CHARACTERISTICS OF BLACK SOUTH AFRICAN ADULT AND ADOLESCENT WOMEN WHO GAVE PREMATURE BIRTH TO GROWTH-RESTRICTED INFANTS AT KALAFONG HOSPITAL, GAUTENG

A thesis presented to the Division of Human Nutrition in the Department of Interdisciplinary Health Sciences of the Faculty of Health Sciences of the University of Stellenbosch in partial fulfilment of the requirements for the degree of Master of Nutrition

by

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DECLARATION

I, the undersigned, hereby declare that the work in this thesis is my own original work and that I have not previously, in part or in its entirety, submitted it at any university for a degree.

8 November 2006
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INTRODUCTION: The objective of the study was to determine the prevalence of certain known risk factors for intra-uterine growth restriction (IUGR) in women who gave premature birth to growth-restricted infants at a large regional hospital (Kalafong) in the Gauteng province of South Africa and to investigate the possible associations between the presence of various risk factors and the severity of growth restriction found in these infants.

METHOD: The study was designed as cross-sectional, descriptive and observational. The subjects included singleton growth-restricted premature infants (n=80), without congenital abnormalities and their mothers (n=80). Anthropometric data [weight, height, mid-upper arm circumference (MUAC) and triceps skinfold thickness (TSF)] were collected from these mothers three to four days post-partum. Infant birth weights were recorded at birth, while the lengths and head circumferences were recorded within 2 days post-partum. Additional information, such as birth spacing, maternal age, smoking habits and alcohol use, was collected by personal interview and blood pressure data and HIV status was obtained from medical records. Data capturing and descriptive statistics were done using Microsoft Excel and comparative analytical statistics were performed with the Statistical Package for the Social Sciences (SPSS), version 12.0.

RESULTS: The study demonstrated a high prevalence (69%) of infants born with a birth weight <3rd percentile. In the sample, 81% of the mothers were aged 17-34 years and most (93%) had their children 18 months or longer apart. Malnutrition prevalence was moderate. In 58% of the mothers the BMI was normal (18.5-24.9 kg/m²) and in 47% the upper arm muscle area (UAMA) was between the 10th-85th percentile. Grade III overweight occurred in 3% and TSF ≤5th percentile occurred in 35% of the mothers. About half (51%) of the mothers in the sample population had hypertension during the second trimester of pregnancy. Smoking and alcohol use during pregnancy was rare (1% and 6% respectively) and the prevalence of HIV infection in the mothers was 26%. The prevalence (16%) of Grade II overweight among the mothers of symmetric growth-restricted (SGR) infants was higher than among the mothers of
asymmetric growth-restricted (AGR) infants (7%). Of the hypertensive mothers, 55% had infants with SGR compared to 45% with AGR (p=0.47). Although rare, smoking occurred only in mothers with AGR infants (3%). No significant differences were found between the smoking and non-smoking group (p=0.21). Although the use of alcohol was more prevalent at 6% in mothers with SGA infants and 7% in mothers with AGR infants, no significant associations were found (p=0.95). Although not significant (p=0.76), there was a higher prevalence of HIV infection in mothers with SGR infants at 29%, compared to 23% of mothers of AGR infants.

CONCLUSION: Although further studies are needed before intervention strategies can be planned and implemented, the findings of this study suggest that apart from the usual factors (maternal age and nutritional status, smoking and alcohol use during pregnancy and birth spacing) that may influence intra-uterine growth, hypertension may contribute greatly to IUGR in this study population.
INLEIDING: Die doel van die studie was om die voorkoms van sekere risikofaktore, wat bekend is daarvoor dat dit kan bydra tot intra-uteriene groeivertraging (IUGV), te bepaal in vroue wat prematuur geboorte gegee het aan groeivertraagde babas in ‘n groot streekshospitaal (Kalafong), in die Gauteng provinsie van Suid Afrika en om die moontlike verband tussen die voorkoms van verskeie risikofaktore en die graad van groeivertraging in die babas te ondersoek.

METODE: Die studie was ontwerp as ‘n deursnit, beskrywend en waarnemende studie ontwerp. Die steekproef bestaan uit enkelgebore, groeivertraagde, premature babas (n=80) sonder enige kongenitale afwykings en hul moeders (n=80). Antropometriese data [liggaamsgewig, lengte, bo-arm omtrek (BAO) en triseps velvou dikte (TVD)] is drie tot vier dae post-partum by die moeders ingesamel. Die geboortemassas van die babas is by geboorte gemeet terwyl die lengtes en skedelomtrekke binne twee dae post-partum gemeet is. Addisionele inligting soos geboortespasiëring, ouderdom van die moeder, rookgewoontes en alkohol gebruik tydens swangerskap, was met behulp van ‘n persoonlike onderhoud verkry, terwyl bloeddrukdata en MIV status uit die hospitaallêer verkry is. Microsoft Excel is gebruik om die data te dokumenteer en beskrywende statistiek te bereken. Die Statistical Package for Social Sciences (SPSS) program, weergawe 12.0, is gebruik vir statistiese ontleiding.

RESULTATE: Die studie het ‘n hoë prevalensie (69%) van babas met ‘n geboortemassa <3de persentiel getoon. In die steekproef was 81% van die moeders tussen 17-34 jaar oud en die meeste (93%) het hul kinders 18 maande en langer uitmekaar gehad. Wanvoeding voorkoms was matig. In 58% van moeders was die liggaamsmassa indeks (LMI) normaal (18.5-24.9 kg/m²) en in 47% was die bo-arm spierarea (BASA) tussen die 10de en 85ste persentiele. Graad III oorgewig het in 3% van die moeders voorgekom en in 35% het die TVD ≤5de persentiel geval. Bykans die helfte van die moeders (51%) was hipertensief tydens die tweede trimester. Tabakrook en alkoholgebruik tydens swangerskap was raar (1% en 6% onderskeidelik) en die voorkoms van MIV infeksie was 26%. Teen 16% het Graad II oorgewig ‘n hoër voorkoms getoon in die moeders van simmetries groeivetraagde
SGV) babas teenoor slegs 7% in die moeders van assimmetries groeivertragde (AGV) babas. In die hipertensiewe moeders, het 55% SGV- en 45% AGV babas (p=0.47) gehad. Alhoewel skaars, het die rookgewoonte slegs voorgekom onder die moeders met AGV babas (3%). Geen betekenisvolle verskille is tussen die rokende en nie-rokende groepe aangetoon nie (p=0.21). Die gebruik van alkohol was meer algemeen in die moeders van beide SGV- (6%) en AGV (7%) babas, maar geen betekenisvolle verbande is gevind nie (p=0.96). Alhoewel nie betekenisvol nie (p=0.76), het MIV infeksie, meer voorgekom onder moeders van SGV- as AGV babas (29% teenoor 23%).

GEVOLGTREKKING: Alhoewel verdere navorsing nodig is voordat intervensiestrategieë beplan en geïmplementeer kan word, dui die bevindinge van hierdie studie nietemin aan dat benewens die gewoontelike risikofaktore vir IUGV (ouderdom en voedingstatus van die moeder, rook en alkohol gebruik tydens swangerskap en geboortespasieëring), hipertensie ’n groot bydra mag lewer tot IUGV in hierdie studiepopulasie.
### English abbreviations

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<td>AIDS</td>
<td>acquired immunodeficiency syndrome</td>
</tr>
<tr>
<td>AGR</td>
<td>asymmetric growth-restricted</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index</td>
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<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
</tr>
<tr>
<td>ICU</td>
<td>intensive care unit</td>
</tr>
<tr>
<td>IUGR</td>
<td>intra-uterine growth-restriction</td>
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<tr>
<td>IQ</td>
<td>intelligence quotient</td>
</tr>
<tr>
<td>LBW</td>
<td>low birth weight</td>
</tr>
<tr>
<td>LDL</td>
<td>low density lipoprotein cholesterol</td>
</tr>
<tr>
<td>MUAC</td>
<td>mid-upper arm circumference</td>
</tr>
<tr>
<td>NCRSP</td>
<td>Nutrition Collaborative Research Support Program</td>
</tr>
<tr>
<td>PI</td>
<td>ponderal index (Rohrer’s index)</td>
</tr>
<tr>
<td>SGA</td>
<td>small-for-gestational-age</td>
</tr>
<tr>
<td>SGR</td>
<td>symmetric growth-restricted</td>
</tr>
<tr>
<td>TSF</td>
<td>triceps skinfold (thickness)</td>
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UAMA : upper arm muscle area

**Afrikaanse afkortings**

AGV : asimetries groeivertraagde

BAO : bo-arm omtrek

BASA : bo-arm spierarea

IUGV : intra-uteriene groeivertraging

LMI : liggaamsmassa indeks

MIV : menslike immuniteitsgebrekvirus

SGV : simmetries groeivertraagde

TVD : triseps velvoudikte
LIST OF DEFINITIONS

Abruptio placentae
Premature separation of the placenta\textsuperscript{36}

Appropriate for gestational age (AGA)
A description of the size for gestational age on an intra-uterine growth grid of an infant whose birth weight is between the 10\textsuperscript{th} and 90\textsuperscript{th} percentile\textsuperscript{36}

Asymmetric growth restriction (AGR)
A form of growth restriction that results when there is failure to gain weight or loss of weight of the fetal trunk and limbs, while length and head circumference are relatively spared\textsuperscript{8}

Chorioamnionitis
Inflammation of the fetal membranes\textsuperscript{38}

Gestational age
The age of an infant at birth as determined by the length of the pregnancy or a clinical assessment\textsuperscript{38}

Gravida
The number of pregnancies a woman has experienced\textsuperscript{18}

Intra-uterine growth restriction (IUGR)
A fetal growth impairment resulting in a birth weight at or below the 10\textsuperscript{th} percentile for age and gender, and a fetus that has not reached its full growth potential\textsuperscript{36}

Low birth weight (LBW)
A birth weight below 2500 g\textsuperscript{36}

Multiparous
Having given birth to more than one infant\textsuperscript{18}
Necrotising enterocolitis
Acute inflammation and death of the bowel mucosa

Parity
The number of previous deliveries

Polycythemia
An increase in the total blood cell mass

Preeclampsia
Pregnancy-induced hypertension with proteinuria developing after the 20th week of gestation

Premature infant
An infant born before 37 weeks of gestation

Primiparous
One previous delivery

Small for gestational age (SGA)
Birth weight below the 10th percentile of the standard weight for gestational age

Symmetric growth restriction (SGR)
Occurs when there is early intra-uterine insult resulting in a small baby with weight, length and head circumference below the 10th percentile

Vernix caseosa
An unctuous substance composed of sebum and desquamated epithelial cells

Very low birth weight (VLBW) infants
Birth weight below 1500 g
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CHAPTER 1: INTRODUCTION AND PROBLEM STATEMENT

1.1 Introduction

Preterm delivery is the most important cause of perinatal mortality and morbidity in the developed world. The prevalence of preterm delivery in developed countries is 6-10% and although the mortality rate for very low birth weight (VLBW) infants has decreased over the past decades, there is still a high proportion of infants with neurodevelopmental abberations.\(^1,2\) In a nationwide South African survey, the low birth weight (LBW) (<2500 g) prevalence was found to be 19.6% in metropolitan areas and 16.5% in rural areas.\(^3\) Perinatal morbidity and mortality of infants are related to growth restraints in utero which present as LBW.\(^3\) The evidence that LBW infants are at risk perinatally and that they have higher rates of subnormal growth, morbidity and neurodevelopmental abberations in childhood, is well documented.\(^4,5\)

1.2 Intra-uterine growth restriction (IUGR)

Approximately 30% of LBW infants in the United States have intra-uterine growth restriction (IUGR) and are born after 37 weeks. In developing countries, approximately 70% of LBW infants have suffered IUGR.\(^6\) IUGR is not a specific disease, but a manifestation of many possible fetal and maternal disorders. Because clinical management, counselling and ultimate outcome are largely dependent on the aetiology, it is important for the clinician to ascertain the specific causes of growth failure.\(^7\)

1.3 Aetiology of intra-uterine growth restriction (IUGR)

The aetiology of preterm birth is multifactorial and involves complex interactions between fetal, placental, uterine, maternal and environmental factors. IUGR is associated with medical conditions which interfere with: circulation and placental efficiency; the development and growth of the fetus; and the general health and nutrition of the mother. IUGR may in fact be a normal fetal response to nutritional or oxygen deprivation.\(^6\)
1.4 Patterns of growth restriction

Symmetric growth restriction (SGR) is characterised by smaller dimensions in skeletal and head size as well as abdominal circumference and is considered to be indicative of an early intrinsic insult to fetal growth. SGR infants have a weight, height and head circumference that fall below the 10th percentile. Growth is symmetrically impaired because the insult happens at a time when fetal growth occurs primarily by cell division.

In contrast, asymmetric growth restriction (AGR) is the consequence of extrinsic factors, usually resulting from the inadequate availability of substrates for fetal metabolism, or placental factors in the latter stages of pregnancy. In the latter pattern, the length, musculoskeletal dimensions and head circumference are spared, and the abdominal circumference is decreased because of subnormal liver size. An essential feature of AGR is a birth weight below the 10th percentile for gestational age and a loss of subcutaneous fat. Minimal or absent vernix caeosa is characteristic and the facial appearance is one of alertness. The skin is thickened and desquamating with a parchment quality and muscle tone is increased. These factors generally present later in pregnancy at a time when fetal growth occurs primarily by an increase in cell size rather than cell number.

1.5 Prognosis

Recent retrospective studies by Baker et al have shown that adults who had been small for gestational age (SGA) infants, had elevated blood pressure; thin infants (low ponderal indices), which indicates low weight in relation to height, developed high blood pressure and non insulin dependent diabetes, while disproportionate infants, i.e. AGR infants (short in relation to head circumference) were shown to be at risk as adults for raised blood pressure, elevated serum low density lipoprotein (LDL) cholesterol, and fibrinogen levels. Infants affected by severe IUGR of any cause may fail to catch-up in growth and as a result be stunted and short in stature as adults.
1.6 Significance of the study

Due to the fact that the causes of SGR and AGR are disparate, it is possible that distinguishing between them might provide useful information for diagnostic and counselling purposes. AGR infants are likely to do fairly well if adequately fed post-natally. They do however appear to have a higher prevalence of major anomalies, such as aneuploidy (any deviation from an exact multiple of the haploid number of chromosomes, whether fewer or more) when compared to SGR infants. The symmetrically small infants appear to have been programmed early in utero, and in general do less well. Often more than one risk factor is present in women who give birth to growth restricted infants. However, the type of risk factors seem to vary in different population groups, making it worthwhile to investigate specific population / demographic groups to identify which of the known risk factors play a role in that particular group. In certain developed countries, smoking appears to play an important role in IUGR, whereas maternal malnutrition and HIV infection appear to be important contributors to IUGR in developing countries. In a South African study conducted at Tygerberg Hospital in the Western Cape province, it was found that hypertension played a significant role in the delivery of preterm very low birth weight (VLBW) (<1500 g) infants. They did not however indicate whether these infants suffered IUGR. If one or two risk factors are identified, specific attainable strategies may be developed to improve pregnancy outcomes in the particular population or demographic group. There are many risk factors for IUGR and only a few (maternal malnutrition, maternal age, maternal hypertension, maternal smoking and use of alcohol, birth spacing and HIV infection) will be investigated.

1.7 Hypothesis

In this study population, the prevalence of one risk factor is higher than any of the other risk factors, namely maternal hypertension and it leads to AGR, because the insult occurs only from the second trimester when fetal growth occurs primarily by an increase in cell size rather than cell number.
CHAPTER 2: LITERATURE REVIEW

2.1 Background

IUGR is seen worldwide and has major implications especially in the developing countries. Prevalence varies from 30-70% in the developed and developing countries respectively. IUGR has a significant impact on health expenditure, because of its effects on the newborn and its consequences later in life. It consists of a spectrum of disorders ranging from acute complications such as peri-natal asphyxia, hypoglycaemia and hypothermia to long term complication such as a sharply increased risk of cerebral palsy, cardiovascular disease and diabetes mellitus. IUGR has distinct and different mechanisms, depending on which stage it occurred at during pregnancy.

2.2 Small for gestational age infants (SGA)

Potential acute problems encountered in SGA infants include: peri-natal asphyxia, hypoglycaemia, hypothermia, pulmonary haemorrhage, meconium aspiration, necrotising enterocolitis, polycythaemia, illnesses related to congenital anomalies, syndromes or infections. Due to suppressed immune function, infections occur more readily in SGA infants.9

2.3 Symmetric growth restriction (SGR)

Conditions such as chromosomal abnormalities, teratogenic agents (e.g. alcohol), infections or severe maternal hypertension may lead to SGR.6 A head circumference below the 10th percentile at birth and an abnormal neurological examination in the newborn period are associated with poor growth and later microcephaly.9 In terms of long-term outcomes, studies have shown a broad range of outcomes ranging from normal to small decreases in IQ to a sharply increased risk of cerebral palsy. The worst outcomes have been observed in the more severely growth-restricted infants who are preterm.2,7
2.4 Asymmetric growth restriction (AGR)

Most commonly, the disorders that limit fetal metabolic substrate availability causing AGR, are maternal vascular disease (preeclampsia and chronic hypertension), decreased utero-placental perfusion, placental infarction, poor maternal nutrition, severe physical exertion late in pregnancy, smoking during pregnancy and the amniotic fluid infection syndrome. When comparing AGR infants with SGA infants, it was found by Dashe et al. that AGR infants were more likely to have major anomalies than SGR infants or appropriate for gestational age (AGA) infants. A neonatal outcome composite including one or more of respiratory distress, intraventricular haemorrhage, sepsis or neonatal death, was more frequent among AGR than SGR infants and SGR infants were not found to be at increased risk of morbidity compared with AGA infants.

