Ethnic and Maternal Determinants of Fetal Growth in Normal Pregnancies.

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Abstract

Background, hypotheses and aims.

Standard ultrasound biometry charts are derived from a European population. It is known that there is a difference in birthweight in babies born to mothers of different ethnic groups.

The aim was to evaluate the rate of growth in fetuses from different maternal ethnic groups using standard and novel ultrasound biometry measurements in normal pregnancy.

The hypotheses are that:

1. fetal growth in different ethnic groups is characterised by different growth patterns of skeletal and soft tissue biometry.
2. the difference in fetal growth between these ethnic groups is due to maternal anthropomorphic characteristics.

Methods

This was a longitudinal observational ultrasound study.

Participants were healthy pregnant women whose primary ethnicity was European (NZE), Māori, Pacific Island or Indian. Only pregnancies with normal outcomes were included.

Each participant was scanned at 4 weekly intervals from between 16 and 18 weeks to delivery.

Ultrasound measurements were Biparietal Diameter, Head Circumference, Humeral Diaphyseal Length, Abdominal Circumference and Femur Length. 3D ultrasound measurements were Thigh Circumference, partial Thigh Volume, Arm Circumference and partial Arm Volume.

Neonatal measurements were birthweight, head circumference, crown-heel length and thigh circumference.

Statistical analysis included multilevel linear mixed effects modelling, which accounts for correlation of longitudinal measurements.

Results

Maternal characteristics were similar, except for weight, between the ethnic groups.
There were significant differences in the longitudinal growth of skeletal growth parameters – BPD, HC and HDL particularly with slower growth rate in the Indian fetuses compared to the referent NZE.

Fetal soft tissue measurements showed different growth velocity compared to skeletal biometry from early third trimester. The increase in growth in the soft tissue was greater in the heavier ethnic group as well as in the height, and weight tertiles.

Multilevel modelling removed any significance for height and weight in the fitted equations leaving ethnic group.

**Conclusions**

Appropriate ethnic characteristics should be included in customised biometry charts.

Growth velocity of soft tissue may be useful to determine growth abnormalities, especially after 34 weeks. Soft tissue growth may help distinguish fetal growth restriction or SGA or if macrosomia is pathological in Pacific Island diabetics.
Acknowledgements

My grateful thanks go to my wife Sue, for her continual support and encouragement. An undertaking, such as a thesis, cannot be completed without sacrifices by other family members.

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The women and their families who gave up their time during the pregnancy.

Mike and Kylie, my son and daughter in law, for reading the draft and giving advice on writing. This was a little different from their usual science fiction and children’s story writing.

CMDHB librarians for prompt provision of reference articles.

Ethical Permission

Ethical permission for this study was given by the Northern Y Ethics committee Ref no NTY/06/05/032.

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<tbody>
<tr>
<td>ArmCirc</td>
<td>Arm Circumference</td>
</tr>
<tr>
<td>AVol</td>
<td>Arm partial Volume</td>
</tr>
<tr>
<td>AC</td>
<td>Abdominal Circumference</td>
</tr>
<tr>
<td>AGA</td>
<td>Appropriate for Gestational Age</td>
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<tr>
<td>ANOVA</td>
<td>Analysis of Variance</td>
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<tr>
<td>ASUM</td>
<td>Australasian Society for Ultrasound in Medicine</td>
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<tr>
<td>BF%</td>
<td>Percentage Body Fat</td>
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<tr>
<td>BPD</td>
<td>BiParietal Diameter</td>
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<td>BMI</td>
<td>Body Mass Index</td>
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<tr>
<td>BW</td>
<td>Birthweight</td>
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<tr>
<td>CHL</td>
<td>Crown Heel Length</td>
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<tr>
<td>CRL</td>
<td>Crown Rump Length</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>CMDHB</td>
<td>Counties Manukau District Health Board</td>
</tr>
<tr>
<td>CV</td>
<td>Coefficient of Variation</td>
</tr>
<tr>
<td>DOHaD</td>
<td>Developmental Origins of Health and Disease</td>
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<tr>
<td>E</td>
<td>New Zealand European (alternative to NZE) to allow alphabetical priority for reference level.</td>
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<tr>
<td>EFWH</td>
<td>Estimated Fetal Weight (Hadlock 4)</td>
</tr>
<tr>
<td>EFWL</td>
<td>Estimated Fetal Weight (Lee)</td>
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<tr>
<td>FGR</td>
<td>Fetal Growth Restriction</td>
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<tr>
<td>FL</td>
<td>Femur Length (Femoral Diaphyseal Length)</td>
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<tr>
<td>GA</td>
<td>Gestational Age</td>
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<tr>
<td>GDM</td>
<td>Gestational Diabetes Mellitus</td>
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<tr>
<td>GP</td>
<td>General Practitioner</td>
</tr>
<tr>
<td>g</td>
<td>grams</td>
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<tr>
<td>GV</td>
<td>Growth velocity</td>
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<tr>
<td>HC</td>
<td>Head Circumference</td>
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<tr>
<td>HCN</td>
<td>Head Circumference (Neonatal)</td>
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<tr>
<td>HDL</td>
<td>Humeral Diaphyseal length</td>
</tr>
<tr>
<td>ICC</td>
<td>Intra Class Correlation Coefficient</td>
</tr>
<tr>
<td>IGA</td>
<td>Individualised Growth Assessment</td>
</tr>
<tr>
<td>IOM</td>
<td>Institute of Medicine</td>
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<tr>
<td>IUGR</td>
<td>Intrauterine Growth Restriction</td>
</tr>
<tr>
<td>IVF</td>
<td>In Vitro Fertilisation</td>
</tr>
<tr>
<td>LGA</td>
<td>Large for Gestational Age</td>
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<tr>
<td>LMP</td>
<td>Last Menstrual Period</td>
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<tr>
<td>LOA</td>
<td>Limits of Agreement</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>LOS</td>
<td>Length of Stay</td>
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<tr>
<td>m</td>
<td>metres</td>
</tr>
<tr>
<td>mm</td>
<td>millimetres</td>
</tr>
<tr>
<td>NZDepI</td>
<td>New Zealand Deprivation Index</td>
</tr>
<tr>
<td>NZE</td>
<td>New Zealand European</td>
</tr>
<tr>
<td>OR</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>PCA</td>
<td>Principal Components Analysis</td>
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<tr>
<td>PI</td>
<td>Pacific Islander</td>
</tr>
<tr>
<td>PMR</td>
<td>Perinatal Mortality Rate</td>
</tr>
<tr>
<td>QLab</td>
<td>Quantification software for Philips Ultrasound (Trade Mark)</td>
</tr>
<tr>
<td>R</td>
<td>or R squared</td>
</tr>
<tr>
<td>RR</td>
<td>Relative Risk</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SGA</td>
<td>Small for Gestational Age</td>
</tr>
<tr>
<td>SGAcust</td>
<td>Small for Gestational Age customised</td>
</tr>
<tr>
<td>SGApop</td>
<td>Small for Gestational Age by population centiles</td>
</tr>
<tr>
<td>SOMANZ</td>
<td>Society of Obstetric Medicine of Australia and New Zealand</td>
</tr>
<tr>
<td>ThC</td>
<td>Thigh Circumference</td>
</tr>
<tr>
<td>ThCN</td>
<td>Thigh Circumference (Neonatal)</td>
</tr>
<tr>
<td>TOBEC</td>
<td>Total Body Electrical Conductivity</td>
</tr>
<tr>
<td>TVol</td>
<td>Thigh partial Volume</td>
</tr>
<tr>
<td>Z score</td>
<td>observed growth rate – group mean growth rate) / (group growth rate SD).</td>
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CHAPTER 1

INTRODUCTION AND BACKGROUND

1.1 Background and Overview.
The descriptions of normal fetal growth and normal size at birth are challenging concepts, not the least because there are many factors which influence these measures. ‘As recently as 1968, little was known about human fetal growth. Kloosterman, described knowledge at that time in the following way; ‘How intrauterine growth processes during a normal pregnancy evolve and what regulates these processes in humans is practically unknown. The fact is that fetal growth velocity differs and that it is malpractice to use birth weight as a measure for maturity at birth. An early born giant and a late born dwarf with a similar birth weight can differ largely in maturity and development.” (Verburg 2007).

Many studies have demonstrated a difference in mean birthweight at term between ethnic groups (McCowan L 2004). It is possible that differences in birthweight are related to ethnicity. It is also possible that the apparent differences are due to the differences in height and or weight of the mother, or other maternal characteristics, possibly operating through the concept of maternal constraint.

Many basic issues in the assessment of fetal growth have yet to be addressed (such as whether fetuses of different race/ethnic groups have similar growth patterns and what is normal fetal growth at different stages of gestation (Zhang J 2010)?

If differences in measurements of longitudinal fetal growth between ethnic groups are demonstrated, are they due to the ethnicity, or do they relate to other maternal characteristics such as height, weight or BMI?

This thesis reports a longitudinal study of the growth of individual normal fetuses in terms of various fetal biometric measurements and relates these to maternal ethnicity, height, weight and BMI.

1.2 Why birthweight matters.
The terms estimated fetal weight and fetal growth are often used almost interchangeably in the medical literature. However they are not the same. Growth is a dynamic assessment of parameters that are measured on at least two occasions separated by a period of time. The summation of the growth of all fetal parameters contributes to the eventual birthweight.
1.2.1 Short term consequences of abnormal birthweight

Normal birthweight is a surrogate measure for appropriate fetal health and nutrition.

Birthweight is often categorised as large for gestational age (LGA), appropriate for gestational age (AGA), or small for gestational age (SGA). Abnormal birthweight (LGA or SGA) is associated with an increased likelihood of perinatal complications. Thus, screening for, and management of, abnormal fetal growth are important aspects of antenatal care.

Graafmans (Graafmans WC 2002) used birth registries from 7 European countries to compare modal birth weights to country specific perinatal mortality curves. That study showed the perinatal mortality nadir shifted in the same direction as the modal birth weight, suggesting that there is an ideal birth weight and that ideal is related to population characteristics.

**Fig 1.1** Comparison of birthweight distribution (A) and perinatal mortality curves (B) in two different populations. (Graafmans WC 2002) – reproduced with permission.
The Graafmans’ graph only demonstrates the end point of fetal growth, which is the birthweight, and is irrespective of the rate at which that weight was achieved. An ideal classification of fetal growth should have the ability to distinguish accurately between normal and abnormal growth as determined by associated perinatal morbidity and mortality, or even life-course morbidity.

Zhang stated that, at most gestational weeks, perinatal morbidity and mortality rates increase when the fetal size moves farther away from the “optimal” size (Zhang J 2010). Again this statement does not mention a rate of growth to determine the fetal size.

Small for Gestational Age (SGA) is usually defined as a birthweight or estimated fetal weight below the 10th centile for gestational age (Thompson JM 2001) although some definitions use 5th or 3rd centiles (Zhang J 2010), while others use less than 2 standard deviations below the mean (Maršál K 2009).

Intrauterine Growth Restriction (IUGR) is defined as a failure of the fetus to reach its growth potential (Goldenberg RL 1997). IUGR may be considered a postnatal diagnosis after appropriate paediatric assessment of the neonate. Intrauterine growth restriction is also known as Fetal Growth Restriction (FGR). This latter terminology makes it clearer that it is the fetus that is small.

Due to confusing terminology, there is an obvious lack of uniform diagnostic criteria. At present, many authors do not distinguish between the terms ‘small for gestational age’ (SGA) and ‘intrauterine growth restriction’ (IUGR). These two clinical entities are not the same. The term ‘SGA’ should be used for an infant who has failed to achieve a weight threshold (usually defined as the 10th percentile). Conversely, an IUGR infant has, by definition, not reached his/her genetic growth potential due to a lack of nutrition that has occurred in utero. The birthweight of the IUGR baby may or may not be below the 10th percentile. Thus an IUGR fetus may or may not be SGA but IUGR always implies a pathological process (Bamber C 2004).

Growth-restricted fetuses are at increased risk of intrauterine fetal death, fetal distress in labour, birth asphyxia, admission to the neonatal unit and infant death, whereas SGA fetuses may be constitutionally small and not be at the same risk of adverse perinatal events (Bamber C 2004).

For the purposes of this thesis SGA was defined as a birth weight below the 10th centile for gestational age using customised birthweight centiles (see section 1.6.8).

The terms macrosomia and Large for Gestational Age (LGA) are used to describe excessive birth weight. There is controversy in the literature as to whether macrosomia should be defined as an actual birth weight of >4000 g (Boulet SL 2003) or 4500 g (Mocanu EV 2000) for term babies, or as a birthweight > 90th centile on a population (Jolly MC 2003) or a customised chart (Larkin JC 2011).
Macrosomia defined as a birth weight >4500 g has been reported to affect 3.4% of live-born infants (Heiskanen N 2006), although this depends on the incidence of diabetic pregnancies as well as the population. A birthweight of > 4500 g was more common in Pacific Island mothers (23 out of 266) and did not occur in mothers from the Indian subcontinent (0 out of 73) in a study of 611 women (Parry G 2009 unpublished data).

Macrosomia defined as birthweight > 4500 g, and especially > 5000 g is associated with increased risks of stillbirth, neonatal mortality (especially because of birth asphyxia), birth injury, neonatal asphyxia, meconium aspiration and caesarean delivery (Zhang X 2008).

Macrosomia is associated with a risk of prolonged labour, maternal trauma, perinatal mortality, asphyxial injuries, meconium aspiration, shoulder dystocia, soft-tissue trauma, humeral and clavicular fractures, brachial plexus and facial palsies (Salomon 2010).

Pasupathy (Pasupathy D 2011) compared adverse birth and neonatal outcomes between term infants defined as macrosomic by absolute birthweight compared with large for gestational age (LGA) defined by customised centiles. That study demonstrated both maternal and fetal consequences of LGA. In LGA defined by customised centiles caesarean section was increased 1.6 times compared to LGA defined as >4000 g. There was a similar increase for post-partum haemorrhage. Adverse birth and neonatal outcomes were more common when LGA was defined by customised centiles compared to fetal macrosomia defined as birthweight >4000 g but AGA.

Larkin (Larkin JC 2011) concurred with the above findings and found that customised LGA infants carried increased risk of shoulder dystocia, third- or fourth-degree laceration, and cephalopelvic disproportion. LGA (customised) infants that did not meet conventional criteria for LGA/macrosomia were at increased risk of all measured outcomes.

In this thesis LGA was defined as weight above the 90th centile for gestational age using customised birthweight centiles.

The terms IUGR and macrosomia have not been used in this thesis except when quoting from the literature.

1.2.2 Long term consequences of abnormal birthweight.
As well as immediate peripartum consequences there are long term consequences of an abnormal birthweight. Epidemiological studies over the last 15 years have demonstrated that size at birth (both small and large) is associated with an increased risk of adult cardiovascular disease and type 2 diabetes (Barker 1997; Hales CN 2001; Ozanne SE 2004).

Durmuş and Mook-Kanamori (Durmuş B 2010; Mook-Kanamori 2010) have described a positive association between fetal and postnatal growth rates and the risk of obesity during early
childhood. However, the relationship between birth weight and obesity is complicated. Durmuş demonstrated that children growing in the highest quintile of estimated fetal weight during the first half of pregnancy have a higher peak weight velocity during the first month after birth. On the other hand, children with a birth weight in the lowest quintile also have an increased peak weight velocity, a phenomenon which is associated with an increased risk of obesity and higher blood pressure in adulthood.

Pryor (Pryor LE 2011) found that maternal BMI (odds ratio, 2.38; 95% confidence interval, 1.38-4.54 for maternal overweight and 6.33; 3.82-11.85 for maternal obesity) and maternal smoking during pregnancy (2.28; 1.49-4.04) were associated with an increasing BMI trajectory in childhood compared to those with a normal BMI trajectory.

Mehta (Mehta SH 2011) studied diabetes in pregnancy and childhood obesity, in an inner-city, African-American population and found that diabetes and maternal prepregnancy BMI were significant determinants of childhood obesity. When large-for-gestational age (LGA) was added into the model, diabetes was no longer significant (p=0.105); only LGA (p=0.008) and maternal prepregnancy BMI (p=0.032) were significantly associated with childhood obesity.

In a meta-analysis of 20 publications Yu (Yu Z 2011) found that that high birth weight (>4000 g) was associated with increased risk of childhood obesity (odds ratio [OR], 2.07; 95% confidence interval [CI], 1.91-2.24) compared with subjects with BW ≤ 4000 g. Subgroup analyses based on different growth and developmental stages (pre-school children, school children and adolescents) also revealed that high birthweight was associated with increased risk of obesity from childhood to early adulthood.

**Summary:** There are short and long term consequences of having an abnormal birthweight. To allow comparison between studies it is important to use standard definitions of abnormal birthweight. The long term consequences of abnormal birthweight may be confounded by the influence of postnatal feeding on growth in childhood.

**1.2 Factors influencing birthweight**

Fetal growth determines size at birth. Therefore factors influencing size at birth are those which influence fetal growth. Some of the currently known factors include maternal, fetal and paternal factors as well as external factors.

