CORRELATION BETWEEN CORD BLOOD INSULIN/IGF-1 AND EARLY POST NATAL GROWTH IN SMALL FOR GESTATIONAL AGE BABIES.

THESIS

SUBMITTED IN THE PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF M.D. PEDIATRICS

OF

DR M.G.R MEDICAL UNIVERSITY, TAMILNADU,INDIA.

EXAMINATION TO BE HELD IN APRIL 2016

DECLARATION

This is to declare that this dissertation titled, **"CORRELATION BETWEEN CORD BLOOD INSULIN/IGF-1 AND EARLY POST NATAL GROWTH IN SMALL FOR GESTATIONAL AGE BABIES"** is my original work done in the partial fulfilment of the rules and regulations for MD Paediatrics examination of the Tamil Nadu Dr.M.G.R Medical University, Chennai to be held in April 2016

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CERTIFICATE

This is to certify that the dissertation titled " **CORRELATION BETWEEN CORD BLOOD INSULIN/IGF-1 AND EARLY POST NATAL GROWTH IN SMALL FOR GESTATIONAL AGE BABIES**" is a bonafide original work done by Dr Abhilasha Smith during her academic term April 2014- March 2016,in the department of Child Health, Christian Medical College Vellore in partial fulfillment of the requirement for the Master in Child Health examination of the Tamil Nadu Dr.M.G.R Medical University, Chennai to be conducted in April 2016.

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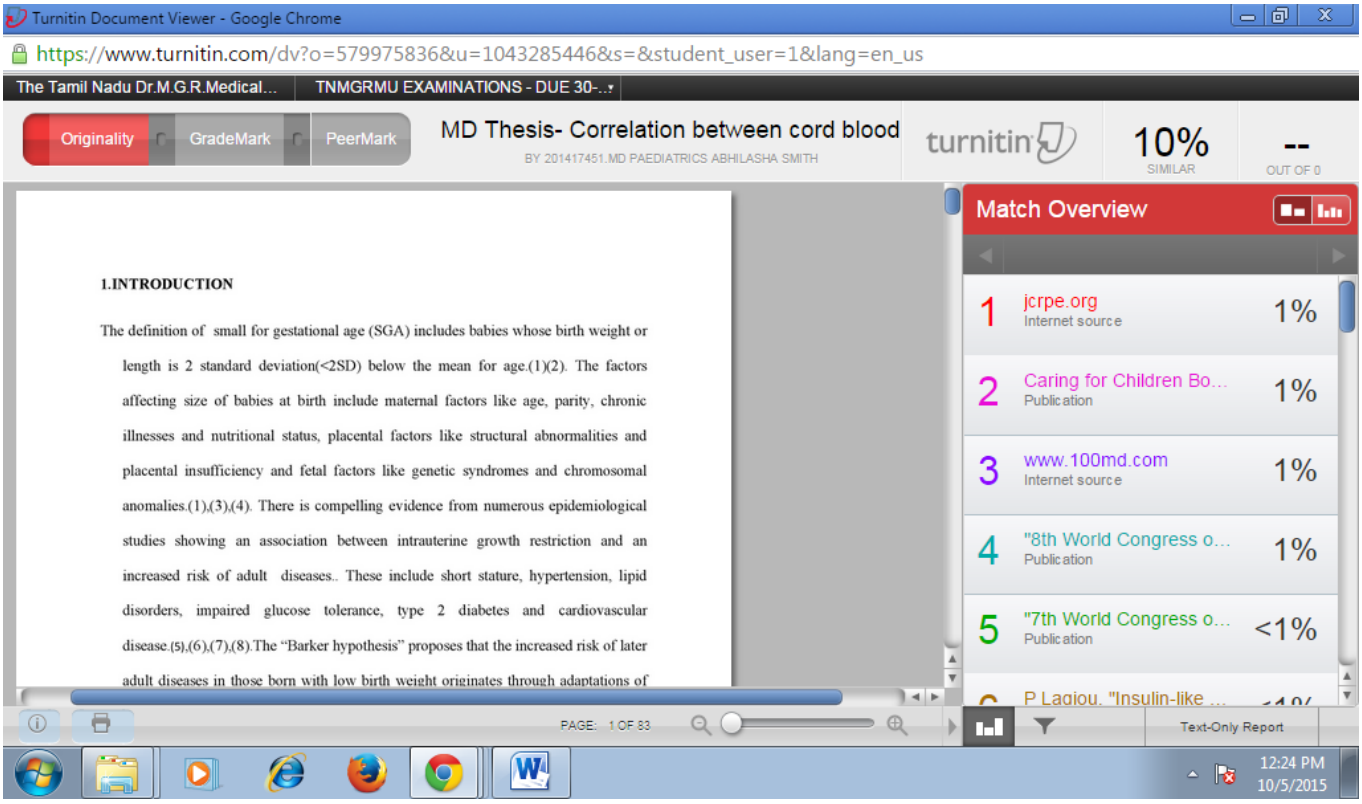
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1.INTRODUCTION
The definition of small for gestational age (SGA) includes babies whose birth weight or length is 2 standard deviation(<2SD) below the mean for age.(1)(2). The factors affecting size of babies at birth include maternal factors like age, parity, chronic illnesses and nutritional status, placental factors like structural abnormalities and placental insufficiency and fetal factors like genetic syndromes and chromosomal anomalies.(1),(3),(4). There is compelling evidence from numerous epidemiological studies showing an association between intrauterine growth restriction and an increased risk of adult diseases.. These include short stature, hypertension, lipid disorders, impaired glucose tolerance, type 2 diabetes and cardiovascular disease.(5),(6),(7),(8).The "Barker hypothesis" proposes that the increased risk of later adult diseases in those born with low birth weight originates through adaptations of
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Contents

ABSTRACT

TITLE OF THE ABSTRACT: CORRELATION BETWEEN CORD BLOOD INSULIN/IGF-1 AND EARLY POST NATAL GROWTH IN SMALL FOR GESTATIONAL AGE BABIES.

DEPARTMENT: PEDIATRICS

NAME OF THE CANDIDATE: ABHILASHA SMITH

DEGREE AND SUBJECT: MD PEDIATRICS

NAME OF THE GUIDE: DR SARAH MATHAI

OBJECTIVES: To compare the levels of insulin, glucose and IGF-1 in term born AGA and SGA babies and demonstrate difference in IGF-1 and insulin resistance as measured by the HOMA-IR index. To demonstrate any difference in catch up growth in AGA and SGA babies and its correlation with diet and these hormonal parameters at 3.5 and 6 months.

METHODS: Maternal and Neonatal details were collected at birth and recorded. Cord blood samples for measurement of glucose , insulin and IGF-1 were taken from 60 infants(30 AGA and 30 SGA). Using this information, HOMA-IR was calculated.

The cohort was followed up at 3.5 and 6 months and a growth assessment was done. The dietary history was also collected. Infants were categorized as adequately, inadequately and rapidly growing based on the catch up growth at 3.5 months in both the AGA and

SGA arms. Glucose, insulin and IGF-1 levels were taken at 6 months. The hormonal profiles at birth and at 6 months were correlated to the growth rates.

Data analysis was done using the SPSS version 21. The Mann whitney U test was used to compare the two groups.

RESULTS: The SGA babies were lighter, shorter and had a smaller head circumference at birth compared to the AGA babies. The cord blood insulin (P=0.0002) and IGF-1(<0.01) were higher in AGA group. There was a linear correlation between the birth weight and the cord blood insulin (p=0.01) and IGF-1(p<0.01).The growth velocity at 3.5 months was similar between the AGA and SGA groups, however, the SGA babies continued to be shorter and lighter than the AGA ones. Insulin and IGF-1 levels at birth had no correlation with catch up growth.

KEY WORDS: Small for gestational age, Insulin, IGF-1, Catch up growth.

1.INTRODUCTION

The definition of small for gestational age (SGA) includes babies whose birth weight or length is 2 standard deviation(<2SD) below the mean for age.(1)(2). The factors affecting size of babies at birth include maternal factors like age, parity, chronic illnesses and nutritional status, placental factors like structural abnormalities and placental insufficiency and fetal factors like genetic syndromes and chromosomal anomalies.(1),(3),(4). There is compelling evidence from numerous epidemiological studies showing an association between intrauterine growth restriction and an increased risk of adult diseases.. These include short stature, hypertension, lipid disorders, impaired glucose tolerance, type 2 diabetes and cardiovascular disease.(5),(6),(7),(8).The "Barker hypothesis" proposes that the increased risk of later adult diseases in those born with low birth weight originates through adaptations of the fetus when it is undernourished.(7),(9). These adaptations can be metabolic, endocrine or cardiovascular and may permanently change the structure and function of the body through changes in insulin metabolism and body fat distribution.(10).

Among the factors which affect the intrauterine growth of the fetus, maternal nutrition is probably the most important one . Hormones which play a key role in fetal growth are insulin and insulin like growth factor (IGF) system(11).

. Insulin is the key regulator of IGF-1 during the intrauterine life. While IGF-2 affects the embryonic growth, IGF-1 is the major growth regulator in late gestation.(12). Low levels of IGF-1 and IGF-2 are reported in the cord blood samples of SGA infants.(5).Nutrition

seems to play a major role in the postnatal regulation of IGF-1 in early infancy.(13) Thereafter by 6-12 months growth hormone(GH) and IGF-1 levels rise leading on to catch up growth.(5). Therefore most of the post natal growth occurs in a GH dependent fashion. Catch up growth usually occurs in the first 6 months and is completed by 2 years of age.(12). It is postulated that the risk of later adult diseases is higher in infants who showed rapid catch up growth.(14)As the physical activity is fairly similar in children between 0-6 months of age, diet and hormonal milieu play an important role in their growth during this period.

India has probably the largest number of low birth weight (LBW) babies in the world and from the Mysore and Pune data, we know that Indian babies have a "thin-fat" phenotype, which predisposes them to an unfavourable metabolic profile in adulthood.(15),(16). There are only few longitudinal studies from India assessing the serial changes in hormonal profile and catch up growth in SGA babies. Therefore we planned this study to compare the hormonal milieu and catch up growth of SGA and AGA infants between birth and 6 months of age.

AIMS AND OBJECTIVES

2.AIMS AND OBJECTIVES

1. To compare the levels of insulin, glucose, and IGF-1 at birth in term born AGA and SGA infants and demonstrate difference ,if any, in the IGF-1 levels as well as insulin resistance as measured by HOMA-IR index.

2.To demonstrate the difference in catch up growth in SGA and AGA infants at 3 months of age and its correlation with diet.

3. To demonstrate the difference in catch up growth in SGA and AGA infants at 6 months of age and its correlation with

a. increments in IGF-1 level and HOMA-IR .

b. diet in the first 6 months of life

4. To demonstrate the correlation between weight and height gain at 6 months independently with IGF-1 level.

LITERATURE REVIEW

SECTION 1:

DEFINITIONS RELATED TO BIRTH & BIRTH WEIGHT USED IN THIS STUDY

The definitions used for the various terms related to birth and birth weight in this study are as follows:

Term birth is defined as delivery between 37 to 42 completed weeks of gestation.

Low birth weight (LBW) is defined as birth weight <2500 gm.

Small for gestational age (SGA) is defined as birth weight less than the 10th percentile of the index population's distribution of birth weights by gestation i.e. the lowest 10% of birth weights (ref Peter Lee et al 2001). **The reference for this study is** taken from a recent publication of the birth weight centile charts from rural community based data in southern India.(17).

Appropriate for gestational age (AGA)is defined as birth weight between the 10^{th} and 90^{th} centile for gestational age as per the reference above(17).

CATCH UP GROWTH is defined as the infant reaching a length and weight =/>the third percentile(-2SD).(3).A change in Z score ≥0.67 can also be considered as catch up.(18).

Postnatal growth was evaluated for the first 3 months after birth. The terms related to postnatal growth used in this study are as follows:

ADEQUATELY GROWING: During the first 3 months, if the infant has the expected weight gain of 20-30gms/day, length gain of 3.5cm/month and an increase in head circumference of 2cm/month the infant is considered to be growing adequately.(19)

INADEQUATELY GROWING: During the first 3 months, if the infant'sweight gain is <20gms/day, length increase is < 3.5cm/month and increase in head circumference is <2cm/month then the infant is considered as showing inadequate growth..

RAPIDLY GROWING: During the first 3 months, if the infant's weight gain is >30gms/day, length increase > 3.5cm/month and increase in head circumference >2cm/month then the infant is considered to have rapid growth.

The definition of adequate growth has been taken from the Nelson's Textbook of Pediatrics, 19th edition.

SECTION 2:

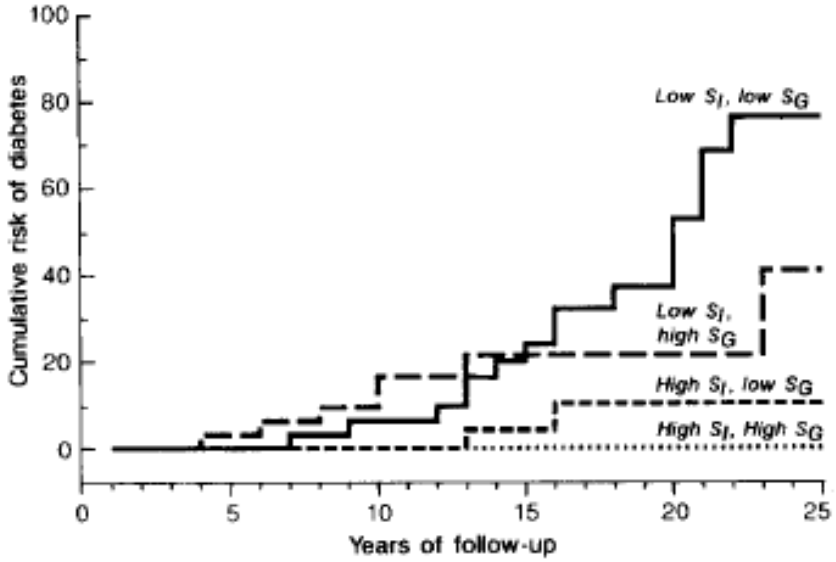
REDUCED INSULIN SENSITIVITY AND COMPENSATORY HYPERINSULINAEMIA- THE LINK BETWEEN LBW AND DISEASES OF METABOLIC SYNDROME:

One of the most consistent findings in those who were born SGA was a reduction in insulin sensitivity. This has been demonstrated in all age groups from birth to adulthood (20),(21),(22). . It appears that reduced insulin sensitivity occurs early and probably *in utero* in SGA subjects.(23).

Insulin sensitivity is defined as the ability of insulin to stimulate tissue glucose uptake and suppress endogenous glucose production. To maintain euglycaemia in the presence of reduced insulin sensitivity, the pancreatic ß cells increase insulin secretion resulting in compensatory hyperinsulinaemia. Eventually the pancreas cannot compensate any further and type 2 diabetes mellitus manifests.

In an elegant study by Martin et al where they followed up a cohort for 25 years ,the predictive power of isolated insulin resistance was well documented.(24). In 155 subjects followed up with intravenous glucose tolerance test(IVGTT) for 6-25 years they demonstrated that an isolated reduction in insulin sensitivity had a 40% cumulative risk of development of diabetes in first degree relatives of type 2 diabetics as compared to a

risk of less than 5% with those having normal insulin sensitivity . This is summarized in the figure below.(Figure 1).