2.5 Risk factors for IUGR

2.5.1 Maternal malnutrition

Maternal nutrition is highly associated with fetal growth and birth weight, especially in developing countries, where a considerable percentage of the population suffer acute or chronic malnutrition. An inadequate availability of nutrients during gestation is probably the single most important environmental factor to influence pregnancy outcome. Nutrition is the major intrauterine environmental factor that alters expression of the fetal genome and may have lifelong consequences. This phenomenon is termed “fetal programming” and it has led to the recent theory that alterations in fetal nutrition and endocrine status, may result in the developmental adaptations that permanently change the physiology, structure and metabolism of an infant. This predisposes the individual to metabolic, endocrine and cardiovascular disease in adulthood. Although physiological adjustments in nutrient utilisation and metabolism are geared toward improving the utilisation of dietary nutrients during pregnancy, the adjustments may be inadequate to meet the demands for pregnancy and lactation if the woman is in poor nutritional status at conception. An adequate supply of nutrient is required to maintain the delicate balance between the needs of the mother and those of the fetus. An inadequate supply will cause a state of
biological competition between the mother and the fetus in which the well-being of both organisms are at serious risk. The consequences of this undesirable situation on the fetus are well known, but the consequences of malnutrition on the mother are less well documented.12,13 Pre-pregnancy weight and weight gain in pregnancy can affect intrauterine growth, as maternal calorie intake and nutritional stores are the only source of fetal energy.14 In situations of marginal nourishment, there is some evidence that mothers adjust their metabolic demands, hence potentially sparing nutrients for the development of the fetus. However, where there is chronic malnutrition, the limits of adaptation might be exceeded and fetal growth might be restricted.4 Inadequate protein and energy intake may be common among some poorer mothers in developing counties and could contribute to fetal growth restriction.4 Fetal growth seems most vulnerable to maternal dietary deficiencies of nutrients such as protein and micronutrients, during the peri-implantation period and the period of rapid placental development.13 Life-long undernutrition of the mother, extended into pregnancy, may be more serious for the baby than an acute nutritional disturbance during pregnancy in the previously well-nourished mother. Where maternal malnutrition is rare, other nutritional and non-nutritional factors, discussed below, may influence the infant’s size at birth.12 Malnutrition reduces placental-fetal blood flow and stunts fetal growth. Impaired placental syntheses of nitric oxide (NO), which is a major vasodilator and angio-genesis factor, and polyamins (key regulators of DNA and protein synthesis), may provide an explanation for poor IUG in response to the two extremes of nutritional problems with the same pregnancy outcome.11 There is growing evidence that maternal nutritional status can alter the stable alterations of gene expression of the fetal genome, through DNA methylation and histone modifications. This may provide a molecular mechanism for the impact of maternal nutrition on fetal programming and genomic imprinting.11

2.5.2 Maternal birth weight

There is a positive association between the mother’s birth weight and the birth weight of her offspring. Women born small are on average smaller in adult life than those with higher birth weights and they have significantly reduced uterine size when compared with girls with appropriate birth weights. This could explain the maternal birth weight-offspring birth weight association.15
2.5.3 Maternal age

Women younger than 16 years of age, primiparous women older than 35 years and gravida women older than 40 years, are reported to be at increased risk of delivering IUGR infants. Young girls who conceive within 2 years of menarche, and who consequently may enter pregnancy with low nutrient reserves due to the recent use of nutrients for their own growth, are at risk of having insufficient nutrient stores to meet the demands of pregnancy and the growth of the fetus.

2.5.4 Maternal hypertension

2.5.4.1 Pregnancy-induced hypertension and preeclampsia

Pregnancy-induced hypertension is probably the best described contributor to IUGR in developed countries. It is estimated that hypertension contributes up to one third of all cases of fetal growth restriction. Pregnancy-induced hypertension, particularly if associated with proteinuria and/or preeclampsia, entails a greater risk of IUGR. A longer duration of hypertension results in a higher degree of IUGR. In a South African study, it was found that hypertension contributed to 44.7% of preterm deliveries of very low birth weight (VLBW) infants at Tygerberg Hospital in the Western Cape province, although they did not indicate whether these infants were growth-restricted.

2.5.4.2 Calcium and preeclampsia

Several recent studies have linked hypertension and preeclampsia to hypocalcaemia, but the specific role of calcium in the development of hypertension during pregnancy is not clear. An increased prevalence of hypertension during pregnancy has been reported in parts of the world where dietary intake of calcium is low and conversely, in areas with high dietary calcium intakes, the incidence of hypertension is low. There is mounting evidence that 1.0 to 2.0 g of supplemental calcium per day will reduce the incidence of preeclampsia, especially in patients who consume 600 mg or less calcium in their diet. Calcium supplementation also may reduce the incidence of preterm labour in some high-risk populations. In a systematic review of
randomised trials, it appeared that women at high risk of gestational hypertension and those with a low calcium intake stood to benefit from calcium supplementation during pregnancy.\textsuperscript{15}

\subsection*{2.5.4.3 Role of magnesium in preeclampsia}

Magnesium deficiency in women often accompanies SGA and it has been shown to cause umbilical arterial spasm, suggesting the possibility of a causal association with SGA.\textsuperscript{19}

\subsection*{2.5.4.4 Low-dose aspirin and preeclampsia}

A meta-analysis of six early clinical trials indicates that prophylaxis with low-dose aspirin prevents 65\% of clinical preeclampsia while causing no apparent harm to the mother or her fetus. Particularly encouraging is the fact that low-dose aspirin appears to be more effective in preventing the more severe proteinuric forms of pregnancy-induced hypertension and in reducing the incidence and severity of IUGR. In a systemic review and meta-analysis by Ruano \textit{et al}\textsuperscript{20} low-dose aspirin had no statistically significant effect on the incidence of preeclampsia in the low risk group overall, but it seemed to have a small beneficial effect in the high risk group. It was therefore concluded that low-dose aspirin was mildly beneficial in terms of reducing the incidence of preeclampsia in women at risk of developing preeclampsia.\textsuperscript{8}

\subsection*{2.5.4.5 Obesity and preeclampsia}

Obesity is probably the most common cause of insulin resistance and it is a definite risk factor for developing pregnancy-induced hypertension as well as preeclampsia. It was found in a study by Stone \textit{et al}\textsuperscript{21} that the only risk factors associated with the development of severe preeclampsia were severe obesity in all patients and a history of preeclampsia in multiparous patients. Although severe obesity may be associated with preeclampsia due to the confounding presence of chronic hypertension, patients with chronic hypertension were excluded in the study. This supports the concept that high BMI is an independent risk factor for severe preeclampsia.\textsuperscript{21}
2.5.4.6 Vitamin C and vitamin E in the prevention of preeclampsia

In a randomised, placebo controlled trial, by Poston et al\textsuperscript{22} it was found that a supplement of 1000 mg vitamin C and 400IU vitamin E during pregnancy in the study group, did not prevent preeclampsia, more LBW babies were born to mothers who were supplemented and IUGR prevalence was the same in the study and control groups. They concluded that supplementation of these amounts of vitamins during pregnancy, was contra-indicated.\textsuperscript{22}

2.5.4.7 Folic acid, hyperhomocysteinemia and preeclampsia

Woman with preeclampsia tend to experience many of the same clinical features, such as insulin resistance and atherosclerotic changes in blood vessels, as do women at risk of heart disease. High serum levels of homocysteine are related to these same conditions, giving rise to the theory that folic acid deficiency and hypercysteinemia may be related to preeclampsia.\textsuperscript{19} Women with homocysteinemia are over four times more likely to have preeclampsia or eclampsia than are women with low homocystein levels. Although it is not known whether adequate folic acid intake will reduce preeclampsia and its symptoms, it does appear to normalize plasma homocystein levels in pregnant women with preeclampsia.\textsuperscript{19} There is evidence that maternal periconceptional folate status is important for the closure of the neural tube and supplementation during pregnancy is recommended worldwide.\textsuperscript{15}

2.5.4.8 Omega (ω)-3 fatty acids and the risk of preeclampsia

Only a few trials of the effectiveness of ω-3 fatty acid supplements or fish consumption in the prevention of preeclampsia have been reported. It is speculated that prostacyclin levels would be increased while thromboxane levels would be decreased by these fatty acids and that vasoconstriction would be lowered as a result. Results of these trials are however mixed, but it appears that ω-3 fatty acids may increase birth weight and gestational age at delivery somewhat. It may however not affect the occurrence of preeclampsia.\textsuperscript{19}
2.5.4.9 Ethnicity-related differences in prevalence of hypertension in South Africa

Charlton et al\textsuperscript{23}, conducted studies in Johannesburg and Cape Town to determine an association between blood pressure and sodium, potassium and calcium excretion in South African subjects. From their findings, they suggested that there was diminished activity of the sodium-potassium ATPase pump in Black compared to White subjects with hypertension. They found urinary Ca excretion in White normotensive and hypertensive participants to be almost double that of Black participants. In Black and Coloured participants, a higher proportion of hypertensives, compared to normotensives, had a low renin status. They concluded that dietary differences together with a possible predisposition to a low rennin status in Black and Coloured adults, may contribute to ethnic-related differences in blood pressure.\textsuperscript{23}

2.5.5 Maternal smoking

Environmental factors such as smoking and poor socioeconomic circumstances interact and contribute to increased delivery of infants before 32 weeks of gestation.\textsuperscript{2} The maternal behaviour which most affects fetal growth is smoking, including passive smoking.\textsuperscript{16} The mechanisms through which cigarette smoking may affect birth weight include: reduced expansion of plasma volume, increased maternal plasma carbon monoxide and consequently increased fetal blood carbon monoxide, increased maternal blood viscosity and consequentially, increased fetal blood viscosity.\textsuperscript{17,19} It was shown that there is an association between reduced birth weight and cigarette smoking which is dose-related, i.e. a function of the number of cigarettes smoked by the mother.\textsuperscript{16} Women who stopped smoking before the 16\textsuperscript{th} week of gestation had babies with similar birth weight patterns as non-smokers. Multi-variant analyses have shown smoking to be independently associated with incidence of IUGR.\textsuperscript{16} Birth weight may be decreased by 135-300 g if the mother smokes during pregnancy.\textsuperscript{7} The older the mother, the stronger the effect of smoking on the rate of IUGR.\textsuperscript{20} The male fetus seems to be influenced more by smoking than the female fetus and the association of smoking and lower birth weight seems to be independent of maternal weight or nutrient intake.\textsuperscript{15} Smoking during pregnancy may contribute to AGR.\textsuperscript{24} Since passive smoking reduces birth weight and since smoking mothers frequently are
married to smoking husbands, this is a truly familial risk factor, even when the mother stops smoking during pregnancy.\textsuperscript{16} Smokers also tend to drink more alcohol than non-smokers.\textsuperscript{19} Evidence from a meta-analysis of randomised controlled trials shows that antenatal smoking cessation programmes can lower the incidence of preterm births.\textsuperscript{2}

\section*{2.5.6 Maternal use of alcohol}

Use of alcohol during pregnancy is associated with an increased rate of spontaneous abortion, abruptio placentae and LBW. Some evidence suggests a relationship between maternal alcohol use and the size of the offspring\textsuperscript{25} and mental impairment. Intra-uterine alcohol exposure is an important cause of microcephaly, which results in long-term growth failure in addition to substantial neuro-developmental delay. Prospective studies have shown that as maternal alcohol consumption increases, the incidence of births of IUGR infants increases.\textsuperscript{25} Even moderate alcohol consumption during pregnancy clearly has a negative effect on fetal birth weight.\textsuperscript{16} A growth-restricting effect on the fetus was usually found at a much lower level of alcohol consumption than that required to produce fetal alcohol syndrome. Owing to the different tolerance levels of individuals for alcohol, the question of how much moderate drinking is safe during pregnancy, has not been answered. Health care providers are therefore advised to promote abstinence from alcohol among pregnant women.\textsuperscript{26}

\section*{2.5.7 Birth spacing}

Women with short inter-pregnancy intervals are at increased risk for delivering pre-term, LBW or SGA infants. In the United States, women with inter-pregnancy intervals of <8 months were 14-47\% more likely to have very premature and moderately premature infants than women with intervals of 18-59 months. Similar results were found in other studies.\textsuperscript{13,14} The risk of LBW or pre-term birth among women with early or closely spaced pregnancies in the United States is at least 50\% greater than that of adult women with an inter-pregnancy interval of 18-23 months.\textsuperscript{14} An adequate supply of nutrients is probably the single most important environmental factor affecting pregnancy outcome and women with closely spaced pregnancies are at increased risk of entering a reproductive cycle with reduced reserves.\textsuperscript{13,14} Maternal
nutrient depletion may contribute to the increased incidence of pre-term births and fetal growth restriction among these women as well as the increased risk of maternal mortality and morbidity. Poor iron and folic acid status has been linked to pre-term births and fetal growth restriction. Supplementation with food and micronutrients during the inter-pregnancy period may improve pregnancy outcomes.

2.5.8 Parity

There may be an association between parity and birth weight. Primigravidae are more likely to give birth to SGA infants than multiparous women, however Carr-Hill et al concluded that the increase in birth weight from one child to the next was more closely related to maternal weight before each successive pregnancy than to parity.

2.5.8.1 Multiple pregnancy

About a third of multiple infant pregnancies deliver preterm infants showing IUGR when compared with singleton infants. Monozygotic twins tend to be more growth restricted than dizygotic twins and a similar association has been reported in mono-amniotic twins.

2.5.9 Altitude

With increasing height above sea level, the atmospheric pressure is reduced and with it the partial pressure of oxygen is decreased. Sabrevilla et al showed a marked reduction in birth weight in infants born at extremely high altitudes and McCullough et al found a greater proportion of infants with IUGR among those born at high altitude in the Rocky Mountains than those born in Denver. It has been shown by Gibson et al that there is an inverse relationship between mean birth weight and maternal haemoglobin levels in pregnancy. The high haemoglobin levels were associated with low increases in plasma volume and this may be the real reason for the negative association between altitude and fetal growth.
2.5.10 HIV infection

There are discrepancies between studies in developed countries, which fail to show effects of HIV on pregnancy complications and outcome, and studies from Africa, which generally do. Similar discrepancies are found with regard to birth weight outcomes in HIV infected women. Several studies in Africa report a decrease in birth weight in pregnancies where the mother is HIV-infected. There is evidence that a decrease in fetal size at birth is related to the stage of maternal HIV disease. Significantly reduced birth weight, length and head circumference were also found in infants born to women with AIDS when compared with HIV-infected women who had not progressed to AIDS.

2.5.11 Other factors

Other factors which could contribute to IUGR include: (1) fetal factors such as chromosomal abnormalities, multifactorial congenital malformations, multiple gestations (twins) and infections; (2) placental factors like small placenta, circumvallate placenta and chorioangioma and (3) maternal factors like renal disease, vascular disease, thrombophilic disorders, toxaemia, chronic illness and sickle cell anaemia.

2.5.12 Interaction of factors

The pathophysiology of fetal growth restriction involves the fetus, the placenta, the mother, and a permutation of combinations of the three. Interactions among maternal nutrition, placental dysfunction and hormonal regulation have been recognised. Since restricted fetal growth is a description rather than a diagnosis, a single pathology is unlikely.

2.5.13 Long-term consequences of low birth weight (LBW)

Adults exposed in utero to the Dutch famine in the third trimester of pregnancy, had poorer glucose tolerance and slightly higher mean systolic blood pressures, than an unexposed group, but the latter difference was not statistically significant. In a study
done by Campbell et al\textsuperscript{15} on the effects of maternal diet on later blood pressure, it was found that if the maternal protein intake was above 50g per day, the systolic blood pressure decreased with increasing percentage of energy intake derived from carbohydrates. If the protein intake was lower, systolic pressure increased with increasing percentage of energy intake derived from carbohydrates.\textsuperscript{15} It was found in autopsies of children who died before the age of 13 years, that children with lower birth weights had faster aortic fatty streak lesion progression when compared to children with normal birth weights.\textsuperscript{15} Reduced fetal growth has also been associated with differences in body composition in adult life that may predispose to cardiovascular disease and diabetes.\textsuperscript{11} The authors found that adult men between the ages of 64 and 72 years with a history of LBW had a higher percentage body fat and fat mass, a lower percentage fat-free soft tissue, a lower muscle-to-fat ratio and a higher trunk-to-limb fat ratio, when compared to men of the same age, who were born with a birthweight above 4.23 kg.\textsuperscript{10} A very large study conducted by Strauss\textsuperscript{15} showed that subjects born SGA from the 1970 British birth cohort had significant deficits in academic achievement up to the age of 16 years, and at 26 years they were less likely to have professional or managerial jobs than those born of appropriate size. These differences remained after adjustment for social, demographic, and other fetal or neonatal factors.\textsuperscript{15} In a study conducted by Mittendorfer-Rutz et al\textsuperscript{28} it was found that individuals of short birth length, adjusted for gestational age, born fourth or more in birth order, born to mothers with a low educational level and those whose mothers were aged 19 or younger at the time of delivery, had a raised risk of attempted suicide. The most significant predictor of suicide was LBW, adjusted for gestational age and teenage motherhood.\textsuperscript{28}

2.6 Assessment of nutritional status

2.6.1 Assessment of nutritional status of the infant

2.6.1.1 Anthropometry of the infant

Anthropometry is still the most practical method of evaluating/assessing maternal and neonatal nutritional status. It is simple, reliable and inexpensive, and is easily applied at the primary care level by community health workers.\textsuperscript{9}
2.6.1.2 Estimation of gestational age

The estimation of gestational age is crucial, as anthropometric data in infants is age-dependent and therefore meaningless unless interpreted in terms of gestational age. Currently, early ultrasound evaluation of the fetus is considered the gold standard for evaluating gestational age before birth. However, without early sonar, other methods are employed to determine gestational age. The postpartum assessment of gestational age by neurological criteria only was originally described by French doctors and simplified by Amiel Tison. The examination involves the assessment of posture, passive and active tone, reflexes and righting reactions. Dubowitz described and developed a scoring system that combines physical criteria with the neurological assessment. The gestational age of an infant is calculated by adding the scores of both examinations. The disadvantage of the Dubowitz scoring system is that it involves the assessment of eleven physical criteria and ten neurological findings, which is time consuming. Although the physical criteria allow clear distinction of infants with varying gestational ages greater than 34 weeks, the neurological criteria are essential to differentiate infants between 26 and 34 weeks, as physical changes are less evident. Ballard and her colleagues abbreviated the Dubowitz scoring system to include only six neurological and seven physical criteria. The accuracy and reliability of the abbreviated Ballard scoring system have been confirmed and the assessment can be performed in a significantly shorter period of time to facilitate accurate gestational age assessment, particularly in sick infants. Regardless of the method used, the assessment of gestational age using neurological and physical criteria is accurate to about a two week range.