Maternal factors include:
1. Ethnicity
2. Parity
3. Maternal age
4. Maternal diet
5. Maternal phenotype
6. Maternal prepregnancy BMI
7. Maternal weight gain in pregnancy
8. Uterine constraint
9. Medical disease e.g. diabetes, Hypertension of Pregnancy
10. Maternal smoking
11. Heritability

Paternal factors include
1. Height
2. Ethnicity

Fetal factors include
1. Fetal gender
3. Gestation at birth
4. Multiple pregnancy
5. Congenital abnormalities

Placental factors include
1. Confined Placental Mosaicism
2. Abnormal Placental Development

External Factors include
1. Environment e.g. altitude
2. Socioeconomic.

The influence of a number of these factors is discussed below. Some of these factors may act together e.g. ethnicity and socioeconomic status may influence environment, nutrition and smoking.

1.3.1 Maternal Factors

1.3.1.1 Ethnicity
Studies in the United States and United Kingdom have documented substantial ethnic differences in birth weight and rates of SGA (Singh GK 1994; MacDorman MF 2002; Alexander GR 2003; David RJ 1997; Vangen S 2002). Black infants had a mean birth weight that was approximately 250 gms lower than white infants in a study from the United States (Singh GK 1994). In Norway, mean birth weight in infants of Pakistani women was about 300 gms lower than the mean birth weight in infants of Norwegian women (Vangen S 2002).
A study by Westerway highlighted differences in birth weight between the Caucasian and Vietnamese babies seen in the Western Sydney Health birth statistics in 1996, with lower birthweight in the Vietnamese (Westerway SC 2005).

Denham (Denham M 2001) compared black and white term neonates in the USA by sampling a low income stratum, and using five anthropometric measures in addition to birth weight. Race was self-determined. White male neonates were significantly larger than black male neonates in birth weight, length and head and arm circumference. Among female neonates none of the anthropometric dimensions differed between blacks and whites, suggesting an effect of fetal gender as well as ethnic group.

This same study (Denham M 2001) used principal components analysis to reduce the anthropometric dimensions to two summary measures: body size and composition. When controlling for social and biological variables, race and infant sex were significant predictors of body composition, but not body size. This study highlighted that a long lean baby and a short fat baby with a very different body composition could have the same birthweight.

In a study from Hawai’i, Crowell (Crowell DH 2007) found that Samoans consistently displayed significantly the largest mean birth weight, whether based on single or mixed racial-ethnic parentage. After covariate adjustment mean birth weight was significantly related to Samoan maternal racial-ethnic parentage followed by Samoan paternal racial-ethnic parentage. The conclusion was that maternal ethnicity has a key role in determining birth-weight.

**Summary:** The literature has shown in many studies that there is a difference in mean birthweights in different ethnic groups. Ethnicity is therefore an important factor to take in to account in any study of fetal growth. The Crowell study demonstrated that it is maternal rather than paternal ethnicity that is the more important contributing ethnicity.

**1.3.1.2 Parity**

It is well described that the firstborn infant is smaller than the second or third. Infants of primiparous pregnancies were lighter, shorter, had smaller head circumferences and were also thinner (lower ponderal index) at birth compared with other infants (Ong KK 2002). Many other studies have confirmed that increasing parity is associated with increasing birthweight (Meis PJ 1995; Kramer MS 1999; Thompson JM 2001; Dunger DB 2007).

The magnitude of the reduction in birth size of a firstborn infant is about 200 g, which is not dissimilar to the effect of smoking (Gluckman PD 2004).
1.3.1.3 Maternal age

Women over 35 years of age have been found in several studies to have an elevated risk of SGA (Meis PJ 1995; Kleijer ME 2005; Odibo AO 2006). Others have found advanced maternal age was either not a risk factor for SGA or the effect of maternal age was no longer significant after adjustment for associated factors (Kramer 1987; Lang JM 1992; Spinillo A 1994; Kramer MS 1999).

A recent population-based, cross-sectional study of North Carolina births from 1999 to 2003 (Swamy GK 2010) demonstrated that birth order exerted a greater influence on birthweight than maternal age. Race-specific modelling in that study of non-hispanic white, hispanic and non-hispanic black showed among all racial subgroups, birth order had a greater influence on birthweight than maternal age, with the largest incremental increase from first to second births. Among non-hispanic black, birth order accounted for a smaller increment in birthweight than for non-hispanic white and hispanic women.

In teenage pregnancies (Khashan AS 2010) showed that birthweight was reduced in the first (mean difference = -24 g; [95% CI: -40, -7]) and second (mean difference = -80 g; [95% CI: -115, -46]) time mothers aged 14-17 compared to the reference group (age 20-29). However, in that study, Khashan commented that the association between young maternal age and birthweight could be partly related to the confounding effects of smoking after adjustment for smoking.

Cooper (Cooper LG 1995) using univariate analyses indicated that the youngest adolescents were at greatest risk for negative birth outcomes including very preterm and preterm delivery, low birth weight, SGA, and neonatal mortality. Logistic regression analyses showed similar results, with the exception that SGA rates were not different.

Therefore the conclusion was that, in teenage pregnancies, the risk is that of preterm birth rather than SGA.

1.3.1.4 Maternal diet

Maternal nutritional status before and during pregnancy is important for the growth and development of the fetus (Thompson DM 2008).

Dietary patterns

Knudsen (Knudsen VK 2008) studied dietary patterns and related these to birthweight. Two major dietary patterns were defined: the first pattern was characterized by red and processed meat and high-fat dairy intake. The second pattern was characterized by intake of vegetables, fruits, poultry and fish. Women were classified into three classes according to their diet: the first class had high intake of foods of the first dietary pattern, and was classified as 'the western diet', the second class preferred foods of the second pattern and was classified as the 'health conscious'; and the third one had eaten foods of both patterns, and was classified as the
'intermediate'. The odds ratio of having a small for gestational-age infant (with a birth weight below the 2.5th percentile for gestational age and gender) was 0.74 (95% CI 0.64-0.86) for women in the health conscious class compared with women in the western diet class.

**Green leafy vegetables**
Green leafy vegetable intake during pregnancy has been positively associated with birth weight in a study in rural Indian women (Rao S 2001) and in a large Danish cohort (Mikkelsen TB 2006).

**Fruit**
The above quoted studies also investigated the relationship between fruit intake and infant birth weight. In the Indian study, fruit consumption at 28 weeks was associated with higher birth weight. A similar finding was noted by Mikkelsen (Mikkelsen TB 2006) who reported that the associations were stronger in women with BMI< 20.34.
A New Zealand study found that low intake of fruit around the time of conception was associated with a tendency to increased SGA (OR1.49 (95% CI 1.0-2.24)) (Mitchell EA 2004).
In mothers with SGA infants, McCowan (McCowan LM 2010) showed that one of the independent risk factors for normotensive-SGA was low pre-pregnancy fruit intake and one of the protective factors was a high pre-pregnancy green leafy vegetable intake.

**Milk**
In a comparison of pregnant women drinking ≥ 6 glasses/day with those drinking 0 glasses/day, Olsen concluded that milk intake in pregnancy was associated with higher birth weight for gestational age, lower risk of SGA, and higher risk of LGA (Olsen SF 2007).

Heppe (Heppe DH 2011) found that maternal milk consumption of >3 glasses/d was associated with greater fetal weight gain in the third trimester of pregnancy, which led to an 88-g (95% CI: 39, 135 g) higher birth weight than that with milk consumption of 0 to 1 glass/d. In addition, head circumference tended to be 2.3 cm (95% CI: -0.0, 4.6 cm) larger when mothers consumed >3 glasses/d. Maternal milk consumption was not associated with length growth. Maternal protein intake (p for trend = 0.01), but not fat or carbohydrate intake from dairy products was associated with higher birth weight. The association seemed to be due to milk protein, or milk components closely associated with protein, rather than to the fat or carbohydrate fraction of milk.

**1.3.1.5 Maternal Exercise**
Clapp (Clapp JF 2000) reported that previously physically inactive women who were assigned at gestation week 8 to exercise for 20 minutes 3-5 times per week for the remainder of pregnancy, gave birth to significantly heavier newborns than the control women (3750 g vs. 3490 g, p= 0.05).
Hopkins (Hopkins SA 2010) reported opposite results and concluded that regular exercise (five sessions of 40 min stationary cycling per week) was associated with lower birth weight (3426 g vs. 3569 g).
Haakstad (Haakstad LAH 2011) observed that the prevalence of newborns with birth weight ≥ 4000 g was 9.6% (n=5) in the exercise group vs. 17% (n=9) in the control group of that study.

A Cochrane review from 2010 concluded that in the few studies that have examined exercise as a determinant of birth weight, the results were inconsistent (Kramer MS 2010).

1.3.1.6 Maternal phenotype

The importance of the maternal phenotype has been shown in cross-breeding experiments and embryo transplant experiments in animals (Walton A 1938; Gluckman PD 1997). These studies thus indicate that maternal size is a major determinant of fetal growth (at least in the 2nd part of pregnancy) (Barker DJ 1993).

Brooks (Brooks AA 1995) investigated the relative role of environmental and genetic factors in the determination of birth weight following ovum donation. The only discernible factors that significantly influenced birth weight were gestational age and recipient's weight. Donor weight, her own birth weight, and the birth weight of the donor's own children were not significantly correlated with the birth weight of the child following ovum donation. It was concluded that the environment provided by the human mother is more important than her genetic contribution to birth weight.

Leary (Leary S 2006 (a)) in a study from many countries showed that mother-baby relationships were phenotypically similar across populations, although some were stronger in developing countries. Maternal height was generally the strongest predictor of neonatal length, maternal head circumference of neonatal head circumference, and maternal skinfold thickness of neonatal skinfolds. The conclusion was that differences in maternal body composition accounted for a large part of the geographical variation in neonatal phenotypes.

Leary in another paper using the same cohorts (Leary S 2006 (b)) compared several studies of body proportions in newborns of at least 37 weeks from several different geographic areas. In this study neonates in Europe were the largest, followed by Jamaica, East Asia (China), then Africa and South Asia. Birthweight varied widely between countries (mean values 2730 g to 3570 g), but in contrast, head circumference was similar in all except China (markedly smaller). The main difference in body proportions between populations was the head to length ratio, with small heads relative to length in China and large heads relative to length in South Asia and Africa. Other characteristics seen in specific populations included relative adiposity in the Indian neonates; they were smaller in all dimensions than European neonates, but their subscapular skinfolds were similar. Also, the Chinese neonates had short legs but long bodies, while those from India had short bodies but long legs.

In all settings, females were smaller than males, first borns were smaller than infants from subsequent births, and neonatal size increased as mothers became older. Despite these differences in overall size across the sex, parity and maternal age subgroups, within each
country, neonates were a similar shape in each subgroup; e.g. females were smaller than males in China, but both had small heads in relation to length.

1.3.1.7 Maternal prepregnancy Body Mass Index (BMI)
Neonates born to mothers who have a normal BMI have significantly less total fat and more lean mass than neonates born to overweight/obese mothers (Hull HR 2008). Silliman (Silliman K 1995) measured neonatal and maternal body fat. At birth, maternal adiposity (% body fat) was significantly associated with infant adiposity ($r = 0.37$, $p < 0.05$).

Frisancho (Frisancho AR 1997) performed anthropometric measurements on 4,952 mothers and their neonates from a Peruvian urban population. Based on age-specific percentiles, the mothers were separated into categories of short and tall stature, high and low fat, and high and low muscle mass. The study reported that: (1) tall and short mothers characterized by similar subcutaneous fat and upper arm muscle area had newborns with similar birth weight and length; (2) mothers characterized by high subcutaneous fat had heavier and fatter, but not longer, newborns than mothers with low subcutaneous fat; (3) mothers characterized by high upper arm muscle area had heavier, leaner and longer newborns than mothers with low upper arm muscle area; (4) mothers characterized by high muscle and high fat had heavier and longer newborns than mothers with high muscle and low fat; but (5) mothers characterized by high muscle and low fat had heavier and longer newborns than mothers with low muscle and high fat. On the basis that subcutaneous fat and arm muscle area reflect calorie and protein reserves respectively, it was concluded that an increase in maternal calorie reserves results in increased infant fatness but a lesser increase in linear growth.

1.3.1.8 Maternal weight gain
Reynolds (Reynolds RM 2010) demonstrated that higher offspring percentage body fat was independently associated with higher pregnancy weight gain, independent of maternal BMI. There were similar significant associations between increased maternal BMI, greater pregnancy weight gain, and increasing parity with greater offspring waist circumference, BMI, and fat mass index.

Crane (Crane JM 2009) found that the effects of gestational weight gain on pregnancy outcome depend on the woman's pre-pregnancy BMI. Pregnancy weight gains of 6.7-11.2 kg in overweight and obese women and less than 6.7 kg in morbidly obese women were associated with a reduction in the risk of adverse outcome. In women with normal pre-pregnancy BMI, excess weight gain was associated with increased birth weight ≥ 4000 g (OR 1.21; 95% CI 1.10-1.34). In overweight women, excess weight gain was associated with increased birth weight ≥ 4000 g (OR 1.30; 95% CI 1.15-1.47). In women who were obese or morbidly obese, excess weight gain was associated with increased birth weight ≥ 4000 g (OR 1.20; 95% CI 1.07-1.34). In women who were of normal weight, overweight, or obese, the rate of birth weight<2500 g or birth weight ≥
4000 g was lower in women with recommended weight gain than in those with excess weight gain.

Cedergren (Cedergren M 2006) agreed that outcome depended on pre-pregnancy BMI and found that there was a 2-fold increased risk of LGA among average and overweight women with excessive weight gain.

Rode (Rode L 2007) also found that birth weight greater than or equal to 4,000 g increased with an increasing weight gain in underweight and normal-weight women, but the association was less apparent in overweight and obese women.

Hedderson (Heddersson MM 2006) adjusted for age, race-ethnicity, parity, plasma glucose screening value, and difference in weeks between delivery and time when last weight was measured and found that women who gained more than recommended by the Institute of Medicine (IOM) were three times more likely to have an infant with macrosomia (odds ratio [OR] 3.05, 95% confidence interval [CI] 2.19-4.26) than women whose weight gain was in the recommended range. Women who gained less than the IOM recommendations were less likely than women in the recommended range to have an infant with macrosomia (OR 0.38, 95% CI 0.20-0.70).

1.3.1.9 Maternal constraint

Gluckman (Gluckman PD 2004) stated that the major non-genetic factor determining the size of the fetus at term is maternal constraint. This term refers to a set of poorly defined processes by which maternal and uteroplacental factors act to limit the growth of the fetus, presumably by limiting nutrient availability and/or the metabolic-hormonal drive to grow.

Maternal constraint can be divided into supply-limited constraint (e.g. maternal size) and demand-driven constraint (e.g. twinning).

There are clearly many genetic factors that might influence the growth of the fetus and placental function, but it has been recognized for many years that fetal growth is relatively more sensitive to the fetal environment; which, in turn, is primarily determined by maternal physiology and placental function. Classically, this has been demonstrated in studies of the correlations in birth weights within families. While siblings have correlated birth weights, the genetic variance ($r^2$) is only about 0.4, suggesting that environmental influences are as dominant as genetic influences.

Furthermore, when the correlation for birth weight is examined for half siblings with the same mother, it is about 0.5, whereas it is very low for half siblings with the same father; this suggests limited involvement of the paternal genome in determining birth size. In contrast, maternal birth size and infant birth size are correlated, showing a maternal intergenerational effect on birth size.
Maternal constraint seems to be about having a fetus appropriate for the maternal size for parturition and postnatal nurturing. The neonatal phenotype is the outcome of the conditions prevailing during the pregnancy.

1.3.1.10 Maternal Medical disease

Medical diseases, such as hypertension of pregnancy, have an increased association with SGA babies (Heard AR 2004), whereas gestational diabetes is more likely to be associated with large for gestational age babies (Wong SF 2006).

Hypertensive disease in pregnancy

It is well recognised that pre-eclampsia is associated with an increased risk of infants being born small for gestational age (Xiong X 1999; Odegard RA 2000; Xiong X 2004; Rasmussen S 2003) and that the risk is greatest in women with early onset disease. Early onset pre-eclampsia is associated with abnormal placental perfusion whereas this is uncommon in later onset pre-eclampsia (Escudero C 2009)

Recent data from a large cohort of nulliparous pregnancies (n =1847) quantified the risk of SGA according to the gestation at delivery in women with pre-eclampsia and gestational hypertension. The risk of SGA by customised centiles was greater in women with pre-eclampsia needing delivery <34 weeks and between 34 and 37 weeks compared with those delivered at term, that is, >37 weeks (57.1% SGA at <34 weeks (RR: 3.1 (95% CI: 2.3–4.2)), 31.7% SGA at 34–36. 6 weeks (RR: 1.7 (95% Cl: 1.2–2.5) and 18.3% SGA at term (RR: 1.0)) (Groom KM 2007). A similar pattern of increasing SGA was also found in gestational hypertension (57.6% SGA at <34 weeks (RR: 4.8 (95% CI: 3.4–6.6), 30.5% SGA at 34–36.6 weeks (RR: 2.5 (95% CI: 1.8–3.5) and 12.1% SGA at term (RR: 1.0)) (Groom KM 2007).