This graph shows the cumulative risk of Type 2 Diabetes Mellitus according to insulin sensitivity and glucose effectiveness.(Adpated from Martin BC, Lancet 1992 Oct 17;340(8825)925-9)

Although elevated insulin levels ensures euglycaemia, the chronic hyperinsulinaemic state has adverse effects on other organ systems. The role of insulin in the pathogenesis of type 2 diabetes mellitus , hypertension and cardiovascular diseases has been well documented .

Facchini *et al* categorized 208 healthy adult subjects into those with normal, moderate and marked insulin resistance using insulin suppression tests. Over a period of 4-11 years those with moderate or marked insulin resistance had a marked increase in the rate of type 2 diabetes mellitus as well as other diseases like hypertension, coronary heart disease, cerebrovascular accidents and even cancer,(25). None of these events occurred

in the most insulin-sensitive tertile as compared to 28 clinical events in 25 individuals of the least insulin sensitive tertile. In this study insulin resistance was noted to be an independent predictor of all the 5 clinical events. This is summarized below in the figure below.

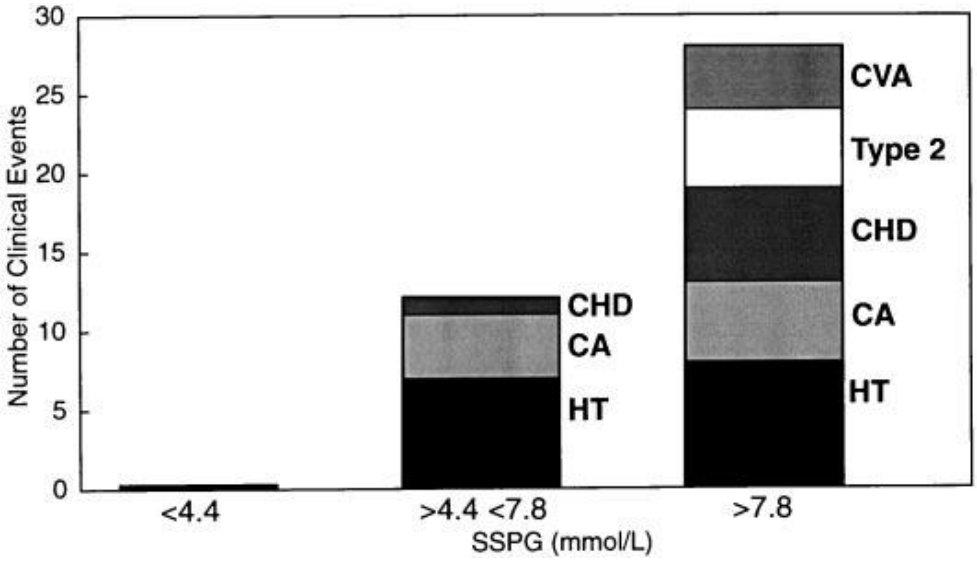


Figure2. Long term risks of insulin resistance (Adapted from Facchini FS et al. *JCEM* 2001; 3574-78 .

Among the major lifestyle factors which affect insulin sensitivity are diet and exercise (26). Unhealthy diet includes high carbohydrate, habitual high fat and low fibre diets as well as excessive fast food consumption and these have all been independently shown to be associated with insulin resistance (27). Sedentary lifestyle including physical inactivity, snacking during TV watching etc also contribute to obesity and adversely affect insulin sensitivity. These are modifiable risk factors.

SECTION 3:

FETAL GROWTH, HORMONAL REGULATION AND CATCH UP GROWTH:

Intrauterine growth occurs in three distinct phases: (5)

5)1)The first 16 weeks is a period of cell hyperplasia.

2)16-32 weeks is a period of cell hyperplasia and hypertrophy

3)The final growth phase from 32-40 weeks consists of rapid cellular hypertrophy(5).

Normal intrauterine growth and size at birth depends upon the interaction between various maternal, genetic, hormonal and environmental factors.(5)(3). Of these perhaps the most important are the maternal factors which include maternal undernutrition, illnesses such as preeclampsia, infections, andtoxins such as cigarette smoke, alcohol. Maternal nutrition plays a key role in the fetal growth. While undernutrition in early pregnancy results in symmetric or proportionate SGA babies, undernutrition in late pregnancy results in asymmetric SGA babies. Placental insufficiency including abruption, infarction and infection also affect fetal growth adversely.

The genetic factors which affect fetal growth include parental height, maternal age ,congenital malformations and chromosomal anomalies(3)..The insulin and IGF system

plays an important role in fetal growth. Environmental factors include maternal health and nutritional status.

Hormones also play a major role in fetal growth and is discussed next.

HORMONAL REGULATION OF FETAL GROWTH

Unlike postnatal growth the hormones which play a major role in the regulation of fetal and placental growth and development are insulin and insulin like growth factor (IGF) system which includes IGF-1,IGF-2 and the IGF binding proteins IGFBP-1, IGFBP-2 and IGFBP3.(28). These peptide hormones bind to specific receptor tyrosine kinases on the target tissues and bring about a variety of metabolic effects. Together they form the IGF axis which is responsive to a variety of environmental stimuli like nutrient and oxygen delivery.(29).

IGF-2 primarily affects embryonic growth while IGF-1 promotes fetal growth in the late gestation.(12), (30),(31),(32).IGF-1 is produced by the fetal liver and its important actions are promotion of substrate uptake by the fetus, inhibition of catabolism and placental lactate production. Thus it helps in the nutrient supply to the placenta and the fetus. The predominant regulator of fetal IGF-1 production is fetal insulin which in turn is regulated by the fetal glucose availability. This is in contrast to postnatal growth where IGF-1 secretion is primarily mediated by growth hormone.

The IGF-1 system regulates fetal growth in response to nutrient availability, which means that in conditions of maternal malnutrition there is decrease in fetal growth with low levels of fetal IGF-1 and altered IGF binding proteins.(12).

Insulin facilitates fetal growth by its direct action on lipogenesis thereby increasing fetal adiposity . It also exerts its action indirectly by stimulating the IGF-1 . IGF-2 has dual actions. Binding to the IGF-1 receptor brings about its biological actions which includes embryonic growth, while binding to the IGF-2 receptor decreases the circulating levels of IGF-2.Thus the IGF-2 receptor acts as a clearance receptor .

In experimental knock out models it has been shown that deletion of the IGF-1 gene leads to severe IUGR. In case of IGF-2, knock out of the IGF-2 receptor leads to embryonic overgrowth while knock out of IGF-2 leads to poor embryonic growth.(12)(5).

Thus, in instances of IUGR, the sensitivity of the fetal tissue to IGF-1 appears to be disturbed. It has also been observed that cord blood levels of IGF-1 and 2 are lower in SGA babies compared to babies born appropriate for gestational age(AGA)(11),(33).The terms intrauterine growth retardation (IUGR) and small for gestational age(SGA) are often used interchangeably, however they are not synonymous.

IUGR describes a condition where there is failure of the fetus to reach its genetic growth potential.(34). It can be symmetric, where all the fetal organs are proportionately decreased as a result of an insult during early gestation or asymmetric where the abdominal viscera and subcutaneous tissue experience a greater decrease in size

compared to the size of the brain.(5).This process occurs later during gestation and demonstrates the ability of the fetus to adapt to an unfavourable environment by redistribution of blood flow to the vital organs.

On the other hand, SGA describes a baby whose birth weight or length is less than 2 standard deviations below the mean for age.(1).However there is much overlap between the two conditions.

Therefore size at birth is not always an indicator of the fetal growth trajectory. Fetuses which have intrauterine growth deceleration , may either result in SGA babies or they may show catch-up growth and be born with appropriate birth weight. Thus birth weight is not a true index of fetal well being..

THE NUTRIENT PIPELINE AND FETAL RESPONSES TO A DISTURBED PIPELINE

After birth, the levels of IGF-I and GH rise significantly in most SGA babies and are probably responsible for the catch-up growth.Maternal health and homeostasis, utero placental blood flow and metabolism affect the supply of nutrients to the growing fetus.(12). Parental ages, severe maternal exercise in the late trimester, cardiac disease and chronic infections play a significant role in fetal growth. The placenta in itself is metabolically active and consumes 40-60% of the glucose and oxygen extracted from the maternal circulation.

In IUGR, the level of this extraction rises further leading on to fetal malnutrition. If the amount of glucose available to the fetus is decreased, the insulin and IGF-1 levels decline and growth is affected. In the presence of uteroplacental disease, there is a redistribution of blood flow to the brain, heart, adrenals and placenta leading on to asymmetrical pattern of fetal growth.

CONSEQUENCES IN INFANTS BORN SMALL FOR GESTATIONAL AGE(Importance of size at birth)

In the late 1980s Professor Barker and his colleagues in Southampton made landmark observations linking LBW with adult onset diseases like coronary heart disease, type 2 diabetes, chronic bronchitis, hypertension, stroke and hyperlipidemia(35). . These observations were subsequently confirmed by several epidemiological studies from across the world thereby suggesting a relationship between early life events such as intrauterine growth restriction and later adult diseases.(7),(8).These initial studies led to the proposition of the Barker hypothesis‘ which suggested that adverse events *in utero* leading to reduced fetal growth, permanently alter the structure and physiology of the offspring, such that the risk of heart disease and diabetes in later life was increased(36). There is now overwhelming evidence that early life events have persistent, long lasting consequences and these effects have been best described in term LBW subjects. During“critical periods” of fetal development the fetal tissues grow by rapid cell division. Different organ systems have different critical periods. Barker proposed that any adverse intrauterine environment, for example, insufficient nutrition or oxygenation

during these critical periods results in fetal survival adaptations(37).These adaptations include alterations in the growth rates of the various organ systems such as to favour brain development at the expense of the less important abdominal organs and skeletal muscle. These adaptations result in variable phenotypes depending on the timing of the *in utero* insult. Late *in utero* nutritional insufficiency results in infants with LBW and disproportionate head size, length and weight. In contrast, proportionately small babies are likely to have faced undernutrition during early gestation. Programming is defined as the event/ events occurring during a critical period of development of the organism resulting in long term changes in its structure and function. Programming therefore forms the basis for the association between intrauterine adversity and increased risk of later diseases.

Programming results in fetal adaptations which can be metabolic, endocrine or cardiovascular and may permanently change the structure and function of the body through changes in insulin metabolism and body fat distribution.(10).

Several mechanisms have been proposed to explain fetal programming. According to the ―thrifty genotype‖ hypothesis proposed by Neel in 1962, during times of insufficient nutrient supply, thrifty genes are selected in the fetus which cause a fast insulin trigger‖ and enhanced capacity to store fat, which in later life increases the risk of obesity and type 2 diabetes mellitus(38). Hales et al proposed the thrifty phenotype‖ hypothesis which stated that during conditions of adverse intrauterine environment the fetus undergoes certain adaptations to ensure growth of vital body organs like brain at the expense of

other ”non essential‘ organs(39). These adaptations may subsequently become detrimental if the postnatal environment is discordant with that *in utero* .(14),(40).

The “ **fetal salvage hypothesis”** proposed that peripheral insulin resistance develops in the undernourished fetus which reduces the number and function of peripheral glucosetransporters (41). After birth persistent insulin resistance causes compensatory hyperinsulinaemia; progressive ß cell exhaustion eventually leading to ß cell failure and type 2 diabetes mellitus.

THE “FETAL INSULIN” HYPOTHESIS developed by Hattersley and Tooke proposed that glucose sensing, insulin secretion and insulin resistance in the fetus are genetically mediated(42). The polygenic genetic factors that increase insulin resistance both *in utero*
as well as in adult life would produce 2 phenotypes- a small thin baby as well as an adult with insulin resistance, hypertension, atherosclerosis and type 2 diabetes mellitus, particularly when associated with obesity.

In 2004 Barker proposed the term “developmental plasticity” to explain the developmental origins of adult disease. According to this theory, the fetus undergoes adaptations *in utero* to suit a predicted postnatal environment and when the postnatal environment is different from that which was predicted *in utero* the individuals may be at risk of adverse outcome(43). Gluckman et al proposed the term ―predictive adaptive response‖(PAR) wherein during periods of developmental plasticity, the fetus makes adaptations which need not necessarily have immediate benefit but is made in expectation

of a future environment.(44). If the predicted and the actual future environment are similar these predictive adaptive responses are appropriate and facilitate survival. However if there is a mismatch between these two environments these PAR increase the risk of later diseases.

Thus, when there is an abundance of nutrition in post natal life as opposed to the "famine" *in utero,* the underlying insulin resistance predisposes the individual to an increased risk of developing type 2 diabetes mellitus, hyperlipidemia etc. Similarly cardiovascular changes also occur in response to fetal stress and persist in adult life leading on to complications like hypertension and coronary artery disease.(45). These effects are augmented by rapid catch up growth.

Let us look at the effect of fetal programming on some of the major organ systems of the body.

CARDIOVASCULAR SYSTEM:

Many studies have shown an association between IUGR and cardiovascular complications in later life. Other than low birth weight, 3 factors play a role in the development of hypertension.

Firstly, accelerated catch up growth is postulated to increase the risk(7).

Secondly, altered angiotensin activity during fetal programming(7) and

Finally, increased catecholamine production and proliferation of renin producing juxtaglomerular cells(7)

It is postulated that the cardiovascular remodeling which occurs as a stress response in utero persists in adult life leading on to a dilated cardiomyopathy like heart remodeling, vascular dysfunction and hypertension .(45)(9).

ENDOTHELIAL DYSFUNCTION

Fetal growth restriction leads to increase in the lipid concentrations and increased sympathetic tone. Also there is reduction in IGF-1 levels which might cause vessel wall thickening.(7).

According to recent work done by Skilton and coworkers in 2007 comparing the aortic intima media thickness(aIMT)of infants with low birth weight with normal controls, it was found that the aIMT was greater in IUGR infants than normal controls.(46).

Similarly, carotid wall thickness was shown to be higher in IUGR infants by Crispi et al.(47). This change persisted into adulthood. The increase in arterial wall thickness was postulated to be a result of vascular remodeling occurring in fetal life.

RENAL CONSEQUENCES

It has been shown that IUGR infants have reduced number of nephrons at birth.(7).

This leads to a decrease in the glomerular filtration surface area. The glomerular filtration rate is thereby maintained by increase in the renal blood flow which in turn causes

glomerular hypertension and hypertrophy (hyperfiltration hypothesis by Brenner and coworkers). In 2005,Keijzer and Veen showed a positive correlation between birth weight and GFR, at the same time a negative correlation between creatinine levels and birth weight.(48). Therefore it was suggested that the risk of hypertension and renal failure was higher in IUGR individuals.

NEURODEVELOPMENTAL OUTCOMES

Poor academic performance, cognitive impairment, behavioural problems, language and visuomotor impairment and learning difficulties are some of the neuropsychiatric issues reported in subjects born SGA(7).