2.6.1.3 Growth charts

The Babson 1976 “fetal-infant growth graph” for preterm infants is commonly used in neonatal intensive care units (ICUs). Its limits include the small sample size which provides low confidence in the extremes of the data, the 26 weeks start and the 500 g graph increments. An updated graph was published in 2003. The new chart allows a comparison for preterm infants as young as 22 weeks of gestation, first with intrauterine and then with post term references and it may replace the one developed by Babson and Benda in 1976. The 10th percentile of this chart is accurate to the
source data prior to 36 weeks and it could therefore be used for the assessment of size for gestational age for infants smaller than 2 kg. There were agreements and differences between this newer data with that of Babson and Benda. The agreements suggest that the Babson and Benda curves had fairly accurate depictions of infant size, which may account for the continued popularity of this chart. The differences may reflect the small sample size of the early chart and the use of only maternal dates for the gestational age. The larger sample sizes used in the development of the new chart, may provide better confidence in the extreme percentiles.29

2.6.1.4 Neonatal weight for gestational age

During intrauterine life, serial measurements of the fetus are feasible only with ultrasound and have not proven to be sufficiently valid or precise to serve as a standard for assessing fetal growth. Therefore weight for gestational age at birth is often used to categorise an infant for having experienced normal, subnormal (SGA) or IUGR or supranormal growth in utero. SGA and IUGR are often used synonymously, as it is very difficult in individual cases to determine whether or not birth weight is the result of true in utero growth restriction. In fact, the higher the SGA degree, the greater the likelihood that SGA is the result of IUGR.12

2.6.1.5 Ponderal index

Rohrer’s ponderal index \[ \text{PI} = \text{birth weight (g)} \times 100 / \text{height (m)}^3 \] is another parameter that has been proposed to describe abnormal growth. Infants with a low PI are classified as disproportional or AGR.9 The advantage of the PI in full-term infants greater than 48.5 cm in length, is that race, gender and gestational age do not affect the ratio. For term infants, a PI above 2.32 is acceptable. In pre-term infants it is affected by gestational age, and related variations in soft tissue mass, especially fat.17 Many investigators have reported higher neonatal mortality rates among disproportional IUGR infants, but better early catch-up growth and better prognosis for long-term growth and development than for proportional IUGR infants.12
2.6.2 Anthropometry of the mothers

2.6.2.1 Maternal body mass index (BMI)

Because initial maternal weight loss immediately after delivery is essentially uniform regardless of antepartum weight, gestational weight gain or infant birth weight, the use of postpartum BMI provides an accurate reflection of the total maternal ‘energy pool’. It was found during the Nutrition Collaborative Research Support Program (NCRSP) that maternal BMI early in pregnancy was little different from postpartum BMI. The NCRSP was a cross-country (Egypt, Mexico and Kenya) research project, investigating relationships between marginal malnutrition and human function, including pregnancy outcome. They found low maternal BMI in early pregnancy to be associated with lower birth weight in all three projects. Early pregnancy BMIs of the women in the study were unavailable and therefore post-partum BMIs were chosen as it were in the NCRSP research project.

2.6.2.2 Maternal mid-upper arm circumference and triceps skinfold measures

Maternal mid-upper arm circumference (MUAC) and triceps skinfold (TSF) thickness are anthropometric measurements that have been used in epidemiological studies. Data on the validity of MUAC to predict LBW babies were obtained in a study by Lechtig and they set the lower limit for MUAC at 23.5 cm. Lechtig found a correlation between maternal MUAC and birth weight which, when compared to other predictive factors such as weight gain during pregnancy and uterine height, arm circumference had a similar predictive value even if gestational age is not known. MUAC is therefore an ideal measure at community level in resource poor areas. Mid-arm muscle area (UAMA), which can be calculated from the MUAC and TSF measurements as follows: \( UAMA = MUAC - \left( TSF \times \pi \right)^2 / 4\pi \) and reflects the lean body mass. Body fat stores increase the most between the 10th and 20th week of pregnancy or before the fetal energy requirements are highest. The levels of stored fat tend to decrease before the end of the pregnancy, in the third trimester due to continual withdrawal of nutrients by the fetus. There is an earlier switch from predominantly carbohydrate to predominantly fat utilisation, a phenomenon termed “accelerated starvation.” To satisfy this need maternal hepatic glucose production
increases, which depletes glycogen stores. The fetus also withdraws amino acids from the maternal circulation, resulting in low levels of blood amino acids, thereby limiting the potential for hepatic gluconeogenesis from amino acids and increasing breakdown of fats. The increased levels of free fatty acids inhibit the uptake and oxidation of glucose, preserving glucose for the fetus and the central nervous system.\textsuperscript{19}

2.7 Lactase deficiency in the South African Black population

A high prevalence (>60\%) of primary adult lactase deficiency was found in the majority of the world’s populations. The occurrence is generally high in the Black populations of Africa. Breath hydrogen analysis was carried out by Segal \textit{et al}\textsuperscript{33} to determine the prevalence of lactase deficiency in different tribes of the South African population. Lactase deficiency was common (78\%), despite the fact that the largest tribes, namely the Zulu and Xhosa, are cattle herders and milk drinkers. This apparent anomaly is due to the consumption of a traditional fermented buttermilk, which has a low lactose content, instead of fresh milk. The most important reason for lactase deficiency in the South African Black population is that they originated in the West and Central African zones of non-milking and took up dairying and milk use fairly recently. They therefore have not had enough time for genetic selection for lactase deficiency through life.\textsuperscript{33}

2.8 Concluding remarks

Fetal growth restriction is the consequence of complex pathology. Often more than one risk factor is present in women who give birth to growth restricted infants. However, the type of risk factors seems to differ in different population groups.
CHAPTER 3: METHODOLOGY

3.1 Study Design and Ethics

3.1.1 Study type

The study was cross-sectional, observational and descriptive in nature.

3.1.2 Ethical considerations

The research protocol (Appendix A) for this study was submitted to and approved (Ref No N05/02/019) by the Human Research Committee of the Faculty of Health Sciences of the University of Stellenbosch, Tygerberg, South Africa, and the Ethics Committee of the Health Science Faculty of the University of Pretoria, South Africa. Confidentiality was ensured throughout the study process.

All costs incurred in the execution of the study were covered by the researcher. This did not include incentives for subjects or remuneration for the researcher or staff involved in the study.

3.2 Sampling and Induction

3.2.1 Sampling method

The total number of live births of preterm infants during September 2005 to the first week in January 2006 at Kalafong Hospital was 114. Each of these live preterm infants born was weighed initially in the neonatal ICU upon arrival. All singleton infants born prematurely were selected from the 114 and screened for possible inclusion into the study. Birth weight and gestational age were used to determine whether they were growth-restricted or appropriate for age. A sample of 80 mothers, with premature infants found to be growth-restricted, was recruited without exception, unless the mother or infant exhibited characteristics stipulated in the exclusion criteria.
3.2.2 Selection criteria

3.2.2.1 Inclusion criteria

The following individuals qualified for inclusion in the study:

- Women born in South Africa
- of any race,
- of any age, religion, language or ethnicity (women under 18 years required consent from a parent),
- who gave birth to singleton, premature (before 37 weeks of estimated gestational age\(^2\)), growth-restricted infants (birth weight <10\(^{th}\) percentile for gestational age\(^6\)),
- at Kalafong Hospital, Tswane, Gauteng and
- who provided signed informed consent to participate in the study and agreeing to all procedures.

3.2.2.2 Exclusion criteria

The following individuals were excluded from the study:

- Women with proven congenital abnormalities as described by a genetics consultant from the University of Pretoria
- Women with terminal illness other than AIDS, e.g., cancer
- Women with diagnosed chorioamnionitis, Rubella, toxaemia and sexually transmitted diseases, not including HIV
- Women with chronic diseases like vascular disease, sickle cell anaemia, renal disease, diabetes mellitus and thrombolytic disorders
- Women who gave birth to infants with proven genetic disorders and dysmorphism as assessed by the genetics consultant)
3.2.3 Written consent

Each participant was provided with an informed consent and information form. The form was administered by the researcher and where there was a problem with understanding, a translator was employed to clarify the information. The translator usually assists the registrars who conduct research in the paediatric ICU. The standard informed consent form used by the Faculty of Health Sciences of the University of Stellenbosch was adapted for this study and was available in English, Sotho and Zulu (Addenda 6, 7 and 8 respectively).

3.3 Data Collection

The researcher visited the paediatric ICU and maternity unit at Kalafong Hospital daily during week days (from the first week in September 2005 to the first week in January 2006), to assess the nutritional status of all singleton infants born prematurely. Infants born during weekend days were screened on Mondays. They were weighed by the registrar on call as they entered the neonatal ICU, as is the procedure during weekdays. For the purpose of the study, the researcher weighed every potential infant during weekdays to verify accuracy of the first measurement done by the registrar. The same scale is used by the researcher and all registrars. For the infants who were identified as growth-restricted by the researcher, through anthropometric evaluation, the mothers were approached immediately to determine whether she and the infant qualified for inclusion.

3.3.1 Anthropometric data of infants

3.3.1.1 Infant weight

The researcher did all the measurements on the infants entering the unit from Mondays to Fridays. For infants born on weekend days, weight was recorded routinely by the registrar of Paediatrics who attended the birth. The same SECA 346 mobile electronic baby scale (with a gradation of 10 g) is used by all doctors and dieticians and the infants were always weighed naked. The scale is calibrated annually and was last calibrated in February 2005. The study was conducted 6 months later.
The scale was placed on a flat, hard surface that allowed it to sit securely without rocking or tipping. Infants were weighed on a pan-type scale that is accurate to within 10g. Any cushion or towel used in the pan was either in place when the zero adjustments were made on the scale or its weight (independently measured) was subtracted from the infant’s weight.22 What ever practice was used, it was uniformly followed and noted in the infant’s file. Infants were set down supinely in the middle of the pan. The average of two measurements was recorded numerically to the nearest gram. If measurements appeared unusual, they were repeated.25 This is the standardised technique used in research.32

### 3.3.1.2 Infant length

Length and head circumference were recorded by the researcher, each weekday morning and as the length and head circumference will not change significantly within 72 hours of birth, infants born on weekend days were measured on Monday mornings using the same measuring board (Nestlé) each time for length and the same non-elastic plastic measuring tape for the head circumference. Recumbent length was obtained with the infant lying down on its back. The measuring board consists of a perspex headboard and moveable footboard that are perpendicular to the backboard. The board was placed on a flat, hard surface and measurements were taken to the nearest millimetre. Reliability was increased by having an assistant hold the infant’s head, while the researcher held the feet and ensured that the legs were fully extended and the heels were at a 90 degrees angle to the measuring mat.25 This is the standardised technique described in the literature.32

### 3.3.1.3 Infant head circumference

The head circumference was measured while the infant was lying on its back. A non-elastic measuring tape was employed, and measurements were done twice. The average of the two measurements was calculated and recorded. The measurement was taken just above the eyebrows, above the ears and around the back of the head, so that the maximum circumference was measured.32 The tape was kept in the same plane (Frankfurt plane) on both sides of the head and pulled snug to ensure accurate readings as is prescribed by the literature.32 Measurements were recorded to the
nearest millimetre. This method has been standardised and used extensively in research.

3.3.1.4 Stratification

Stratification for birth weight, length and head circumference was done as follows: A - <3rd percentile (severe growth restriction); B - 3rd-10th percentile (moderate growth restriction); and C - >10th percentile (normal). Ponderal index (PI) [(weight (kg) / length (m^3))] was recorded, but not stratified. Term infants normally have a PI >2.32 kg/ m^3 and if they have lengths greater than 48.5 cm, this ratio is not affected by race, gender or gestational age. In preterm infants, it is affected by gestational age and therefore a cut-off was not used.

4.3.2 Anthropometric data of the mothers

3.3.2.1 Maternal weight

Weight was determined 3 days after delivery to ensure that most of the oedema had subsided. For the women who still had excessive oedema, 5 days were allowed before weighing. An electronic scale (SECA Viva 750 from Life Max, calibration class IV, 2005), measuring the weight to the nearest 0.1 kg, was used. Validity can potentially be influenced by the clothing worn by the subjects and was controlled for by asking the subject to remove all extra layers of clothing. To ensure privacy, all anthropometric measurements were conducted in a private room, adjacent to the ward. To control for variations during the course of the day, all subjects were weighed at more or less the same time of day, namely before breakfast. Subjects were required to void their bladders before weighing.

3.3.2.2 Maternal height

The height of the mothers was measured using a portable free standing stadiometer height stand (model HS from Scales 2000 with a range from 140-200 cm) and was recorded to the nearest 0.5 cm. BMI was determined using the weight and height measurements. BMI is the weight (kg) divided by the square of the height (m).
BMI $\leq$ 18.5 kg/m$^2$ was classified as underweight, 18.5-24.9 kg/m$^2$ was considered normal, 25-29.9 kg/m$^2$ was described as Grade I overweight, 30-39 kg/m$^2$ Grade II overweight, and $\geq$ 40 kg/m$^2$ was classified as Grade III overweight.34

3.3.2.3 Maternal triceps skinfold

The TSF measurement was performed on the posterior aspect of the dominant arm, midway between the lateral projections of the acromion process of the scapula and the inferior margin of the olecranon process of the ulna. Standard techniques were used.32 Three measurements were taken, 15 seconds apart, and the mean was recorded. Measurements were taken with Harpenden metal callipers, which exert a jaw tip pressure of 10 g/mm$^2$ throughout the calliper’s full measurement range. The caliper was calibrated in August 2004, by a reputable company (Lifemax). Readings were recorded to the nearest millimetre. Every 10th patient, starting with the first patient, were measured by a colleague and the difference between the readings of the researcher and colleague were compared to published standards (<2 mm to either side), to ensure interpersonal differences of measurements were acceptable. The same callipers were used by the colleague and measurements were done within 5 minutes of the researcher’s measurements, to standardise the instrument and time of day. The same standardised techniques were used by both the researcher and the colleague.

3.3.2.4 Maternal mid-upper arm circumference

MUAC was measured midway between the lateral projections of the acromion process of the scapula and the inferior margin of the olecranon process of the ulna. The right arm was measured using a non-elastic plastic tape measure. The circumference was measured to the nearest millimetre and repeated three times. The mean of the three measurements was calculated and recorded.32 The UAMA was calculated as described in 4.4. The UAMA was interpreted using the percentiles for UAMA from Frisancho (Addendum 3).32
3.3.3 Questionnaire

Additional information such as maternal age, birth spacing, maternal smoking, maternal use of alcohol and maternal HIV status, was gathered by personal interviews with the mothers. The data was captured on a specifically tailored form (Addendum 9). Stratification for maternal age was done as follows: A - ≤16 years; B -16-35 years; C – 35- 40 years and D- >40 years. Stratification for birth spacing was as follows: A - >18 months between pregnancies and B - <18 months between pregnancies. Where language was a barrier, the research assistant, who was also employed to explain the consent form, was used as an interpreter, even when a consent form chosen in a language other than English was chosen.

3.3.4 Medical records

3.3.4.1 Blood pressure data

Medical records were utilised to record blood pressure data from the second trimester of pregnancy. If the mean blood pressure as measured and calculated by the gynaecologist was >140/90 mmHg in a previously normotensive woman, or if proteinuria was >300 mg per 24 hours in the absence of infection, or if there was significant oedema in the presence of hypertension, the women were classified as hypertensive by the gynaecologist. This was then recorded in the patient’s file and this information was utilised by the researcher. If the hypertension was well-controlled with medication, the woman was classified as normotensive. This information was documented on the data capturing sheet (Addendum 9).

3.3.4.2 HIV status

Voluntary counselling and testing for HIV in the maternity ward is routine practice at Kalafong Hospital. Women who come to the maternity unit are given the option to test for HIV as they may then be eligible for nevirapine therapy to decrease the chances of vertical transmission of the virus from the mother to the infant. Most women give consent to testing as they want to access the anti-retroviral therapy for themselves and their infants. The researcher therefore needed only to get consent from
the mother to be able to use the results, if she had consented earlier. No new test was required. If the mother refused HIV testing the first time, the researcher still determined the other risk factors and recorded the HIV status as undetermined.