Chronic hypertension

Population-based studies from several countries have shown that chronic hypertension, one of the most common medical conditions in pregnancy, is associated with increased SGA (Allen VM 2004; Zetterstrom K 2006; Gilber WM 2007). SGA is more common with superimposed pre-eclampsia, 48% versus 21% in chronic hypertension with superimposed pre-eclampsia compared with chronic hypertension alone, (RR: 2.30 (95% CI: 1.85–2.84)) (Chappell LC 2008). Sibai (Sibai BM 1983) reported that women with mild chronic hypertension did not have increased SGA unless they developed superimposed pre-eclampsia. McCowan (McCowan LM 1996) also reported higher rates of SGA in women with chronic hypertension and superimposed pre-eclampsia (OR: 5.6(95% CI: 1.8–16)) but in contrast to Sibai (Sibai BM 1983) also found increased SGA in women with chronic hypertension without preeclampsia (OR: 2.9 (95% CI: 1.6–5.0)).
**Diabetes with vascular disease**
Large for Gestational Age (LGA) is typically associated with diabetes but vasculopathy (retinopathy and/or nephropathy and/or pre-existing hypertension) is associated with increased SGA. Haeri (Haeri S 2008) in a prospective study of 340 diabetic women reported odds ratios for SGA up to 10.4 depending on the type of vasculopathy.

Howarth (Howarth C 2007) using customised birth weight centiles also found diabetic women with vascular disease had increased SGA (OR: 6.0(95% CI: 1.5–23)).

**Placental Abruption**
Large studies in women with placental abruption have shown increased rates of SGA (Kramer MS 1997; Nath CA 2008; Ananth CV 1999). The risk of SGA is greater for infants born preterm compared with those born at term, suggesting more marked placental pathology with preterm abruption.

**1.3.1.11 Maternal smoking**
In Western countries smoking is one of the most important pathological factors which is associated with a reduced birthweight.

Cigarette smoking by pregnant women has a dose dependent relationship with reduced birthweight (Abel 1980; Cliver SP 1995; Bernstein IM 2005; Hebel JR 1988).

In an ultrasound based study Bernstein (Bernstein IM 2000) demonstrated reduced fetal abdominal circumference growth as well as thigh circumference growth between 27 and 37 weeks in smokers.

Compared with infants of nonsmokers, at birth, infants of smokers were lighter, shorter, and had smaller head circumferences but were no different in the ratio of weight-for-height (ponderal index \( p=0.7 \)) (Ong KK 2002). Kallen (Kallen 2000) using the Swedish Medical Birth Registry, demonstrated that there was an increased risk of small head circumference for gestational age in women who smoked. ORs (with 95% CI) were for any smoking, <10, and \( \geq 10 \): 1.58 (1.55-1.61), 1.48 (1.45-1.51), and 1.74 (1.70-1.79), respectively.

Smoking cessation programs in pregnancy have been shown to reduce the rates of low birth weight and preterm birth (Lumley J 2004). McCowan (McCowan LM 2009) has shown that in pregnant women who stopped smoking before 15 weeks gestation, rates of SGA and spontaneous preterm birth did not differ from rates in non-smokers.
1.3.1.12 Heritability

Heritability is the proportion of variability of a phenotype which can be explained by shared genes and environment.

In a parent-offspring cohort amongst more than 100,000 families, the fetal genetic contribution to birth weight was suggested to be around 31%, while for birth length it was about 27% (Lunde A 2007) Maternal genetic factors accounted for 22% and 19% of the variance in birth weight and length, respectively.

The relatively higher fetal weight heritability estimates for maternal weight than for paternal weight is most likely a reflection of a shared maternal-fetal environment rather than shared genetic factors (Mook-Kanamori 2010) (see maternal constraint). It has been estimated that 62% of the variation of birth weight of the human fetus results from the intrauterine environment, compared with 20% and 18% from maternal and paternal genes (Godfrey K 1996). The intrauterine environment is therefore has a greater influence than genetic influences.

1.3.2 Paternal Factors

1.3.2.1 Height

In half-sibling studies, the predominant influence of the mother compared with the father, on birth weight has been demonstrated. There is a stronger correlation between the birth weights of half-siblings, who share the same mother than half-siblings who share only a father (Penrose L 1952).

Among half-siblings, related through only one parent, those with the same mother have similar birthweights, the correlation coefficient being 0.58. The birthweights of half-siblings with the same father are, however, dissimilar, the correlation coefficient being only 0.1 (Morton M 1995).

Several studies have examined the contribution of paternal height and/or weight to infant birth weight (Morrison J 1991; Wilcox MA 1995; Klebanoff MA 1998; Magnus P 2001). In most studies, paternal height but not weight was found to have an independent effect on birth weight with the tallest fathers having infants with birth weight 150–180 g heavier than the shortest fathers (Morrison J 1991; Wilcox MA 1995). As maternal height and weight have a more marked influence on infant birth weight than paternal size (Leary S 2006 (a)) adjustment for paternal characteristics has been considered unnecessary and impractical when defining SGA (Wilcox MA 1995).

Veena (Veena SR 2009) commented that birth weight is a composite measure, encompassing bone, fat and lean mass. The main purpose of that paper was to use anthropometry and principal components analysis (PCA) to describe maternal and newborn body composition, and
associations between them, in an Indian population. They also compared maternal and paternal measurements (body mass index (BMI) and height) as predictors of newborn body composition. In this Indian study they showed that parental height predicted neonatal leg length \( (p = 0.003) \) and concluded that newborn adiposity is related to maternal nutritional status and parity, while newborn length is genetically determined.

### 1.3.2.2 Paternal ethnicity

Simhan (Simhan H 2008) described the contribution of paternal race and parental racial discordance to preterm birth. Regardless of maternal race, paternal black race is associated with increased odds of preterm birth. Additionally, among white-black couples, the odds of preterm birth are greater if the mother is black than if the father is black. These data support the notion of a differential contribution of race on preterm birth depending on the parent of origin.

Bennett (Bennett A 2008) demonstrated that babies born at altitude with two Andean parents weighed 252 g more than their European counterparts, with the protective effect being proportional to the amount of Andean parentage and independent of maternal parity, body size, smoking, or socioeconomic status. Paternal compared with maternal transmission raised birth weight 81 g for a given ancestry group. They concluded that indigenous high-altitude ancestry protected against hypoxia-associated fetal growth reduction in a dose-dependent fashion consistent with the involvement of genetic factors. Further, some of the genes involved appeared to be influenced by parent-of-origin effects, given that maternal transmission restricted and paternal transmission enhanced fetal growth.

Crowell (Crowell DH 2007) performed a comparative study of racial-ethnic, gestational age and mean birth-weight differences in Hawai’i. Samoans consistently displayed significantly the largest mean birth weight whether based on single or mixed racial-ethnic parentage. After covariate adjustment mean birth weight was significantly related to Samoan maternal ethnicity, followed by Samoan paternal ethnicity.

Crowell (Crowell DH 2010) confirmed their findings in a birth weight analysis of single primiparous infants of Samoan, Caucasian, Chinese, Filipino, Hawaiian/Part Hawaiian and Japanese racial ethnic groups.

Khoury (Khoury MJ 1987) studied differences in the role of genetic factors in prematurity and intrauterine growth retardation with the use of data on 312 Amish singleton live children ascertained from Amish records in Lancaster County, Pennsylvania. Birth and death certificates were obtained on all children, and inbreeding coefficients of child, mother, and father were computed by use of the path method of tracing common ancestors in a unique genealogic registry of Amish ancestors dating back to the 1700s. Multivariate analysis with linear and log linear models showed that a lower mean gestational age and a higher risk of prematurity (less than 37 weeks) and borderline maturity (37 to 38 weeks) were significantly associated with increased
maternal inbreeding but not child or paternal inbreeding. On the other hand, a higher risk of intrauterine growth retardation (less than the tenth percentile in birth weight for gestational age) and mild intrauterine growth delay (tenth to twenty-fifth percentile) were associated with increased child inbreeding but not maternal or paternal inbreeding. The analysis suggests the presence of genetic heterogeneity in the etiology of prematurity and intrauterine growth retardation; while prematurity is mostly related to the maternal genotype, intrauterine growth retardation is related to the fetal genotype. The study reemphasizes the need for separating low birth weight into prematurity and intrauterine growth retardation in genetic and epidemiologic studies.

The conclusion is that the paternal influence on mean birth weight is less than maternal influence and that paternal influence may be most likely related to gestational age at delivery.

1.3.3 Placental Factors

1.3.3.1 Confined Placental Mosaicism (CPM)
In over 20% of pregnancies with idiopathic IUGR, chromosomal mosaicism confined to extra embryonic tissues (CPM) has been observed. CPM is the most common form of constitutional chromosomal mosaicism which is defined as at least two cell lines with different chromosomal complements in a fetoplacental unit derived from a single zygote. In CPM only the placenta is affected unlike in generalised chromosomal mosaicism where both the fetus and the placenta are involved (Lestou VS 1998).

1.3.3.2 Abnormal Placental Development
Alterations in trophoblast differentiation occur in various pathophysiological situations and underlie pregnancy disorders, such as preeclampsia and fetal growth restriction (IUGR) (Macara L 1996).

Preeclampsia and IUGR are associated with defects in endovascular invasion, where some spiral arteries are not invaded at all and some are superficially invaded, leading to lack of the normal physiological adaptation of spiral arteries to pregnancy, reduced blood flow into the intervillous space, and relative hypoxia/ischemia (Sebire NJ 2004; Scifres CM 2009).

Evers (Evers IM 2003) found that histological abnormalities such as the presence of nucleated fetal red blood cells, fibrinoid necrosis, villous immaturity and chorangiosis were observed more often in the diabetic placentae compared with the control placentae. These differences in histology were particularly observed when they compared both AGA-groups. LGA-control placentae showed a high incidence of histological abnormalities, almost comparable to the diabetic placentae. Only fibrinoid necrosis was significantly more common in the LGA-diabetic placentae. The difference between AGA- and LGA-diabetic placentae was related to relative placental weight. Placentae from LGA-non-diabetic women showed several similarities to those of women with diabetes.
Placentas with a displaced cord show markedly reduced transport efficiency, reflected in a smaller birth weight for a given placental weight. Placentas with a non-central cord insertion have a sparser chorionic vascular distribution, as measured by the relative vascular distance (Yampolsky M 2009).

1.3.4 Fetal Factors.

1.3.4.1 Fetal gender
Lampl (Lampl M 2009) demonstrated that fetal gender modified the effects of maternal height and weight on birth weight. This study used a linear mixed effects model to analyse the interaction of different effects in 3495 pregnancies from Santiago, Chile. Interaction terms between sex, maternal height, and maternal weight identified that male infants were more influenced by maternal weight among shorter mothers and more influenced by maternal height among lighter mothers, compared to female infants. A male advantage of 60 g occurred among neonates of the shortest and lightest mothers, compared to 150 and 191 g among short and heavy mothers, and tall and light-weight mothers, respectively.

Pang (Pang MW 2003) demonstrated that fetal gender had a statistically significant influence on the final regression models of biparietal diameter, head circumference and femur length in a population that was 98% Chinese.

Hindmarsh (Hindmarsh PC 2002) used anthropomorphic measurements at birth and analysed them by principal components to explain shape at birth. Birth measures were also related to antenatal growth measurements to determine the strength of ultrasound evaluation in determining subsequent growth. There was statistically significant sexual dimorphism in all measures at birth, with males heavier, longer, and leaner than females.

Melamed (Melamed N 2011) performed a retrospective study on the effect of fetal sex on intra-uterine growth patterns of ultrasound biometry measurements and their ratios. Sex-specific regression models for the mean values of these measurements at each gestational week were generated. They concluded that female fetuses grow significantly slower than male fetuses, and these differences are observed from early gestation.

This same group (Melamed N 2011) compared the accuracy of sonographic fetal weight estimation between male and female fetuses using 3,672 sonographic weight estimations performed within 3 days prior to delivery, using 8 different regression models. They found that in seven out of the eight models tested, a male fetus was associated with a significantly lower systematic error compared with a female fetus (-1.2% to 2.1% vs. 2.3% to 6% respectively, P<0.001). On multivariate analysis, fetal sex was independently associated with sonographic accuracy so that the likelihood of a weight-estimation within 10% of birthweight was 30% higher for male compared with female fetuses. This association was independent of birthweight.
Thompson (Thompson JMD 1994) showed that there is a difference of 100 g between males and females in NZ newborn.

Fetal gender may not always be ascertained before delivery because of parental wishes or because it has not been imaged.

1.3.4.2 Gestation at birth

Gestation at delivery is the variable with the most important influence on birthweight. In the United States several studies have shown that risk of preterm or very preterm delivery is increased in black, Mexican- American and Asian women (Shiono PH 1986; Schieve LA 1996). In the United Kingdom an increased risk of preterm delivery is observed in Afro-Caribbean and African women (Aveyard P 2002).

Troe (Troe EJ 2008) in his PhD thesis of the ‘Ethnic differences in fetal growth, birth weight and infant mortality’, studied 1494 women from Rotterdam, The Netherlands. He demonstrated that, compared to the Dutch population, shorter gestational age was of more common in the Antillean and Surinamese populations, which was consistent with previous studies in the Netherlands indicating that preterm birth is more frequently seen in the black (mainly Surinamese Creole) and Hindustani populations. In that study, there was a higher proportion of preterm births (<37 weeks) in the black population, compared to the Dutch population. Thus the influence of ethnicity on birthweight in previous studies may be, at least in part, related to length of gestation. Troe stated in the study that it was insufficiently powered to comment whether socioeconomic status was a co-confounder.

1.3.4.3 Multiple pregnancy

Twins are born both smaller and earlier than singletons (Buckler JM 2004). Twin growth rate in humans has been documented ultrasonographically to be reduced in late gestation. The supposition is that this reduced rate of growth and the shortened gestational length are secondary to constraints of uterine size (Bloomfield FH 2006). There are some human data to support this hypothesis. In multiple pregnancies in which fetal number was reduced early in pregnancy, either spontaneously or medically, fetal size and gestation length are related to the initial number of fetuses, rather than the number present at delivery (Alexander JM 1995; Pinborg A 2005).

1.3.4.4 Congenital Abnormality

Congenital abnormalities are an important cause of abnormal birthweight. Dolan (Dolan SM 2007) examined data from a large, prospective multi-centre trial, the First and Second Trimester Evaluation of Risk (FASTER) trial. A singleton liveborn with a birth defect was 3.6 times more likely to have low birth weight at less than 2,500 g (95% CI 3.0-4.3) and 11.3 times more likely to be very low birth weight (VLBW) at less than 1,500 g (95% CI 8.5-15.1).
Suresh (Suresh GK 2001) found major birth defects were present in 823 (4.3%) of 19,228 VLBW infants from 147 hospitals. The most common categories were chromosomal anomalies (20%); named syndromes, sequences, and associations (19%); and gastrointestinal (14%), cardiovascular (11%), and nervous system (10%) anomalies.

Chromosomal abnormalities are more common in antenatal statistics than in post natal series. Snijders (Snijders RJ 1993) performed fetal blood karyotyping in 458 fetuses referred for assessment of growth restriction at 17 to 39 weeks’ gestation. The fetal karyotype was abnormal in 89 (19%) of the cases. The most common chromosomal defect in the group referred at < 26 weeks’ gestation was triploidy; in those referred at ≥ 26 weeks, it was trisomy 18. Compared with those fetuses with a normal karyotype, the chromosomally abnormal group had a higher mean head circumference/abdominal circumference ratio.

Less commonly congenital abnormalities are found in LGA fetuses. Vora (Vora N 2009) describes the features of fetal overgrowth syndromes, including Pallister-Killian, Beckwith-Wiedemann, Sotos, Perlman, and Simpson-Golabi-Behmel. The overgrowth syndromes have significant clinical and molecular overlap, and are associated with developmental delay, tumours, and other anomalies.

### 1.3.5 External Factors

#### 1.3.5.1 Environment

Yip (Yip R 1987) measured the effect of altitude on birth weight. With 500 m gradations for altitude, a curvilinear dose-response relationship of birth weight reduction with increasing altitude was demonstrated. In comparison with neonates born at sea level, neonates born at higher altitudes (greater than 2000 m) had a twofold to threefold increase in intrauterine growth restriction.

Birthplace is also important in ethnicity studies. Li (Li D 1990) looked at the South East Asian population born in the USA and compared the birthweight with those who were born outside the USA. They showed an average increase in birthweight of 100 g in the children whose mother was born in the USA compared to those who were not. This may be related to dietary changes or socioeconomic differences.

Kinabo (Kinabo J 1993) examined the data of 19,783 full term singleton babies in Tanzania to determine the effect of seasonal variation on birth weight. Mean birth weight was low during the rainy season and high during the dry season, a period immediately after harvest. This observation was suggested to mean that mean birth weight varies with season. However, it may be a surrogate for nutritional intake due to food availability in different seasons and therefore would not be an independent effect.
1.3.5.2 Socioeconomic
A measure of socioeconomic status used in New Zealand is the Deprivation Index (NZDepI). It is based on nine variables, including income, employment, access to telephone, access to car, single parent family, educational qualifications, whether the property is owned and number of people per bedroom in a house. These variables are combined to provide a deprivation score for each meshblock in New Zealand. Meshblocks are geographical units defined by Statistics New Zealand, containing a median of approximately 90 people. The index of deprivation ranges from 1 to 10, where 1 represents the areas with the least deprived scores and 10 the areas with the most deprived. It should be noted that deprivation scores apply to areas rather than individual people.