CATCH UP GROWTH- THEORIES AND IMPLICATIONS

Catch up growth is defined as the infant reaching a length and weight =or>the third percentile (-2SD).(3). Catch up growth usually starts early after birth and is completed by 2 years of age.(1). About 10-15% of children born SGA fail to achieve to catch up growth.(5).

Karlberg has designed the **infancy-childhood-puberty growth model** based on normal growth among infants. Growth is divided into 3 phases.

1) The infancy phase begins in mid gestation and lasts upto 3 years of age. This phase represents the postnatal continuation of fetal growth.

2) The childhood phase begins from 6-12 months of age till puberty.

3) The pubertal phase starts from puberty until the attainment of the final height.

Growth hormone (GH) begins to exert its action from 6-12 months of age(5). This leads to a rise in the GH dependent IGF-1 production, leading to increase in the growth velocity.

SGA infants show the maximum catch up growth during the first 6 months of life. Those who fail to show catch up by 6 months , are postulated to suffer from difficulty in transition to the GH dependent growth or malfunction of the GH-IGF-1 axis.Infants born small for gestational age have lower levels of insulin and IGF-1.It is postulated that in tissues chronically deprived and depleted of these, a substantial rise in concentration during rapid catch-up growth leads to early development of insulin resistance.(5).

Those infants who show early and complete recovery in form of rapid catch up growth are at the highest risk of metabolic disturbances.(1),(49).

There are 2 models proposed for governing catch up growth:(5),(50).

1) The neuroendocrine model: This states that each individual has a genetically programmed age appropriate set point for body proportions. This mechanism situated in the central nervous system is able to judge the mismatch between the actual and target size and adjust the growth rate accordingly.

2)The growth plate model: This model suggests that growth is a localized process occurring at the individual growth plates as is evidenced by local catch up growth after transient suppression of growth at a particular growth plate.

However neither of the two can completely explain the underlying mechanisms of catch up growth.

Thus one can conclude that catch up growth depends upon genetic, nutrirional and hormonal factors especially the GH-IGF-1 axis. Children who fail to show catch up growth may have a persistent defect in the GH-IGF-1 axis.

SECTION 4:

STUDIES RELATED TO THIS THESIS

1.SIZE AT BIRTH AND CORD BLOOD LEVELS OF INSULIN, IGF-1 AND OTHER HORMONES IN TERM HUMANS INFANTS.

IGF axis plays a major role in fetal growth , therefore cord blood insulin and IGF-1 levels are expected to correlate with the birth size. In an African American and White cohort, ***Vidal*** et al (51)observed that infants with higher IGF-1 levels were larger at birth (p=0.0001) after adjusting for factors like, race, gender, gestational age at delivery, maternal BMI and smoking. In this study a strong positive correlation was also found between infants with high IGF-1 levels and maternal obesity (BMI>30 kg/m2).

Maternal obesity drives the fetal IGF axis and increases the risk of higher birth weight and childhood obesity.

Smerieriet al observed (52) a positive effect of cord blood IGF-2 on birth weight and length whereas IGFBP-2 had a negative effect on both birth weight and height.

Other parameters such as insulin, cortisol and IL-6 did not seem to have a major role in determining birth size in this study.

Ken Ong and co-workers studied the correlation between size at birth and cord blood levels of Insulin,IGF-1,IGF-2,IGFBP-1 and 3 and the soluble IGF-2 binding receptor.(53). A total of 199 term newborns were studied.

It was found that insulin, IGF-1 and IGFBP-3 were positively related to birth weight and ponderal index. Positive correlation was also found between the IGF2/IGF-2 R ratio with all parameters at birth.

Akcakus et al looked at the relationship between intrauterine growth, IGF-1 and IGFBP-3 and bone mineral status in newborn babies.(54)

IGF-1 levels were noted to be highest in LGA followed by AGA and SGA babies ($p<0.01$).

Karamizadeh etal observed that in addition to cord blood IGF-1, maternal IGF-1 and cortisol levels were also low in SGA babies.

Similarly, adipose tissue hormone, adiponectin was also noted to be low in SGA babies at birth.(55).Similar to other studies, these investigators also reported a positive correlation of IGF-1 level and birth weight.

An Indian study was done by ***SubarnaMitra*** etal to look at how fetal growth was affected by maternal anthropometry and metabolic profile.(56).

The mean level of cord blood insulin was higher in LGA when compared to SGA babies. (p 0.007). Birth weight was correlated with maternal weight (p 0.0002) and maternal BMI

(p 0.0001). Also cord blood insulin had a positive correlation with all anthropometric parameters at birth except ponderal index and chest circumference.

Claudio Chiesa while confirming a positive correlation of IGF-1 and IGFBP-3 with all anthropometric measurements at birth observed that ghrelin and insulin had no correlation with the birth measurements(57), whereas., leptin levels were found to have a trend towards a positive correlation with the birth length. (p=0.05).

2.GENDER SPECIFICITY OF INSULIN, INSULIN LIKE GROWTH FACTOR-1 AND OTHER HORMONES ON PRENATAL GROWTH

Lourdes Ibanezetal observed that (58) the cord insulin and IGF-1 were higher in term girls when compared to term boys both in the SGA and AGA group($p<0.01$) concluding that these hormones were gender specific .

However in a similar study done by ***SubarnaMitra*** etal in India.(59), no gender based differences in the anthropometry and cord blood insulin in term Indian could be demonstrated.

In a recent Indian study done by ***Wiley*** etal (60) girls had a higher IGF-1 level than boys at birth ($p<0.03$). Cord blood IGF-1 was associated with sum of skin fold thickness positively ($p<0.001$) apart from most other anthropometric parameters.

3. BIRTH WEIGHT, INSULIN AND HOMA-IR IN TERM BORN NEWBORNS:

Sahasrabuddhe etal did a pilot study in India and found that, (61) the insulin and glucose levels in full term normal pregnancies was 6.75 ±2.96 mIU/ml and 91.69±27.05 mg/dl respectively.

While lower weight babies had lower glucose and higher insulin values, the heavier babies had higher glucose and lower insulin values.

Hyperinsulinemia, as defined by insulin levels >19 was found in 4 out of 121 babies (3.3%). Three out of the four had low birth weight<2500gms.

HOMA was greater than 2.5 in 18% of babies and showed a positive correlation with hypothyroid mothers.

The overall incidence of low birth weight was more in complicated pregnancies (31.25%) as compared to uncomplicated pregnancies (20%).

Simental et al, observed in his study that (62). LGA babies showed a strong association with hyperinsulinemia (OR 5.02,CI 1.15-22.3 and p=0.01).

Both LGA and SGA babies exhibited similar HOMA-IR values, however cord blood glucose was higher in SGA babies.

4. INSULIN/ IGF-1 AXIS AND POST NATAL GROWTH

Dizdarer et al (63),demonstrated that serum glucose levels were lower in term SGA babies than in term AGA babies,($p<0.05$.) and Insulin levels were higher in term SGA infants , than term AGA infants ,($p<0.05$).

Similarly, HOMA-IR values were higher in term SGA than in term AGA,($p<0.05$) and

IGF-1 levels were lower in term SGA when compared with term AGA infants .

HOMA-IR values were higher at 3 and 6 months in well growing SGA children compared to both not well growing SGA and AGA children.

IGF-1 levels were higher at 3 and 6 months in well growing SGA babies compared with those not well growing.

Orbak etal looked at the association between maternal and fetal serum IGF-1,IGFBP-3 and leptin levels and early post natal growth in SGA babies.(64).

It was noted that slower growing SGA babies had lower cord blood IGF-1 values when compared to the normally growing ones, concluding that IGF-1 played a role in post natal growth.. Also significant positive correlations were found between birth weight and cord blood leptin, IGF-1 and IGFBP-3 levels ($p<0.001$).

Ken Ong etal observed that (13) that IGF-1 levels at 5 years were positively correlated to weight ($p<0.0005$) and height ($p<0.0005$) at 5 years however it was unrelated to the cord blood IGF-1 levels.

It was also found that the IGF-1 levels at 5 years were correlated to the rate of weight gain between 0-2 years ($p<0.0005$) with higher levels in children showing post natal catch up growth.

5. CHANGES IN INSULIN SENSITIVITY IN EARLY POST NATAL LIFE AND ITS ASSOCIATION WITH CATCH UP GROWTH:

Tong-yan Han etal from China looked at the association between catch up growth and insulin sensitivity of SGA born babies at 3 months of life.(65).and found that SGA babies had higher fasting insulin and HOMA-IR levels suggestive of insulin resistance.

Mericq etal did a study to look at changes in insulin sensitivity in small and appropriate for gestational age infants from birth to three years(66).

SGA infants had lower insulin levels than AGA infants (p 0.03) at 48 hours of life. However by three years of age the fasting insulin levels were higher in the SGA group,($p=0.005$).

SGA infants also had a higher HOMA-IR at 3 years of age compared to AGA infants.

At 3 years of age, the rate of weight gain was the most important factor determining fasting insulin levels(r=0.47,p=0.003),indicating development of insulin resistance.

In this context, ***Iniguez*** et al observed that , SGA infants had lower IGF-1 levels at birth which quickly rose till 3 years of age, when levels became higher than that of AGA infants.

IGF-1 levels at 1 year were associated with gain in length (p=0.049), in contrast IGF-1 levels at 3 years was associated with weight gain.

Associations between insulin resistance and low birth weight was studied by ***Nestor Soto*** et al.(21). He observed that SGA infants were shorter, lighter and had a smaller head circumference at birth when compared to AGA infants.

While at 48 hours the fasting glucose levels of SGA and AGA infants was comparable , the fasting insulin levels were lower in the SGA group<0.01.

Furthermore,fasting insulin levels were higher in SGA infants with WCUG when compared to SGA without WCUG and AGA.

It was seen that increase in length in the 1st year of life was the only independent factor affecting post load insulin secretion at 1 year.(p<0.01).

Ibanez and coworkers to demonstrated the association of catch up weight gain on early onset adiposity and insulin resistance in SGA children..(20).

SGA infants gained weight faster than the AGA counterparts between 2 and 4 years of age. Between 2 and 4 years of age, the increase in body fat and adiposity were higher in SGA children.It was also seen that the lean body weight was lower in SGA children.

At 2 years of age, SGA children had lower insulin levels and HOMA ,however between 2-4 years, although the mean IGF-1 levels were similar between both the groups, fasting insulin levels increased in the SGA group.

Milovanovic et al, observed that (22).SGA babies had a lower ponderal index(24.8±1.8 vs 26.3±3.1) and were thinner than AGA babies.

At 4 years of age, SGA children were lighter than AGA children. Also plasma glucose 2 hours after oral glucose load was higher in SGA when compared to the AGA counterparts (p=0.006).

Insulinogenic index, as calculated by (insulin 30- insulin 0)/(glucose 30- glucose 0) was lower in the SGA children (p=0.02).

There was symmetrical catch up in weight and height which was independent of the post natal feeding practices.

It was also found that SGA children had a lower glucose stimulated insulin secretion at 4 years of age when compared to the AGA children.

METHODOLOGY

INTRODUCTION :

This section details the Materials and Methods used in this study**.** The study was approved by the Institutional Review Board and Ethics committee (IRB min no 9088 dated 6.10.2014). Informed written consent was obtained from the mothers of all the participants at recruitment into the study.

STUDY SETTING:

The recruitment and collection of data at birth were done in the labour room, neonatal intensive care unit and post natal wards of the Christian Medical College Vellore. Follow-up of this cohort at 3.5 months and 6 months was done in the Paediatric endocrinology outpatient clinic of the institution. All recruitment was done by the primary investigator of the study.

SAMPLE SIZE CALCULATION:

In a similar study published earlier (63), the mean difference in IGF-1 levels at birth between AGA and SGA babies was 28.5%, standard deviation in AGA group was 28.42 and that in the SGA was 22.40. Using an Alpha error of 1% and Power of 90%, 24 neonates would need to be recruited in each arm. Considering a dropout rate of 10% , this would equate to 27neonates in each arm. We recruited 60 neonates, 30 each in the SGA and AGA arms of this study.

STUDY POPULATION:

All babies born at term between 37-42 weeks of gestation in CMC hospital during the study period were eligible for the study. Subjects were excluded if they had :

1. Birth asphyxia
2. Mothers with intrauterine infections
3. Major systemic illness
4. Major congenital anomalies
5. Chromosomal anomalies or genetic syndromes

STUDY PERIOD:

Recruitment for the study commenced in December 2014. The major recruitment occurred between December 2014 and February 2015 This was planned with a view to enable follow-up of these infants till 6 months of age. To achieve target sample size, few subjects were recruited in August 2015 also.

METHODOLOGY:

MATERNAL DETAILS AT BIRTH:

Maternal pregnancy details were collected from the mother's hospital records in the labour room and postnatal wards. Maternal age, parity, gestational age at delivery and mode of delivery were noted. Maternal risk factors like pregnancy induced

hypertension (PIH), gestational diabetes (GDM), and thyroid disorders if present were documented.

Although maternal height and weight at the first visit to the hospital were available, this information could not be used to calculate the maternal BMI because of non-uniformity of the data. As it is common local custom to have antenatal care elsewhere and have delivery at another hospital, the first visit to our hospital ranged from 8 weeks of pregnancy to the time of delivery.

NEONATAL DETAILS AT BIRTH:

Physical examination of the neonate was done by the primary investigator to confirm term gestation and to rule out major systemic illness, congenital anomalies, chromosomal or genetic syndromes. Anthropometry included weight, length and head circumference for all babies recorded within 24 hours after birth by the primary investigator. Weight was measured using an electronic infant scale with a precision of 10 gms(Global weighing system Essae DS-252). Recumbent length was measured using an infantometer .Occipitofrontal head circumference was measured using a flexible measuring tape. Using weight and length measurements , ponderal index was calculated using the formula (weight in grams/length in cm^3)x 100. Subjects were followed up in the NICU/postnatal wards till they were discharged from the hospital.

Cord blood samples were collected for insulin, glucose and IGF-1 assays in appropriate tubes and were sent to the laboratory immediately. The samples had unique code

numbers. Glucose samples were analysed immediately, Insulin and IGF-1 samples were centrifuged and sera were frozen at -20°C till analysis. Using glucose and insulin values, HOMA-IR was calculated using the formula : fasting insulin (µU/ml)x fasting glucose (mmol/L)/22.5

All mothers were advised to give exclusive breast feeds till 6 months of age. Contact details of the family were collected and they were advised to return for follow-up at 3.5 and 6 months as per the study protocol .

AT 3.5 MONTHS FOLLOW UP:

All subjects had their weight, length and head circumference measured by the primary investigator as described earlier. . Body mass index(BMI) was calculated using the formula weight in kg/height in m^2.

Details of the infant's diet as well as any significant illness during this period were documented. In addition a brief developmental assessment of the infant was done by the primary investigator.

Catch up growth was calculated for all babies in terms of gm/kg/day and cm/month for gains in weight, length and head circumference respectively. Weight gain was calculated from the 11^{th} postnatal day for all babies. . Differences in the catch up growth between AGA and SGA infants was calculated and recorded. Catch-up growth was then correlated with the insulin/ IGF-1 at birth.