3.4 Calculation of derived parameters

Derived parameters were calculated using the following formulas:

\[
\text{Body mass index (BMI) (kg/m}^2\text{)} = \frac{\text{weight (kg)}}{\text{height (m)}^2}
\]

\[
\text{Ponderal index (PI) (kg/m}^3\text{)} = \frac{\text{weight (kg)}}{\text{length (m)}^3}
\]

\[
\text{Mid-upper arm muscle area (UAMA) (cm}^2\text{)} = \frac{[\text{MUAC} - (\text{TSF} \times \pi)]^2}{4\pi}
\]

3.5 Statistical analyses

The data was captured electronically with Microsoft Excel and controlled for accuracy of transfer with regular cross-referencing. SPSS (Statistical Package for the Social Sciences) version 12.0 (Chicago IL) was used for the analytical statistics. The t-test assessed whether the means of two groups were statistically different from each other and the Independent Sample t-test compared the means of two groups on a given variable. The Chi-Square test is a non-parametric test, used most frequently to test the statistical significance of results reported in bivariate tables. The Pearson's chi-square test is one of the most common types of chi-square significance test. It was used to test the hypothesis of no association between columns and rows in tabular data. It can be used even with nominal data. Fischer’s exact test can be used for data in a 2x2 contingency table. It is an alternative to the Chi-square test. For a 2x2 table, Fischer’s exact test is computed when a table has a cell with an expected frequency of <5.
CHAPTER 4: RESULTS

4.1 Sample Characteristics

4.1.1 Sample selection

From the 114 live preterm births, 80 subjects (mothers) were recruited in the Neonatal ICU unit of Kalafong Hospital, where their infants were admitted for medical management. Some of the other infants (n=13), not included in the study were also growth restricted, but were excluded due to factors like diabetes in the mother (n=2), twin births (n=6), triplet births (n=3) and congenital abnormalities (n=2). Of the 114 live preterm births, 21 were AGA. The 80 women selected, had given premature birth to infants with a birth weight for gestational age, below the 10th percentile as plotted on the revised Babson and Benda (2003) growth chart. All the infants were singletons and had no congenital abnormalities or dysmorphic features. The mothers were excluded if they had chorioamnionitis, Rubella, toxaemia and sexually transmitted diseases, not including HIV; as well as chronic diseases like diabetes mellitus, vascular disease, sickle cell anaemia, renal disease, and thrombolytic disorders.

4.1.2 Characteristics of the growth-restricted infants

The range for gestational age at birth of the infants in the sample was between 28 and 37 weeks. Fifty five (68.8%) of the infants had a birth weight below the 3rd percentile. Thirty nine (48.8%) of the infants had a length below the 3rd percentile, 23 (28.8%) had a length between the 3rd and 10th percentile and 26 (32.5%) had a length above the 10th percentile. Twenty of the 80 infants (25%) had a head circumference below the 3rd percentile, 34 (43.5%) fell between the 3rd and 10th percentile and the 26 remaining (32.5%) had a head circumference above the 10th percentile. This renders 49 (61.3%) of the infants SGR and 31 (38.7%) to be AGR (Figure 4.1). The mean ponderal index was 2.13 [Standard Deviation (SD) 2.02], ranging from 1.35 to 3.458 kg/m³.
4.1.3 Characteristics of the mothers

4.1.3.1 Age of mothers

The mothers’ ages ranged from 16 to 42 years. The majority of mothers (81.3%) were between the ages of 17-34 years. There was only one mother (1.3%) younger or equal to 16 years, with the remaining 17.6%, 35 years or older. When comparing the ages of mothers with SGR and AGR infants, the majority of mothers fell in the age category of 17-34 years with 77.6% of mothers having SGR infants and 87.1% of mothers having AGR infants. A higher percentage of mothers (20.4%) with SGR infants were 35 years or older, compared to 12.9% of mothers with AGR infants. In both groups there were very few mothers who were older than 40 years, 4.1% of mothers with SGR infants and 3.2% of mothers with AGR infants (Figure 4.2).

The Pearson's chi-square test was used to compare the age classification of mothers of 34 years and younger and mothers of 35 years and older. No significant difference was found between mothers with SGR and AGR infants, as far as these two age categories were concerned (p=0.389).
Figure 4.2  Age categories of mothers included in the study (n=80)
No significant difference was found when women <34 y were compared to women >34 years in SGR and AGR groups.
When comparing mean ages of women in SGR and AGR group, no significant difference was shown.

When considering the age of all mothers, a mean of 27.76 (SD 6.31) was obtained.
When using the t-test for independent samples to compare the mean age of mothers with SGR infants (27.73y; SD 6.48) to those with AGR infants (27.81y; SD 6.14), no significant difference between the two mean ages was found (p=0.961).

In conclusion it can be said that although it appears as though there were more mothers of ages 35 and higher who had SGR infants, the age differences between these two groups of mothers were too small to be significant and no conclusions could be made as far as age was concerned, except to say that the majority of all mothers in this sample were between the ages 17 and 34 years.

4.1.3.2 BMI of mothers

More than half of the mothers (57.5%) had a normal BMI classification (18.5 to 24.9 kg/m²) while 26.3% fell between 25 and 29.9 (Grade I overweight); 12.5% fell between 30 and 39 (Grade II overweight); 2 (2.5%) were grade III overweight and only 1(1.3%) was underweight (BMI <18.5). The mean BMI was
25.48 kg/m² (SD 5.30) and the BMIs ranged from 16.46-45.28 kg/m².
There were 61.3% of mothers of AGR infants and (55.1%) of mothers with SGR infants who had a normal BMI classification (18.5-24.9kg/m²) (Figure 4.3). When looking at these percentages, it seems as if there was a higher percentage (44.2%) of mothers with SGR infants, compared to 35.5% of mothers with AGR infants who were overweight (Grade I, II, III), while a higher percentage (61.3% compared to 55.1%) of mothers with AGR infants was of normal weight (BMI 18.5-24.9kg/m²).
To determine whether this difference was significant, a Pearsons chi square test was performed. The one underweight mother was excluded (to make a 2x2 table comparison possible for a chi-square test), while all overweight mothers (Grade I, II and III) were grouped together and compared to those with a normal weight. The Pearson’s chi square test however indicated that there was no significant difference between mothers with SGR and AGR infants as far as being of normal weight or being overweight (Grade I, II and III) was concerned (p=0.472).

When looking at the BMI of all mothers, an average of 25.5 kg/m² (SD 5.30) was obtained. When using the t-test for independent samples to compare the average BMI of mothers with SGR infants, mean 25.9 kg/m² (SD 5.82) with those with AGR infants, mean 24.8 kg/m² (SD 5.31), no significant difference between the two mean BMI scores was obtained (p=0.363) (Figure 4.3). In conclusion it can thus be said that the type of growth restriction in the infants could not be linked to the BMI of the mother.
Figure 4.3  BMI classification of mothers included in the study (n=80)
T-test for difference between mean BMI scores among mothers with SGR and AGR infants showed no significant difference.
No significant difference between mothers with SGR and AGR infants as far as normal weight or being overweight was concerned.

4.1.3.3 Triceps skinfold thickness of mothers

The arm anthropometry showed that 28 (35%) of the mothers had a TSF <5th percentile; 51 (63.8%) had a normal TSF thickness (5th-85th percentile) and 1 (1.3%) had an above normal measurement (>85th percentile) (Figure 4.4).

Almost two-thirds of mothers (63.8%) fell between the 5th and 85th percentile for TSF. There were a higher percentage of mothers (65.3%) with SGR infants that fell between the 5th and 85th TSF percentile, compared to 61.3% of mothers with AGR infants. When a Pearsons chi square test was performed to compare the mothers of SGR and AGR infants with regard to having a TSF between the 5th and 85th percentile or <5th percentile, the difference was not significant (p=0.626) (Figure 4.4).
One mother was excluded, because she was the only one with a TSF >85th percentile and therefore fell outside of the 2x2 table used for the chi-square test.
Figure 4.4  Triceps skinfold thickness classification of mothers included in the study (n=80)
No significant difference in TSF between mothers with SGR and AGR infants.

4.1.3.4 Mid-upper arm circumference of mothers

The mid-upper arm circumference showed 3 mothers (3.8%) to have a low (<5<sup>th</sup> percentile) circumference; 66 (82.5%) had a normal measurement (between the 5<sup>th</sup> and 85<sup>th</sup> percentile) and 11 (13.8%) had a circumference above the >85<sup>th</sup> percentile. The greater majority of mothers (82.5%) fell between the 5<sup>th</sup> and 85<sup>th</sup> percentile for MUAC, with 13.8% above the85<sup>th</sup> percentile (Figure 4.5). None of the mothers with SGR infants fell beneath the 5<sup>th</sup> percentile, with 83.7% between the 5<sup>th</sup> and 85<sup>th</sup> percentile, and 16.3% above the 85<sup>th</sup> percentile. As far as mothers with AGR infants were concerned, there were 9.7% who had a MUAC <5<sup>th</sup> percentile, 80.6% with a MUAC falling between the 5<sup>th</sup> and 85<sup>th</sup> percentile and 9.7% with a MUAC >85<sup>th</sup> percentile (Figure 4.5). When comparing the mothers of SGR and AGR infants with regard to having a normal or above normal MUAC, three mothers with a MUAC <5<sup>th</sup> percentile were excluded (they comprise a separate group which would make the use of a chi-square test impossible) and the Pearsons chi-square test showed no significant difference between the groups (p=0.498). This result should be interpreted with
caution, as some of the cell numbers were less than five. If Fischer’s exact test was used to compare the two groups of mothers (those with SGR and AGR infants) with regard to having a MUAC between the 5<sup>th</sup> and 85<sup>th</sup> percentile or >85<sup>th</sup> percentile, no significant difference was found (p=0.737).

![Figure 4.5 Mid-upper arm circumference classification of mothers included in the study (n=80)](image)

No significant difference in MUAC in mothers with SGR and AGR infants (n=3 excluded in <5<sup>th</sup> percentile group).

4.1.3.5 Upper arm muscle area (UAMA) of mothers

The derived parameter, mid-upper arm muscle area (UAMA), showed that only one (1.3%) of the women had a muscle mass < 5<sup>th</sup> percentile; 37 (46.3%) had a normal muscle mass (5<sup>th</sup>-85<sup>th</sup> percentile) and 42 (52.5%) had a UAMA >85<sup>th</sup> percentile. The majority of mothers (52.5%) fell above the 85<sup>th</sup> percentile for UAMA, with 46.3% between the 5<sup>th</sup> and 85<sup>th</sup> percentile. (Figure 4.6) There was a slight, but not significant difference between mothers with SGR and AGR infants. The majority of mothers with SGR infants fell above the 85<sup>th</sup> percentile, while the majority of mothers (54.8%) with AGR infants fell between the 5<sup>th</sup> and 85<sup>th</sup> percentile. When a Pearsons chi-square test was performed to compare the mothers with SGR and AGR infants with regard to
UAMA, 1 mother was excluded in the category <5\textsuperscript{th} percentile as a 2x2 table could then be used to calculate Pearson’s chi square. No significant difference was found (p=0.171) (Figure 4.6).

![Figure 4.6 Upper arm muscle area classification of mothers included in the study (n=80)](image)

No significant difference in UAMA in mothers with SGR and AGR infants (n=1 excluded in <5\textsuperscript{th} percentile)

### 4.1.3.6 Birth spacing

Fifty seven (71.25\%) of the multiparous women had their latest infant more than 18 months apart from their previous child, whereas 6 of the multiparous women (9.5\%), had their children within 18 months of each other. Seventeen (21.3\%) of the women, were primiparous and the other 78.8 \% had other children. In total, 7.5\% of the women in the sample had their children spaced closer together than 18 months (Figure 4.7).

Almost all (92.5\%) mothers had their children more than 18 months apart. The same pattern was evident among mothers with SGR (91.8\%) and AGR (93.5\%) infants (Figure 4.7). Fisher’s exact test was performed, as the cell numbers in the category
≤18 months, were below 5 in both groups of mothers. No statistically significant difference was found between the two groups of mothers (p=1.00). The mean period of birth spacing could not be analysed, as the exact spacing in months was not documented. The researcher only distinguished between the period ≤18 months.

4.1.3.7 Hypertension prevalence during pregnancy

Of the 80 women, 41 (51.3%) had high blood pressure from the 2nd trimester of pregnancy (>140/90 mmHg) and 39 (48.75%) were normotensive. One woman (1.3%) was normotensive due to medication. She had been hypertensive before the pregnancy. More than half of the mothers (51.3%) reported hypertension during the second trimester. There were a higher percentage of mothers (55.1%) with SGR infants with hypertension during the second trimester, compared to those with AGR infants (45.2%) (Figure 4.8).

To try and determine if there was a significant difference between the two different groups of mothers related to hypertension during the second trimester, the Pearsons

![Figure 4.7 Birth spacing in mothers included in the study (n=80)](image)
A chi-square test was used. (The one respondent that indicated that her hypertension during the second trimester was controlled with medication was excluded from the analysis to facilitate statistical analyses using a 2x2 table. It was unclear whether she had any other underlying pathology, and as a result, she represented a third group). It was found that, mothers with SGR and AGR infants did not differ significantly as far as the presence of hypertension during the second trimester of pregnancy was concerned (p=0.466).

![Figure 4.8 Prevalence of hypertension during the second trimester of pregnancy in mothers (n = 80)](image)

No significant difference in presence of hypertension in mothers with SGR and AGR infants.

**4.1.3.8 Smoking prevalence during pregnancy**

Only one (1.3%) of the women smoked during pregnancy and alcohol use during pregnancy was very low (6.3%) in this sample. Almost all mothers (98.8%) said that they did not smoke during their pregnancy. The only smoker had an AGR infant. A Pearson's chi-square test was done, although both groups of mothers had less than 5 respondents in the “Yes” category. The difference was insignificant (p=0.206). Fischer’s exact test was also used to determine the significance of the difference
between the two groups, because some cells contained less than 5 respondents (p=0.387). There was no significant difference found (Figure 4.9).

![Smoking prevalence graph]

**Figure 4.9** Prevalence of smoking during pregnancy in mothers included in the study (n=80)
No significant difference in prevalence of smoking during pregnancy between the SGR and AGR mothers.

### 4.1.3.9 Prevalence of alcohol use in the mothers during pregnancy

Almost all mothers (93.8%) said that they did not make use of alcohol during their pregnancy. Of the 12.6% who used alcohol, 6.1% has SGR infants and 6.5% had AGR infants, making the difference between the groups insignificant. Pearson’s chi square was performed to compare the difference between the prevalence of alcohol use during pregnancy in these two groups (p=0.953). Some cells contained less than 5 respondents and therefore Fischer’s exact test was performed (p=1.000). Both tests showed that there was no significant difference between the two groups (Figure 4.10).
4.10 Prevalence of alcohol use in mothers included in the study (n=80)

No significant difference in alcohol use during pregnancy between mothers with SGR and AGR infants.

4.2 HIV infection prevalence in the mothers

Most mothers (93.8%) were aware of their HIV status, with 67.5% reporting their status as negative, and 26.3% confirming it as positive; 69.4% of mothers who were HIV negative had SGR infants while 64.5% of the mothers who tested negative, had AGR infants; 28.6% of mothers with SGR infants were HIV positive while 22.6% of mother with AGR infants were HIV positive (Figure 4.11).

When excluding all respondents with an undetermined HIV status, and using a Pearsons chi square test to compare type of growth with HIV status (positive status vs. negative status), no significant difference was demonstrated between mothers with SGR infants and AGR infants as far as their HIV status was concerned. (p=0.764).
4.3 Summary of the prevalence of risk factors measured in mothers with symmetric and asymmetric growth-restricted infants

The prevalence of the risk factors for IUGR investigated in this study is summarised for mothers with SGR and AGR infants respectively (Figure 4.12).

Mothers who smoked totalled 1.3% and all of them (3.2% of total sample) had AGR infants (p=0.206). Of the 6.3% of mothers who reported alcohol use during pregnancy, 6.5% had AGR infants and 6.1% had SGR infants (p=0.953). Most mothers (92.5%) had their infants spaced more than 18 months apart, but of the 7.7% who had closely spaced pregnancies, 6.5% had AGR infants and 8.2% had SGR infants. Only one woman (1.3% of the total) was younger or equal to 16 and she had a SGR infant (2%). In the total sample, there were 17.6% of women who were older than 35 years and 12.9% of them had AGR infants and 20.4% had SGR infants. In total, the women with the AGR infants who were younger or equal to 16 and older than 34, were 22.4% (p=0.389). The MUAC was normal (between the 5th and 85th percentile) in 82.5% of the mothers and 9.7% of the mothers who had a low MUAC (<5th percentile) had AGR infants. Of the 13.8% of mothers who had a high MUAC...
(>85th percentile), 9.7% had AGR infants and 16.3% had SGR infants. The women with high or low MUAC, were therefore 19.4% in AGR infants and 16.3% in SGR infants (p=0.498). Of the 26.3% of mothers who tested positive for HIV, 22.6% of the mothers had AGR infants and 28.6% of the mothers had SGR infants (p=0.764). Only 1.3% of the women had a low (<18.5) BMI and all of them (3%), had AGR infants. Of the women with BMIs above 24.9 kg/m², 35.5% had AGR infants and 44.8% had SGR infants. The total of mothers with BMIs above the 85th percentile or below the 5th percentile in the AGR infant group was 38.7% and in the SGR infant group was 44.8% (p=0.472). A high percentage of mothers (35%) had a low (<5th percentile) TSF and 38.7% of them had AGR infants and 32.7% had SGR infants. The mothers who had above average TSF, totalled 1.3%, and all of them (2%) had SGR infants. In total, the women with above or below average TSF in the AGR infant group totalled 38.7% and 34.7% were in the SGR infant group (p=0.626). Only 1.3% of the mothers had a low (<5th percentile) UAMA and all of them (3.2%) had AGR infants. In the AGR group, 45.1% had an UAMA > 85th percentile or below the 5th percentile and in the SGR group 59.2% had an UAMA > 85th percentile or below the 5th percentile (p=0.171). The prevalence of hypertension was high in this study population (51.3%) and 45.2% of them had AGR infants and 55.1% of them had SGR infants (p=0.466).
Figure 4.12 Summary of the prevalence of risk factors in mothers included in the study with symmetric growth restricted and asymmetric growth-restricted infants
CHAPTER 5: DISCUSSION

5.1 The Findings

5.1.1 Characteristics of infants in the study

The prevalence of IUGR in infants born premature in this study population was very high (70.2%) and 68.8% of these infants had birth weights below the 3rd percentile. In South Africa the prevalence of infants born with a LBW was found by to be 19.2% in the metropolitan areas and 16.5% in rural areas\textsuperscript{3} with the developed world showing a lower prevalence of 6 - 10%. IUGR is estimated at 30% in the United States of America\textsuperscript{6}, but 70% in developing countries, which compares closely to the prevalence observed in this small study population. The prevalence of SGR was much higher (61.3%) than the prevalence of AGR (38.7%), which indicates that factors such as infections, severe maternal hypertension, chromosomal abnormalities and teratogenic agents such as alcohol, could play an important role in the growth in utero of the study population.\textsuperscript{6} The exclusion criteria however eliminated chromosomal abnormalities and chorioamnionitis. Hypertension and alcohol use were recorded and it appeared that alcohol use was not prevalent (6.3%).