In a New Zealand study Craig (Craig ED 2004) demonstrated that preterm birth and SGA were positively associated with teenage pregnancy and increasing NZDepI. However in the same study, Ekeroma (Ekeroma AJ 2004) found that despite residing in areas of high socioeconomic deprivation, which is associated with poor pregnancy outcomes for Māori and European/other women, Pacific women in these areas had better pregnancy outcomes, with lower preterm and SGA rates. An explanation for that may be due to the protective effect of obesity. SGA was defined by population centiles. Mantell (Mantell CD 2004) in another paper from that study also showed that Māori women experienced significant socioeconomic gradients in rates of SGA, with risk for Māori women in the most deprived NZDepI areas being double that of Māori living in affluent areas. No adjustment was possible in these studies for important confounders such as maternal BMI or smoking.

1.3.6 Summary
The literature shows that birthweight is influenced by many factors. Because birthweight is the measured outcome of fetal growth all those factors that are important for birthweight are also important in the assessment of the normality of growth in an individual fetus. Some of these factors can be easily measured, such as maternal height and weight. Other factors, such as maternal constraint, cannot be measured.

This thesis has concentrated on the maternal factors involved with fetal growth that are part of the normal antenatal clinical assessment i.e. parity, maternal height, weight and ethnicity. Factors that have been discussed above, such as smoking and maternal medical disease were exclusion criteria during recruitment, with the aim to remove confounding variables and to obtain a normal maternal phenotype in our study population. Other maternal characteristics data, such as diet and physical activity, which are not routinely collected, were also not included.

Fetal gender information was not collected antenatally but it was collected at delivery for post-delivery analysis.
1.4 Assessment of gestational age

The early assessment of gestational age is important for accurate assessment of fetal growth. Traditional thinking is that early growth is principally controlled genetically and occurs at a constant exponential rate with little biological variation (Pedersen NG 2008). Therefore the earlier in pregnancy gestational age is assessed, the more reliable the assessment will be.

1.4.1 Ultrasound dating of pregnancy

Menstrual age, taken as the first day of the last menstrual period (LMP), is used interchangeably with the term gestational age. Ultrasonic fetal measurement charts for the various parameters are based on menstrual age / gestational age. Assignment of gestational age based on LMP may cause problems with estimating the date of delivery. A discrepancy between observed and expected fetal size at the first ultrasound examination may principally reflect aspects of the menstrual history and, in particular, cycle length. Kramer (Kramer MS 1988) investigated the validity of GA estimation by LMP compared to ultrasound BPD measurement at 16 to 20 weeks in term, pre-term and post-term pregnancies and found that one in four pre-term and seven in eight post-term pregnancies were classified incorrectly when using LMP.

Up to 40% of women may have a discrepancy between menstrual dates and early ultrasound assessment of fetal size, despite accurate recall of the last menstrual period (Geirsson RT 1991; Nakling J 2005).

The accuracy of dating pregnancies by a certain LMP compared with ultrasound dating was tested by Campbell (Campbell S 1985), Waldenstrom (Waldenstrom U 1990) and Tunon (Tunon K 1996) who all found that a BPD between fourteen and twenty weeks was more reliable than a certain LMP in predicting the date of delivery.

Early ultrasound is commonly considered to provide a more valid estimation of gestational age than LMP dating (Taipale P 2001; Bennett KA 2004). Embryological studies have observed uniform development of the human embryo with small differences in size and age at different embryonic stages (Deter RL 1999). First-trimester growth studies in individual fetuses indicate that there is a change in length growth rate between 9 and 10 weeks, menstrual age. This is consistent with a shift in development from organogenesis to growth. However, disparities in growth may also occur at an early stage of pregnancy some of which may be due to chromosomal or structural abnormalities. Many of these abnormalities would be detected later in an individual pregnancy by appropriate screening.

1.4.2 Ultrasound measurement error

Correct cursor placement is critical for accurate measurements. Some of the early ultrasound systems used a very crude form of callipers, which could only measure in increments of five millimetres. Modern systems measure to an accuracy of half a millimetre and combined with the
high resolution of the scanning equipment, the ease of measuring fetal parameters has been
greatly improved. The fetal head and abdominal circumference charts formulated by Campbell
(Campbell S 1975), Hadlock (Hadlock FP 1982) and Deter (Deter RL 1982) used a digitised map
measurer on a polaroid image for measuring circumference. The possibilities for error were large
and yet their charts are still in common use.

In 1975, Robinson and Fleming published a critical evaluation (Robinson HP 1975) of a two-year
old preliminary communication on sonar CRL measurements (Robinson. 1973). The beam-width
effect was given particular focus in the analysis of random and systematic measurement errors,
resulting in a “corrected” CRL-table. The beam-width problem was hardly raised again until 20
years later, when Jago (Jago JR 1994) in a small-scale study found the FL significantly longer
when measured with an old scanner than with a new one.

Økland (Økland I 2011) looked at whether technical improvements reducing the beam width in
modern ultrasound machines affect fetal measurements in the lateral plane. Since the non-axial
measurements are typically influenced the most, this effect may have clinical implications for
ultrasound-based fetal age assessment, particularly femur length and Crown Rump Length
(CRL). Overall, the beam width was 1.08 mm narrower with the new machines than with the old
machines (95% CI, 0.50–1.65).

The lack of knowledge of technical development and its consequences for ultrasound equipment
in clinical use cause systematic errors, particularly in first trimester assessment of GA, giving
dating errors of up to half a week (Pretorius DH 1984; Pexsters A 2010) and erroneous risk
estimations in prenatal screening (Koster MP 2008). With the use of a modern scanner and an
old dating chart, the FL/CRL will be considered ‘too short’ (Jago JR 1994), fetal age is then
 underestimated and the predicted date of delivery is set too late, which of course may have
clinical consequences (Økland I 2011).

This thesis has accepted these potential errors and used the Australasian Society for Ultrasound
in Medicine (ASUM) charts (ASUM website www.asum.com.au) as confirmation of gestational
age, as these are the charts in common usage within the community and the thesis is assessing
growth rather than gestational age. The ASUM charts were derived from measurements of 500
patients between 5 and 11 weeks gestation age, performed in 27 ultrasound practices with
modern equipment. The population scanned was from a multicultural community in Sydney,
Australia.
1.5 Ultrasound Biometry

1.5.1 History
Antenatal ultrasound has become one of the clinicians’ most important tools for assessing fetal age, growth and wellbeing.
Obstetric ultrasound has been in use since the late nineteen fifties when Ian Donald and his team at the University of Glasgow’s Department of Midwifery began work on measuring the fetal head. In 1957 Donald, an Obstetrician, and Brown, an engineer, developed the world’s first compound contact scanner (Donald I 1958), which was a hand held system, followed in 1964 by the first commercial mechanical system. Donald (Donald I 1962) first measured the size of the fetal head with ultrasound.

Campbell (Campbell S 1969) developed a reproducible method for measurement of the BPD. The data for the early studies was collected on A mode, static B mode scanners and first generation real time systems with linear array transducers. Circumference measurements for both the head and abdomen studies were performed utilizing a hand held map measurer on a ‘Polaroid’ image. The margins for error were increased when compared with the state of the art real time sector ultrasound systems with electronic measuring facilities currently used for fetal assessment. The majority of these early studies were collected from predominantly white, middle class populations. There were no generally accepted criteria to follow for chart production, for example de Crespigny (de Crespigny L 1989) defined the week of gestation as being completed weeks (and days), whilst Hadlock (Hadlock FP 1982) used half weeks as the end point. This factor alone gave variations between charts of half a week.

1.5.2 Standard Biometry
Standard ultrasound biometry used to assess fetal size, gestation age and growth are the
- Biparietal Diameter (BPD)
- Head Circumference (HC)
- Abdominal Circumference (AC)
- Femur Diaphyseal Length (FDL or commonly shortened to FL)
All measurements are subject to error.
This error can be due to
- machine error if the machine has not been calibrated correctly
- resolution error, which is an inherent part of the physics of ultrasound
- observer error due to incorrect selection of the anatomical plane used for measurement as well as incorrect placement of the measuring callipers
- inter-observer variation
- incorrect selection of charts with the measurement that has been used being plotted on a chart that has been generated using a different measurement technique
- population error due to the graph being generated from a population with different characteristics
- error created with the use of modern equipment in conjunction with old charts, as outlined in section 1.4.2.

Smulian (Smulian JC 2001) showed in more than 1000 fetuses that, in his population, AC < 10\textsuperscript{th} centile from published nomograms had false negative rates that ranged from 11.3\% to 90.5\%, and for the more than 90\textsuperscript{th} centile these rates were 0 to 66.4\% across gestational ages from 10 to 40 weeks. That study concluded that institution-specific nomograms for fetal abdominal circumference measurements were important to avoid incorrect categorization of outer centiles.

1.6 Methods of assessment of normal growth

Fetal growth is measured in an attempt to detect abnormal growth. Much of the assessment to detect growth rate has measured biometry and size from cross-sectional data rather than growth from longitudinal data and is therefore not a true assessment of fetal growth rate.

Owen investigated various ways of interpreting serial biometry to try to predict fetal growth (Owen P 1998). These calculations include growth per day and percentage growth per day resulting in generation of a growth velocity (Owen P 1996; Owen P 1998).

Longitudinal data may be used to calculate conditional centiles, which are ‘individualized’ growth standards. For example, the clinician may wish to know whether a fetus has grown slowly given (or conditional on) its gestational age and its size some weeks previously (Royston P 1995).

Because longitudinal studies are based on a small number of fetuses, the centiles produced for estimating size compared with a cross-sectional study may be less precise. Serial measurements on an individual fetus are highly correlated so that the effective sample in such a study is likely to be nearer the number of fetuses than to the total number of observations with special statistical techniques for centile determination needed to correct for the correlation between measurements if the centiles have been generated from longitudinal data (Royston P 1995).

Goldenburg (Goldenburg RL 1989) noted that differences in study methods may be as, or more, important than population differences in defining the 10\textsuperscript{th} and 90\textsuperscript{th} percentile boundaries for normal fetal growth. He looked at studies that used the 10\textsuperscript{th} percentile cut-off point and analysed the factors that gave differing measurements in these studies. There were differences in how gestational age was calculated – whether it was ‘rounded’ up or down, whether it was given in completed weeks or in weeks and days. There were also differences in exclusion criteria, whether the measurements were controlled for sex of the infant and race and parity of the mother. He called for a single standard using the same gestational age calculation, as well as controlling for sex, ethnicity, parity and BMI, to allow appropriate comparisons.
1.6.1 Definition of fetal growth

Fetal growth has usually been evaluated solely from birth weight. However, birthweight is a simplistic surrogate for fetal growth rate. Birth size must be considered with respect to gestational age. A birth weight of 2300 g does not have the same significance at 35 weeks (normal preterm birth weight) as it does at 38 weeks (small, term fetus). As mentioned above (section 1.3.1.1), Denham (Denham M 2001) has also highlighted that a long lean baby may have the same birthweight as a short fat baby born at the same gestation.

One should always keep in mind the difference between fetal size, which represents a single measurement point, and fetal growth, which is a dynamic process and necessitates assessment of fetal measurements at two or more time points. The two concepts contain completely different information (Owen P 1996).

When considering the associations between birth weight and health outcomes, it is important to remember that birth weight is a single, cross sectional summative measure taken at the end of a long period during which growth is rapid but not linear. The same birth size can be obtained by quite different intrauterine growth trajectories (Bloomfield FH 2006).

![Diagram of fetal growth trajectories](image_url)

Rapid initial growth ----. Growth slowing ........ Steady growth ———

**Fig 1.2 .Fetal growth trajectories.** (Bloomfield FH 2006) Reproduced with permission.

Different fetal growth trajectories can result in similar birth weights. The graph shows three exaggerated hypothetical growth trajectories: rapid growth in the first half of pregnancy with slowing thereafter (long dashed line); a similar initial trajectory followed by a period of slow growth before there is intrauterine catch-up growth (short dashed line); initially slower growth with acceleration in the last half of gestation (solid line).
Furthermore, adverse environmental and/or genetic influences may have different effects during various periods of pregnancy. Therefore, the study of fetal growth trajectories using multiple measurements may be more informative than the study of a single measurement such as birth weight (Mook-Kanamori D 2010).

Fetal growth can be assessed from the rate of change of the individual biometric measurements or a combination of these measurements in equations that have been developed to give estimated fetal weight.

1.6.2 Commonly used population references and standards
Regardless of which percentile is applied to estimate fetal size or growth, a reference or a standard is required. A population reference is often established on the basis of a large sample size (ideally representing the underlying population), with a study population that includes both low-risk and high-risk pregnancies and both normal and abnormal perinatal outcomes. On the other hand, a standard usually is based on low-risk pregnancies with a normal outcome. When the “population reference” and the “standard” are applied to an individual fetus or infant, interpretations of the findings differ. The use of a population reference will yield a relative fetal size in relation to the total population; a standard will assess a fetal size in comparison to normally grown fetuses. Thus, a standard may have more clinical utility than a population reference (Zhang J 2010).

The development of fetal growth standards based exclusively on birth weights is flawed as fetal growth restriction is frequently associated with preterm delivery. A review by Reeves et al examined the performance of a variety of the growth characterizing standards that have been employed to define abnormal growth and examines their performance in the prediction of adverse perinatal outcome (Reeves S 2008). The conclusion was that “Population-specific standards are more applicable than generalised growth curves since individual populations have better outcomes with different birthweights. The key to modelling a growth standard is to identify the most appropriate ‘normal’ population. IUGR is associated with preterm delivery, so using population birth weight standards for preterm gestations is inappropriate. Both individualised growth standards as proposed by Gardosi (Gardosi J 1992) and cross-sectional standards as proposed by Hadlock (Hadlock FP 1991) and modified by Bernstein (Bernstein IM 1994) employ different approaches to generate a fetal growth standard. Both used birth weight for term and estimated fetal weight for preterm gestations. Gardosi used an optimum birthweight to further customise the growth curve using maternal factors. The two methods have yet to be compared head-to-head, but both approaches appear to improve the identification of the fetus/newborn at risk of fetal growth restriction beyond that achieved with traditional birth weight-derived growth curves.”
In most clinical and epidemiologic research, birthweight-for-gestational-age references have been used to assess size at birth (Brenner WE 1976; Lubchenco LO 1976; Williams RL 1982; Zhang J 1995; Kramer MS 2001; Alexander GR 2003). These references were developed with very large, mostly population-based databases. They provide birth-weight percentiles by each gestational week. However, infants who are born preterm are more likely to be growth restricted (Weiner CP 1985; Secher NJ 1987; Ott 1993; Hediger ML 1995; Bukowski R 2001; Morken NH 2006). Thus, their birthweight does not represent all fetuses in utero at a given preterm gestational week. The 10th percentile of the birthweight reference in preterm, for example, is substantially lower than the 10th percentile of the ultrasound-based fetal weight reference (Maršál K 1996; Cooke R 2007). Consequently, a population birthweight reference will significantly under diagnose SGA infants in preterm births.

A study by Salomon confirmed these findings in a French population using 18,989 single non-anomalous fetuses. The growth curves were significantly different in preterm gestations. The 50th percentile of the birth weight standard matched the 10th percentile of the estimated fetal weight standard from 28 to 32 weeks gestation (Salomon LJ 2007).

The presumption from all these studies is that the estimated fetal weight equation is accurate. However, these equations have been shown to have a range of accuracy (see section 1.7).

Fig 1.3. Growth curves in preterm fetuses. (Salomon LJ 2007) Reproduced with permission.

The solid lines are the mean, 10th and 90th centiles for the estimated fetal weight standard. The dashed lines are the equivalent lines for the birthweight.
Numerous ultrasound-based fetal weight references have been published since the early 1980s (Ott WJ 1982; Marsal K 1996). Most of these were cross-sectional references that were based on either retrospective databases (Snijders RJ 1994; Kurmanavicius J 1999; Kurmanavicius J 1999; Jung SI 2007) or prospective data collection (Hadlock FP 1991; DG Altman 1994; Jacquemyn Y 2000; Leung TN 2008). In these studies, each pregnant woman contributed data from only 1 observation. The relatively large sample sizes in these studies provided relatively stable estimates.

Selection bias (e.g. why a woman received an ultrasound examination at a gestational week when a routine ultrasound examination is not usually performed) may have affected the ability to generalise from these references to the general population. Prospective studies improve the data quality by confirming gestational age early, scheduling examinations systematically, and having strict protocols with the measurements that are performed by fewer highly trained sonographers. Nonetheless, cross-sectional studies can provide a reference only for fetal size, not fetal growth velocity. Longitudinal studies with repeated measurements on the same fetus are required to study true fetal growth (Owen P 1996). This is the basis of the study design reported in this thesis.

Population graphs that are out of date also do not account for the second-generation phenomenon. (Li D 1990) An average annual increase of 18 g in birthweight (100 g mean birth weight increase from 1980 to 1986) has been reported in South East Asian patients delivered in Washington whose birthplace was coded as outside USA. A similar temporal change of birth weight during the same period of time was not observed among infants of US-born Asian mothers.