Nelson Textbook of Paediatrics describes the weight, length and gain in head circumference during normal growth in children(19) . Based on these recommendations, our subjects were arbitrarily classified into 3 categories:

a. Inadequately growing: weight gain <20gms/day, length increase of < 3.5cm/month and increase in head circumference of <2cm/month.
b. Adequately growing: weight gain 20-30gms/day, length increase of 3.5cm/month and increase in head circumference of 2cm/month.
c. Rapidly growing: weight gain >30gms/day, length increase of > 3.5cm/month and increase in head circumference of >2cm/month.

The correlation between these 3 categories of growth and their hormonal parameters at birth was investigated.

DETAILS AT 6 MONTHS FOLLOW UP:

At 6 months of age, details of the infant's diet as well as any significant illness during this period were documented. In addition a brief developmental assessment of the infant was done by the primary investigator. Anthropometric measurements like weight, length and head circumference were noted . Fasting (4 hours post feed) blood samples was collected for S.insulin, IGF-1 and glucose assays only in SGA babies. However due to limitation of time, the 6 months follow up study could not be completed and follow up will continue after submission.

HORMONE ASSAYS

Cord blood glucose was measured by the hexokinase test using the COBAS 8000 analyser.

S. Insulin and IGF-1 levels were as measured by chemiluminiscence assay using SIEMENS IMMULITE 2000 XPi. The coefficient of variance was 7 for both insulin and IGF-1.

DATA ENTRY AND ANALYSIS:

Data was prospectively entered in Epidata software version 3.1 and analysis was done using SPSS version 21..

Student's t test was used for comparison of means whereas Mann whitney U test was used for comparison of differences between the SGA and AGA groups.

1. Neonatal parameters including gestational age, anthropometric measurements and ponderal index were compared between the groups. .

2. The effect of maternal age, parity and risk factors (gestational diabetes and hypertension) on birth weight was noted.

3. The mean insulin and IGF-1 levels were calculated at birth for both SGA and AGA babies and the difference was analysed using the Mann-Whitney U test.

4. For those available, HOMA-IR was compared between the two groups.

5. Linear regression was done with insulin and IGF-1 levels across all gestational ages and birth weights.

6. Anthropometric variations at 3.5 months between AGA and SGA were recorded and differences in catch up growth was noted between the 2 groups.

7. Subjects were divided into adequately growing, inadequately growing and rapidly growing based on catch up growth and differences in SGA and AGA groups noted.

8. The catch-up growth at 3.5 and 6 months was correlated with the hormonal parameters at birth.

9. Comparison of our data with data from other studies was done using unpaired t test.

10. Results were expressed as median ±SDS. P value was considered significant if

< 0.05.

RESULTS

This section is divided into three subgroups:

1. Results of the baseline parameters at birth

2. Results of the follow-up study at 3.5 months

3. Results of the follow-up study at 6 months

1. Results of the baseline parameters at birth

Baseline characteristics

There were 30 subjects in the SGA group and 30 in the AGA group. All except one set of SGA twins were born singleton. Excluding them did not affect the statistical analysis, therefore they were included in the analysis. Similarly there were 3 babies who were large for gestational age In view of their very small number they were also included in the analysis.

The baseline characteristics of the cohort are shown below in Table 1.

TABLE 1: BASELINE CHARACTERISTICS

	N	MEAN	SD	P value
BIRTHWEIGHT(gms)				
SGA	30	2031.667	209.9767	**<0.01**
AGA	30	3188	478.627	
LENGTH(cm)				
SGA	30	44.96667	2.092406	**<0.01**
AGA	30	49.23333	2.062528	
HEAD CIRCUMFERENCE(cm)				
SGA	30	31.33667	1.119262	<**0.01**
AGA	30	33.98	1.07	
GESTATIONAL AGE(wks)				
SGA	30	38.03667	0.937158	<**0.01**
AGA	30	39.31667	1.004845	
PONDERAL INDEX				
SGA	30	2.236333	0.239878	<**0.01**
AGA	30	2.658	0.286265	

As expected, SGA babies were lighter, shorter and had smaller head circumference as compared to the AGA group. In addition they had lower Ponderal index as compared to the AGA group. Interestingly, although all the infants were born at term, there was a difference between the gestational ages between the groups with the SGA group being born earlier.

TABLE 2: GENDER WISE DISTRIBUTION OF THE COHORT IS SHOWN BELOW IN TABLE 2.

AGA/SGA	MALES	FEMALES	P value
SGA	15 (50%)	15(50%)	
AGA	13(43.33%)	17(56.67%)	0.605
TOTAL	28(46.67%)	32(53.33%)	

There were no differences in the number of males and females either in the SGA or AGA group.

FIGURE 3.1:GENDER WISE DISTRIBUTION OF SGA INFANTS

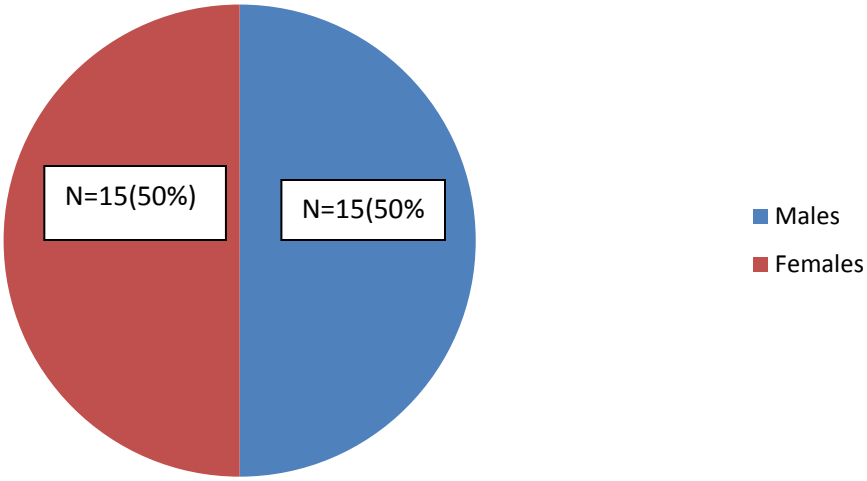
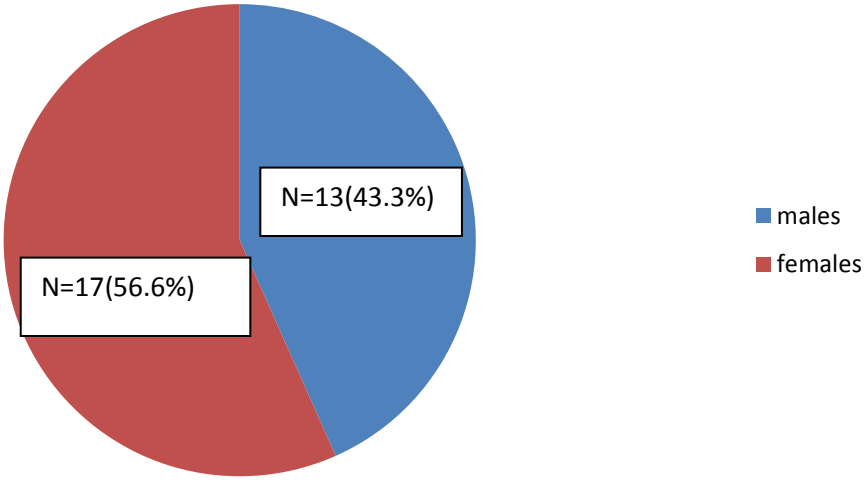


FIGURE 3.2:GENDER WISE DISTRIBUTION OF AGA INFANTS



THE CORD BLOOD LEVELS OF INSULIN AND IGF-1 IS SHOWN BELOW IN TABLE 3.

VARIABLE	**SGA**	**AGA**		**SGA**	**AGA**
CORD INSULIN(µU/ml)			**CORD IGF-1(ng/ml)**		
N	30	30		30	30
MEDIAN	2	2.45		25	43.4
MIN	2	2		25	25
MAX	6.55	34.7		47	156
P-VALUE	**0.002**			**<0.01**	

Cord blood insulin & IGF-1 levels were significantly lower in the SGA group as compared to the AGA group.

Because of inadequate sampling and delay in reaching the laboratory, cord blood glucose values were available only for 21 babies .Therefore HOMA-IR could be calculated only for 21 babies and is shown below in Table 4.

Table 4.Cord blood Glucose & Insulin levels /HOMA-IR

PARAMETER	**SGA(N=5)**	**AGA(N=16)**	**P VALUE**
GLUCOSE(mg/dl)	74	94.625	
INSULIN(µU/ml)	3.028	8.225	
HOMA-IR	0.616(±0.457)	1.9675(±2.0727)	**0.17**

.

HOMA-IR appeared to be higher in the AGA babies although there was no statistical difference .

There was no gender wise difference in the cord blood insulin and IGF-1 levels within the SGA and AGA group of subjects This is shown below in Table 5.The AGA boys were heavier, longer and had a larger head circumference compared to the AGA girls. Whereas in the SGA group, the boys tended to be longer with a larger head circumference.

TABLE 5.: GENDER WISE DIFFERENCE BETWEEN THE SGA AND AGA INFANTS FOR CORD BLOOD INSULIN AND IGF-1.

	SGA			**AGA**		
	Males	**Females**	**P**	**Males**	**Females**	**P**
WEIGHT(gms)	2054.667	2008.667	**0.558**	3473.08	2970.00	**0.002**
LENGTH(cm)	45.667	44.2667	**0.066**	50.38	48.35	**0.004**
HEAD CIRCUMFERENCE (cm)	31.7867	30.8867	**0.026**	34.46	33.62	**0.022**
INSULIN(µU/ml)	2	2	**0.39**	3.07	2.34	**0.62**
IGF-1(ng/ml)	25	25	**0.52**	50.96	47.53	**0.75**

TABLE 6: COMPARISON BETWEEN BASELINE NEONATAL CHARACTERISTICS OF TERM AGA BABIES IN OUR STUDY WITH OTHER INDIAN STUDIES.

	Our Study		**S.MITRA etal, Puducherry**(59)			
	MALES (n=13)	**FEMALES (n=17)**	**MALES (n=26)**	**FEMALES (n=24)**	**Pm**	**Pf**
Weight(gms)	3473.08± 371.89	2970± 441.54	3080± 540	2920± 380	0.0241	0.70
Length(cms)	50.38±1.55	48.35±1.99	48±2	47±1	0.0006	0.0067
Head Circumference (cms)	34.46±0.749	33.62±1.153	34.09±1.73	33.23±1.57	0.46	0.38
Insulin(µU/ml)	5.33±6.15	5.69±8.2	15.15±15.93	11.77±10.95	0.0396	0.0603

Pm- p value is for comparison of males between the 2 studies.

Pf- p value is for comparison of females between the 2 studies.

The table shows that there was a significant difference among the birth weight of boys between the 2 studies. The length was also significantly different among both the sexes. In the term AGA group, Vellore boys were heavier and longer than the ones from Puducherry, and our girls were longer than the Puducherry girls.

Despite being lighter and shorter the boys in the Puducherry cohort had higher insulin levels. , girls showed a trend towards higher insulin levels.

TABLE 7: COMPARISON BETWEEN BASELINE NEONATAL CHARACTERISTICS OF TERM BABIES IN OUR STUDY WITH INTERNATIONAL STUDIES.

OUR STUDY		**Weight (gms)**	**Length (cms)**	**Insulin (µU/ml)**	**IGF-1 (ng/ml)**
AGA (n=13)	**M**	3473.08±371	50.38±1.55	5.33±6.15	50.97±35.66
(n=17)	**F**	2970±441	48.35±1.99	5.69±8.2	47.53±24.13
SGA (n=15)	**M**	2054.66±232	45.66±1.95	2.59±1.25	28.06±7.13
(n=15)	**F**	2008.66±190	44.26±2.05	2.28±0.54	28.46±13.98
DIZDARER et al(63)					
AGA (n=10)	**M**	3568±347.87	51.2±3.45	6.835±3.98	69.07±28.42
(n=5)	**F**	3230±543.98	50.3±3.4		
SGA (n=8)	**M**	2167±790.90	46.25±4.41	7.445±4.47	40.52±22.4
(n=15)	**F**	1972±567.70	45.53±3.36		
P1-AGA	**M**	**0.5391**	**0.4521**		
	F	**0.2830**	**0.1172**		
SGA	**M**	**0.6067**	**0.6582**		
	F	**0.8173**	**0.2218**		
IBANEZ et al(58)					
AGA (n=24)	**M**	3400		5.6±0.9	64±6
(n=24)	**F**	3400		9.4±1.1	84±5
SGA (n=24)	**M**	2300		3.3±0.6	41±4
(n=24)	**F**	2300		6.3±0.8	59±5
P2-AGA	**M**			**0.8323**	**0.0863**
	F			**0.0338**	**0.0001**
SGA	**M**			**0.0221**	**0.0001**
	F			**0.0001**	**0.0001**

P1- p value is for gender wise comparison of weight and height between Indian babies and those from Turkey (Dizdarer).

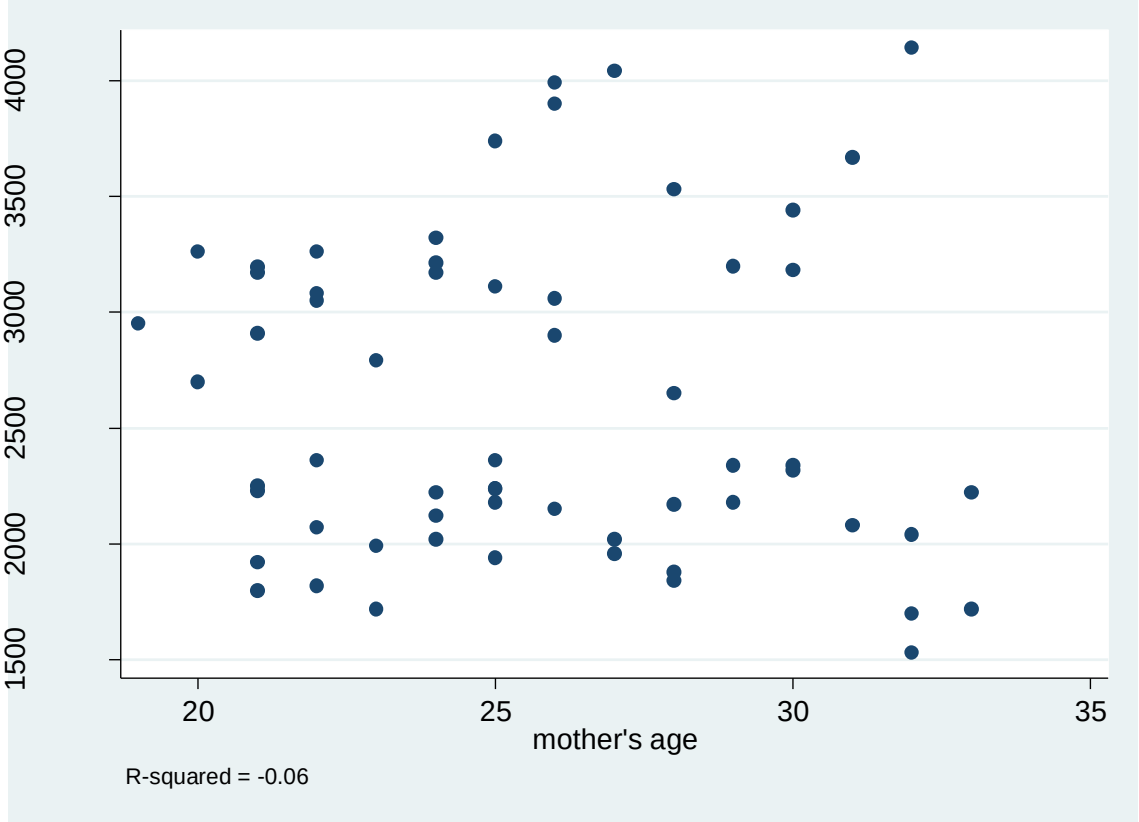
P2- p value is for gender wise comparison of insulin and IGF-1 levels between Indian and Spanish babies (Ibanez).