5.1.2 Risk factors in the mothers included in the study

5.1.2.1 Smoking during pregnancy in the mothers

The literature describes the smoking habit during pregnancy as one of the greatest contributors to delivery before 32 weeks and LBW in the developed countries\textsuperscript{16}. In developing countries, other factors seem to play a more important role, like maternal malnutrition and HIV infection. In this study population, 11.3% of infants were born before 32 weeks and the prevalence of smoking in the study population mothers was only 1.3%. Smoking is said to contribute to AGR and in this study, all the mothers who reported smoking had AGR infants. The low prevalence of smoking in this population seems to support the findings of the literature, that smoking is not a great contributor to IUGR in developing countries, compared to other risk factors of which the prevalence is higher. Mothers have had no prior counselling to warn them of the
dangers of smoking during pregnancy. They could however have been influenced by the advertisement on cigarette packets, which warn them about the dangers of smoking, during pregnancy. During the hospitalisation period, none of the mothers who reported not smoking, smoked on the premises. There is a facility for them where they may smoke and only the few mothers who reported smoking, were observed smoking in the facility.

5.1.2.2 Maternal nutrition

Maternal malnutrition, characterised by marginal nutritional stores seems to play a very important role in developing countries. This study population did not demonstrate a high prevalence of this risk factor, as 57.5% of women in this study population had a normal BMI, 26.3% were Grade I overweight, 12.5% were Grade II overweight and 2.5% were Grade III overweight. A normal or high AMA, which indicates muscle mass, was found in 98.7% of mothers and 63.8% had a normal TSF, which indicates fat reserves. An interesting finding was however the moderate prevalence (35%) of mothers with a TSF below the 5th percentile, despite a normal or above average BMI and UAMA. The literature describes a phenomenon called “accelerated starvation”, which occurs during the last trimester of pregnancy, when fat is used predominantly as fuel instead of carbohydrates, when fetal demands are very high. It is possible that marginal intake of nutrients in this period, could accentuate the loss of fat in favour of carbohydrates or muscle protein. The high prevalence (52.5%) of mothers with a high muscle mass could possibly be attributed to weight bearing exercise in addition to good nutrition. The mothers in this population group make use of public transport. They therefore carry their parcels and children over great distances, which exercise the arms and legs.

5.1.2.3 Primiparity

Primiparity was present in 21.3% of the mothers in the study. The literature reports primiparity as a risk factor for IUGR, although the woman’s weight does contribute to the pregnancy outcome. As already reported, below average maternal weight in this study sample was uncommon and therefore the infants of these primiparous women
were most probably not worse off than the infants of the mothers who had previously given birth.

5.1.2.4 Age of mothers

Women younger than 16 years of age, primiparous women older than 35 years and *gravida* women older than 40 years, are reported to be at increased risk of delivering IUGR infants. The prevalence of women \( \geq 35 \) years and \(<16\) years was low (20.1%) in this study population. Maternal age therefore does not seem to be a common risk factor in this study population.

5.1.2.5 Birth spacing

The risk of LBW or pre-term birth among women with early or closely spaced pregnancies in the United States is at least 50% greater than that of adult women with an inter-pregnancy interval of 18-23 months. An adequate supply of nutrients is probably the single most important environmental factor affecting pregnancy outcome. Women with closely spaced pregnancies are at increased risk of entering a reproductive cycle with reduced reserves, but this risk factor did not seem to play a significant role in this study population, as 92.5% of mothers had their infants more than 18 months apart.

5.1.2.6 Alcohol use during pregnancy

Even moderate alcohol consumption during pregnancy clearly has a negative effect on fetal birth weight. Alcohol use during pregnancy was rare (6.3%) in this study population. Of the 5 mothers who reported alcohol use, 4 used small quantities (<200 ml wine or beer per day) during the first few weeks of pregnancy, when they were unaware that they were pregnant. They discontinued the use when they discovered the pregnancy. There was only the 1 woman who continued the use of alcohol for the duration of the pregnancy. Alcohol use is associated with SGR infants and in this population 13.3% of the women who used alcohol, had SGR infants compared to the 4.6% who had AGR infants. This is however not necessarily significant, as the size of the population was small. When using subjective measures
such as questioning to gather data, there is always the possibility of bias, in reporting results. The mothers were questioned alone to ensure that they would not be influenced by other mothers included in the study and they have not had any prior counselling, to warn them against the dangers of alcohol consumption during pregnancy.

5.1.2.7 HIV infection in mothers

The prevalence of HIV infection in this study population was 26.3%. In developing countries, HIV infection seems to contribute greatly to IUGR. The women who have progressed to AIDS seem to have infants who were more growth restricted than those who have not progressed so far. In this study population, women who tested positive for HIV were often tested after the birth of their infants. They were therefore unaware of their status during pregnancy and most probably still in the asymptomatic phase of the disease. CD4 counts had not been evaluated in any of these women, which made it difficult to determine the stage of HIV disease. When looking at the growth patterns in the infants of the women who tested positive for HIV, more women had SGR infants (28.6%) than AGR infants (22.6%). It is however not possible to deduct anything from this difference, because the study population was small and the stage of the disease in each individual women was undetermined.

5.1.2.8 Hypertension in the mothers

Pregnancy-induced hypertension is probably the best described contributor to IUGR in developed countries. It is estimated that hypertension contributes up to one third of all cases of fetal growth restriction. Pregnancy-induced hypertension, particularly if associated with proteinuria and/or preeclampsia, entails a greater risk of IUGR. A longer duration of hypertension results in a higher degree of IUGR. In a South African study, it was found that hypertension contributed to 44.7 % of preterm deliveries of VLBW infants at Tygerberg Hospital in the Western Cape province, although they did not indicate whether these infants were growth restricted. In this study population the prevalence was 51%.
The risk factors for pregnancy induced hypertension and preeclampsia are numerous, including marginal calcium and magnesium intake during pregnancy \(^{17,18,19}\) and obesity, which leads to insulin resistance.\(^{21}\) The nutrient intake of the mothers was not determined in this study, but it could be included in a follow-up study, as hypertension seems to possibly contribute significantly to IUGR in this study population, with 51.3% of mothers being hypertensive. No routine supplementation is provided at Kalafong Hospital Ante-natal Clinic. All the mothers in this study population were Black and lactose intolerance is very prevalent in the South African Black population. The calcium and magnesium content of dairy products is high and if dairy is excluded due to lactose intolerance, the daily intake of calcium and magnesium will be marginal. The presence of hypertension towards the end of the pregnancy was documented in all the women. There was however not always a record of blood pressure during early pregnancy, because a large percentage of the women were never examined during the early stages of their pregnancy. The period of insult from this risk factor is therefore not always known. It was therefore not possible to investigate whether the duration of the insult influenced the growth pattern of the infant. There was a higher percentage (55.1%) of mothers with hypertension who had SGR infants, compared to 45.2% with AGR infants, but the difference was not greatly significant (p=0.466). If the period of insult was known, it could possibly have shown that the SGR infants were exposed to the insult during an earlier stage of pregnancy. Overweight (Grade I, II and III) occurred in 41.3% of mothers in this study and as overweight is an independent risk factor for hypertension, it could have contributed significantly to hypertension prevalence. Of the hypertensive mothers, 48.8% were overweight, 55% of them Grade I, 40% Grade II and 5% Grade III.

5.1.2.9 Socio-economic factors

Poor socio-economic circumstances seem to contribute to premature birth and LBW.\(^{16}\) Although this factor was not investigated in this study, information from the patients’ folder indicated that most of the women in the study population were unemployed, single and dependent on welfare grants. They were classified as H1, meaning on admission they reported an income of less than R1200 per month. This risk factor ought to be explored in future research.
5.2  Estimation of gestational age

Most women who have their infants at Kalafong Hospital do not report for follow-up assessment at the ante-natal clinic from the first trimester. Some arrive at the hospital for the first time when they are already in labour. As a result, the gestational age of the infants is not confirmed by early sonar - which is the gold standard for determination of gestational age. The women usually report the pregnancy to have been unplanned, yet wanted and are therefore also unable to recall the last day of their last menstruation. This method of determining gestational age is therefore also not used often. The Ballard scoring system is consequently used most often, because it includes clinical as well as neurological signs of maturity. The problem with the Ballard scoring system is that it can over-estimate maturity by up to 2 weeks, because a fetus who experiences severe restrictions in utero, shows accelerated maturation, which can then influence the Ballard estimation. Some of the infants included in this study were however so growth-restricted that they would still have fallen below the 10th percentile had their gestational ages been taken as 2 weeks earlier.

5.3  Anthropometric measurements of the mothers

To ensure uniformity in the anthropometric measurements of the mothers, the researcher did all the measurements, using the same equipment and procedures as were described in the protocol. Inter-observer variability was controlled for by having every tenth subjects’ MUAC and TSF re-measured by a Registered Dietitian. The measurements were all within 2 mm from each other and when other measurements were used to classify according to the percentiles, the classification remained the same as for the measurements taken by the researcher. It is this assumed that the anthropometric measurements were fairly reliable. The measurements of the infants were also done as described in the protocol and repeated at random by the researcher to ensure reliability.

5.4  Sample selection

Seasonal differences can influence the number of premature infants born, but there is no evidence documented, that it would influence fetal growth in the same way as the
risk factors discussed in the literature overview, if the population is not reliant on subsistence farming, where the dry season influences maternal nutrition. In the past two years, there has been no pattern in the statistics at Kalafong Hospital, suggesting that the number of preterm infants born is influenced by season. To diminish bias, every infant born during the study period, was screened for possible inclusion. Premature infants were selected, as they stay in hospital longer and therefore their mother’s nutritional status can be determined post-partum, when they are not as edematous. Full-term infants are discharged within two days of birth, without being screened for congenital abnormalities. It would be impossible for one researcher to screen all infants born at the hospital, if full term infants were included. Acute complication related to IUGR in premature infants result in long periods of hospitalisation, whereas the full term infants are often discharged within a few days, without any acute complications.

5.5  Limitations of the study

5.5.1  Study design

The descriptive nature of the study aimed to describe certain risk factors in women who gave premature birth to IUGR infants. The sample size was small, but as the study did not intend to investigate aetiology, but simply to investigate and describe a particular demographic group, it was still useful and can serve as the basis for further case-control and intervention studies. The sample size was determined by the average statistics of infants born during a 4 month period at Kalafong NICU. Further studies could include a greater sample size, which can be determined statistically. Confounders are always a problem with this type of study and therefore the exclusion criteria were aimed at minimising known confounders, so that the strength of the finding for each risk factor investigated would be maximised.

5.5.2  Assessment of nutritional status of mothers

The BMI, UAMA and TSF were used to determine the nutritional status of the mothers. These parameters are measured objectively, which is an advantage and it indicates macronutrient intake. The assumption is however made that if macronutrient
intake is low, micronutrient intake will be low as micronutrients are present in sources supplying macronutrients. A high intake of macronutrients does not however always ensure sufficient intake of micronutrients as diets can be low in nutrient dense foods. A diet high in refined starches could therefore provide adequate macronutrients, but lack micronutrients, such as folic acid for example. Although the majority of women in this sample appeared well nourished, it is possible that they were malnourished due to a lack of micronutrients, which was not investigated.
CHAPTER 6: CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

Of the LBW infants born in this sample population, 68.8% had a birth weight <3rd percentile. A higher prevalence of SGR infants (61.3%) was found with 38.7% being AGR.

Hypertension was found in (51.3%) of the mothers from the second trimester and (52.3%) of hypertensive mothers in the study had AGR infants. The only woman who had a BMI <18 was hypertensive, HIV negative and showed no other risk factors that were investigated in the study. Of the hypertensive mothers, 28.5 % had a TSF <5th percentile.

Only 4 women in the study population had an MUAC <23.5 cm and all had at TSF <5th percentile. They all had a normal UAMA (5th-85th percentile) and one of the 4 women had a BMI <19 kg/m². All of these women with a low MUAC, were normotensive and had no history of smoking or alcohol use. One of these women had her infant within 18 months of the previous one and all of the women were HIV negative.

The other known risk factors were not found to be highly prevalent, except for HIV, which contributed 26.3% of the total mothers in the study sample. There was a higher prevalence, although insignificant, of HIV infection among mothers of SGR than AGR infants (40% compared to 23.1%) (p=0.764). The BMI of the HIV infected mothers was mostly normal (71.4%) to high (28.6%) as was the UAMA (52.4% normal; 42.9% high and 4.8% low). The TSF thickness was however normal in 61.9% of the women, low in 33.3% (<3rd percentile) and high in 4.8% of these women, despite the normal to high BMI, indicating some peripheral fat loss in the women with low TSF thickness measurements, which has been described as “accelerated starvation”, during the last trimester of pregnancy, in the literature. Increased nutritional needs due to HIV infection and opportunistic infections could accentuate the utilisation of fat during the last trimester of pregnancy in these HIV-infected
women and together with the “accelerated starvation” phenomenon, could explain the low TSF in the presence of a normal BMI.

Other known risk factors investigated in this study occurred infrequently and were not significant. The differences between mothers with SGA infants and mothers with AGR infants were not statistically significant.

The risk factor with the highest prevalence in this study population was hypertension. The possible aetiology of pregnancy-induced hypertension is multifactorial, but there may be one or two significant factors which increase the risk for developing hypertension. This could pave the way to preventative strategies, such as calcium supplementation for example, which are implementable and applicable. Strategies to address the spread of HIV are already in place.

6.2 Recommendations

Follow-up studies should be done to ascertain the prevalence of risk factors not investigated in this study as well as the occurrence of factors that predispose to hypertension. Women attending the hospital for other reasons ought to be encouraged to attend the ante-natal clinic from early pregnancy and, if possible, before conception to facilitate early intervention, where applicable.
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Addendum 1

RESEARCH PROTOCOL

Investigation into the presence of various risk factors in Black South African women who gave premature birth to growth-restricted infants at Kalafong Hospital, Gauteng

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1. TITLE

Characteristics of Black South-African adult and adolescent women who gave premature birth to growth-retarded infants at Kalafong Hospital, Gauteng

2. LITERATURE REVIEW

2.1. Introduction

Intrauterine growth restriction (IUGR) is not a specific disease, but a manifestation of many possible fetal and maternal disorders.\(^\text{1}\) Perinatal morbidity and mortality of infants are related to growth restraints in utero which presents as low birth weight.\(^\text{2}\) The evidence that low birth weight (LBW) infants (<2500g) are at risk perinatally and that they have higher rates of subnormal growth, morbidity and neurodevelopmental problems in childhood, is well documented.\(^\text{2,3}\)

2.2. Patterns of growth retardation

Symmetrical growth restriction is characterised by smaller dimensions in skeletal and head size as well as abdominal circumference and is considered to be indicative of an early intrinsic insult impairing fetal growth. Growth is symmetrically impaired because the insult happens at a time when fetal growth occurs primarily by cell division.\(^\text{2}\) In contrast, asymmetrical growth restriction is the consequence of extrinsic factors, usually resulting from the inadequate availability of substrates for fetal metabolism. In this pattern, the musculo-skeletal dimensions and head circumference are spared, and the abdominal circumference is decreased because of subnormal liver size and a paucity of subcutaneous fat. Most commonly, the disorders that limit fetal metabolic substrate availability are maternal vascular disease and decreased utero-placental perfusion. These factors generally present later in pregnancy at a time when fetal growth occurs primarily by an increase in cell size rather than cell number.\(^\text{2}\)
2.3. **Prognosis**

Recent, retrospective studies by Baker and colleagues have shown that adults who were small for gestational age (SGA) babies, had elevated blood pressure, thin babies (low ponderal indices) developed high blood pressure and non insulin dependent diabetes, while disproportionate babies (short in relation to head circumference) were shown to be at risk as adults, for raised blood pressure, elevated serum LDL cholesterol, and fibrinogen levels.\(^2\) Infants affected by severe IUGR of any cause may fail to catch-up in growth and as a result be stunted and short as adults.\(^4\) Furthermore, potential problems encountered in SGA infants include: peri-natal asphyxia, hypoglycaemia, hypothermia, pulmonary haemorrhage, meconium aspiration, necrotizing enterocolitis, polycythemia, illnesses related to congenital anomalies, syndromes or infections.\(^4\) Due to suppressed immunity, infections occur more readily in SGA infants.\(^4\)

Because the causes of symmetric and asymmetric growth restriction are disparate, it is possible that distinguishing between them might provide useful information for diagnostic and counselling purposes.\(^1\) AGR babies are likely to do fairly well if adequately fed post-natally. The symmetrically small infants appear to have been programmed early in utero, and in general do less well.\(^4\)

2.4. **Risk factors for IUGR**

2.4.1. **Maternal malnutrition**

An inadequate availability of nutrients during gestation is probably the single most important environmental factor influencing pregnancy outcome. Although physiological adjustments in nutrient utilisation and metabolism are geared to improve the utilisation of dietary nutrients during pregnancy, these adjustments may be insufficient to meet the demands for pregnancy and lactation if the woman is in poor nutritional status at conception. An adequate supply of nutrient is required to maintain the delicate balance between the needs of the mother and those of the fetus. An inadequate supply will cause a state of biological competition between the mother and the fetus in which the well-being of both organisms are at serious risk. The
consequences of this undesirable situation on the fetus are well known; the consequences of under nutrition on the mother is less well documented. Pre-pregnancy weight and weight gain in pregnancy can affect intrauterine growth, as maternal calorie intake and nutritional stores are the only source of fetal energy. In situations of marginal nourishment, there is some evidence, that mothers adjust their metabolic demands, hence potentially sparing nutrients for the development of the fetus. However, where there is chronic under nutrition, the limits of adaptation might be exceeded and fetal growth might be restricted.