Population norms also do not account for the well-established effect of smoking on birth weight. The effect of this omission, especially in settings with high rates of maternal smoking, is similar to the effect of prematurity, and results in falsely lowered norms for fetal growth caused by inclusion of fetuses whose growth has been impaired by maternal smoking. Nor do population norms account for physiological determinants of fetal growth (maternal height, weight, parity, ethnicity and fetal sex). Charts developed in the 1970’s will have included a greater population of smokers than recent charts, which may partly explain some of the increase in birthweight seen over that time.

Population charts need to be appropriate for and derived from the population they apply to. Ultrasound charts in NZ have been derived from a UK (Campbell S 1969) or a Texas (Hadlock FP 1985) population and may not apply to our Pacific Island or Asian population. Charts from a multicultural study from Sydney as used by ASUM (Westerway SC 2000) are more modern, but the multicultural population has a high proportion of Vietnamese and therefore may not apply to our New Zealand population.
Cross-sectional ultrasound data obtained on 392 fetuses of middleclass white mothers in Texas was used by Hadlock (Hadlock FP 1985) to generate a commonly used fetal weight software package widely used in New Zealand. If the biometry charts are not appropriate for the different populations it could be argued that the Hadlock formula may also not be appropriate. Lee (Lee W 2009) has shown that the original Hadlock formula was no longer appropriate for his Detroit population and developed a modified Hadlock equation.

1.6.2.1 Ethnic growth/biometry studies:
A cross-sectional study of 524 singleton pregnancies showed ethnic differences in fetal biometry between Belgian, Turkish and Moroccan people (Jacquemyn Y 2000). Turkish and Moroccan individuals had a higher birth weight compared to the Belgian participants. These differences could however be partly explained by differences in BMI, parity and smoking between the groups. Longitudinal studies in the UK showed the same growth pattern in different ethnic groups, even though the EFW mean was different (Mongelli M 1995; Spencer JAD 1995).

Plot of mean (± 2 SD) values of estimated fetal weight (solid and dotted lines) from longitudinal data of 20 Bangladeshi fetuses. Linked crosses indicate mean values from longitudinal data of 60 Anglo-Saxon fetuses.

Fig 1.4 Difference in EFW in different ethnic groups. (Spencer J 1995) reproduced with permission
Fig 1.5 Difference in EFW in different ethnic groups - Mongelli graph (Mongelli M 1995) reproduced with permission.

Pang (Pang MW 2003) in a prospective longitudinal study of 533 Chinese pregnant women, showed that maternal and pregnancy characteristics had a significant effect on fetal biometry and can be seen as early as 24 weeks GA. The measurements in that study were from 24 weeks and therefore the difference may have occurred earlier. Despite commenting that smoking has an effect on fetal growth this paper did not state whether smoking was an exclusion criteria. Within Pang’s study it was demonstrated in Chinese women that increased fetal head size and abdominal circumference were significantly associated with extremes of maternal age. Maternal height had a statistically significant influence on biparietal diameter. Maternal booking weight had an influence on fetal abdominal circumference and femur length. Fetal sex was found to have a statistically significant influence on final regression models of biparietal diameter, head circumference and femur length. Parity had an influence on fetal head circumference and abdominal circumference. Maternal and pregnancy characteristics had only a minimal effect on the femur diaphysis length.

Therefore Pang’s study illustrates that the differences found in ethnic growth studies may be due to maternal and other characteristics.

There were similar differences in humeral and femoral length found in a small study from Malaysia investigating Malay, Chinese and Indian populations (Raman S 1996). Other studies from Holland (Drooger JC 2005) and Peru (Merialdi M 2005) have all produced similar findings. The Peruvian study was performed at sea level to exclude altitude as a confounder.

In contrast Hadlock (Hadlock FP 1990) failed to demonstrate significant differences in standard in utero fetal biometry measurements; biparietal diameter (BPD), head circumference (HC),
abdominal circumference (AC), femur diaphyseal length (FDL), in 300 black and hispanic fetuses from 20 to 41 weeks compared to their white middleclass group. Hadlock’s study is limited because menstrual age was calculated from a remembered LMP in patients who had not taken the oral contraceptive pill in the previous 3 months. There were no confirmatory early scans and some of the measurements were cross sectional measurements taken in the third trimester.

In a Canadian study by Kierans (Kierans WJ 2008) showed that, despite their lower mean birth weights and higher SGA rates (when based on a population standard), Chinese and South Asian infants had lower perinatal mortality risks throughout gestation. The opposite pattern was observed for First Nations (Indigenous North American Indian) births. This group had higher mean birth weights, lower SGA rates, and higher perinatal mortality risks. When SGA was based on ethnic-specific standards, however, the pattern was concordant with that observed for perinatal mortality. The concordance of perinatal mortality and SGA rates when based on ethnic-specific standards, and their discordance when based on a single standard, strongly suggests that the observed ethnic differences in fetal growth are physiologic, rather than pathologic, and make a strong case for development and utilisation of ethnic-specific standards (Kierans WJ 2008).

In a longitudinal ultrasound study of Peruvian women from a poor district at sea level in Lima, Merialdi (Merialdi M 2005) compared the biometry in pregnancy with charts from another Peruvian population (Krampl E 2000) as well as charts from Europe and the USA. When compared, using Z-scores, with ultrasound-based reference fetal size charts obtained from North American and European populations, fetuses from the studied population appeared to grow more slowly with advancing gestational age. This trend was not observed when a Peruvian population, similar to the one studied, was used as a reference. This group concluded that fetal growth in this Peruvian population may not be adequately assessed by using reference charts obtained from other populations. This has implications for the use of growth standards in antenatal management.

In summary there is good evidence to suggest that there are ethnic differences in fetal biometry. However, as is shown in Pang’s study, ethnicity was only one of several factors that influenced fetal size. In that study of a single ethnic group, different biometry measurements were variously associated with maternal age, maternal height and maternal booking weight. Merialdi’s study implies that each population should develop its own reference centiles.

In the assessment of growth, however, a standard that is based on an ethnic group of low-risk pregnancies with a normal outcome may have more clinical utility than a population reference as recommended by Zhang (Zhang J 2010).
1.6.3 The standard approach to defining fetal size abnormality

Most clinicians and researchers use SGA, IUGR and Fetal Growth Restriction (FGR) interchangeably. However, this practice is problematic. Fetuses with a weight <10th percentile are not necessarily growth restricted (they may be constitutionally small but healthy). On the other hand, a weight of >10th percentile does not necessarily denote “normal” fetal growth. For example, the rate of fetal growth may undergo pathologic decline in late gestation. In such a case, the birthweight may still be >10th percentile, but the fetus may have experienced growth restriction and incurs an increased risk of perinatal death and morbidity (Stratton JF 1995; Owen P 1997).

1.6.4 Early Pregnancy Growth studies

Longitudinal studies of first trimester growth have shown that growth is not linear (Blaas HG 1998; Deter RL 1999).

Bottomley found that the rate of increase in CRL was higher in women of black ethnic origin compared with white, and increased with advancing maternal age. As CRL is used to date pregnancies, and this influences further growth assessment, consideration should be given to the use of individualized growth charts which take account of maternal factors recently shown to influence first trimester growth (Bottomley C 2009). Mook-Kanamori (Mook-Kanamori D 2010) also demonstrated that maternal age was positively associated with first-trimester fetal crown to rump length (difference: 0.79 mm (95% CI: 0.41, 1.18) per standard deviation increase).

Salomon 2011 (Salomon L 2011) looked at an IVF pregnancy cohort and suggested that fetuses which are smaller or larger than expected in the first trimester are at increased risk of abnormal birth weight (SGA and macrosomia, respectively).

Fetal size in early pregnancy was analysed at 11–14 weeks and a one-point increase in the CRL Z score (i.e. a 3.6-mm increase in CRL at 11 or 14 weeks) was associated with a 39% decrease in the risk of delivering an SGA infant. Conversely, a one-point increase was associated with a 62% increase in the risk of delivering a macrosomic infant (defined as >4000 g).

The relationship between early fetal growth and the subsequent course of pregnancy is difficult to interpret. It may be that the same genetic or environmental factors influence growth in both the first trimester and later pregnancy. A suboptimal environment, as a result of factors such as abnormal placentation, may affect growth earlier than previously thought. Alternatively, environmental factors (nutritional, hormonal, etc.) encountered during the first trimester might permanently affect fetal growth potential. It is also possible that some fetuses may be physiologically small throughout pregnancy. A recent study has shown that maternal physical characteristics and lifestyle habits influence first-trimester fetal growth based on CRL. Higher diastolic blood pressure and a higher haematocrit were both associated with shorter CRL, as were maternal smoking and a lack of folic acid supplementation (Mook-Kanamori D 2010).

Height, weight or BMI were not significant in this study. The significant factors for analysis were
the same factors that were used for recruitment inclusion i.e. maternal age, education and using folic acid, which presents a possible bias in that study.

1.6.5 Growth velocity
Growth is can be defined as rate of change in a parameter measured over a given time period. In fetal growth studies this interval should not be less than 2 weeks. Stefos used an interval of 4 weeks in his calculation of slope before 26 weeks of pregnancy to predict growth later in the pregnancy (Stefos T 1989).

Bertino has taken the relative growth velocity (as a percentage of the size attained at 40 weeks and plotted that against menstrual age. This shows differing growth patterns for different parameters. The skeletal parameters Biparietal Diameter (BPD), Head Circumference (HC), Occipito Frontal Diameter (OFD) and Femur Length (FDL) all peak around 20 weeks, whereas the Abdominal Circumference (AC) as a reflection of soft tissue shows a later peak and a more steady velocity.

The Head Volume (HV) peaks later again. Because this is a relative velocity as a percentage of size at 40 weeks, this reflects the relative proportion of the head size and brain development in the human fetus until late in the pregnancy.

Fig 1.6. Relative growth velocity. (Bertino E 1996) Reproduced with permission
It is apparent from Bertino’s graph (Bertino E 1996) above, that relative growth velocity of the individual parameters are different and peak at different times. This is reflected clinically in the different proportions of head size to abdominal size at different gestational ages.

It is also interesting to look at the abdominal circumference velocity graph below and note that the peaks of growth velocity for different centiles do not occur at the same gestational age. This is not the relative velocity, but the measured velocity. The slope of the graph at each centile, before and after the peak is very similar, but the rate of growth in mm per day is different even early in pregnancy for those that may develop large or small babies.

Bertino has used measurements 10 weeks apart. Clinically requests are often made for measurements 2 weeks apart. It has been suggested that 3 - 4 weekly intervals are more appropriate for growth assessment (Deter RL 1986; Owen P 2001).

Abdominal Circumference (AC) growth velocity (mm per week) as a function of gestational age (weeks).

**Fig 1.7 Abdominal circumference growth velocity** (Bertino E 1996). Reproduced with permission.
Milani (Milani S 2005) demonstrated that neonates in the upper third of birthweight distribution (3618+/−43 g, mean+/−SEM) had, at 22 weeks of gestational age, AC growth velocity higher by 0.55+/−0.10 mm/week than those in the lower third (2902+/−36 g). Neonates in the upper third of crown heel length distribution (51.7+/−0.21 cm) had, at 20 weeks gestational age, FDL growth velocity higher by 0.11+/−0.05 mm/week than those in the lower third (48.2+/−0.18 cm). Neonates in the upper third of head circumference distribution (35.7+/−0.13 cm) had, at 18 weeks, HC growth velocity higher by 0.57+/−0.20 mm/week than those in the lower third (33.3+/−0.11 cm).

Owen (Owen P 1996) performed ultrasound at 4 weekly intervals and derived velocity standards for standard biometry parameters. That study used a mixture of cross sectional and longitudinal data and showed that the rate of growth of the fetal head as represented by the BPD is maximal in the late second trimester with a gradual reduction in velocity towards term. A similar pattern of growth was seen with femur length measurements. The pattern of growth of the Fetal Abdominal Area (FAA) demonstrated a gradual rise in growth rate over the second and early third trimester, reaching maximum velocity at 33 weeks of gestation with a steady decline in velocity thereafter.

Owen’s graphs are similar to Bertino’s. The pattern of growth of the fetal abdominal area is similar to that of abdominal circumference.

Others have suggested that growth as modelled in a fitted growth curve in normal pregnancy is constant until 26 to 30 weeks and then slows down (Rossavik IK 1984; Pineau JC 2003; Pineau JC 2006; Guihard-Costa AM 2000).

Lampl and Jeanty performed weekly FL and EFW from 13 weeks in 44 pregnancies. Growth patterns in individual fetuses were investigated and they described growth (in mm/day) as pulsatile (Lampl M 2003). Measurement was done by one author and there were no intra observer error measurements performed to determine if this could be explained by measurement error when performed weekly.

**1.6.6 Proportionality and Ratios**

The above curves suggest that as pregnancy progresses the proportions or ratios of biometry may be different at gestational ages. The concept of proportion has been used clinically for many years to differentiate symmetrical and asymmetrical growth restriction (Wladimiroff JW 1997).

Padoan (Padoan A 2004) has shown that fetal growth-restriction fetuses have disproportionate reduction in fat mass compared with lean mass. Fetal growth-restricted fetuses have reduced subcutaneous fat and lean mass compared with control fetuses; a further reduction occurs in subcutaneous fat concentration compared with the reduction in lean mass when fat is normalized for body size, with either head circumference or femur length.
Lim (Lim JM 2000) in a study from Malaysia has suggested differences in fetal body proportions exist between some races. The longer femur diaphysis length noted in certain races did not necessarily imply that the corresponding crown-heel length was longer. There was no significant difference in relationship of the neonatal crown-heel length and the femur diaphysis length between the Malay and Chinese populations, but the relationship in the Indian population was significantly different from both the Chinese and Malay. For a given femur diaphysis length, the crown-heel length of the Indian population was found on average to be 1.1 cm shorter than the crown-heel length of the Malay and Chinese populations.

Hindmarsh (Hindmarsh PC 2002) stated that in a low risk population delivering at term, body shape was largely determined by proportionality between anthropometric measures.

Indexes of body proportionality standardized for birth weight, potential maternal and fetal determinants of fetal growth and proportionality were assessed by Kramer (Kramer MS 1990). Infants who were growth-retarded, those with taller mothers, those whose mothers had severe pregnancy-related hypertension, and males tended to be longer and thinner and had larger heads for their weight, although these variables explained only a small fraction of the variance in the proportionality measures.

In diabetic pregnancies Mello (Mello G 2000) demonstrated that offspring of diabetic mothers with poor glycaemic control in the third trimester had significantly greater means of ponderal index and thoracic circumferences, and significantly smaller cranial/thoracic circumference ratios with respect to controls.

1.6.7 Longitudinal Growth
An overwhelming majority of fetal growth assessments done today would not be true growth assessments but are serial comparisons compared with cross-sectional reference ranges (Kiserud T 2009).

Several longitudinal ultrasound growth studies have been conducted in the past 25 years. Although some of them had small numbers Deter (20), Marsal (86), Gallivan (67), (Deter RL 1982; Marsal K 1996; Gallivan S 1993), others had sample sizes, which ranged from approximately 200 (Mongelli M 1995; Di Battista E 2000) to 634 women (Johnsen SL 2006; Johnsen SL 2006). Most of the larger studies were performed in Europe, predominantly in white women. The Johnsen study used multilevel modelling for the growth of fetal head, abdomen and femur and produced charts for assessing fetal size and growth which could be adjusted for maternal and fetal factors to suite individual pregnancies.

Fry (Fry AG 2002) constructed three models for defining fetal growth during the third trimester; longitudinal ultrasound estimates of fetal weight obtained serially, cross-sectional ultrasound estimates of fetal weight, and cross-sectional birth weight data. Derived regression lines
depicting fetal size across gestation were significantly different from each other. Significant weekly variations in fetal weight gain were observed within the raw cross-sectional data sets, both for ultrasound-estimated fetal weight (range 91-278 gms/week) and birth weight (65-309 gms/week). Fry concluded that each of the methods used to model normal fetal weight gain in the third trimester defined a distinct pattern of fetal growth.

The cross sectional and longitudinal measurements were very close at all gestations. Below 34 weeks the difference between the ultrasonically derived measurements and birthweight at that early gestation was the most apparent.

Fig 1.8 Smoothed growth curves through the third trimester. (Fry AG 2002). Reproduced with permission

All equations define a statistically unique curve when compared to each other in pair-wise fashion (partial f test, p<0.05). Live birth weight is represented by the solid line, longitudinal ultrasound estimates of the fetal weight by the dotted line and cross sectional ultrasound estimates of fetal weight by the dashed line. Both ultrasound estimates below 34 weeks are greater than the actual birthweight, suggesting that the Hadlock 3 formula is inaccurate for estimating fetal weight between 24 and 34 weeks gestation. However the EFW and birthweights at the gestation below 34 weeks were not in the same patients. This study may be flawed by the fact that babies born before 34 weeks are more likely to be SGA.