The Vellore cohort was similar to the Turkish cohort in anthropometry and hormonal parameters.

The Spanish babies were controlled for birth weight. However, their AGA girls and SGA boys and girls had higher insulin and IGF-1 levels compared to our cohort.

This comparison shows that anthropometric measurements among AGA and SGA babies are similar in India, and Turkey. However gender differences were noted in the study done by *Ibanez* with cord blood insulin and IGF-1 being higher in girls than in boys.

FIGURE 5:THE CORRELATION BETWEEN MATERNAL AGE AND BIRTH WEIGHT IS SHOWN IN FIGURE 1 BELOW.



Low birth weight babies (babies weighing < 2500 gms) are scattered across all the maternal ages (20-35 years). Athough not significant, there was a trend (p=0.59) towards increasing birth weight (weighing> 3500gms) with increase in maternal age > 25 years.

Eleven of the 59 mothers had gestational diabetes. All of them were on diet control and none were receiving medication for diabetes. Shown below in Table 8 is the correlation between maternal gestational diabetes (GDM) and the birth parameters.

Maternal GDM and Offspring birth weight

GESTATIONAL DIABETES	**N**	**MEAN BIRTHWEIGHT(gms)**	**SD**	**P value**
YES	11	2660	943.9041	**0.79**
NO	48	2598.571	629.7354	

Maternal GDM and Offspring cord blood insulin level

GESTATIONAL DIABETES	**N**	**MEDIAN (INSULIN)µU/ml**	**MIN-MAX**	**P-VALUE**
YES	11	2	2-6	**0.61**
NO	48	2	2-34	

Maternal GDM and Offspring cord blood IGF-1 level

GESTATIONAL DIABETES	**N**	**MEDIAN (IGF-1)ng/ml**	**MIN-MAX**	**P VALUE**
YES	11	25	25-80	**0.89**
NO	48	27	25-156	

Table 8 shows that maternal gestational diabetes did not have a significant impact on the offspring's birth weight and cord blood insulin or IGF-1 levels.

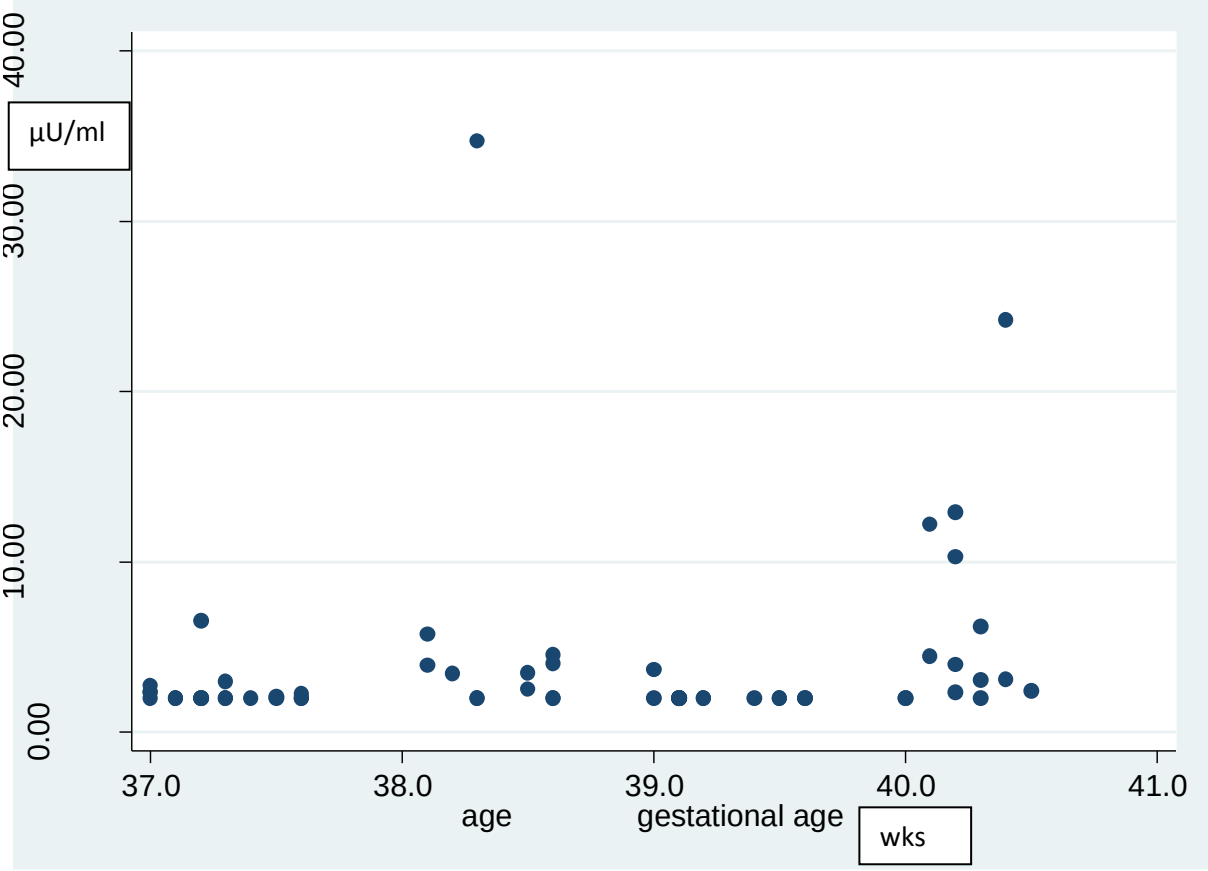
Although the sample size of mothers with GDM were limited, there was no difference in their offspring's SGA and AGA outcome as shown below in Table 9.

TABLE 9: SGA/AGA BIRTH IN RELATION TO MATERNAL DIABETES MELLITUS.

GESTATIONAL DIABETES	**SGA**	**AGA**	**TOTAL**
YES	6 (54.55%)	5 (45.45%)	11
NO	24 (48.98%)	25 (51.02%)	48
TOTAL	30	30	

The impact of gestational age on cord blood insulin across 37-42 weeks of gestation was studied and is shown in Figure 6 below.

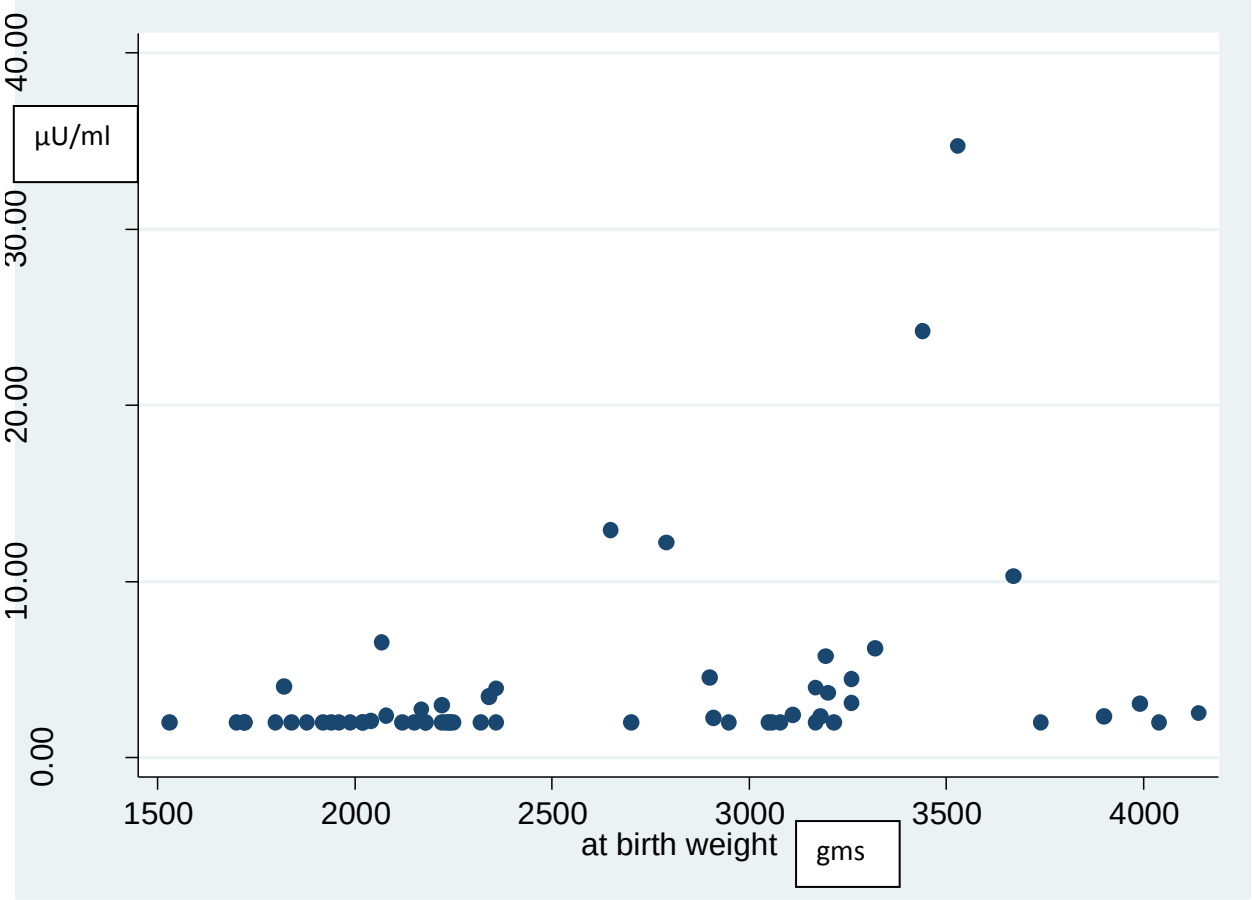
FIGURE 6: CORRELATION BETWEEN GESTATIONAL AGE AND CORD BLOOD INSULIN.



This graph shows that there was no correlation between gestational age and cord blood insulin levels. (p=0.12).

The impact of birth weight on cord blood insulin was studied and is shown below in Figure 7.

FIGURE 7: CORRELATION BETWEEN BIRTH WEIGHT AND CORD BLOOD INSULIN.

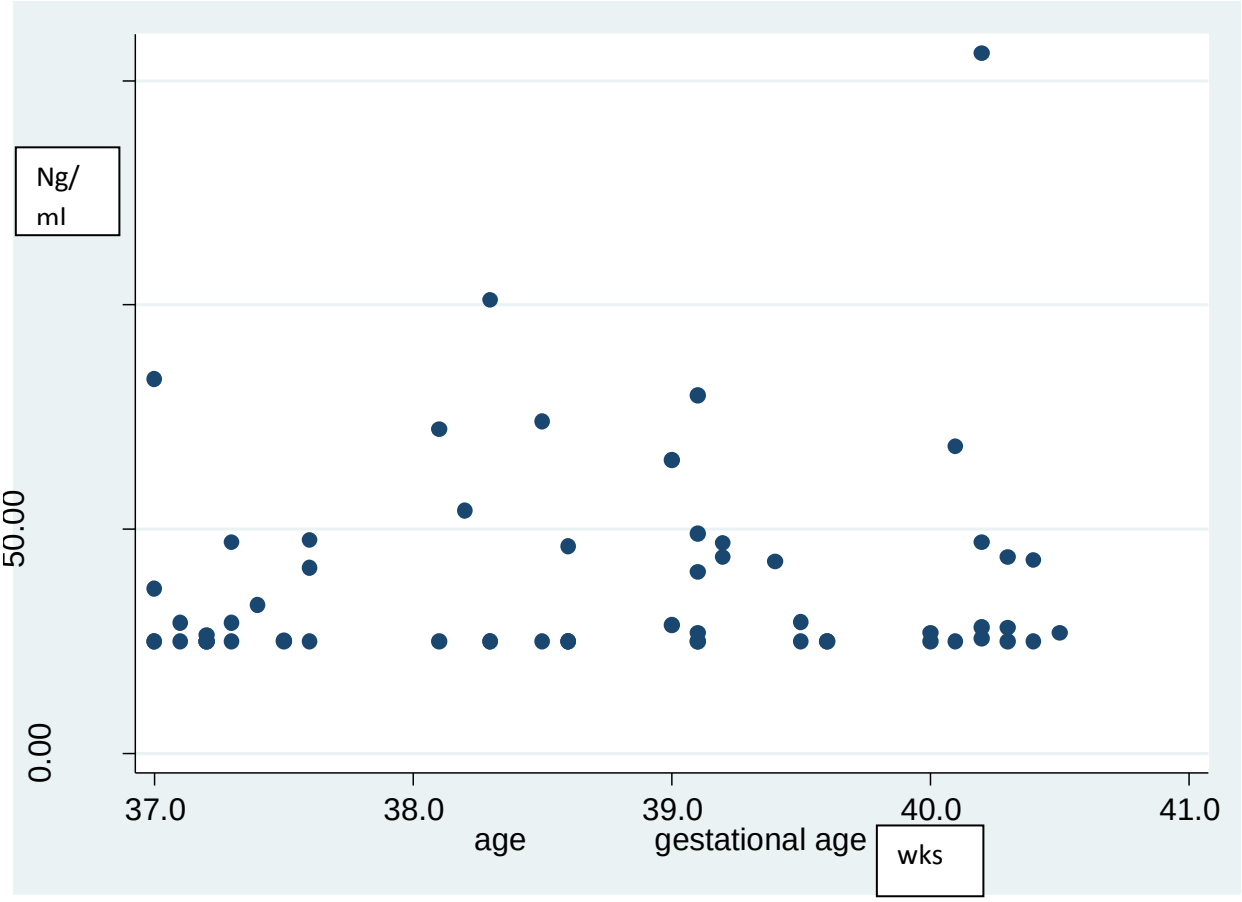


As shown in the graph above, there was a linear correlation between birth weight and cord blood insulin levels (p=0.01). Across the birth weights, there was increase in cord blood insulin leves. With increase in birth weight, the insulin levels tended to increase.

Likewise, the impact of gestational age and birth weight on cord blood IGF-1 level was also studied.

Shown in Figure 8 below is the correlation between gestational age and cord blood IGF-1 level .

FIGURE 8: CORRELATION BETWEEN GESTATIONAL AGE AND CORD BLOOD IGF-1.