Inadequate protein and energy intake may be common among some poorer mothers in developing counties and could contribute to fetal growth retardation. Where maternal malnutrition is rare, other nutritional and non-nutritional factors, discussed below, may influence the infant’s size at birth.

2.4.2. Maternal age

Women younger than 16 years of age, primiparous women older than 35 years of age and gravida women older than 40 years, are reported to be at increased risk of delivering IUGR infants. Young girls who conceive within 2 years of menarch and who, consequently may enter pregnancy with low nutrients reserves, due to the recent use of nutrients for their own growth, are at risk of having insufficient nutrient stores to meet the demands of pregnancy and the growth of the fetus.

2.4.3. Maternal hypertension

Pregnancy-induced hypertension is probably the best identified contributor in IUGR in the developed countries. It is estimated that hypertension contributes up to one third of all cases of fetal growth retardation. Pregnancy-induced hypertension, particularly if associated with proteinuria and/or pre-eclampsia, entails a greater risk of IUGR, A longer duration of hypertension results in a higher degree of IUGR. Several recent studies have linked hypertension and pre-eclampsia to hypocalcaemia, but the specific role of calcium in the development of hypertension during pregnancy is not clear. An increased prevalence of hypertension during pregnancy has been reported in parts of
the world where dietary intake of calcium is low and conversely, in areas with high dietary calcium intakes, the incidence of hypertension is low.7

2.4.4. Maternal smoking

The maternal behaviour which most affects fetal growth is smoking, including passive smoking. It was shown that there is an association between reduced birth weight and cigarette smoking which is dose-related i.e. a function of the number of cigarettes smoked by the mother.7 Women who stopped smoking before the 16th week of gestation have babies with similar birth weight patterns as non-smokers. Multi-variant analyses have shown smoking to be independently related to the incidence of IUGR.7 Smoking during pregnancy may contribute to asymmetrical growth retardation.4 Since passive smoking reduces birth weight and since smoking mothers frequently are married to smoking husbands, this is a truly familial risk factor, even when the mother stops smoking.7 Some of the mechanisms through which cigarette smoking may affect birth weight are: reduced expansion of plasma volume, increased maternal plasma carbon monoxide and consequentially, increased fetal blood carbon monoxide, increased maternal blood viscosity and consequentially, increased fetal blood viscosity. Smokers also tend to drink more alcohol than non-smokers.7

2.4.5. Maternal use of alcohol

Use of alcohol during pregnancy has been associated with an increased rate of spontaneous abortion, abruptio placentae and LBW. Some evidence suggests a relationship between maternal alcohol use and the size of the offspring.8 Prospective studies have shown a dose-related increase in the number of IUGR babies with maternal alcohol consumption. A growth restricting effect on the fetus was usually found at a much lower level of alcohol consumption than that required to produce fetal alcohol syndrome. Even moderate alcohol consumption during pregnancy clearly has a negative effect on fetal birth weight.7 Owing to the different tolerance levels of individuals for alcohol, the question of how much moderate drinking is safe during pregnancy, has not been answered. Health care providers are therefore advised to promote abstinence from alcohol among pregnant women.8
2.4.6. Birth spacing

Women with short inter-pregnancy intervals or pregnancies at a young age, are at increased risk for delivering pre-term, LBW or SGA infants. In the United States, women with inter-pregnancy intervals of <8 months were 14-47% more likely to have very premature and moderately premature infants than were women with intervals of 18-59 months. Similar results were found in other studies. The risk of low birth weight or pre-term birth among women with early or closely spaced pregnancies in the United States is at least 50% greater than that of adult women with an inter-pregnancy interval of 18-23 months.5

An adequate supply of nutrients is probably the single most important environmental factor affecting pregnancy outcome. Women with early or closely spaced pregnancies are at increased risk of entering a reproductive cycle with reduced reserves. Maternal nutrient depletion may contribute to the increased incidence of pre-term births and fetal retardation among these women as well as the increased risk of maternal mortality and morbidity.5 Poor iron and folic acid status has been linked to pre-term births and fetal growth retardation. Supplementation with food and micronutrients during the inter-pregnancy period may improve pregnancy outcomes.5 No routine supplementation is provided at Kalafong Hospital Ante-natal Clinic.

2.4.7. HIV infection

There are discrepancies between studies in the developed countries, which fail to show effects of HIV on pregnancy complications and outcome, and studies from Africa, which generally do. Similar discrepancies are found with regard to birth-weight outcomes in women with HIV.9 In Africa, several studies report a decrease in birth weight in pregnancies where the mother is HIV infected.9 There is evidence that a decrease in fetal size at birth is related to the stage of maternal HIV-disease. Significantly reduced birth weight, length and head circumference were also found in babies born to women with AIDS when compared with HIV-infected women who had not progressed to AIDS.9
2.4.8. Other factors

Other factors which could contribute to IUGR include: (1) fetal factors such as chromosomal abnormalities, multi factorial congenital malformations, multiple gestations (twins) and infections; (2) placental factors like small placenta, circumvallate placenta and chorioangioma and (3) maternal factors like renal disease, vascular disease, thrombophylic disorders, toxaemia, chronic illness and sickle cell anaemia.

2.4.9. Interaction of factors

The pathophysiology of fetal growth retardation involves the fetus, the placenta, the mother, and a combination of the three. The complexity involves different reasons for the restricted growth, acting independently or in combination. Interactions among maternal nutrition, placental dysfunction and hormonal regulation are recognised. Since restricted fetal growth is a description rather than a diagnosis, a single pathology is unlikely.

2.5. Evaluation of nutritional status

2.5.1. Anthropometry

Anthropometry is still the most practical method of evaluating maternal and neonatal nutritional status. It is simple, reliable and cheap, and is easily applied at the primary care level by community workers.

2.5.2. Maternal BMI

Because initial maternal weight loss immediately after delivery is essentially uniform regardless of ante-partum weight, gestational weight gain or infant birth-weight, the use of post-partum body mass index (BMI) provides an accurate reflection of the total maternal "energy pool". It was found during the Nutrition Collaborative Research Support Program (NCRSP), that maternal BMI early in pregnancy was little different from post-partum BMI. The NCRSP, was a cross-country research project,
investigating relationships between marginal malnutrition and human function, including pregnancy outcome. They found low maternal BMI in early pregnancy, to be associated with lower birth weight in all three projects.¹⁰

2.5.3. Mid-upper arm circumference

Maternal mid-upper arm circumference (MUAC) and triceps skinfold (TSF) thickness are anthropometric measurements that have been used in epidemiological studies.² Data on the validity of MUAC to predict LBW babies were obtained in a study by Lechtig.¹¹ The lower limit set by the researchers in this study, was 23.5 cm. He found that there was a correlation between maternal MUAC and birth weight, which when compared to weight gain during pregnancy, uterine height and percentage of weight for height, arm circumference had a similar predictive value even if gestational age is not known. MUAC is therefore an ideal measure at community level in low income areas.¹¹ Mid-upper arm muscle area (UAMA), which can be calculated from the MUAC and TSF measurement, reflects the lean body mass.⁶

2.5.4. Neonatal weight-for-gestational age

During intrauterine life, serial measurements of the fetus are feasible only with ultrasound and have not proven to be sufficiently valid or precise to serve as a standard for assessing fetal growth. Therefore, weight-for gestational-age at birth is often used to categorise an infant as having experienced normal, subnormal (SGA) or intrauterine growth restriction or supra normal growth in utero. SGA and IUGR are often used synonymously, as it is very difficult in individual cases to determine whether or not birth weight is the result of true in utero growth restriction. In fact, the higher the SGA rate, the greater the likelihood that SGA is the result of IUGR.⁶

2.6. Concluding remarks

Fetal growth restriction is the consequence of complex pathology. Often more than one risk factor is present in women who give birth to growth restricted infants. However, the type of risk factors seem to differ in different population groups,
making it worth while to investigate specific population / demographic groups to identify which of the known risk factors seem to play an important role in that particular group. If one or two risk factors are identified, specific attainable strategies can be developed to try and improve pregnancy outcomes in the particular population or demographic group.

3. Objectives

3.1. Background to the study

At Kalafong Hospital, 24% of all infants are born prematurely and about half of these infants are SGA. Reports from developed Western nations indicate that about one-third of all LBW infants are not truly premature, but are SGA instead, whereas evidence from developing countries suggest that a much higher proportion of their LBW infants may be SGA. It has been demonstrated in several studies, that the incidence of IUGR decreases as a country becomes more developed.\(^{12}\)

IUGR presents with LBW infants, who constitute up to 74% of perinatal mortality.\(^{12}\) During the first year of life, the risk of mortality in LBW infants is twenty times greater. These growth restricted infants show inadequate catch-up growth, leading to stunting and short stature as adults. Unsatisfactory neurological development is common in these children and in adulthood, the girls who were growth restricted infants, often give birth to SGA infants.\(^{12}\) Factors contributing to IUGR include: maternal malnutrition, adolescent pregnancy, short birth intervals, poor socio-economic factors, HIV infection, low-grade amniotic fluid infection, maternal hypertension, to name but a few.\(^{13}\) To identify the known risk factors which probably contribute most significantly to IUGR in this specific population group, could open the possibility for intervention programmes to decrease the incidence of growth retardation. In so doing the quality of life for infants could improve, while saving money on the medical management.
3.2. **Research Problem**

In this study, the mothers of these growth retarded infants are to be investigated in an effort to determine whether one single or several characteristics, known to increase the risk of intra-uterine growth retardation, are present among pregnant women in this demographic area.

3.3. **Research Aim**

To determine the prevalence of known risk factors for intra-uterine growth restriction, in women who give premature birth to growth retarded infants at Kalafong Hospital.

3.4. **Specific Objectives**

- To describe the prevalence of various maternal risk factors for intra-uterine growth restriction which include: nutritional status, age, hypertension during pregnancy, smoking, use of alcohol, birth spacing and HIV status.
- To investigate the possible associations between the presence of various risk factors and the severity of growth restriction found in the infants.

4. **STUDY PLAN**

4.1. **Study Design**

Study domain: The study is exclusively in the quantitative domain.
Study design: A cross-sectional, descriptive, observational study.
Study techniques: Objective anthropometric measurements, utilisation of information in existing medical records and short interview to extract further information not recorded in medical records.
4.2. Study Population

4.2.1 Sample selection

The study population will be recruited among South-African adult and adolescent women who give birth to single premature growth restricted infants at Kalafong Hospital in the Gauteng Province of South Africa during the study period. Women, who exhibit any of the exclusion criteria, will not be included in the study. The data will be collected between November 2004 and January 2005.

4.2.2. Sample size

The study will comprise at least 80 individuals. The data will be collected until 80 individuals are included. Based on current birth statistics at Kalafong Hospital, this should take between 3 and 4 months. This is a descriptive and not a case control study. These 80 individuals should be enough to make the study statistically meaningful.

4.2.3. Inclusion criteria

- South-African-born women of any race
- of any age, religion, language and ethnicity (women under 18 years will need consent from a parent)
- who gave birth to single, premature, growth restricted infants (prematurity defined as birth before 37 weeks of estimated gestational age and growth restriction in a neonate, defined as a birth weight less than the 10th percentile for gestational age)
- at Kalafong Hospital
- who consent to participate in the study, agreeing to all procedures
4.2.4. Exclusion criteria

- Women with proven congenital abnormalities as described by a genetics consultant, Dr. E Honey
- Women with terminal illness other than AIDS, e.g. cancer
- Women with diagnosed chorioamnionitis, Rubella, toxaemia and sexually transmitted diseases, not including HIV
- Women with chronic diseases like vascular disease, sickle cell anaemia, renal disease, diabetes mellitus and thrombolytic disorders
- Women who gave birth to infants with proven genetic disorders and dysmorphism as assessed by Dr E Honey (genetics consultant)

5. Method

5.1. Data collection

The researcher will visit the paediatric ICU unit and maternity unit at Kalafong daily during week days to assess the nutritional status of all infants born prematurely. For those infants who are identified as growth restricted, by the researcher, through anthropometric evaluation, the mothers will be approached immediately to determine whether she and the infant qualify for inclusion.

5.1.1. Anthropometric data of neonates

5.1.1.1. Infant weight

The researcher will do all the measurements on the babies entering the unit, from Mondays to Fridays. For infants who are born on weekend days, weight is recorded routinely by the Registrar of Paediatrics who attends the birth. The same SECA electronic baby scale is used by all doctors and dietitians and the infants are always weighed naked. The scale is calibrated annually and was last calibrated in February 2004. Scales should be placed on a flat, hard surface that will allow them to sit securely without rocking or tipping. Infants should be weighed on a pan-type scale
that is accurate to within 10g. Any cushion or towel used in the pan should either be in place when the zero adjustments are made on the scale or its weight should be subtracted from the infant’s weight. What ever practice is used, it must be uniformly followed and noted in the infant’s file. Infants will be set lying down in the middle of the pan. The average of two measurements will be recorded numerically to the nearest gram. If measurements appear unusual, they will be repeated. This is the standardised technique used in research.

5.1.1.2 Infant length

Length and head circumference will be recorded by the researcher, each weekday morning and as the length and head circumference will not change significantly within 72 hours of birth, infants born on weekend days will be measured on Mondays using the same measuring board (Nestle) each time for length and the same non-elastic plastic measuring tape for the head circumference. Recumbent length will be obtained with the infant lying down on its back. The measuring board consists of a perspex headboard and moveable footboard that are perpendicular to the backboard. Measurements will be taken to the nearest millimetre. Reliability will be increased by having a second person hold the infants head, whilst the researcher holds the feet and ensures that the legs are fully extended and the heels are at a 90 degrees angle to the measuring mat. This is the standardised technique used in research.

5.1.1.3 Infant head circumference

The head circumference will be measured whilst the infant is lying on its back. A non-elastic measuring tape will be employed, and measurements will be done twice. The average of the two measurements will be calculated and recorded. The measurement will be taken just above the eyebrows, above the ears and around the back of the head, so that the maximum circumference is measured. The tape will be in the same plane on both sides of the head and pulled snug. Measurements will be recorded to the nearest millimetre. This method has been standardised and used extensively in research.
Stratification for birth weight, length and head circumference will be done as follows: A <3rd percentile (severe growth retardation); B 3rd-10th percentile (moderate growth retardation); C >10th percentile (normal).

Ponderal index (PI) \([\text{weight (kg)}/\text{length (m}^3\text{)}]\) will be recorded, but not stratified. Term babies normally have a PI greater than 2.32 kg/m\(^3\) and if they have lengths greater than 48.5 cm, this ratio is not affected by race, gender or gestational age. In preterm infants, it is affected by gestational age and therefore a cut-off will not be used.

5.1.2. Anthropometric data of mothers

5.1.2.1. Maternal weight

Weight will be determined 3 days after delivery to ensure that most of the oedema has subsided. For women who still have excessive oedema, 5 days can be allowed before weighing. An electronic SECA scale, measuring the weight to the nearest 0.1 kg, will be used. Validity can potentially be influenced by the clothing worn by the subjects, as well as the time of day the measurements are taken. The variation in clothing will be controlled for by asking the subject to remove all extra layers of clothing. To ensure privacy, all anthropometric measurements will be conducted in a private room, adjacent to the ward. To control for variations during the course of the day, all subjects will be weighed at more or less the same time of day, namely before breakfast. Subjects will be required to void before weighing.

5.1.2.2. Maternal height

The height of the participants will be measured using a portable stadiometer. The height will be recorded to the nearest 0.5 cm. BMI will be determined using the weight and height measurements taken. BMI being the weight (kg) divided by the square of the height (m). A BMI below 18.5 kg/m\(^2\) will be classified as underweight, a BMI between 18.5 and 24.9 kg/m\(^2\) will be considered normal, a BMI between 25 and 29.9 kg/m\(^2\) will be described as grade I overweight, a BMI between 30-39 kg/m\(^2\) grade II overweight and a BMI above or equal to 40 kg/m\(^2\) will be classified as grade III overweight.
5.1.2.3. Maternal triceps skin fold

The TSF measurement will be performed on the posterior aspect of the dominant arm, midway between the lateral projections of the *acromion* process of the scapula and the inferior margin of the *olecranon* process of the ulna. Standard techniques will be used. The measurements will be taken, 15 seconds apart and the average will be recorded. Measurements will be taken with a Harpenden metal calliper, which exerts a jaw tip pressure of 10 g/mm² throughout the calliper’s full measurement range. The calliper was calibrated in August 2004, by a reputable company. Readings will be recorded to the nearest millimetre. Every 10th patient, starting with the first patient, will be measured by a colleague and the difference between the readings of the researcher and colleague will be analysed statistically to measure interpersonal differences of measurements. The same calliper will be used by the colleague and measurements will be done within 5 minutes of the researcher’s measurements, to standardise the instrument and time of day. The same standardised techniques will be used by both the researcher and the colleague and if there are still significant differences in measurement, another colleague will be used, whose technique might differ. Measurements can also be repeated to make sure that they are as accurate as possible.

5.1.2.4. Maternal mid upper arm circumference

The MUAC will be measured midway between the lateral projections of the *acromion* process of the scapula and the inferior margin of the *olecranon* process of the ulna. The right arm will be measured using a non-elastic plastic tape measure. The circumference will be measured to the nearest millimetre and repeated three times. The average of the three measurements will be calculated and recorded. The UAMA will be calculated as follows: $UAMA = MUAC - \left( \frac{TSF \times \pi}{2} \right)^2 / 4\pi$. The UAMA will be interpreted using the percentiles for UAMA from Frisancho (Addendum 3).

5.1.3. Questionnaire

Additional information such as maternal age, spacing between births, maternal smoking, maternal use of alcohol and maternal HIV status, will be gathered by
personal interview with the mothers. The data will be captured on a specifically tailored form. (Addendum 9). Stratification for maternal age will be done as follows: A: ≤16 years; B: 16-35 years; C: 35-40 years and D: >40 years. Stratification for spacing between pregnancies will be as follows: A: >18 months between pregnancies and B: ≤18 months between pregnancies. Where language is a barrier, the research assistant, who will also be employed to explain the consent form, will be used as an interpreter.