Johnsen (Johnsen SL 2004) measured BPD and HC before 20 weeks and developed new charts which gave 3-8 days higher GA assessment than the charts presently in use. Maternal age, multiparity, fetal gender, breech position and shape of fetal head affected GA estimation by 1-2 days when using BPD (p = 0.0001-0.02). Only maternal age and fetal gender affected GA estimation when using HC (p = 0.001). Therefore HC was suggested as the more robust method to estimate GA.
Johnsen (Johnsen SL 2006) used the cohort as above to establish GA and then performed serial measurements in the same patients in order to assess longitudinal fetal growth. Reference percentiles for the growth of Mean Abdominal Diameter (MAD), AC and FL showed continuous growth in gestational week 10-40, while BPD and HC showed a slightly blunted growth toward the end of pregnancy.

In that same cohort (Johnsen SL 2006) Johnsen measured intrauterine growth expressed by EFW. This showed a continuous pattern until term. Males were calculated to be 5% heavier than female fetuses at 20 gestational weeks and 3% at 40 weeks. Otherwise, the fetal and maternal effects on intrauterine growth correspond to a weight shift of 1.3% for breech/non-breech, 2.5% for each increase in maternal height tertile, and -4% for smoking/nonsmoking. Maternal age higher than 34 years had a significant increased EFW of 4.5% compared with maternal age less than 24 years. Maternal weight, body mass index, and parity did not influence the EFW.

de Jong (de Jong CLD, 1998) used longitudinal growth of fetal weight in the third trimester of high risk pregnancies with subsequent normal outcome and concluded that physiological variables affect fetal weight gain and need to be taken into account when fetal growth is monitored in high risk pregnancies. de Jong (de Jong CLD 1999) also compared the longitudinal fetal growth in the third trimester in high risk pregnancies with adverse perinatal outcome. Those with a normal outcome had an average growth of 24.2 g/day whereas those with an adverse outcome had an average growth of 20.9 g/day (p<0.05).

1.6.8 Customised birthweight centiles

The customised antenatal growth charts developed by Gardosi (Gardosi J 1995) are based on a regression model for birth weight, fitted to a very large group of neonates. The determinants in this model are maternal height and weight, ethnic origin, parity and fetal gender. After calculation of the “term optimal weight” for a fetus, a fetus-specific intrauterine growth curve for EFW can be constructed, using a proportionality equation linking EFW during gestation to birth weight. An important assumption for this approach is that the proportionality equation is correct for each fetus. It also assumes that the effect of each biometric measurement has the same proportionality during pregnancy.

Customised birth weight centiles are used to classify the size of the baby at birth. They adjust newborn weight for maternal height, weight, ethnicity and parity, and more accurately identify infants that are at risk of neonatal morbidity and perinatal mortality than traditional population birth weight centiles which are largely derived from European births (McCowan LM 2005; Battin MR 2007). Internationally, customised birth weight centiles have been shown to better identify at-risk pregnancies (Figueras F 2007, Figueras F 2007, Clausson B 2001, Gardosi J 2011).

New Zealand customised birth weight centiles were generated using a birth cohort from 1993 to 2000 (McCowan LM 2004). At that time height, weight and smoking status were not routinely
collected, limiting numbers available for inclusion and women who smoked could not be excluded. The ethnic groups that had sufficient numbers for development of customized centiles were NZ European, Māori, Samoan, Tongan, Chinese and Indian. The coefficients obtained in NZ European women are virtually identical to those obtained for European women in Australia, America and Europe (Mongelli M 2007).

Inclusion of women who smoked in this original dataset is likely to have falsely lowered the optimum birth weights for Māori as 45% of Māori women smoke during pregnancy (New Zealand Health Information Service 2007).

Anderson (Anderson NH 2011, personal communication) updated the New Zealand customised birthweight centile calculator. The variables included in this multivariable analysis were those that have previously been found to be associated with birthweight (Gardosi J 1995) i.e. maternal height, weight, parity, ethnicity, gestation, and infant gender. Additionally the pathological variables of diabetes, hypertensive disease and cigarette smoking were included as they also have a significant influence on birthweight (Mongelli M, Gardosi J 2009, Varvarigou A. 2010).

McCowan (McCowan LME 2005) has shown in the New Zealand setting that the use of customised birthweight centiles is associated with the detection of SGA pregnancies with perinatal morbidity. Groom (Groom KM 2007) has shown that this relationship is still evident at different gestational ages, especially preterm.

Others have suggested that customised birthweight centiles are not useful in the prediction of morbidity (Zhang X 2007; Hutcheon JA 2008; Zhang J 2010; Zhang J 1995).

Hutcheon suggested that a non-customised but intrauterine-based standard has a similar ability to predict risk for stillbirth and early neonatal mortality compared with a customised birthweight standard (Hutcheon JA 2008) and that customising birthweight percentiles for maternal characteristics has "little justification" (Hutcheon JA 2011).

Gardosi has responded to this using the stepwise improvement of birthweight prediction as illustrated in Figure 1.9 (below). This figure shows progressive small increases in $R^2$ occurs with the addition of maternal characteristics. The higher the value of $R^2$ in the model means the better explanation of the variables that are used to predict the outcome. Gardosi states that the data illustrated is contrary to Hutcheon’s statement that there is no “additional value in customising for maternal characteristics” (Gardosi J 2011).

Despite this difference of opinion between the Hutcheon’s group and Gardosi, Zhang from that group suggests there is an important difference to be found in some maternal characteristics. In a study that group performed on women with short stature they state that the effect of maternal short stature or primiparity on perinatal mortality is partly mediated through SGA birth. Thus, birthweight differences resulting from these maternal characteristics appear also to have an important pathological component (Zhang X 2010). This finding agrees with that of Gardosi
(Gardosi J 2009) who found that parity and increasing maternal BMI had an effect on perinatal mortality rates.

Fig 1.9. Accuracy of birthweight prediction and maternal characteristics. (Gardosi J 2011). Reproduced with permission.

Law (Law T 2011) compared body fat percent (BF%) and neonatal outcomes of preterm small for gestational age (SGA) infants based on customised (SGAcust) versus population (SGApop) growth curves in 204 preterm low birthweight (<2500 g) infants using air-displacement plethysmography. In that study customised growth curves reclassified 30% of the preterm, low
birthweight infants from AGA to SGA compared to a commonly used population-based growth curve developed for preterm infants. Customised growth curves better identified low infant BF%, neonatal morbidity risk, and length of stay in the Neonatal Unit.

Mikolajcyk (Mikolajcyk RT 2011) used the fetal-weight reference developed by Hadlock and the notion of proportionality proposed by Gardosi and made the weight reference easily adjustable according to the mean birthweight at 40 weeks of gestation for any local population. They used data from 24 countries in Africa, Latin America, and Asia. They compared their reference with that of Hadlock (non-customised) and with that of Gardosi (customised) and found that their generic reference for fetal-weight and birthweight percentiles could be easily adapted to local populations and had a better ability to predict adverse perinatal outcomes than the non-customised fetal-weight reference, and was simpler to use than the individualised reference without loss of predictive ability.

1.6.9 Z scores
To facilitate comparisons of growth rate between ultrasound examinations performed at different gestational weeks, growth rate can be standardized according to the gestational age at the time of the scans. A Z-score can be thus calculated for each fetus by subtracting the mean growth rate for all fetuses that were scanned at the same interval, and dividing by the standard deviation (sd) of the growth rate for this group: $Z$-score = (observed growth rate − group mean growth rate) / (group growth rate sd). A Z-score of -1 from the mean corresponds to the 16th centile and a Z-score of -2 corresponds to the 3rd centile.

Merialdi (Merialdi M 2005) has used Z-scores to compare fetal biometry charts in a Peruvian population. Z-scores close to 0 suggested that the average of the measurements do not differ from the mean of the reference centiles. That study suggested that fetal growth in the Peruvian population may not be adequately assessed by using reference charts obtained from other populations.

1.6.10 The individualised approaches to assess fetal growth by ultrasound.
It has been suggested that the key to detect fetal growth abnormality is to develop a method that can identify the growth assessment for individual fetuses.

Several approaches have been proposed over the past 25 years. Rossavik and Deter (Rossavik IK 1984) first proposed a mathematical model for fetal growth. Their model assumed that all fetal biometric parameters follow a definable growth pattern throughout pregnancy. Regression analysis was used to obtain optimal coefficient estimates for the Rossavik function. Based on that model, the authors developed an individualised growth assessment, in which an individualised fetal growth curve is created based on early ultrasound examinations. The assessment requires a minimum of 2 ultrasound examinations separated by 4–8 weeks before 26
weeks of gestation. This curve was used to predict late fetal growth in the same fetus (i.e. each fetus becomes its own control). Implicitly, this model assumed that fetal growth is not affected by external factors (pathologic or environmental) before 26 weeks of gestation.

Concerns regarding this approach have been raised that fetal growth abnormality can be demonstrated as early as the first trimester, as well as the fact that it requires multiple ultrasounds (Reeves S 2008) and it appears to have little advantage over already established birthweight fetal growth curves (Shields LE 1993; Ariyuki Y 1995; Pineau JC 2003; Pineau JC 2006).

Deter’s (Deter RL 1992) approach however does appeal, in that it assesses the growth, using the Rossavik model, of that fetus within its environment of maternal factors such as parity, ethnicity, maternal BMI, smoking and fetal gender. Any abnormal growth is then defined as the percentage deviation from the expected growth trajectory. This fits well with the definition of IUGR being a failure to reach expected growth potential. It does not relate growth to comparison with population data or standards.

Pineau (Pineau JC 2003) compared four mathematical models of fetal head growth (a linear-quadratic model, a linear-cubic model, the Rossavik model and a new two-phase model, which they had developed to take into account an alteration in growth kinetics at 30 gestational weeks. All the models had good coefficients of determination \((R^2)\). However the standard error estimates (SEE) of the two-phase model were much lower \((0.13 \leq \text{SEE} \leq 0.57)\) than the SEE of the three other models when computed over the whole gestational period \((0.49 \leq \text{SEE} \leq 2.69)\); nevertheless, when the three other models were computed for the two successive periods, their SEE decreased, and data fitting was improved. Pineau (Pineau JC 2006) did a similar study for femur and abdominal circumference and found a simple linear-quadratic equation gave the best fit of all the models.

Although this study purported to compare the Rossavik model, each fetus was measured only once. It was therefore a cross-sectional study and did not follow the original Rossavik method which needs at least two measurements of the same fetus to generate that individual’s growth curve. These Pineau studies were the only studies, to the author’s knowledge, that are independent of the Rossavik and Deter group to publish on the Rossavik model.

1.6.11 What are the basic differences between individualised growth assessment (IGA) of Deter and the customized birth weight percentiles of Gardosi? The Gardosi method is limited to estimated fetal weight (EFW) whereas IGA looks at fetal biometry.

IGA makes no assumptions about the shape of individual growth curves or their relationship to percentile lines generated in cross-sectional studies of growth.
The Gardosi method assumes that individual estimated weight growth curves have the shape of the 50th percentile line determined by Hadlock in a cross-sectional growth study of estimated weight in a European cohort. This method also assumes that if growth is normal, individual EFW growth curves will be the same as percentile lines.

In IGA, the expected values to which actual measurements are compared are derived only from Rossavik regression model specified from the measured slope of the individuals 2nd trimester growth curve and the duration of growth.

The Gardosi method starts by determining the optimal birth weight at 40 weeks, based on maternal height, weight and parity and a regression model derived from a postnatal reference sample. The percentile line of the Hadlock study that gives this expected birth weight at 40 weeks is then chosen as the expected individual growth curve for that fetus. Actual EFW values at different time points are compared to normal ranges, constructed around expected values that are derived from the variability characteristics of the postnatal reference sample (assuming without proof that prenatal variability is constant and the same as that found in the postnatal sample). These ranges contain the biological variability of growth between fetuses.

The optimal weight is based on the physiological variables of maternal ethnicity, height, weight and parity and is optimized by exclusion of pathological variables such as smoking, hypertension, diabetes that can influence fetal growth.

Anderson (Anderson NH 2011) has specifically included coefficients for these pathological variables in the most recent New Zealand centile calculator to enable growth to be optimized in those patients who have these pathological conditions. This means that these conditions can be accounted for and eliminated so that the final centiles do not include pathology and are therefore optimized.

In IGA, the difference between expected and measured values of a growth parameter at a given time point is compared to the measured prediction variability seen in a normally growing fetus. This variability is due only to measurement and modeling errors and does not contain any of the biological variability of growth between different fetuses. Thus with IGA, detection of a growth abnormality only requires that the difference between the expected and measured value be greater than the prediction error in normally growing fetuses.

Both of these approaches have the same aim i.e. to detect early growth restriction.

The individualised growth assessment of Deter relies on having 2 scans before 26 weeks. This is unusual in a normal New Zealand clinical scenario. The production of the growth curve is mathematically complicated and uses software that is not commercially available.

The method of Gardosi uses parameters that can be used at any stage of the pregnancy after 24 weeks. The prediction can be performed at clinical presentation and the software to use this is freely available. Although Gardosi assessment uses cross-sectional data, it is the more practical
and easiest to use of the two techniques. It also has had the largest number of studies analyzing its performance in relation to outcomes.

Another form of individual growth assessment is to use conditional centiles.

1.6.12 Conditional centiles
One of the reasons that longitudinal standards for growth are not commonly used in the clinic is most likely that correct statistical analysis of longitudinal fetal data is complicated. There are several methods available for the statistical analysis of longitudinal data, but the most appropriate appears to be the method of describing conditional centiles, employing the technique of multilevel modelling (See section 1.12.1).

Longitudinal data are also more difficult to collect than cross sectional data. Therefore longitudinal graphs are not easily produced.

An alternative is conditional centiles which use individual predictions for the expected normal range of a measurement at the second time of measurement on the basis of the first measurement. Each second-time measurement is thus assigned a centile, which is conditional to the previous measurement in the same fetus. If the parameter measured is on the 50\textsuperscript{th} centile and is on the 5\textsuperscript{th} centile at the next measurement then growth has slowed. If the measurement is on the 5\textsuperscript{th} centile and the next measurement is also on the 5\textsuperscript{th} centile then growth is normal \cite{Owen1998, Beltrand2008, Kiserud2009}. Kiserud \cite{Kiserud2009} and Hooper \cite{Hooper2002} have produced graphs illustrating this. Kiserud has also produced freely available software in an Excel spreadsheet to allow this to be done easily (personal communication).

Fig 1.10. Conditional weight graph. (Hooper PM 2002) reproduced with permission.
The dashed lines represent unconditional 80\% prediction curves. The middle solid line represents the predicted 50\textsuperscript{th} centile for a particular fetus. The lower and upper solid lines represent
conditional 80% prediction curves. As can be seen, the EFW is dropping below the centile line for the given fetus.

The principles of customised reference ranges and conditional reference ranges may be combined, including covariates such as ethnicity and fetal gender, in a model for conditional reference ranges (Johnsen SL 2006; Johnsen SL 2006), providing tools for assessing fetal growth while at the same time taking into account variables that may influence the fetal outcome assessed. Such combined models would further improve the distinction between constitutional and pathological. In clinical surveillance of fetal wellbeing, these methods can be applied using published (Johnsen SL 2004) computerized spreadsheet applications with formulae for unconditional (conventional) and conditional centiles.

In the prediction of low ponderal index in newborn infants, for example, conditional centiles of third-trimester fetal abdominal area performed much better than did unconditional centiles (Owen P 2000).

Using conditional centiles, Pedersen (Pedersen NG 2008) compared the performance of fetal size and growth between the first and second trimesters in predicting subsequent adverse pregnancy outcome (preterm delivery, smallness for gestational age and perinatal death) and found that conditional growth standards (of biparietal diameter) predicted outcome better than did fetal size (biparietal diameter).

1.6.13 Conditional centiles difficulties:

First, if a fetus has already been subjected to growth restraint by the time of the first measurement, then an artificially ‘low’ set of predicted conditional centiles will be generated, based upon the first measurement. This raises the possibility that any further growth restriction will be underestimated. Second, it remains to be established how a series of three or more measurements should best be quantified, i.e. whether the third (or subsequent) measurement should be categorized according to conditional centiles generated from the first or the second measurement. Intuitively, one would expect that the longer the time interval over which growth is measured then the more reliable the measure of growth will be, since the effect of measurement error will be lessened and the magnitude of the growth abnormality will be maximized. However, this will not necessarily be true if a fetus has experienced an abrupt reduction (or acceleration) in growth rate. Third, it has to be realized and accepted that errors or variation in fetal measurement will influence the interpretation of serial changes in fetal size. It is not possible to eliminate intrafetal variation, but this can be minimized by careful ultrasound. Conditional centiles have been produced based on EFW and therefore depend on which equation is used to generate the EFW.

The advantage of using conditional centiles for growth assessment is that they are easy to use and that are individualised for that fetus and its conditions. Graphically it may be more reassuring
to a clinician to show that growth is along the expected centile of an SGA fetus, even if it is along the 10th centile on population centiles.

1.7 Estimation of Fetal weight.
In a Norwegian population, adult weight and height for both men and women increased over a 30-40 years period (Tverdal A 1996). In the same period, birth weight by gestational age (GA) at term has increased 100 g (Skjaerven R 2000), and the proportion of newborn >/4500 g has increased from 3.1 to 4.7% from 1989 to 2000 (Report of the Medical Birth Registry of Norway 2000). This may indicate changes also in the intrauterine growth parameters and a need for correspondingly updated reference ranges for EFW (Johnsen SL 2006).