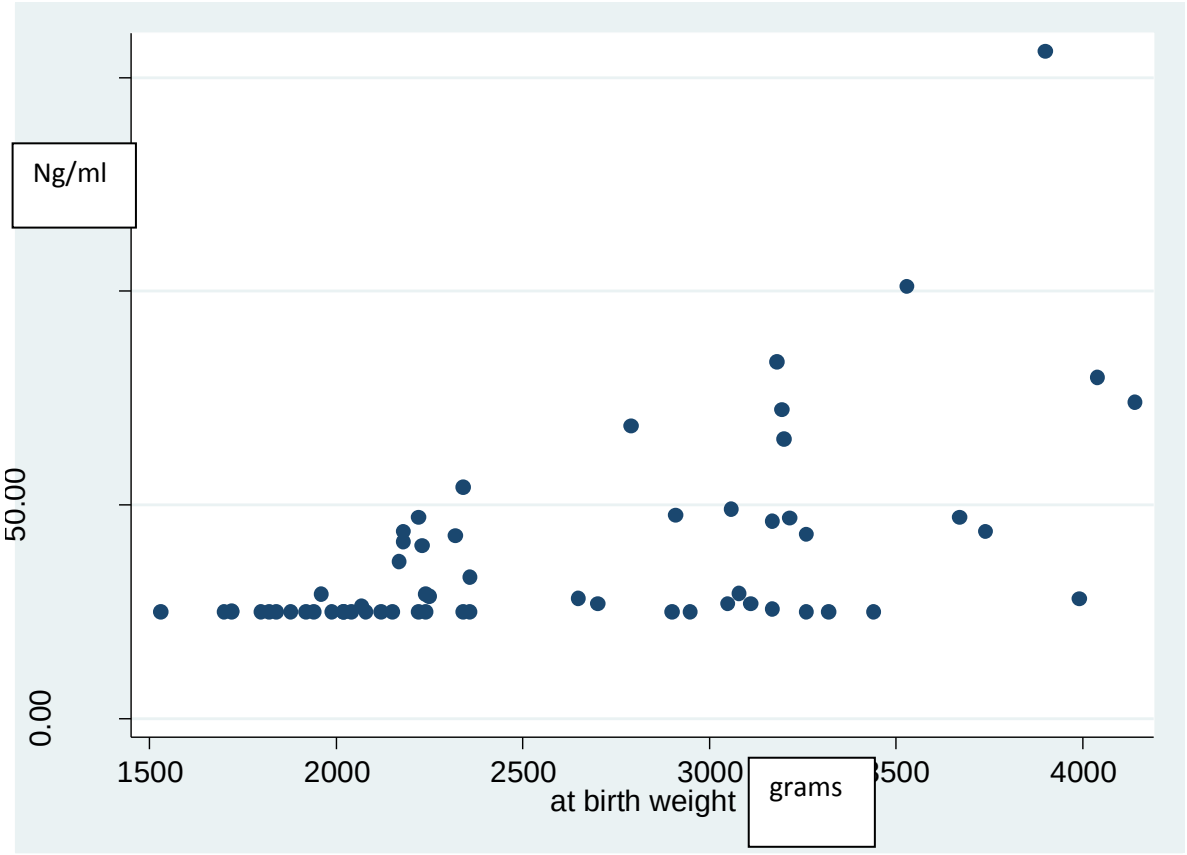


There was no correlation between gestational age and cord blood IGF-1 levels.

(p=0.41).

The correlation between birth weight and cord blood IGF-1 level is shown below in Figure 9.

FIGURE 9: CORRELATION BETWEEN BIRTH WEIGHT AND IGF-1 LEVELS



There was a strong positive correlation between birth weight and IGF-1 levels.

($p<0.01$) across all birth weights.

We also investigated the correlation between ponderal index at birth and the cord blood hormonal parameters and this is shown in Table 10 below.

TABLE 10: CORRELATION BETWEEN PONDERAL INDEX AND CORD BLOOD INSULIN AND IGF-1.

	PONDERAL INDEX	**P-VALUE**
CORD BLOOD INSULIN	0.2	**0.11**
CORD BLOOD IGF-1	0.59	**<0.01**

As is shown above, there was strong correlation between ponderal index and cord blood IGF- at birth. However there was no such correlation between ponderal index and cord blood insulin level.

RESULTS OF THE FOLLOW UP STUDY AT 3.5 MONTHS.

50 of the 60 infants of the initial cohort had completed 3.5 months of age and were eligible to be included in the Follow-up study. Thirty five of them (22 SGA, 13 AGA) returned for follow-up and were included in the study. The anthropometric indices of this cohort are shown below in Table 11.

TABLE 11: ANTHROPOMETRIC INDICES AT 3.5 MONTHS

WEIGHT(gms)	**N**	**MEAN**	**SD**	**P-VALUE**
SGA	22	4475.909	621.7691	**<0.01**
AGA	13	5930.769	933.3404	
LENGTH(cm)				
SGA	22	56.13636	2.932502	**<0.01**
AGA	13	60.76923	2.74329	
BMI				
SGA	22	14.12727	1.33316	**0.004**
AGA	13	15.90769	2.132472	
HEAD CIRCUMFERENCE				
SGA	22	37.34	1.3486	**<0.01**
AGA	13	39.38	1.0636	

As shown in the Table above, at 3.5 months, the SGA babies continued to be lighter, shorter, had smaller head circumference as well as lesser BMI as compared to their AGA peers. .

The follow-up cohort was investigated for any difference in anthropometry based on their gender. This is shown in Table 12 below.

TABLE 12: GENDER WISE DIFFERENCE IN ANTHROPOMETRY AT 3.5 MONTHS.

WEIGHT(gms)	**N**	**MEAN**	**SD**	**P-VALUE**
MALES	16	5086.25	871.9853	**0.71**
FEMALES	19	4957.368	1162.329	
LENGTH(cms)				
MALES	16	58.375	3.138471	**0.44**
FEMALES	19	57.42105	4.018233	
HEAD CIRCUMFERENCE(cms)				
MALES	16	38.40625	1.66552	**<0.01**
FEMALES	19	37.84211	1.518887	
BMI				
MALES	16	14.84375	1.60581	**0.87**
FEMALES	19	14.74211	2.095316	

Boys had larger head circumference as compared to the girls at 3.5 months. In all other parameters they were similar.

Shown below in Table 13 is the comparison of the catch-up growth between the SGA and AGA cohort.

TABLE 13: CATCH UP GROWTH IN SGA/AGA BABIES AT 3.5 MONTHS.

WEIGHT(gms/day)	**N**	**MEAN**	**SD**	**P-VALUE**
SGA	22	25.42455	0.299357	**0.18**
AGA	13	28.93546	0.226427	
LENGTH(cm/month)				
SGA	22	3.270455	0.493447	**0.94**
AGA	13	3.282308	0.448407	
HEAD CIRCUMFERENCE(cm/month)				
SGA	22	1.716364	0.299357	**0.05**
AGA	13	1.527692	0.226427	

This table shows that SGA and AGA babies had similar growth rates in terms of weight and length at 3.5 months of age.

However there was a trend towards larger head circumference in SGA babies as compared to AGA babies.

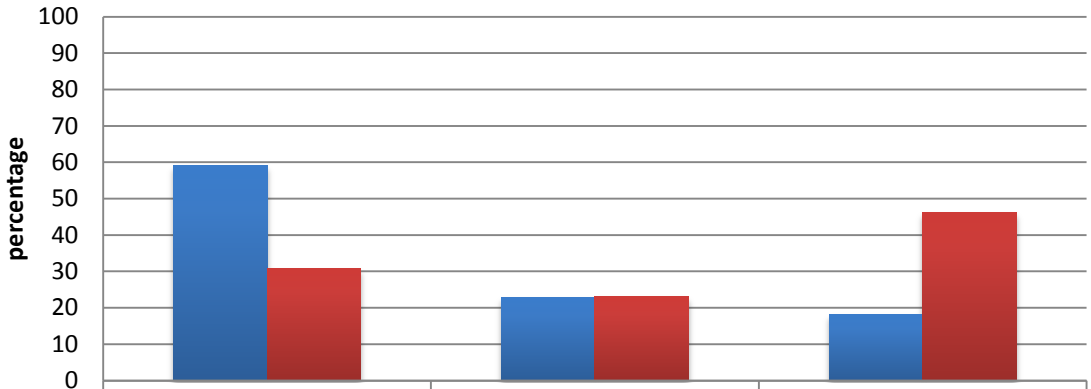
TABLE 14: CATCH UP GROWTH IN AGA/SGA BABIES

	ADEQUATELY GROWING	INADEQUATELY GROWING	RAPIDLY GROWING
WEIGHT			
SGA(n=22)	13(59.1%)	5(22.7%)	4(18.2%)
AGA(n=13)	4(30.8%)	3(23.1%)	6(46.2%)
LENGTH			
SGA(n=22)	7(31.8%)	9(40.9%)	6(27.3%)
AGA(n=13)	2(15.4%)	7(53.8%)	4(30.8%)

At 3.5 months, 59.1% of the SGA babies were adequately growing while 46.2% of AGA babies were rapidly growing in terms of increase in weight.

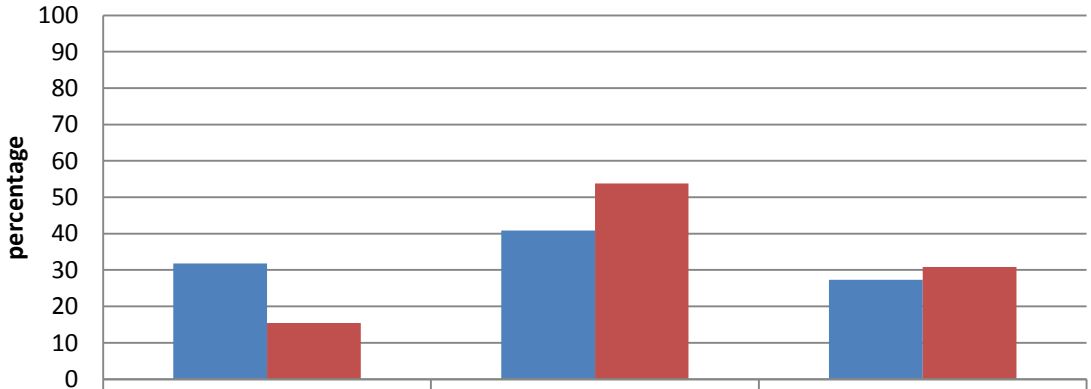
Majority of the babies were inadequately growing in terms of length at 3.5 months.

FIGURE 10.1:WEIGHT CATCH UP IN SGA/AGA INFANTS



	adequately growing	inadequately growing	rapidly growing
SGA	59.1	22.7	18.2
AGA	30.8	23.1	46.2

FIGURE 10.2:LENGTH CATCH UP IN SGA/AGA INFANTS



	adequately growing	inadequately growing	rapidly growing
SGA	31.8	40.9	27.3
AGA	15.4	53.8	30.8

We looked at the effect of cord blood insulin level on the infants' catch-up growth at 3.5 months in terms of weight & length as is shown below in Figure 11 & 12 respectively.

FIGURE 11: CORRELATION BETWEEN CORD BLOOD INSULIN AND WEIGHT GAIN AT 3.5 MONTHS.

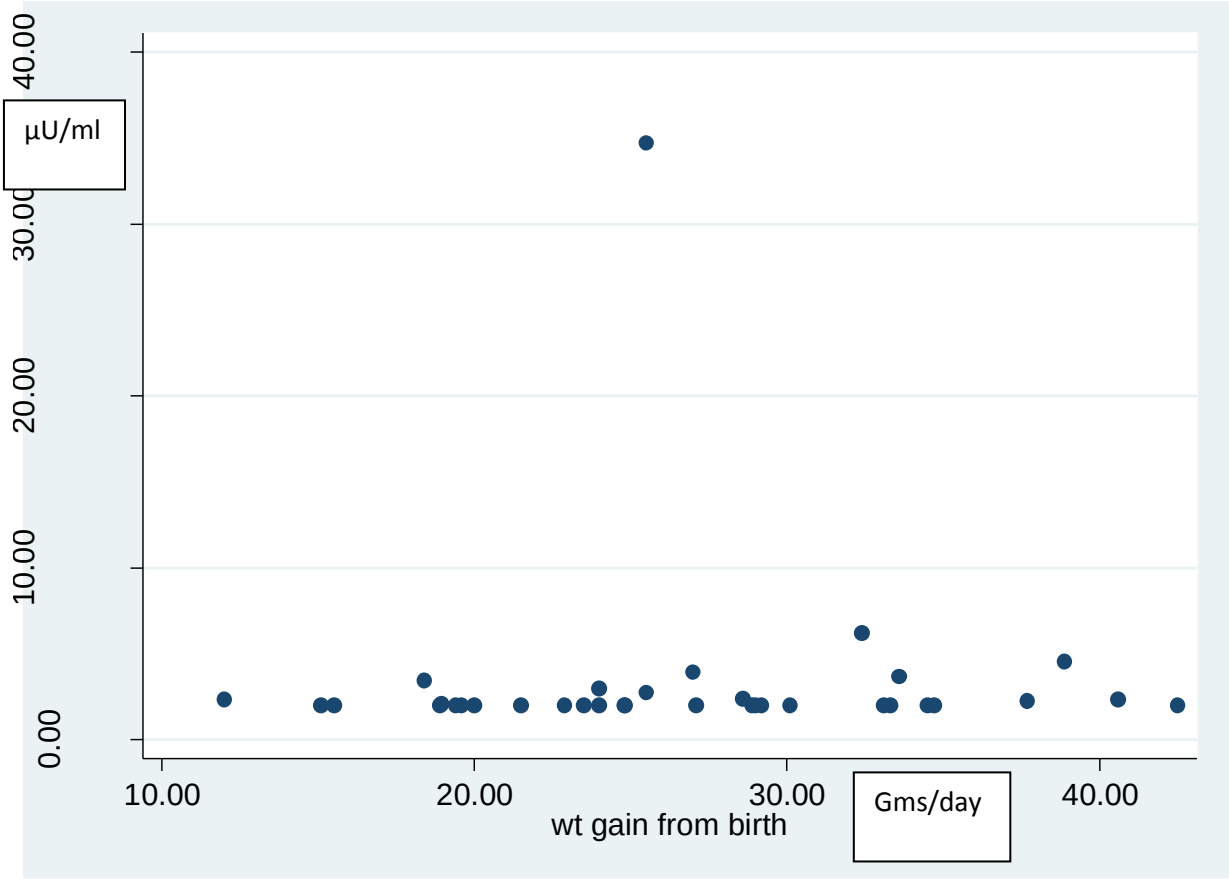
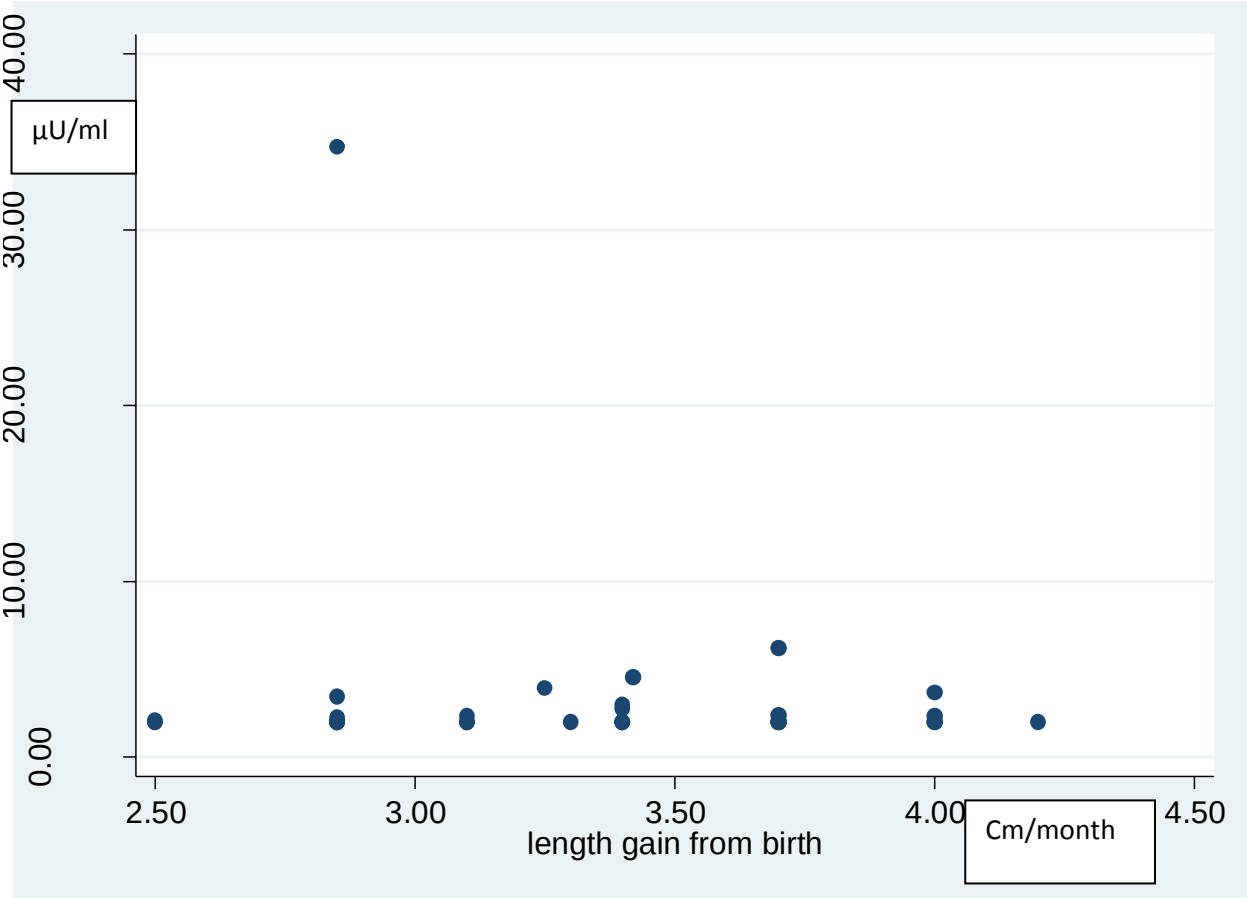