5.1.4. Medical records

Medical records will be utilised to record hypertension from the second trimester of pregnancy. If the mean blood pressure is >140/90 mmHg in a previously normotensive woman, or if there is proteinuria >300 mg/24 hours in the absence of infection or if there is significant oedema in the presence of hypertension, the woman will be classified as hypertensive. If the blood pressure is well controlled with medication, the woman will be classified as normotensive. This information will be documented on the data capturing sheet (Addendum 9).

HIV testing in the maternity ward is standard practice at Kalafong Hospital. Women who come to the maternity unit are given the option to test for HIV as they are then eligible for Nevirapine therapy to decrease the chances of vertical transmission of the virus from the mother to the infant. Most women give consent to testing as they want to make use of the anti-retroviral therapy for themselves and their infants. The researcher therefore needs only to get consent from the mother to be able to use the results, if she consented earlier. No new test will be required. If the mother refused HIV testing the first time, the researcher will still determine the other risk factors and record the HIV status as undetermined.
6. DATA ANALYSIS

6.1. Analysis of data

Data will be analysed by the researcher with the assistance of a statistician appointed by the Department of Human Nutrition of the Faculty of Health Sciences, University of Stellenbosch.

6.2. Statistical Methods

Both descriptive and inferential statistics will be used to analyse the data. The frequency of each risk factor will be determined. The relationship between each risk factor and the severity of growth retardation will be investigated statistically.

7. ETHICAL CONSIDERATIONS

7.1. Ethical review committee

The study will be submitted for approval to the Committee for Human Research, Faculty of Health Sciences, University of Stellenbosch and the Faculty of Health Sciences Research Ethics Committee, University of Pretoria.

7.2. Informed consent

Each participant will be provided with an informed consent form. The form will be administered by the researcher and where there is a problem with understanding, a translator will be used to clarify the entire form. This translator assists the registrars who conduct research in the paediatric ICU. The standard informed consent form used by the Faculty of Health Sciences of the University of Stellenbosch has been adapted for this specific research study and will be available in English, Sotho and Zulu (Addenda 6, 7 and 8).
7.3. Confidentiality

Patient identification information will be omitted from the study related material to ensure confidentiality. The researcher will be the only person who will have access to this information. Upon entering the study, each participant will be assigned a subject identification number which will be used on all study related material and documents. Participants will be ensured verbally and by means of the informed consent form (Addendum 6), that all conversations and information provided to the researcher will be regarded as confidential. This will be done by either the researcher or the translator. Data collected and information provided to the researcher will only be used for this specific study and will not be shared for any other purpose or projects.

8. BUDGET

Equipment such as scales, calipers, measuring boards and tapes are the property of the Department of Human Nutrition of Kalafong Hospital and will be used, free of charge, with the permission of the department. All further costs will be the responsibility of the researcher.

9. TIME FRAME

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10 RESULTS REPORTING

Data will be reported in a Masters thesis and will be presented at national conferences and submitted for publication in a peer-reviewed dietetics/scientific journal.
REFERENCES

Babson and Benda Growth chart for preterm infants: 22-50 weeks gestation.
Addendum 3

PERCENTILES FOR UPPER-ARM MUSCLE AREA (males and females, 1-74 years)

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Addendum 4

PERCENTILES FOR TRICEPS SKINFOLD THICKNESS (males and females, 6 months - 19 years)

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Percentiles for triceps skinfold thickness (males and females 6 months - 19 years) (NHANES II 1976-1980). Printed with permission by Lee et al.15
PERCENTILES FOR ADULT TRICEPS SKINFOLD THICKNESS (males and females; 18-74 years)

| Race and Age | Number of Examined Persons | Mean | Standard Deviation | 5th | 10th | 15th | 25th | 50th | 75th | 85th | 90th | 95th |
|--------------|----------------------------|------|-------------------|-----|------|------|------|------|------|------|------|------|------|
| All Races*   | 5868                       | 24.9 | 9.8               | 11.0| 13.0 | 15.0 | 17.5| 22.0 | 29.0 | 35.0 | 38.0 | 43.0 |
| 18-24 years  | 1066                       | 20.7 | 8.6               | 10.0| 11.5 | 12.5 | 15.0 | 19.0 | 25.0 | 29.5 | 32.0 | 37.0 |
| 25-34 years  | 1170                       | 23.6 | 9.9               | 10.0| 13.0 | 14.0 | 16.5 | 22.0 | 29.0 | 33.5 | 36.6 | 43.5 |
| 35-44 years  | 844                        | 26.3 | 9.8               | 13.0| 14.5 | 16.5 | 19.5 | 25.0 | 32.6 | 37.0 | 40.3 | 44.5 |
| 45-54 years  | 763                        | 27.5 | 9.7               | 12.5| 15.0 | 17.0 | 20.5 | 27.0 | 34.0 | 38.0 | 40.5 | 45.0 |
| 55-64 years  | 1329                       | 27.2 | 9.5               | 12.0| 15.0 | 17.5 | 21.0 | 26.5 | 33.0 | 37.0 | 40.0 | 43.6 |
| 65-74 years  | 1416                       | 25.7 | 9.0               | 12.0| 14.5 | 16.5 | 19.0 | 25.0 | 31.0 | 35.0 | 37.6 | 42.0 |
| White        | 5868                       | 24.7 | 9.5               | 11.5| 13.5 | 15.0 | 17.5 | 23.5 | 30.5 | 35.0 | 37.5 | 42.5 |
| 18-24 years  | 894                        | 20.8 | 8.9               | 10.5| 11.3 | 13.0 | 15.0 | 19.0 | 25.0 | 29.0 | 32.0 | 37.1 |
| 25-34 years  | 1000                       | 23.3 | 9.4               | 10.5| 13.0 | 14.0 | 16.5 | 22.0 | 28.5 | 33.0 | 36.0 | 42.1 |
| 35-44 years  | 726                        | 26.1 | 9.6               | 12.0| 14.5 | 16.0 | 19.0 | 24.5 | 32.0 | 36.5 | 40.0 | 44.0 |
| 45-54 years  | 647                        | 27.3 | 9.4               | 13.0| 15.0 | 16.5 | 20.5 | 27.0 | 33.0 | 37.0 | 40.0 | 43.1 |
| 55-64 years  | 1176                       | 27.0 | 9.4               | 12.5| 15.0 | 17.5 | 21.0 | 26.0 | 32.6 | 36.5 | 39.1 | 43.1 |
| 65-74 years  | 1345                       | 25.5 | 8.8               | 12.0| 14.5 | 16.5 | 19.0 | 25.0 | 30.5 | 34.0 | 37.0 | 41.1 |
| Black        | 782                        | 26.6 | 11.6              | 10.0| 12.0 | 14.0 | 17.5 | 25.5 | 35.0 | 39.0 | 42.5 | 48.0 |
| 18-24 years  | 147                        | 20.6 | 8.8               | 8.0 | 10.0 | 11.0 | 14.0 | 19.0 | 27.0 | 31.0 | 35.0 | 37.0 |
| 25-34 years  | 145                        | 25.5 | 12.2              | 8.0 | 11.0 | 13.0 | 16.0 | 22.0 | 32.0 | 37.0 | 47.0 | 49.5 |
| 35-44 years  | 103                        | 28.7 | 11.4              | 9.0 | 14.0 | 15.0 | 20.5 | 25.5 | 32.6 | 40.3 | 45.0 | 48.0 |
| 45-54 years  | 100                        | 31.6 | 11.8              | 10.5| 16.0 | 20.0 | 23.5 | 31.5 | 40.0 | 43.5 | 48.5 | 53.1 |
| 55-64 years  | 135                        | 29.5 | 10.8              | 12.5| 14.0 | 18.0 | 22.5 | 28.5 | 38.5 | 42.0 | 43.0 | 46.0 |
| 65-74 years  | 152                        | 20.0 | 10.5              | 11.5| 14.5 | 17.0 | 21.5 | 29.0 | 37.0 | 38.6 | 44.0 | 47.5 |

*Includes all other races not shown as separate categories.

Percentiles for triceps skinfold thickness for males and females (18-74 years) (NHANES II 1976-1980). Printed with permission by Lee et al. 15
PARTICIPANT INFORMATION LEAFLET AND CONSENT FORM (English)

TITLE OF THE RESEARCH PROJECT: Investigation into the presence of various risk factors in South-African women who gave premature birth to growth-retarded infants at Kalafong Hospital, Gauteng

REFERENCE NUMBER: N05/02/019

PRINCIPAL INVESTIGATOR: Marlene Gilfillan

ADDRESS: P O Box 622
Rooihuiskraal
Centurion
0154

CONTACT NUMBER: 012-3186551 (work)

You are being invited to take part in a research project. Please take some time to read the information presented here, which will explain the details of this project. Please ask the study staff or doctor any questions about any part of this project that you do not fully understand. It is very important that you are fully satisfied that you clearly understand what this research entails and how you could be involved. Also, your participation is entirely voluntary and you are free to decline to participate. If you say no, this will not affect you negatively in any way whatsoever. You are also free to withdraw from the study at any point, even if you do agree to take part.

This study has been approved by the Committee for Human Research at Stellenbosch University and the Faculty of Health Sciences Research Ethics Committee University of Pretoria and will be conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.

What is this research study all about?

• The study will be conducted in the Paediatric Intensive Care Unit of Kalafong Hospital. No other site will be utilized. All together, the number of participants recruited will total 80.

• The project aims to determine the prevalence of certain characteristics in women, known to be risk factors for intra-uterine growth restriction, in other words – factors which could have caused the baby to grow slower than expected in the mother’s womb. If there is one factor in this population that occurs very frequently and the factor can be prevented, then measures can be employed to prevent or decrease its occurrence in this hospital. The family planning and anti-natal clinics can become the sites for prevention.

• It is standard practice at Kalafong, that all babies are measured (length and head circumference) and weighed at birth, as it serves as a baseline from which progress is measured. It is also a screening method to identify babies at
risk of developing malnutrition due to increased needs and intolerance to feeds. For the purpose of the study, no additional measures are required and the investigator asks permission to use the measurements of the baby who has been identified as growth retarded (too small for their age). The mothers of the growth retarded babies who are the participants in the study, is asked permission to be measured to determine their nutritional status. These measurements will include: weight, height, arm circumference and triceps skinfold thickness. Additional information such as tobacco, alcohol and narcotic use, age and birth spacing will be gathered by a short interview if the mother consents to the interview and permission is asked to access and gather information from the medical records in the mother’s file. The information that is required from the medical records will include the blood pressure and the HIV status. No further evaluation will be required.

- All premature infants admitted to this unit will be screened for inclusion, without exception.
- No medical treatment is offered and no invasive procedures will be done for the sole purpose of this study.

Why have you been invited to participate?
- You have been invited to participate, because your infant is small for his/her age. By allowing investigation of certain of your characteristics, could help in determining the major risk factor in this population for slowing the growth of babies in the mother’s womb.

What will your responsibilities be?
- You are only expected to answer the questions truthfully and to allow measurements to be taken of you.

Will you benefit from taking part in this research?
You will not benefit from this research in the short term, but if you were to have another baby, you could actually benefit, if preventative measures have been implemented in the family planning and or anti-natal clinic. Other women who give birth in future could also benefit from the preventative measures.

Are there any risks involved in your taking part in this research?
As information is kept confidential, there are no risks involved, as no treatment or invasive procedures are applicable.

If you do not agree to take part, what alternatives do you have?
- If you do not take part, there will be no implications. The infant will receive the same care as infant whose mothers have consented to participate in the study.

Who will have access to your medical records?
- The researcher is the only one who has access to the medical records. The data capturing sheet makes no provision for a name and therefore whoever analyses the data will have no form of identification of the participant. As soon as data is captured and the consent form has been signed, the consent form and data capturing sheets are separated. The researcher will therefore also not know the
identity once all the data has been collected. If the study is published, the identity of participants will be unknown.

What will happen in the unlikely event of some form of injury occurring as a direct result of your taking part in this research study?
The study is purely descriptive, no treatment is offered and involves no invasive techniques. Chances of injury are therefore unlikely.

Will you be paid to take part in this study and are there any costs involved?
You will not be paid to participate in the study nor will you be expected to pay should you participate. It is not expected of you to travel as you are present at the baby’s side every day for the duration of the baby’s stay in the unit.

Is there anything else that you should know or do?
You can contact the Faculty of Health Sciences Research Ethics Committee, University of Pretoria at 012-3398612 or the Committee for Human Research Stellenbosch, at (021) 938-9207 if you have any concerns or complaints that have not been adequately addressed by the researcher

You will receive a copy of this information and consent form, if you desire for your own records

By Signing below, I………………………….. agree to take part in a research study entitled:- Investigation into the presence of various risk factors in South-African women who gave premature birth to growth-retarded infants at Kalafong Hospital, Gauteng

I declare that:
• I have read or had read to me this information and consent form and it is written in a language with which I am fluent and comfortable.
• I have had a chance to ask questions and all my questions have been adequately answered.
• I understand that taking part in this study is voluntary and I have not been pressurized to take part.
• I may choose to leave the study at any time and will not be penalized or prejudiced in any way.
• I may be asked to leave the study before it has finished, if the study doctor or researcher feels it is in my best interests, or if I do not follow the study plan, as agreed to.

Signed at (place)…………………………..on (date) ………………………….. 2004

…………………………..                                                        ………………………
Signature of Participant                                                            Signature of Witness
Declaration by Investigator

I (name ) ........................................................declare that:-

- I explained the information in this document to ........................................
- I encouraged him/her to ask questions and took adequate time to answer them.
- I am satisfied that he/she adequately understands all aspects of the research, as discussed above
- I did/did not use a translator. *(If a translator is used then the translator must sign the declaration below.)*

Signed at *(place)* .............................................on *(date)* .......................... 2005

...........................................  ...........................................
Signature of Investigator  Signature of Witness.

Declaration by Translator

I *(name)* ........................................................declare that:-

- I assisted the investigator *(name)* .......................... to explain the information in this document to *(name of participant)* .......................... using the language medium of Afrikaans/Sotho/Zulu
- We encouraged him/her to ask questions and took adequate time to answer them.
- I conveyed a factually correct version of what was related to me.
- I am satisfied that the participant fully understands the content of this informed consent document and has had all his/her question satisfactorily answered.

Signed at *(place)* .............................................on *(date)* .......................... 2005

...........................................  ...........................................
Signature of Translator  Signature of Witness
FOROMO ENA KE YA DIPATLISISO GO BA TSEA KAROLO (Sotho)

Sehlogo ke projeke ya dipatlisiso: mo go bo-mme le basetsana ba batho baso mo afrika-borwa go bo mme le basetsane ba ba fumanang masea pele go matswalo a bona ba bona. Sepetleleng sa Kalafong, Gauteng

Nomoro ya motsibisi: N05/02/019

Mookamedi mogolo ke: Marlene Gilfillan

Tulo: P O Box 622
      Rooihuiskraal
      Centurion
      0154

Dinomoro tsa mogala: 012-3186551 (mo tirong)

Le a lalediwa go tsa karolo mo patlisisong ya porojeke, kopo ke gore le tsee nako go bala ka kitso e e tla tlhalosiwang ka botlhokwa jwa porojeke. Kopo ke gore le botse dipotso go barutabana kgotsa dingaka ka sengwe le sengwe se le sa se tlhaloganyeng fela mabapi le projeke. Go botlhokwa gore le kgotsofale le go tlhaloganya sentle ka patlisiso e, gore e re raya eng? Le go nna teng ga lona. Gape, karolo ya gago e tla nna e e khutshwane e bile o sa gapeleseke ke sepe go tsa tsaa karolo. Fela ga o ka re nnya, tsotlhe di ka segoame mo lethakore ka gongwe. O ntse o sa gapelediwe ke sepe go ka tlogela ka thuto, ebile le a ontse o dumela go ka tsa tsaa karolo.

Thuto e, e netefaditswe ke ba komiti ya lefapha la patlisiso go tswa Stellenbosch University, e bile re tla bona pono ka thuto le molao kaga lefatshes e tlininking South African Guidelines to Good Clinical Practice gape le Medical Research Council (MRC) thuto go patlisiso.

Thuto ka patlisiso e, ke gore eng?
  • Thuto re tla e bona go tswa go ba lefapha la tlhokomelo ya bana ya maemo a nthla kwa Kalafong (Paediatric Intensive Care Unit). Ga gona mathakore a tla go dirisiwa. Gotlhe, palo ya ba ba tla tsaang karolo ke masome a robedi.
  • Maikemisetso a porojeke e go ela tlhoko ka maemo a mangwe a mosadi, jaaka ngwana yo o tsalwang pele ga letsatsi la gagwe la matsalo. Ga e le gore go na le tsela tsela e nngwe mo bathong e e ka dirang sentle e bile tsela e o e ka dira gore re thibele, teng fao, go ka diriswa mabaka a go thibela kgotsa go fokotsa ditiragalo tse kwa bookelong.
  • Bana ba tla tsewa maemo ka boitekanelo jwa bana. Kago tsu bokete, botelele le tlhogo ja ka tlwaelo. Bomme ba bana ba ba sa itekanelang ba ba tsaang karolo mo thutong, le bona ba tla kadiwa go bona gore ba itekanetse mo phepong. Kalo tla akaretsa bokete, boleele, mabogo le boitekanelo jwa letlalo la diphaka. Koketso yakitso e tla kopangwa ka poisano e khutshwane (interview) le ka lekwalo labookelo.
- Bana ba ba belegwang pele ga nako ba tla Neilwa tlhokomelo ya maemo a nthla.
- Ga go na ditlhare tse di tla neelwang. Gape ga go na tshenyo mo tsamaisong yabotlhokwa jwa thuto.