The study from Johnsen also showed that fetal presentation (breech/non-breech) influenced EFW. This is in agreement with Chauhan who reported that the error with most EFW-models is significantly higher for fetuses in breech than in vertex position (Chauhan SP 1995).

Estimation of fetal weight is calculated from an equation that has been developed from a combination of measured ultrasound parameters.

Dudley (Dudley N 2005) in a review of the literature showed that there was no consistently superior equation to estimate fetal weight. Random errors are large with large intra and inter observer variability.

Unfortunately, to date the sonographic estimation of fetal weight at term has been shown to have margins of error increasing with increasing fetal size (Scioscia M 2008).

An EFW equation has been produced by Combs (Combs CA 1993) from a mathematical model of fetal volume. In that study the formula \(\text{EFW} = (0.23718 \times \text{AC}^2 \times \text{FL}) + (0.03312 \times \text{HC}^3)\) produced smaller systematic errors and smaller absolute errors than either the Hadlock or Shepard formulae both overall and in fetal weight ranges from less than 1000 g to over 4000 g.

Kehl (Kehl S 2011) used postpartum measurements of head circumference, abdominal circumference and thigh length to evaluate new weight equations. The conclusion was that the current accuracy of fetal weight estimation with conventional biometric parameters by two-dimensional ultrasound has reached its limits and further improvement would probably only be achieved through new approaches in ultrasound.

1.7.1 Accuracy of EFW
The accuracy of the identification of abnormal fetal growth obviously hinges on the accuracy of EFW and the accuracy of the fetal biometry equation used to estimate the EFW.

Errors in fetal weight estimation may derive from several sources:
1.8 Other Ultrasound approaches – measurement of Soft Tissue

It has long been known that the human is the mammal with the greatest percent of body fat at term and has an enormous capacity to alter this body compartment as a result of intrauterine growth (Ziegler EE 1976). While fat constitutes only 12–14% of normal birth weight, it has been demonstrated to account for almost half of its variance (Catalano PM 2001). Accumulated fat accounts for more than half of the calories which are accrued by the fetus from 27 weeks to term (Sparks JW 1980).

Most fetal weight is gained during the second half of gestation, when fetal growth is accompanied by an exponential deposition of fat tissue (Enzi G 1981). Bernstein demonstrated that fat mass
grows at a different rate in pregnancy compared to bone growth and lean mass in the second half of the pregnancy (Bernstein IM 1997).

Soft tissue (muscle and fat) can be evaluated using prenatal ultrasonography. As one example, multivariate statistics have been used to demonstrate that decreased soft tissue mass, as indicated by fetal thigh circumference, is one of the earliest manifestations of IUGR (Deter RL 1995).

Partial limb volume is a soft tissue parameter that has also been described for the evaluation of fetal nutritional status (Lee W 2009). Lee performed longitudinal growth studies that demonstrated accelerated soft tissue accretion of the fetal limbs after approximately 28 weeks in pregnancies with normal growth outcome. During the late third trimester of pregnancy, percentage Body Fat (%BF) is most highly correlated with Partial Thigh Volume (TVoI). Similar to actual birth weight, this soft tissue parameter accounts for a significant improvement in explaining the variation in neonatal %BF compared with fetal AC or EFW alone.

Fetal fat has been measured using indicators of abdominal fat, subscapular fat mass, mid-arm fat mass and mid-thigh fat mass (Larciprete G 2003; Schwartz J 2003). The subcutaneous fat mass in growth restricted infants at term is significantly lower than that in normally grown infants (Larciprete G 2005).

2D ultrasound assessment has also been used to look at fat mass in decreased birth weight at high altitude (Galan HL 2001). This reduced birth weight of the newborns in Denver was the result of a reduction in fetal subcutaneous fat tissue and not lean mass.

There have been a number of studies looking at fetal soft tissue with 3D Ultrasound in the assessment of fetal growth (Matsumoto M 2000; Schild RL 2000; Lee W 2001; Lee W 2004; Chang CH 2002; Chang CH 2005).

Schild in an editorial (Schild RL 2009) commented that ultrasound-generated estimates of fetal fat may be useful in the evaluation of fetal growth abnormalities. Fat and lean body mass have long been used in the postnatal nutritional assessment of an individual. In fetal life, weight correlates better with soft tissue thickness than it does with two-dimensional (2D) measurements.

Larciprete (Larciprete G 2003) measured soft tissue parameters (mid-arm fat mass and lean mass (MAFM, MALM), mid-thigh fat mass and lean mass (MTFM, MTLM), abdominal fat mass (AFM) and the subscapular fat mass (SSFM)) every three weeks to define reference values of fetal subcutaneous tissue thickness in 218 healthy pregnancies and in 85 women with gestational diabetes. They found fetal fat mass values, particularly in late gestation, are greater in women with gestational diabetes compared with healthy women.
Moyer-Mileur (Moyer-Mileur LJ 2009) examined the relationship between term newborn percent body fat (%BF) measured by air displacement plethysmography to 2-dimensional ultrasound biometric measures of fetal growth. The mean %BF was 10.9±4.8%. Estimated fetal weight and fetal abdominal circumference had the largest correlations with newborn %BF ($R^2 = 0.14$ and 0.1 respectively, p<0.05); however, stepwise linear regression modeling did not identify any fetal biometric parameters as a significant predictor of newborn %BF. Newborn mid-thigh circumference and Ponderal Index (weight, kg/length, cm$^3$ explained 21.8 and 14.4% of the variability in %BF and gave the best stepwise regression model. The conclusion was that 2D ultrasound did not provide a reliable estimate of newborn percent Body Fat.

Anthropometric ultrasound measurements, indicative of fetal body composition of normal fetuses, have shown a unique exponential pattern of the growth profile during the second half of gestation, both in lean mass and in fat mass (Bernstein IM 1997), suggesting that the measurement of fetal fat could provide a more sensitive and specific marker of abnormal fetal growth.

Recently three-dimensional ultrasound measurements of fetal limb volumes have been reported as the best parameters to estimate fetal weights as well as fetal fat mass when compared with abdominal circumference and traditional estimation of fetal weight (Khoury FR 2009; Lee W 2009).

Chang (Chang FM 1997) studied soft tissue volume measurements of the fetal extremities for a Taiwanese population. Predicted values were developed for fetal thigh volume in 225 singleton fetuses between 20 and 40 weeks’ menstrual age. In that study, single-parameter volume measurement of the fetal arm and thigh, respectively, achieved higher accuracy in predicting weight at delivery than did conventional 2D equations based on several biometric parameters.

Schild (Schild RL 1999) confirmed a greater accuracy of estimated fetal weight by the use of his own formula compared to 2D biometry. However application of published 3D weight formulae (Chang FM 1997, Liang RI 1997) which were derived from East Asian populations to Schild’s predominantly Caucasian population led to gross overestimation of fetal weight stressing the need for population-specific weight formulae.

Neonatal fat mass, as estimated by skinfold thickness measurements, is significantly higher in infants from women with diabetes mellitus and gestational diabetes (Enzi G 1980) Catalano (Catalano PM 2003) studied neonatal body composition using both skinfold thickness measurements and total body electrical conductivity (TOBEC) and confirmed that infants from diabetic mothers have an increased percentage of body fat compared to infants of women with normal glucose tolerance.
Birth weight has been generally used as an indicator of intrauterine growth. However, different growth patterns exist for fetal skeletal growth and fetal weight as was seen from the growth velocity graphs of Bertino (Bertino E 1996). This difference reflects the different dimensionality of length and weight, as well as the possible difference in growth curves between lean mass and fat mass.

In the study of Nobile de Santis,(Nobile de Santis MS 2010) the results indicated that GDM fetuses grow more quickly in all parameters analysed using ultrasound examination, but particularly in non-traditional body composition parameters, where the higher growth differences were observed in fetal fat parameters. This suggests that soft tissue studies, especially fetal fat, may be useful in GDM pregnancies.

This thesis has taken these soft tissue assessment techniques and applied them in a longitudinal manner in normal pregnancies, with subsequently normal outcomes, and compared the growth according to maternal characteristics.

1.9. Assessment of Neonatal Nutrition

1.9.1 Neonatal body composition

After birth, neonatal infant body composition is traditionally evaluated using birth weight and anthropometric measurements, including the ponderal index and skinfold thickness (Beattie RB 1994; Pietrobelli A 2005). Neonatal ponderal index has been suggested as a gold standard (Mondry A 2005) in terms of physical measurement. Others have disputed this with Cole (Cole TJ 1997) suggesting that past 39 weeks gestation, the body mass index was a better measurement of obesity than ponderal index.

Davidson (Davidson S 2011) compared BMI and weight for length ratios for infants born at 33 – 42 weeks gestation because the American Academy of Paediatrics (AAP news 2007) recommends using weight/length (Wt/L) in infants from birth to age 2 and BMI thereafter. The conclusion was that as body proportionality indexes provide an assessment of body mass and fatness relative to length, BMI and Wt/L ratio percentiles be added to weight and length growth curves as a routine intrauterine growth assessment at birth.

Detailed body composition analysis further considers individual components that contribute to total body weight. Humans are unique among mammalian species because their fetuses deposit significant quantities of fat and newborn infants have one of the greatest percentages of body fat at birth (Kuzawa C 1998).

Catalano (Catalano PM 1992) used birth weight and other anthropometric parameters within 24 h of delivery to describe the relationship between newborn body composition and fetal growth. Percentage body fat was estimated from skinfold thickness and ponderal indices. Seventeen
neonates (9%) were SGA (<10\text{th} \text{ percentile}), 147 (78.2\%) were AGA and 24 (12.8\%) were LGA. The correlation between ponderal index and %BF was poor ($R^2 = 0.15$). Despite the fact that neonatal fat mass constituted only 14\% of total birth weight, it explained 46\% of its variance, compared to ponderal index which explained 22\% of the variance in birthweight and correlated poorly with %BF.

Other investigators compared the subcutaneous fat and lean mass area, on antenatal ultrasound, of the fetal thigh in 17 growth-restricted fetuses and 20 normal control subjects (Padoan A 2004). The diagnosis of IUGR in that study was based on a small AC (<2 SD). Growth-restricted fetuses had reduced subcutaneous fat and lean mass compared with normal fetuses, but the IUGR and controls were not matched for gestational age.

Beattie (Beattie RB 1994) proposed supplementary approaches for the evaluation of body composition of neonates (e.g. ponderal index, skinfold thickness and mid-arm circumference measurements) to improve nutritional assessment beyond the use of birth weight alone. Mid-arm circumference measurements have been used as indirect measures of subcutaneous fat and lean body mass in newborn infants. Excler (Excler JL 1985) found mid-arm circumference to be more useful than birth weight, length and head circumference for identifying growth restriction in French infants.

A number of studies have used Principal Components Analysis to evaluate neonatal body composition. This statistical approach investigates the underlying structure of a dataset, by reducing the data to meaningful components. This method enables a large number of correlated variables to be summarized in terms of a relatively small number of uncorrelated principal components. The extent to which the principal components capture the variation in the original variables can be quantified in terms of the proportion of variance explained. The components can aid interpretation and represent meaningful constructs that parsimoniously describe the multivariate data.

Shields (Shields BM 2006) used principal components analysis with varimax rotation to reduce birth weight to two more meaningful components: skeletal size and fat. These components have different associations with known determinants of birth weight, suggesting fat and skeletal size may have different regulatory mechanisms. In particular gestational age was significantly related to skeletal size, in both boys and girls ($r = 0.41$ and 0.52), but not fat. Skeletal size at birth was also associated with parental skeletal size (maternal: $r = 0.24$ (boys), $r = 0.39$ (girls); paternal: $r = 0.16$ (boys), $r = 0.25$ (girls)), and maternal smoking (0.4 SD reduction in boys, 0.6 SD reduction in girls). Fat was associated with parity (first borns smaller by 0.45 SD in boys; 0.31 SD in girls), maternal glucose ($r = 0.18$ (boys); $r = 0.27$ (girls)) and maternal fat ($r = 0.16$ (boys); $r = 0.36$ (girls)).
Denham (Denham M 2001) used principal components analysis to describe differences in neonatal size between black and white babies of low socioeconomic status. Principal components analysis reduced the anthropometric dimensions to two summary measures: body size and composition. When controlling for social and biological variables, race and sex were significant predictors of body composition, but not body size.

Hindmarsh (Hindmarsh PC 2002) examined measurements of birth size were obtained and analysed by principal components to explain shape at birth. There was significant sexual dimorphism in all measures at birth, with males heavier, longer, and leaner than females. Parity, maternal height, and body mass index were important determinants of birth weight (p < 0.001). Cigarette smoking influenced birth weight, length, and head circumference (p < 0.001). Principal component analysis revealed that proportionality was the predominant size/shape at birth (55% of variance explained). A further 18% of variance was explained by a contrast between weight, head circumference, and length versus three skinfolds.

Veena (Veena SR 2009) performed a similar study in India to that performed by Shields. This group showed that of the four maternal components, fat was the strongest and only significant predictor of neonatal fat.

Yajnik (Yajnik CS 2003) examined body size and fat measurements of babies born in rural India and compared them with white Caucasian babies born in an industrialised country. The Indian women gave birth to lighter babies (mean birthweight: 2.7 kg compared with 3.5 kg). Compared to Southampton babies, the Indian babies were small in all body measurements, the smallest being abdominal circumference (z-score: -2.38; 95% CI: -2.48 to -2.29) and mid-arm circumference (z-score: -1.82; 95% CI: -1.89 to -1.75), while the most preserved measurement was the subscapular skinfold thickness (z-score: -0.53; 95% CI: -0.61 to -0.46).

Moyer-Mileur (Moyer-Mileur LJ 2009) demonstrated that newborn mid-thigh circumference (MTC; cm) and ponderal index (PI; weight, kg/length, cm$^3$) explained 21.8 and 14.4% of the variability in %BF, respectively, and gave the best stepwise linear regression model (P < 0.001).

Measurement of mid-thigh circumference has been selected for this thesis as the measurement of normal nutrition based on the study of Moyer-Mileur (Moyer-Mileur LJ 2009) as well as it is a convenient measurement to compare antenatal and postnatal measurements.

1.10 NZ demographic data

1.10.1 National statistics
In 2007 Statistics New Zealand (Health 2010) reported 63,492 mothers gave birth to 64,044 babies.
1.10.2 Ethnicity

The average birthweight of live born babies was 3.43 kg (Table 1.1). Male babies were, on average, heavier (3.48 kg) than female babies (3.38 kg). Asian babies had the lowest average birthweight (3.23 kg), while Pacific babies had the highest (3.55 kg). The average birthweight of babies within each ethnic group has remained fairly constant since 1999. (Health 2010)

<table>
<thead>
<tr>
<th>Ethnic group</th>
<th>Average birthweight (kg) ± standard deviation (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Māori</td>
<td>3.40 ± 0.65</td>
</tr>
<tr>
<td>Pacific peoples</td>
<td>3.58 ± 0.65</td>
</tr>
<tr>
<td>Asian</td>
<td>3.27 ± 0.57</td>
</tr>
<tr>
<td>European</td>
<td>3.53 ± 0.62</td>
</tr>
<tr>
<td>Other</td>
<td>3.41 ± 0.67</td>
</tr>
<tr>
<td>Not stated</td>
<td>3.40 ± 0.68</td>
</tr>
<tr>
<td>Total</td>
<td>3.48 ± 0.64</td>
</tr>
</tbody>
</table>

Table 1.1 National average birthweight of live born babies, by sex and ethnicity, 2007 (Health 2010)

The National data is limited by the publication of birthweight without reference to gestational age. The average birthweights may be biased because of differences in preterm birth rates within the different ethnic groups. In 2007 preterm babies (less than 37 week’s gestation) accounted for 7.1 percent of live births (Table 1.2).

<table>
<thead>
<tr>
<th>Ethnic group</th>
<th>Liveborn babies by gestational age (weeks)</th>
<th>Total</th>
<th>%</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Māori</td>
<td>0.0</td>
<td>0.2</td>
<td>0.5</td>
<td>0.8</td>
</tr>
<tr>
<td>Pacific peoples</td>
<td>0.0</td>
<td>0.2</td>
<td>0.4</td>
<td>0.8</td>
</tr>
<tr>
<td>Asian</td>
<td>0.0</td>
<td>0.1</td>
<td>0.3</td>
<td>0.8</td>
</tr>
<tr>
<td>European</td>
<td>0.0</td>
<td>0.1</td>
<td>0.3</td>
<td>0.7</td>
</tr>
<tr>
<td>Other</td>
<td>0.0</td>
<td>0.3</td>
<td>0.5</td>
<td>0.6</td>
</tr>
<tr>
<td>Not stated</td>
<td>0.2</td>
<td>0.0</td>
<td>0.3</td>
<td>1.0</td>
</tr>
<tr>
<td>Total number</td>
<td>8</td>
<td>72</td>
<td>220</td>
<td>463</td>
</tr>
<tr>
<td>Total percentage</td>
<td>0.0</td>
<td>0.1</td>
<td>0.4</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Table 1.2. Percentage of liveborn babies, by gestational age and ethnicity, 2007 (Health 2010)
In New Zealand Craig (Craig ED 2004) has shown a higher preterm delivery as well as higher SGA in the Māori population, compared to New Zealand European and Pacific Island women.

