), after 1 year (N = 12) and after 2 years (N = 9) GH treatment

			Baseline		1 Year		2 Year	
Patient	Age*	Ht SDS	CA	BA	CA	BA	CA	BA
1	9.9	-4.8	119	60	132	84	144	108
2	9.9	-3.4	119	72	132	90	144	108
3	6.6	-3.5	79	47	93	58	103	94
4	5.5	-3.1	64	60	79	72	91	84
5	7.9	-2.0	90	84	108	108	120	120
6	4.7	-4.5	57	36	69	60	81	72
7	7.0	-2.8	84	60	96	84	110	96
8	5.7	-2.5	66	42	81	57	N/A	N/A
9	7.2	-2.5	81	72	98	83	N/A	N/A
10	7.0	-3.4	77	48	96	54	N/A	N/A
11	4.0	-3.8	42	42	N/A	N/A	N/A	N/A
12	4.9	-2.7	54	48	N/A	N/A	N/A	N/A
13	5.6	-3.4	78	39	N/A	N/A	N/A	N/A
16	11.6	-2.6	137	120	150	144	163	156
17	12	-3.7	143	105	156	120	168	132
14†	N/A	-2.6	71	71	N/A	N/A	N/A	N/A
15†	7.1	-2.9	75	54	N/A	N/A	N/A	N/A
18†	N/A	-3.1	79	58	N/A	N/A	N/A	N/A
19†	N/A	-3.4	70	54	N/A	N/A	N/A	N/A
20†	N/A	-2.2	26	12	N/A	N/A	N/A	N/A

HtSDS = Height SDS; CA = Chronological Age; BA = Bone Age
***Age at start of GH treatment if applicable**
CA & BA expressed in months
† Patients not yet treated with GH

APPENDIX XVII

DXA findings on GH treated patients at baseline (N = 13) and 1 year (N = 12)

Patient	Baseline LBM (kg)	1 Year LBM (kg)	Baseline BMC (kg)	1 Year BMC (kg)	Baseline BMD (g/cm2)	1 Year BMD (g/cm2)
1	N/A	16.17	N/A	0.67	N/A	0.77
2	N/A	25.18	N/A	1.04	N/A	0.90
3	N/A	13.45	N/A	0.54	N/A	0.72
4	9.28	15.11	0.25	0.65	0.83	0.82
5	18.98	25.86	0.79	1.02	0.85	0.87
6	8.43	10.37	0.33	0.39	0.72	0.73
7	12.45	16.54	0.59	0.73	0.84	0.86
8	11.02	14.76	0.47	0.95	0.80	0.77
9	13.81	16.9	0.60	0.74	0.79	0.81
10	11.79	16.55	0.50	0.65	0.81	0.81
11	6.94	N/A	0.28	N/A	0.71	N/A
12	9.82	N/A	0.42	N/A	0.77	N/A
13	9.99	N/A	0.44	N/A	0.79	N/A
14	12.81	N/A	0.60	N/A	0.78	N/A
15	14	N/A	0.58	N/A	0.83	N/A
16	N/A	27.33	N/A	1.17	N/A	0.89
17	15.78	21.76	0.56	1.01	0.87	0.90