**Ke ka nthla ya eng o lalediwa go tsa karolo?**

- O lalediwa go tsa karolo, gonne ngwana o mommye ka dingwaga ka go dumela, dipatusiso tse di tla thusa go thibela kotsi e e tla amang ngwana a saleng popegong ya mmagwe.

**Maikemisetso a gago ke eng?**

- O thhwanela go araba dipotso ka botshepegi le go dumela fa o tsewewa maemo.

**A o ka tswelwa ke mosola ka go tsa karolo mo patlisisong?**

- O ka se tswelwe mosola ka patlisiso mo nakong e e khutshwane, fela fa e le gore o tlo nna le ngwana o ka tswelwa mosola go tsewa maemo.

**A go ka nna le kotsi mo karolo e e tsewang ka patlisiso?**

- Fa kitso e nna sephiri, ga go kotsi, e bile go se tsiamiso e e ka diragatswang ka boema jwa gago.

**Fa o sa dumele go tsaar karolo, ke sefe mo lethakoreng o na naso?**

- Fa o sa tsee karolo, tiragatso e tla be e seteng. Ngwana yo o tshotsweng pele ga nako o tla bona tlhnomokomelo ka go tshwana le yo e leng gore e na mme wa gagwe sa le a tsaar karolo ka thuto.

**Ke mang yo o tla boning tshono ka makwalo a bookelo?**

- Yo o batlisisang ke e ne yo o tla bonang tshono ka makwalo a bookelo. Pampitshana e tshwereng ke datara e ka se neele leina, e bile go se mongwe yo o ka iteng sengwe ka batseakarolo, go fithelela kitso e e bolokiwa ka fa komputeng gape foromo ya maikemisetso e sainewa, e bile yona foromo le kitso e e bolokilweng di a arogangwa. Yo o batlisisang le gona ga a kake a lemoga go fithela sengwe le sengwe, fa e le gore thuto e tla bonagatswa, ba tseakarolo ba ka seke ba itsegale.

**Gotla diragalaeng mo tse di sa utlwiseng monate go dforomo tsa kutlobothoko e e lebileng dipholo mo tseong ya patlisiso thuto?**

- Thuto e bonolo go thhaloganyega, go se o tla amogelang ditlhare gape go se yo o tla beng a sa kgotsofala.

**A go tsea karolo go tla tswhelana ke gore o duele?**

- o ka se bone tuelo ka go tsea karolo, gongwe le wena a sa tswanelwa ke gore o duele go tsea karolo. Go tla be go se boltlokowa gore o tsame, fa o tla be o
tshwanelwa ke go ema ngwana wa gago mo nokeng ka nako tsotlhe fa a tla be a le phapusing e tlhopegileng.

**A gona le sengwe se o se itseng kgotsa o ka se dirang?**

- O tshwanetse go ikopantsha le ba komiti ya dipatlisiso go (021) 9389207 ga o botsa kgotsa ngongorego e e sa thagisiwang ke wa dipatlisiso.
- O tla bona lekwalo kgatiso ka kitso le foromo ya maikemisetso, fa e le gore o batla sengwe le sengwe se se bolokilweng.

Ka tshaeno ka fa tlase, nna……………………………………tumelo ke gore ke tsa karolo mo dipatlisisong tsa thuto.

Tumello :-Popego go bagolo ba mmala motsho go Aforika borwa le basetsana ba ba senang maikemisetso ba ntse ba tshola bana ba ba tsalwang pele ga nako ya matswalo ba feleletsba ba gola maemo a bona a sa itekanela kwa Kalafong Hospital, Gauteng.

**Ke dumela gore:**

- Ke buisitse kgotsa ke buisebitswe kitso yotlhe le foromo ya maikemetso, gape, e kwadiilwe ka loleme le ke le tlhaloganyang, ebile tsotlhe dipotso di arabilwe sentle.
- Ke tlhalogantse gore karolo e ke tla tsayang e tla nna e khutswane, gape ke sa gapelesege go tsaa karolo.
- Ke go tswa go nna go ka tlogela thuto nako nngwe le nngwe, ebile ke ka seke ka atlholwa.
- Ke dumelesega go tlogela thuto e, e se e felelele, fela ngaka kgotsa ba dipatlisiso ba itse gore ke ka go rata game.

Tshaeno kwa……………………………………ka…………………………2005.

………………………………………                 ……………………………..
Tshaeno ya motseakarolo                     Tsaeno ya paki
**Tumallano ka mobatlisi**

Nna (leina)………………………………..ke dumela gore:-

- Ke tlhalosite kitso mo go pampiri ya bopaki go………………………….
- Ke kgotalebitse go botsiwa dipotso le go tsa nako go araba
- Ke kgotsofetse gore tsotlhe tse bothokwa ka dipatlisiso dia tlhaloganyega, mongwe le mongwe a boletse se se mo amang.
- Ke dirisitse kgotsa ga ka dirisa motlhalosi (Tshaeno fa tlase fela fa go diritswe motlhalosi)

Tshaeno  kwa (lefeloe)..........................ka(letsatsi)....................2005.

…………….………………………………..………………….

Tshaeno ya mobatlisi Tshaeno ya paki

**Tumallano ka motlhalosi**

Nna (leina)………………………………..ke dumela gore:-

- Ke thusitse mobatlisi (leina)……………………………ka go tlhalosa kitso mo pampering ya bopaki go ( leina la motseakorolo)……………………………ka go dirisa loleme la go tlhaloganyega.
- Ke kgothaleditse go botsiwa dipotso lego tsayanako go araba.
- Ke bone tsela ya nnete e bontshang mo ke tshwanetseng go nna teng
- Ke kgotsofetse gore batseakarolo ba tlhaloganye bothokwa ba pampiri ya ka botshepegi, ebile dipotso tsa bone di arabilwe gore ba tle ba kgotsofale.

Tshaeno kwa (lefeloe)..........................ka (letsatsi)....................2005

…………….………………………………..………………….

Tshaeno ya motlhalosi Tshaeno ya paki
Addendum 8

IFOMO LEMININGWANE YABANGENELA UCWANINGO (Zulu)

ISIHLOKO NGOHLELO LALOLUCWANINGO: Ubunjalo ngabesifazane abansundu base Mzanzi Afrika abesekhulile kanye nabasathombayo ababelethu isikhathi singakafiki nokungabi kuhle kosana, esibedlela sa se Kalafong e Goli

INOMBHOLO YE LEFELENSI: N05/02/019

UMCUBUNGULI OMKHULU: Marlene Gilfillan

IKHELI: P O Box 622
  Rooihuiskraal
  Centurion
  0154

INOMBHOLO YOCINGO: 012-3186551 (emsebenzini)

Uyamenywa ukuthatha ingxenye kulolucwaningo. Olwalehlelo uyacwelwa ukuba uthathe isikhathi uma ufunza ngeminingwane ethulwe lapha. Lemininingwane yiyona ezochaza kabanzi ngenhloloso yaloluhlelo. Uyacelwa ukuthi ubuze ko tisha no nama kuDokotela umakukhona kuqondisisi noma nafalane, nangendlela omgathinteka ngayo, ukuthi isikhathi singakafiki nokungeni nokungabi kuhle kosana, esibedlela sa se Kalafong e Goli.

Loluhlelo lokufunda luzobanjelwa egunjini elibizwa Paediatric Intensive Care Unit esibedlela sese Kalafong. Akukho elinye igumbi elizosetshenziswa ngaphandle kwaleli. Inani labazothatha ixhaza lizobangu 80

Injongo yaleprojeki ukuhlolisisa izindlela ezingadala ukuba ingane elihamba elihamba kancane kunalelo elifanele nomla elilindelwa esibeleyetheni. Uma ngabe kuyenzeka okunye kwakoloku abantwini bakithi kungavikelwa ngokuthatha izinyathelo ezingadala ukuba kwakoloku kulesisibedlela. Amakliniki ohlelo lomndeni kanye nomla ikliniki okudlala esiba ngaphambi kokubelethwa angaba aziwazi ezixwelela.

Izingane zizolinganiswa zikalwe ukuhlola noma zikhula kahle ngokungakhubazeki. Loluhlelo lufaka nezingane zizaqoqo noma zikhula kahle ngokungakhubazeki. Loluhlelo lubhaka nezingane zizaqoqo noma zikhula kahle ngokungakhubazeki. Loluhlelo lubhaka nezingane zizaqoqo noma zikhula kahle ngokungakhubazeki.

Lumayelana nani lolucwaningo na?

- Loluhlelo lokufunda luzobanjelwa egunjini elibizwa Paediatric Intensive Care Unit esibedlela sese Kalafong. Akukho elinye igumbi elizosetshenziswa ngaphandle kwaleli. Inani labazothatha ixhaza lizobangu 80
- Injongo yaleprojeki ukuhlolisisa izindlela ezingadala ukuba ingane elihamba elihamba kancane kunalelo elifanele nomla elilindelwa esibeleyetheni. Uma ngabe kuyenzeka okunye kwakoloku abantwini bakithi kungavikelwa ngokuthatha izinyathelo ezingadala ukuba kwakoloku kulesisibedlela. Amakliniki ohlelo lomndeni kanye nomla ikliniki okudlala esiba ngaphambi kokubelethwa angaba aziwazi ezixwelela.

Loluhlelo lokufunda lusekelwa ngabe komotin yamalungelo abantu nocwalingo lwe Univesi yase Stellenbosch. Kanti luzoqhutshwa ngenkambo ye international Declaration of Helsinki, South African Guidelines to Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.
lungaqokelele ngemibuzwana (short interview) nangokuhlola umlando ngempilo kaname efayilini. Akukho okunye okuzobye kudingeke ngemuvu kwalokhu

- Zonke izingane ezibelethwe ngaphambi kwasikhathi (premature babies) ezamukelwe kulelihlelo zizothathwa zingabandlululwa.
- Akukho hlelo lokwelashwa olwenganyelwe kanti futhi akakho kulimala kuloluhlelo.

Umenyelweni ukuze uthathe ixhaza?

- Umenywe ngoba ingane yakho ibukeka iyincane kuneminyaka yayo. Ngokuvumela uhlolo oluthile mayelana nesimo sakhe kungasiza ekucwaningeni ngokukhula kancane kwalezizingane esibelethweni sikamame.

Kuzoba yini umsebenzi wakho?

- Ulindelwa ukuthi ukuze uthathe ixhaza?
- Umenywe ngoba ingane yakho ibukeka iyincane kuneminyaka yayo. Ngokuvumela uhlolo oluthile mayelana nesimo sakhe kungasiza ekucwaningeni ngokukhula kancane kwalezizingane esibelethweni sikamame.

Kuzoba yini umsebenzi wakho?

- Ulindelwa ukuthi ukuze uthathe ixhaza?
- Umenywe ngoba ingane yakho ibukeka iyincane kuneminyaka yayo. Ngokuvumela uhlolo oluthile mayelana nesimo sakhe kungasiza ekucwaningeni ngokukhula kancane kwalezizingane esibelethweni sikamame.

Ingabe kukhona isimosobungozi (risk) osithathayo ngokuthatha ixhaza?

- Njengoba yonke iminingwane iyimfihlo akukho simo sobungozi ngoba akukho kwelashwa okwenziwayo

Uma ungavumi ukuthatha ixhaza yiziphi ezinye izindlela onazo?

- Uma ungathathi ixhaza akukho okuzoba inkinga. Ingane yakho izothola ukwelashwa nokunakekelwa njengezinye izingane zawomame abakhona kuloluhlelo lokufunda.

Ngubani ozobe enemvume yokuceina yonke iminingwane yakho?

- Umewenzelwa ukwelashwa nokumakliniki ombucwazi yonke kulelihlelo okuhlela kancane kwalezizingane esibelethweni sikamame.

Kuzokwenzekani uma kungaba nokulimala ngikuleli hlelo lokucwaninga?

- Loluhlelo alwenzelwanga ukululaza, akukho kwelashwa okwenzekayo nokulimazayo ngakho amathuba wokuba umuntu angalimala ake

Uzokhokhela yini nomina ngabe kukhona izindleko ezizingekayo?

- Akukho kukhokhela yini nomina ngabe kukhona izindleko ezizingekayo?

Kukhona yini okunye ofanele ukwazi nomina ukwenze?

- Thintana ne Committee for Human Research e 012-9389207 uma ngabe awugculisekile ngendlela umcwaningi eqhube loluhlelo ngayo. Singakunikeza ulwazi ngaloluhlelo uswatho.
Ngokusayina ezansi mina ........................................... ngiyavuma ukuthatha ixhaza kuloluhlelo: Locwaningo lemfundo yomam abamnyama abadala nabasha base Ningizimu Africa ababalethe izingane ngaphambis kwesikhathi nokukhula kwezingane ezikhubazekile esibhedlela iKalafong, eGauteng.

Ngiyaqiniseka ukuthi:
- Ngiyifundile noma ngifundelwe yonke imininingwane ngolimi engilizwayo futhi engилиqondisisayo.
- Ngibe nalo ithuba lokubuza imibuzo ngaphenduleka kahle.
- Ngiyaqonda futhi ukuthi ukuze ngithathe ixhaza kuloluhlelo ngizithandele mina akukho muntu ongingindezele.
- Uma ngizikhethela ukuye ka noma nini angeke ngaahlwuliswa noma ngayiph indlela
- Ngingatshelwa ukuba ngiyaye ukuthatha ixhaza ngaphambis kokuba ngiqe he ulhlelo uma ngabe udokotela noma umcwaningi wohlelo (researcher) ecabanga ukuba kuzongisiza lokhu noma kwenze ka ukuba ngingalandelini imigomo yaloluhlelo ngokwesivumelwano

Kusayinwe e (indawo) .................... ngomhlaka (date) ................. 2005

........................................
Isiqiniseko somthathixhaza ........................................

........................................
Isiqiniseko sofakazi
Isiqinisekiso somcwaningi

Mina (igama) ……………………………………. ngiyaqinisekisa ukuthi:-
• Ngicazile konke okucukethwe kulomculu ukuze ………………………
• Umthathixhaza abuze imibuzo futhi ngathatha nesikhathi esilingene ukuphendula
• Nganelesekile ukuthi umthathixhaza uqonda konke okuphathelene nohlelo njengoba kusqaziwe
• Ngisebenzise noma angisebenzisanga umtoloki (uma umtoloki usetshenzisiwe kumle asayine lesisivumelwano esingezansi)

Kusayinwe e(indawo) …………………………… ngomhlaka ………………… 2005

........................................  ........................................
Isiqiniseko somcwaningi Isiqiniseko sofakazi

Isiqiniseko somtoloki

Mina (igama) ……………………………………. ngiyaqinisekisa ukuthi:
• Ngisize umcwaningi (igama) ……………………….. ukuchaza ulwazi olucukethwe kulomculuku ku (igama lomthathixhaza) …………………………… ngisebenzisa ulimi lwesizulu
• Simgququzele umthathixhaza ukubuza imibuzo futhi sathatha isikhathi esilingene ukuyiphendula.
• Ngichazile ngabuye ngadlulisa okuphathelene nami njengomtoli
• Ngqiniseko ngomthathixhaza ukuthi konke okucukethwe kulomculu uyakuqondisasa futhi nemibuzo yakhe iphenduliwe.

Kusayinwe e(indawo) …………………………… ngomhlaka ………………… 2005

........................................  ........................................
Isiqiniseko somtoliki Isiqiniseko sofakazi
### Addendum 9

**DATA CAPTURING SHEET**

**NEONATE DATA**

<table>
<thead>
<tr>
<th>Weight: absolute (kg)</th>
<th>A &lt;3rd</th>
<th>B 3rd-10th</th>
<th>C &gt;10th</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight: percentile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length: absolute (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length: percentile</td>
<td>A &lt;3rd</td>
<td>B 3rd-10th</td>
<td>C &gt; 10th</td>
</tr>
<tr>
<td>Head circumference: absolute (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head circumference: percentiles</td>
<td>A &lt;3rd</td>
<td>B 3rd-10th</td>
<td>C &gt; 10th</td>
</tr>
<tr>
<td>Ponderal index (kg/m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**MATERNAL DATA**

<table>
<thead>
<tr>
<th>Age: first 6 digits of ID number</th>
<th>A ≤16</th>
<th>B 16-35</th>
<th>C 35-40</th>
<th>D &gt;40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age classification</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>A &lt;18.5 underweight</td>
<td>B 18.5-24.9 normal</td>
<td>C 25-29.9 GrI overweight</td>
<td>D 30-39 GrII overweight</td>
</tr>
<tr>
<td>BMI classification</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSF (mm)</td>
<td>A &lt;5th</td>
<td>B 5th-85th</td>
<td>C &gt;85th</td>
<td></td>
</tr>
<tr>
<td>TSF percentiles</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MUAC (cm)</td>
<td>A &lt;5th</td>
<td>B 5th-85th</td>
<td>C &gt;85th</td>
<td></td>
</tr>
<tr>
<td>MUAC percentiles</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UAMA (cm²)</td>
<td>A &lt;5th</td>
<td>B 5th-85th</td>
<td>C &gt;85th</td>
<td></td>
</tr>
<tr>
<td>UAMA percentile</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spacing pregnancy (mo)</td>
<td>A &lt;18 mo</td>
<td>B &gt;18 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spacing categories</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure mmHg</td>
<td>A Yes</td>
<td>B No</td>
<td>C Controlled with medication</td>
<td></td>
</tr>
<tr>
<td>---------------------------</td>
<td>-------</td>
<td>------</td>
<td>-------------------------------</td>
<td></td>
</tr>
<tr>
<td>Hypertension during 2nd trimester</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>A Yes</td>
<td>B No</td>
<td>C Yes, stopped before 16 weeks gestation</td>
<td></td>
</tr>
<tr>
<td>Alcohol use</td>
<td>A Yes</td>
<td>B No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV status</td>
<td>A Positive</td>
<td>B Negative</td>
<td>C Undetermined</td>
<td></td>
</tr>
</tbody>
</table>