FIGURE 12: CORRELATION BETWEEN CORD BLOOD INSULIN AND LENGTH GAIN AT 3.5 MONTHS.



As shown in the Figures above, there was no correlation between cord blood insulin levels and weight gain.(p= 0.95) as well as length gain (p=0.48) at 3.5 months of age.

Similarly we also looked at the effect of cord blood IGF-1 level and catch-up growth at 3.5 months as shown below in Figure 13&14 respectively.

FIGURE 13: CORRELATION BETWEEN CORD BLOOD IGF-1 AND WEIGHT GAIN AT 3.5 MONTHS.

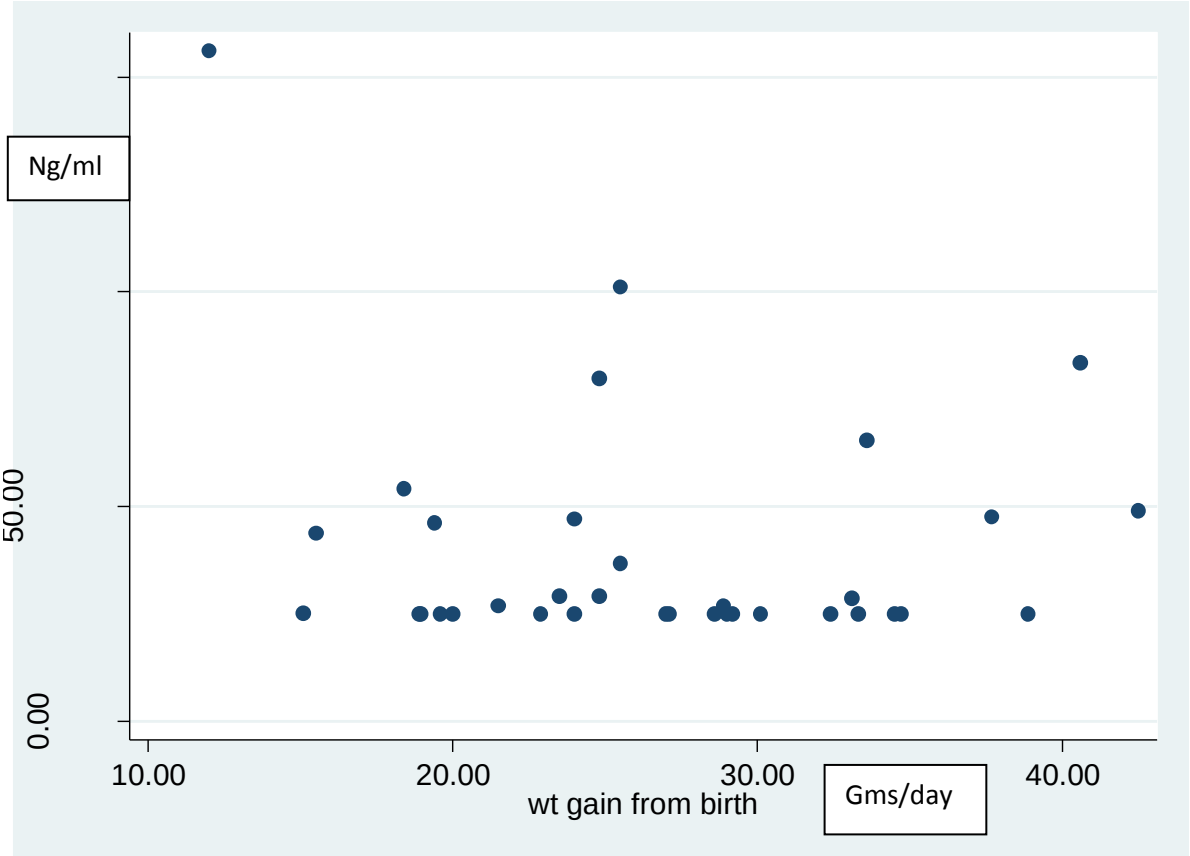
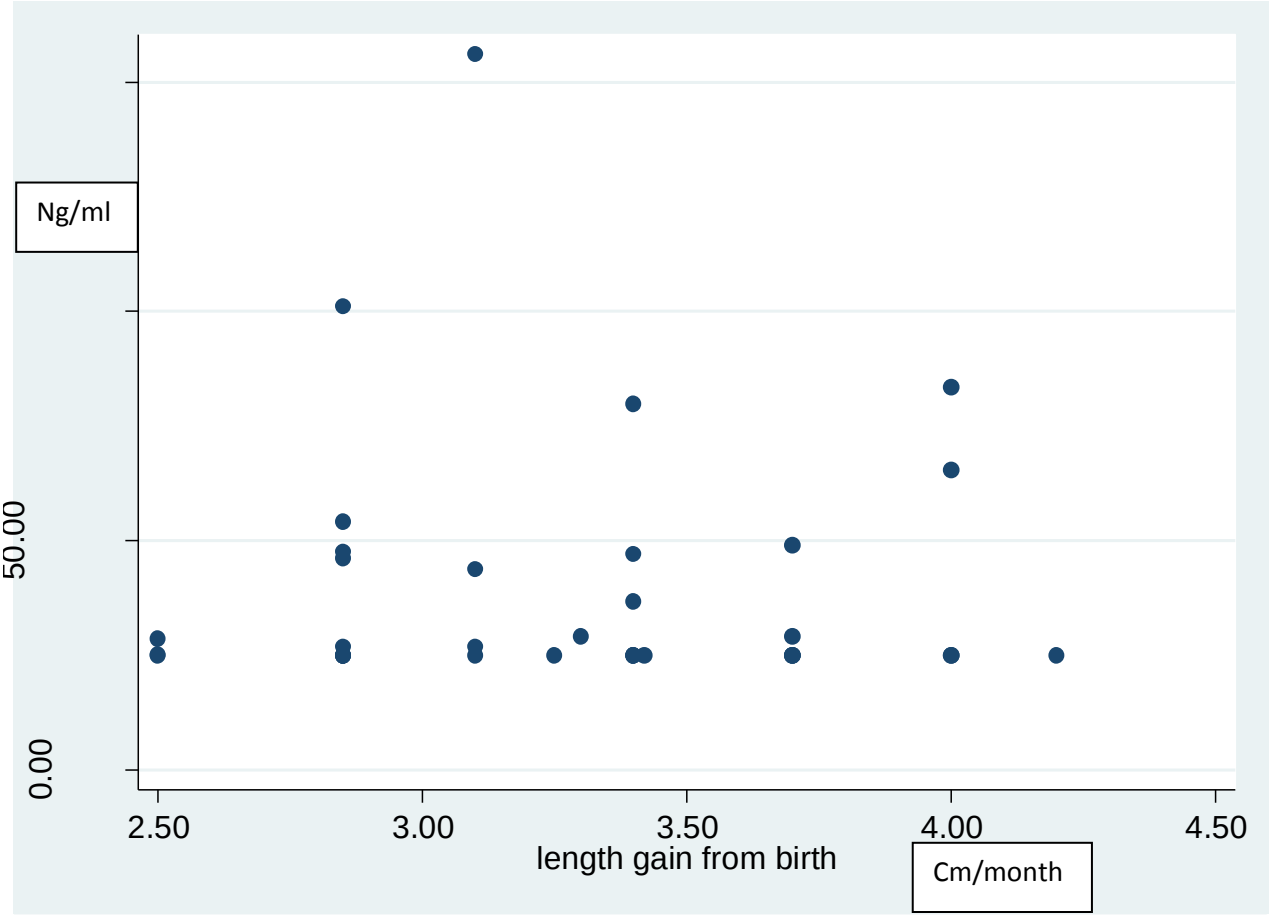


FIGURE 14: CORRELATION BETWEEN CORD BLOOD IGF-1 LEVELS AND LENGTH GAIN AT 3.5 MONTHS.



As shown in the Figures above, cord blood IGF-1 did not impact growth at 3.5 months of age either in terms of weight (p=0.37) or length gain(p=0.98).

RESULTS OF THE FOLLOW UP STUDY AT 6 MONTHS OF AGE

Of the 60 babies in the initial cohort, only 41 babies had completed 6 months of age and were eligible for the 6 months follow-up study. Of these, only 5 babies (4 SGA) returned for follow-up. Because of the limited sample size, the characteristics of each of these subjects are individually described. No statistical analysis was done between the groups.

TABLE 15: ANTHROPOMETRIC INDICES AT 6 MONTHS OF AGE.

PARAMETER	**BABY 1**	**BABY 2**	**BABY 3**	**BABY 4**	**BABY 5**
AGA/SGA	**SGA**	**SGA**	**SGA**	**SGA**	**AGA**
GENDER	boy	girl	boy	girl	Boy
AT BIRTH					
WEIGHT(gms)	2220	2240	2250	2150	3900
LENGTH(cms)	48	46	49	45	50
HC(cms)	30	31	32	32	36
3.5MONTHS					
WEIGHT(gms) **Catch up(g/day)**	4500 24	4480 23.5	5400 33.1	4050 20	5040 12
LENGTH(cms) **Catch up(cm/mon)**	60 3.4	59 3.7	58 2.5	55 2.85	60 3.1
HC (cms) **Catch up(cm/mon)**	37 2	37 2	40 2.28	38 1.7	39 1
6 MONTHS					
WEIGHT(gms) **Catch up(g/day)**	6680 29.06	6040 20.8	6760 18	5960 25.46	6920 25.06
LENGTH(cms) **Catch**	66 2.4	66 2.8	61 1.2	64 3.6	66 2.4

up(cm/mon)					
HC(cms) **Catch up (cm/mon)**	41 1.6	39 0.8	41.5 0.6	41 1.2	41.5 1

During the first 3.5 months, in the SGA group, 3 babies showed adequate catch-up (20-30 gm/day) while one of them showed rapid catch-up. The LGA baby showed catch-down growth with a mean gain of only 12 gm/day.

All had inadequate growth in terms of length and head circumference at 3.5 month.

However at 6 months all except 1 SGA baby had rapid weight catch up(>20 gms/day).

The same baby showed inadequate gain in length and head circumference also.

Hormonal assay was also done during the 6 month Follow-up and results are shown in Table 16 below.

TABLE 16: HORMONAL PARAMETERS AT 6 MONTHS OF AGE:

PARAMETER	**BABY 1**	**BABY 2**	**BABY 3**	**BABY 4**	**BABY 5**
SGA/AGA	SGA	SGA	SGA	SGA	AGA
SEX	BOY	GIRL	BOY	GIRL	BOY
AT BIRTH					
INSULIN	2	2	2	2	2.32
IGF-1	25	29.2	28.7	25	156
AT 6 MONTHS					
GLUCOSE	76	90	95	71	86
INSULIN	3.05	2	3.65	2	2.812
IGF-1	38.4	67.2	32.1	78	25

Although the LGA baby had very high IGF-1 level at birth, his length was only 50 cm. At 6 months he had the lowest level of IGF-1 in the group. His growth parameters showed a catch-down growth.

DISCUSSION

In this study we recruited 60 infants , 30 of them born SGA and 30 born AGA at birth. Their anthropometry and birth details along with the maternal details were recorded and cord blood was sampled for glucose, insulin and IGF-1 levels. They were prospectively followed up at 3.5 months and their growth velocity as well correlation with the hormonal parameters at birth were investigated. Their follow-up at 6 months of age is ongoing. There was no difference between the number of boys and girls in each group at birth.

As expected, the SGA cohort were leaner, shorter and had smaller head circumference than the AGA group (Table 1). We compared the neonatal anthropometry of our infants with other available Indian data. . Only data for term AGA babies were available for comparison. In comparison with the Puducherry cohort, our boys were heavier. In terms of length, both boys and girls in our group were longer. (Table 6, (59)). This difference is significant particularly because more than one third of the Puducherry cohort (8/26) were LGA babies as compared to our cohort where only 2 of the 13 babies were LGA. In comparison with the Nagpur cohort, our babies were heavier at birth(46).. Although Puducherry and Vellore(the location of our study cohort) are geographically closely located in South India the differences in the neonatal anthropometry between the 2 cohorts may be due to the difference in the socioeconomic status of the parents with the Vellore cohort being representative of a higher socioeconomic strata. In addition, India is a very diverse country where each geographical area has unique cultural and dietary practices in addition to numerous other differences and these may also explain the birth

size differences in the various parts of India. . When compared to the international data our cohort was similar to the Turkish cohort in weight and length. (Table 7). When we analysed the neonatal anthropometry between boys and girls in the SGA and AGA groups , the findings were interesting. In the AGA group, as expected, the girls were lighter, shorter and had smaller head circumference than the boys (Table 5). This is the usual growth pattern where females are smaller made than males. However in the SGA group, the only difference was in the head circumference wherein the girls had smaller head circumference than the boys. It is possible that there is an interplay of multiple factors namely genetic/ intrauterine environmental and hormonal which result in fetal growth restriction and this occurs irrespective of the gender. On the other hand, it may also be possible that the male fetuses are relatively more growth retarded than the females such that eventually there is no significant difference in birth size between the genders. Several studies in animal and human models including maternal undernutrition studies have reported sexual dimorphism with an accentuation of adverse phenotype in males(67),(68),(69),(70).

The SGA cohort in our study were born earlier as compared to the AGA cohort although all were born at term. This may be explained by the fact that in view of SGA status as well as the aetiological factors for SGA (for eg.maternal preeclampsia), early termination of pregnancy may have occurred in the SGA group.

We then compared the cord blood hormonal parameters at birth which included insulin, glucose, and IGF-1 levels between our AGA and SGA cohorts. The median insulin level in the AGA group was 2.45 µU/ml when compared to 2 µU/mlin SGA babies (p=0.002).

This is similar to various other studies where the cord blood levels of insulin were found to be higher in term AGA as compared to SGA babies.(In fact there was a positive linear correlation between birth weight and cord blood insulin levels (p=0.01) across the birth weights in our study (Figure 7).

It is well known that insulin with its anabolic action plays a key role in fetal growth and therefore has a positive correlation with the size at birth. However this is in contrast to the findings of Dizdarer et al where the term born SGA group had higher insulin levels at birth as compared to the AGA group.(63).

Simental et al also documented higher insulin level in their SGA cohort, however this did not reach statistical significance because of the very small number of SGA babies in their cohort(62). Higher insulin levels in the SGA group in these studies may be evidence of development of insulin resistance *in utero*.

In comparison with other Indian data, the cord blood insulin levels of the AGA babies in our study was comparable with those of the Nagpur cohort (2,40 ±0.97 vs 6.75±2.96 respectively) (61). However this was in contrast with data from another similar South Indian cohort where the AGA babies had higher insulin levels as compared to our AGA

cohort (10.96±13.28 vs 2.40 ±0.97mIU/ml respectively(p value=0.0008)(56). This was despite the fact that the Puducherry AGA cohort were lighter as compared to our group. While the higher insulin levels could be related to the ambient glucose levels (data of concurrent glucose levels not available)this may also suggest a degree of insulin resistance in them(56). Data on SGA babies is scarce from India, therefore we could not compare our SGA cohort with other Indian data.

HOMA-IR could only be calculated in limited number of subjects in our study because of reasons described earlier. HOMA-IR of our AGA cohort was similar to the Nagpur cohort (1.967 vs 1.52 respectively)(30) . There was insufficient data from the SGA group for comparison. Dizdarer et al have reported increased HOMA-IR in their SGA group when compared to the AGA group ((63). Similarly, HOMA-IR was higher in the SGA cohort of Simental's study although this did not reach statistical significance(62). It is absolutely imperative to assess plasma glucose levels as early as possible after collection in order to obtain correct result .This should be done to prevent glycolysis and uptake of glucose in the sample by the RBS's.The glycolysis can also be prevented by using fluorinated tubes as the fluoride inhibits glycolysis.. This makes it technically challenging. In addition the reliability of cord blood glucose level is questionable as it is dependent on factors such as maternal glucose level, stress of delivery etc. Therefore although fasting levels of insulin and glucose as well as the calculated value of HOMA-IR have been widely used as surrogates for insulin sensitivity in large population studies,

these values as described in the Literature review section cannot be used to precisely evaluate glucose-insulin axis *in vivo*.

IGF-1 is a key hormone regulating fetal growth and it is primarily controlled *in utero* by insulin. As expected our AGA group with greater insulin levels had higher IGF-1 levels as compared to the SGA group(43.4 vs 25µU/ml, $p<0.01$,Table 3). This is consistent with several other epidemiological studies((32),(63),(71). In fact both birth weight and ponderal index showed a strong positive correlation with IGF-1 levels in our study.

In contrast ,in a meta analysis of 11 observational studies reported by Elhdadad et al, the IGF-1 levels in term AGA and SGA babies were comparable(72).In this systematic review, the IGF-1 levels were higher in LGA group as compared to the AGA group thereby concluding an association of IGF-1 and fetal growth only in the higher range of the birth weight spectrum. They also reported higher IGFBP-1 levels in SGA infants and suggested a key role of this hormone in the intrauterine growth of SGA infants.

In the above context, Dizdarer et al's findings were quite interesting. In contrast to most of the other studies including our study, at birth, the SGA group in their study had lower IGF-1 levels despite having higher insulin levels than their AGA group. The authors have suggested insulin resistance and secondary hyperinsulinism playing a role in altering the IGF-IGFBP axis in SGA infants.

Gender specificity in adiposity and its related parameters have been demonstrated in some studies. Healthy girls born at term while being lighter have been documented to

have more adiposity , higher insulin, IGF-1 and leptin levels as compared to boys (73),(74),(75). In an elegant study, **Ibanez**etal reported similar gender specific findings in term born SGA girls((58). Girls born at term, both AGA as well as SGA although had similar birth weight as the boys in their respective group had strikingly higher levels of insulin and IGF-1, In addition AGA girls in their group had greater fat mass (measured by DEXA scan) as compared to boys although there was no genderwise difference among the SGA group. This was in contrast to our findings wherein AGA girls were although lighter at birth than boys, their hormonal parameters were similar. In SGA group there was no gender wise difference either in birth weight or in the hormonal parameters.

Postnatal growth at 3.5 months & 6 months of age

Of the 50 infants who had completed 3.5 months of age by the end of the study period, 35 infants (22 SGA, 13 AGA) were followed up and were included in the study. It was interesting to note that the postnatal growth velocity was similar in the SGA and AGA cohort. We then investigated as to whether there was a difference in weight or length gain between the groups. Both in terms of gain in weight (25.43±0.29 vs 28.94±0.23 gm/kg/day respectively, p=0.18) and in length (3.27±0.49 vs 3.28±0.44 respectively, p=0.94) , the SGA and AGA groups were similar(Table 13) . As the SGA group were smaller than the AGA group at birth in all the anthropometric measurements and in the subsequent months their growth velocity was similar to the AGA group, the SGA group

remained lighter, shorter and with lower BMI than the AGA group at 3.5 months of age(Table 12).

Three patterns of growth have been described in the first year of life in children: normal growth, catch-up growth and catch down growth,(18),(76).Weight and height growth above or below the statistical limits of normal is defined as catch up or catch down growth. This phenomenon of catch up allows the growth restricted babies to reach growth which is similar to healthy babies born at term. When we analysed the growth of our cohort as described in the section on Methodology, approximately half of the AGA group exceeded the expected weight gain as opposed to less than a quarter of the SGA group(Table 14). Close to a quarter from each group had inadequate weight gain and the remaining were growing in the expected normal range. Surprisingly approximately half of the cohort from each group did not show adequate gain in length. In Soto et al's cohort of term SGA and AGA infants, 73% of the SGA group showed weight catch-up but only 52% showed length catch-up by 1 year of age(21).. Interestingly neither the cord blood levels of insulin/ IGF-1 had any effect on either gain in weight or length at at 3.5 months of age in our study.

Rapid postnatal weight gain is known to be associated with adverse hormonal milieu as early as infancy. Dizdarer et al had reported higher insulin and HOMA-IR values in well growing SGA infants at 3 & 6 months of age as compared to the SGA group who did not grow well(63). There were no similar findings in the AGA group even in those who had shown accelerated weight gain. The authors therefore concluded that postnatal

catch-up growth may adversely affect the glucose metabolism in those born SGA in their later life. Similar findings were also reported by Soto et al(77). At 1 year of age their SGA group who showed weight catch-up, developed higher fasting insulin levels *although they were not overweight*. Therefore although it is comforting to note that our SGA cohort, even those who showed adequate postnatal growth, remained smaller at 3.5 months of age, it is important to follow them up longitudinally and assess for early development of insulin resistance. There are no definite recommendations available as to how much and how fast the SGA babies need to grow to remain metabolically healthy.

After early infancy, IGF-1 is mostly influenced by growth hormone. In Dizdarer's study.the well growing SGA group had higher IGF-1 levels at 3 & 6 months of age although on an average the SGA group had lower IGF-1 levels at birth. Similar findings were also reported by Soto et al(21). We did not have sufficient data at 6 months for comparison. Dizdarer eta l speculated that due to the development of early insulin resistance which alters the IGF-IGFBP axis, SGA babies who grow well during infancy have a tendency for decelerated growth in later life and eventually become short adults without reaching their genetic height potential. Currently growth hormone therapy is recommended for children born SGA with poor height velocity to improve their final height outcome.

Reduced insulin sensitivity is a well established early metabolic abnormality in the pathogenesis of adult onset diseases including type 2 diabetes mellitus mellitus, hypertension and Atherosclerosis(35),(78),(79).

The most important environmental factor adversely affecting insulin sensitivity is obesity, in particular abdominal adiposity. s(80),(81),(82). Therefore prevention of obesity remains one of the most important modifiable factors affecting insulin resistance. Catch-up growth in SGA infants is mostly complete by 2-3 years of age. Infancy, in particular, the first 6 months is the period of maximum growth after birth. Rapid growth during infancy has been associated with obesity in later life.. Those with insulin resistance may remain asymptomatic for several years and in later years they may or may not develop diseases linked with metabolic syndrome. This gives a long window period during which interventions such as lifestyle modifications (healthy diet, regular physical exercise) will reduce the impact of insulin resistance.

Our cohort, both the AGA and SGA groups did not demonstrate insulin resistance in terms of hyperinsulinaemia at birth. In addition. on an exclusive breast feed diet, close to 60% of the SGA cohort demonstrated postnatal growth in the “adequate” range. Despite adequate growth the SGA group remained smaller than the AGA group at 3.5 months of age. Current evidence suggests that remaining relatively smaller may benefit them from the risk of developing insulin resistance and metabolic syndrome in later life. However the accelerated weight gain in almost half of the AGA infants is worrying. As insulin

resistance is augmented by obesity it is important that their growth is monitored long term and rapid catch-up weight gain is avoided.

LIMITATIONS

This study has several limitations. One important limitation was the limited sample size during follow-up, particularly at 6 months of age. Correlation of anthropometry and hormonal parameters with the catch-up growth at 6 months would have given us valuable information. Another limitation was insufficient glucose sampling at birth thereby limiting assessment of HOMA-IR. In addition we did not have the maternal pre-pregnancy weight and subsequent BMI for correlation with the birth size.

CONCLUSIONS

1. Insulin and IGF-1 were lower in term born SGA babies in comparison with AGA babies.
2. There was a linear positive correlation between the birth weight and the cord blood insulin and IGF-1 levels across all term gestational ages.
3. With exclusive breast feeding, there was no difference in catch up growth in terms of both weight and length between the SGA and AGA groups at 3.5 months of age, However SGA babies continued to be lighter and shorter than AGA babies at 3.5 months.
4. Long term follow-up of this cohort will give more insight into when, if at all, the SGA subjects catch-up with their peer group in terms of growth. In addition whether this group will develop an adverse metabolic milieu with rapid catch-up growth remains to be seen..

ANNEXURES

INFORMED CONSENT

Christian Medical College, Vellore

Department of Child health-Unit-1

Study title: Correlation between cord blood insulin/IGF-1 and early postnatal growth in small for gestational age babies.

INFORMATION SHEET

You are being requested to take part in this study to see if babies born small for gestational age have lower insulin and IGF-1 level at birth and whether the levels increase with post natal growth leading to insulin resistance and long term health risks.

Why are we doing this study?

It has been observed that babies born small (low birth weight) have an increased risk of developing diseases like diabetes, hypertension, heart disease etc when they are adults. This risk is more if the babies who are born small grow rapidly after birth. Food intake is one of the most important factors affecting the growth of children. In addition there are certain hormones which affect the growth of children before and after birth. In babies who are born small, the hormone levels may be different at and after birth from those who are born with normal birth weight. These hormones as well as the baby's food intake affect the growth in children particularly those who are born small. In this study we plan to look at children born small, their growth and hormonal profile at birth and during the first 6 months after birth. To understand the difference between those who are born small and with normal weight, some of the normal weight babies will also be part of this study.

What will you have to do?

If you give consent for the study, some blood tests and simple measurements (weight, height and head circumference) will be done for your baby at birth. Your baby will not be pricked for tests as these will be taken from the umbilical cord

blood. Both parents weight and height will be recorded. During your hospital visits for vaccination at 3 & 6 months, your child will be measured by the Paediatrician and details of the baby's diet will be collected. At 6 months, babies who were born small will have a single blood test done by the Padiatrician. Mothers will have their weight and height recorded once again.

Can you withdraw from this study after it starts?

Your participation in this study is entirely voluntary and you are also free to decide to withdraw permission to participate in this study. If you do so, this will not affect your usual treatment at this hospital in any way.

What will happen if you develop any study related injury?

As the study involves usual body measurements and a simple blood test by a qualified Paediatrician at 6 months of age, we do not anticipate any study related injury to your child.

Will you have to pay for the blood tests?

The blood test for the study will be done free of cost for you, however if you develop any unrelated illness , you will have to bear the hospital expenses.

Will your personal details be kept confidential?

The results of this study will be published in a medical journal but you will not be identified by name in any publication or presentation of results. However, your medical notes may be reviewed by people associated with the study, without your additional permission, should you decide to participate in this study.

Format for Informed Consent Form for Subjects

Informed Consent form to participate in a research study

Study Title:Correlation between cord blood insulin/IGF-1 and early postnatal growth in small for gestational age babies.

Study Number: _____

Subject's Initials: _____ Subject's Name: _____

Date of Birth / Age: _____

(Subject)

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions. [ ]

(ii) I understand that my participation in the study is voluntary and that I amfree to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

(iii) I understand that the investigators doing the study, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s).[ ]

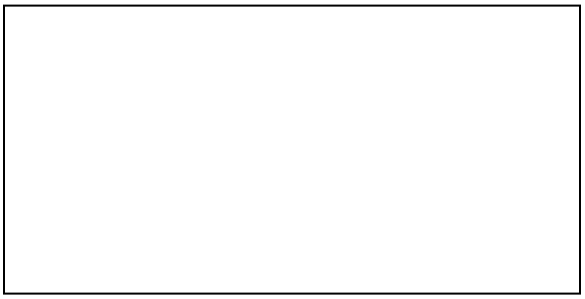
(v) I agree to take part in the above study.[ ]

Signature (or Thumb impression) of the Subject/Legally Acceptable

Date: _____/_____/_____

Signatory's Name: _____Signature:

Or



Representative: _____

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Signature of the Investigator: _____

Date: _____/_____/_____

Study Investigator's Name: _____

Signature or thumb impression of the Witness: _____

Date: _____/_____/_____

Name & Address of the Witness: _____

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