McCowan has shown significant differences in mean birthweights between New Zealand's main ethnic groups, born at gestational weeks from 38 to 41 at National Women's Hospital. Mean birthweights by ethnic group were: European 3521 g, Māori 3467 g, Samoan 3691 g, Tongan 3791 g, Chinese 3418 g, Indian 3192 g and other 3466 g. Tongan and Samoan babies were significantly heavier and Indian babies were significantly lighter than babies from all other ethnic groups (P < 0.001 for all comparisons). Overall Māori babies were approximately 50 g lighter than European babies but this difference was not statistically significant (P = 0.08), whereas Chinese babies were significantly lighter with a mean birthweight 100 g less than European (P < 0.001). (McCowan L 2004)

1.11 Demographic characteristics of pregnancies in the Counties Manukau DHB

In 2007 the Counties Manukau DHB region had the highest number of births in a New Zealand Health Board (8691 births; 14.3 percent of total) (Health. 2010). The largest proportion of Pacific Island (32 percent) mothers resided in Counties Manukau. The figures for the 12 months Dec 2008 to November 2009 show a drop in births to 8057. Of these births 1819 were to Māori, 3056 to Pacific peoples, 422 to Asian, 1980 to European, 614 to Indian and 166 to other.

Socio-economic status: Nearly 34% of the Counties Manukau population live in very deprived areas (based on the NZ Deprivation Index 2006; Deciles 9 and 10 being the 20% relatively most deprived areas in New Zealand). Fifty seven percent of all Counties Manukau Maori and 73% of our Pacific Island people live in decile 9 or 10 areas (Counties Manukau DHB Women’s Health DHB Annual Clinical Report 2009). Many of these patients have minimal or no antenatal care and will arrive, unbooked, in labour to the delivery unit.
<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Females</th>
<th>Males</th>
<th>Total</th>
<th>Mean Birth Weight (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Birth Weight (g)</td>
<td>Number</td>
<td>Birth Weight (g)</td>
</tr>
<tr>
<td>Asian</td>
<td>202</td>
<td>3271</td>
<td>220</td>
<td>3324</td>
</tr>
<tr>
<td>European</td>
<td>974</td>
<td>3397</td>
<td>1006</td>
<td>3583</td>
</tr>
<tr>
<td>Indian</td>
<td>306</td>
<td>3079</td>
<td>308</td>
<td>3212</td>
</tr>
<tr>
<td>Māori</td>
<td>866</td>
<td>3294</td>
<td>953</td>
<td>3380</td>
</tr>
<tr>
<td>Other</td>
<td>91</td>
<td>3302</td>
<td>75</td>
<td>3540</td>
</tr>
<tr>
<td>Pacific Islander</td>
<td>1487</td>
<td>3538</td>
<td>1569</td>
<td>3577</td>
</tr>
<tr>
<td>Grand Total</td>
<td>3926</td>
<td>4131</td>
<td>8057</td>
<td></td>
</tr>
</tbody>
</table>

Table 1.3 Birth weight of live born babies, excluding fetal anomalies, born in CMDHB facilities for the 12 months Dec-08 to Nov-09 by gender and weight after 37 weeks (Saleem F 2010). Percentages may not total to 100 due to rounding.

The data (Table 1.3) confirm the National data that Pacific Island babies have a greater mean birthweight and Asian and Indian babies have a lower mean birthweight than New Zealand European.

A retrospective analysis of 608 patients who had more than one fetal biometry ultrasound, maternal height and weight recorded and who delivered over a 3-month period was performed to provide some baseline population data on ethnicity and maternal BMI (Parry G 2009) (Fig 1.11). Birthweight was customised from maternal ethnicity, height and weight. BMI was classified by the WHO criteria shown in Table 1.4 (WHO Expert Consultation. 2004).
In that population study group only 30% of births were to women of normal BMI, 26% to overweight women, and 42% to women who were Obese by WHO BMI standards.

<table>
<thead>
<tr>
<th>Classification</th>
<th>BMI(kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Principal cut-off points</td>
</tr>
<tr>
<td>Underweight</td>
<td>&lt;18.50</td>
</tr>
<tr>
<td>Severe thinness</td>
<td>&lt;16.00</td>
</tr>
<tr>
<td>Moderate thinness</td>
<td>16.00 - 16.99</td>
</tr>
<tr>
<td>Mild thinness</td>
<td>17.00 - 18.49</td>
</tr>
<tr>
<td>Normal range</td>
<td>18.50 - 24.99</td>
</tr>
<tr>
<td></td>
<td>23.00 - 24.99</td>
</tr>
<tr>
<td>Overweight</td>
<td>≥25.00</td>
</tr>
<tr>
<td>Pre-obese</td>
<td>25.00 - 29.99</td>
</tr>
<tr>
<td></td>
<td>27.50 - 29.99</td>
</tr>
<tr>
<td>Obese</td>
<td>≥30.00</td>
</tr>
<tr>
<td>Obese class I</td>
<td>30.00 - 34.99</td>
</tr>
<tr>
<td></td>
<td>32.50 - 34.99</td>
</tr>
<tr>
<td>Obese class II</td>
<td>35.00 - 39.99</td>
</tr>
<tr>
<td></td>
<td>37.50 - 39.99</td>
</tr>
<tr>
<td>Obese class III</td>
<td>≥40.00</td>
</tr>
</tbody>
</table>

WHO BMI criteria

Table 1.4. The WHO criteria for BMI (WHO Expert Consultation. 2004).

Using the WHO criteria it can be seen that there is a different distribution of obesity across the different ethnic groups (Fig 1.12)
The ethnic groups differed across the BMI ranges with obese class 3 containing Pacific Island, Māori and European mothers. There were no Indian or Asian mothers in this group. In the underweight group there were no Pacific Island patients (Figure 1.12).

Ethnic-specific BMI categories have been described to account for varying body-fat and lean body mass distributions between races. Polynesian adults have a greater lean muscle mass, and Asian adults have a higher percentage of body fat than Europeans at the same BMI (Swinburn B 1999; World Health Organisation 2000; W. H. O. Expert Consultation 2004). Ethnic specific definitions of overweight and obesity have been recommended whereby Māori and Pacific BMI thresholds are raised and Asian BMI thresholds are lowered compared to European (Swinburn B 1999; W. H. O. Expert Consultation 2004) (see Table 1.4). The appropriateness of these criteria in pregnancy are supported by the findings from a single study which showed that Chinese women had an increased risk of pregnancy complications at these lower BMI levels (Leung TY 2008). There are no data investigating ethnic-specific BMI in other ethnicities in relation to adverse pregnancy outcomes.
<table>
<thead>
<tr>
<th>Classification</th>
<th>BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Asian/Indian</td>
</tr>
<tr>
<td>underweight</td>
<td>&lt;18.50</td>
</tr>
<tr>
<td>Normal</td>
<td>18.50-23.49</td>
</tr>
<tr>
<td>overweight</td>
<td>23.50-27.49</td>
</tr>
<tr>
<td>Obese</td>
<td>≥27.50</td>
</tr>
</tbody>
</table>

**Table 1.5. Ethnic-specific BMI categories** (WHO Expert Consultation 2004)

When the BMI of that population study group is classified by ethnic criteria compared to the WHO criteria the distribution of BMI changes (Fig 1.13)

**Fig 1.13 Distribution of BMI according to WHO or ethnic specific criteria** (Parry G 2009)

N = Normal, OW = Overweight, OB = Obese. Underweight, New Zealand European and Others have been removed as they do not change with differences in classification criteria.

The relative changes per ethnic group can be seen as percentages in Table 1.6.
<table>
<thead>
<tr>
<th></th>
<th>NZE (n=84)</th>
<th>Indian (n=70)</th>
<th>Māori (n=128)</th>
<th>Asian (n=37)</th>
<th>Pacific Island (n=269)</th>
<th>Other (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO Underweight</td>
<td>3</td>
<td>6</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnic underweight</td>
<td>3</td>
<td>6</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO Normal</td>
<td>32</td>
<td>30 (42.8%)</td>
<td>32 (25.0%)</td>
<td>28 (75.7%)</td>
<td>28 (10.4%)</td>
<td>6</td>
</tr>
<tr>
<td>Ethnic Normal</td>
<td>32</td>
<td>24 (34.2%)</td>
<td>43 (33.6%)</td>
<td>18 (48.6%)</td>
<td>36 (13.4%)</td>
<td>6</td>
</tr>
<tr>
<td>WHO Overweight</td>
<td>21</td>
<td>22 (31.4%)</td>
<td>39 (30.5%)</td>
<td>5 (13.6%)</td>
<td>53 (19.7%)</td>
<td>8</td>
</tr>
<tr>
<td>Ethnic overweight</td>
<td>21</td>
<td>20 (28.5%)</td>
<td>42 (32.8%)</td>
<td>13 (35.1%)</td>
<td>70 (26.0%)</td>
<td>8</td>
</tr>
<tr>
<td>WHO Obese</td>
<td>30</td>
<td>12 (17.1%)</td>
<td>57 (44.5%)</td>
<td>1 (2.7%)</td>
<td>188 (69.9%)</td>
<td>6</td>
</tr>
<tr>
<td>Ethnic Obese</td>
<td>30</td>
<td>20 (28.5%)</td>
<td>43 (33.6%)</td>
<td>3 (8.1%)</td>
<td>163 (60.6%)</td>
<td>6</td>
</tr>
</tbody>
</table>

Table 1.6 Percentage distribution of obesity by ethnic group according to classification (Parry G 2009)

It is clear that the population of CMDHB is of very mixed ethnicity and obesity. The incidence of obesity is different if BMI is classified by ethnic criteria instead of WHO criteria.

As examples a normal BMI of 24 in a New Zealand European patient represents an overweight BMI in an Indian patient and a BMI of 25.5 is normal in a Pacific Island woman and overweight in an NZE woman.

Since this thesis was investigating the effects of BMI and ethnicity on fetal growth, ethnic BMI classification was used, which allows a better comparison between BMI and fetal growth.

1.12 The Statistical Description of Fetal Growth

1.12.1 Introduction

Statistical techniques appropriate for analysis of longitudinal data involve multilevel modeling. This is also known as hierarchical modeling because of the hierarchical nature of the data.

1.10.1 Multilevel modelling

Fetal longitudinal data are hierarchical in structure, with variation between gestational ages within fetuses and variation between fetuses. Multilevel modelling adequately
represents the underlying structure of the data and allows efficient models to be constructed (Troe EJ 2008).

Repeated measures data arise in a number of contexts, such as child or animal growth, panel surveys and the like. The basic structure is that of measurements nested within subjects, i.e. a two-level hierarchy. The multilevel modelling allows for the fact that repeated measurements will be correlated. The point of multilevel modelling is that a statistical model explicitly should recognise a hierarchical structure where one is present.

Longitudinal data have a hierarchical structure based on two levels of variation: within fetuses between gestational ages (level 1), and variation between fetuses (level 2) (Johnsen SL 2006).

Conventionally, fetal biometric size charts were constructed with ultrasound measurement of each fetus only once. The use of longitudinal data creates a number of statistical problems. The most important drawback is the underestimation of the variability between the subjects as repeated measures are taken in the same individual.

Multilevel modelling offers several advantages over conventional statistics for the processing of longitudinal growth data. First, the interval between each measurement at the individual level need not be fixed. This allows greater flexibility in the process of data collection. It also gives better precision in the assessment of the relationship between the independent and dependent variables as there is no need to aggregate the time factor for analysis.

Second, it allows modelling of variability (intra- and inter-subject) at different levels.

Third, it provides a framework for the calculation of reference intervals for both fetal size and fetal growth using the same set of longitudinal data.

Fourth, covariates such as maternal and pregnancy characteristics can be added into the model allowing development of a customized model for fetal size in individual pregnancies (Pang MW 2003).

Multilevel modelling provides better estimates in answer to the simple questions for which single-level analyses were once used and in addition allows more complex questions to be addressed.

Finally, carrying out an analysis that does not recognise the existence of clustering within a hierarchy at all creates serious technical problems. For example, ignoring clustering will generally cause standard errors of regression coefficients to be underestimated. The point of multilevel modelling is that a statistical model explicitly should recognise a hierarchical structure where one is present. Multilevel modelling provides an efficient way of doing this. (Rasbash J 2009)

Royston (Royston P 1995; Royston P 1995) has shown how to apply multilevel modelling to longitudinal data to produce growth centiles and the same model may also be used to calculate valid size centiles.
Linear mixed effects model (multilevel modelling) accounts for between-subject heterogeneity by incorporating subject specific random effects for both intercept and gradient. These models have been used to motivate three measures of fetal growth: the conditional centile or z-score of a current measurement given an earlier value for the same measurement; the best linear unbiased predictor (BLUP) of the subject specific random effect gradient (which is shown to be invariant to transformations of location and scale), and the standardized residual at a given gestational age, which characterizes departures from the modelled growth trajectory (Gurrin LC 2001).

Other papers quoted above have all used multilevel modelling to analyse longitudinal growth (Pang MW 2003; Johnsen SL 2006; Troe EJWM 2007).

Pang (Pang MW 2003) has constructed customised models of individual fetal biometric parameters rather than fetal weight. The rationale used was that this approach eliminated the potential problem of erroneous estimation of fetal weight using formulae for its calculation. In addition, they reasoned that it allowed direct assessment of the characteristics of any growth aberration by comparison of the deviation of the individual fetal biometric parameters from the expected values i.e. symmetrical vs. asymmetrical growth restriction.

1.12.3 Mathematical Models for Fetal Growth.

Hooper (Hooper PM 2002) developed a model for fetal growth and used it to construct tools for diagnosis of intrauterine growth restriction. In this model fetal weight estimates are first transformed to normally distributed z-scores. The covariance structure over gestational ages is then estimated using a regression model. The diagnostic tools include individual growth curves with error bounds, probabilities to assess whether a fetus is small for its gestational age, and residual scores to determine whether current growth rates are unusual. The methods were developed using data from 13593 ultrasound examinations involving 7888 fetal subjects. The model shows that median fetal growth velocity increases up to a gestational age of 35 weeks and then decreases during the final weeks of pregnancy. When growth is expressed as change in log weight, or equivalently as change proportional to current weight, the model reveals a constant deceleration as gestational age increases from 14 to 42 weeks. (Hooper PM 2002)
Fig 1.14 Velocity of Median Weight curve, (Hooper P, 2002). Reproduced with Permission

Pineau (Pineau JC 2006) compared four mathematical models (a linear-quadratic model, a linear-cubic model, the Rossavik model and a new two-phase model, which had been found to best fit fetal head data). In a previous study Pineau (Pineau JC 2003) attempted to determine the best model describing the kinetics of fetal head growth. The result was a new two-phase mathematical model, computed independently for male and female data, taking into account the increasing inter-subject variability with gestational age, and the decrease in mean growth rate at about 30 gestational weeks.

Pineau tested the same mathematical models on AC and FL data and found the best fitting was obtained with the simplest model: the linear-quadratic one. Furthermore, in contrast to HC, accurate modelling of FL and AC data did not require separate computing of data for males and females.

Mathematical models used to describe the growth of each dimension should be carefully chosen as close as possible to the raw data. This consideration is also relevant for ‘individualized growth charts’ (Pineau JC 2006).

1.12.4 SAMPLE SIZE CONSIDERATIONS

Sample size in longitudinal studies is difficult to compute, especially where a multilevel analysis is to be performed (Twisk J 2006).

To date, precise sample size formulae are unavailable for the longitudinally derived equations and so we must be guided by pragmatic considerations, such as feasibility and resource
requirements, and what has been previously employed in the literature (personal communication from A Stewart, statistician, University of Auckland).

In computing statistical power sample size estimates are needed which have been derived from a similar study design or at least from procedures which have similar assumptions. Similar longitudinal studies have used 20 (Deter RL 1982), 44 (Lampl M 2003) or 87 subjects (Lee W 2004).

For a longitudinal study estimates should be derived from a longitudinal analysis. In addition to estimates of the relevant variance and difference to detect, the computation of statistical power for longitudinal designs typically requires an estimate of the correlation between successive measurements for an individual.

Power and sample size in multilevel modelling. (Snijders T 2005)

Sample size determination in multilevel designs requires attention to the fact that statistical power depends on the total sample sizes for each level.

The power of statistical tests generally depends on sample size and other design aspects; on effect size or, more generally, parameter values; and on the level of significance. In multilevel models, however, there is a sample size for each level, defined as the total number of units observed for this level. E.g., in a three-level study of pupils nested in classrooms nested in schools, there might be observations on 60 schools, a total of 150 classrooms, and a total of 3,300 pupils. On average in the data, each classroom then has 22 pupils, and each school contains 2.5 classrooms. What are the relevant sample sizes for power issues?

Power depends on the parameter being tested, and power considerations are different depending on whether the researcher focuses on, e.g., testing a regression coefficient, a variance parameter, or is interested in the size of means of particular groups. In most studies, attention goes primarily to regression coefficients.

A primary qualitative issue is that, for testing the effect of a level-one variable, the level-one sample size (in the example, 3,300) is of main importance; for testing the effect of a level-two variable it is the level-two sample size (150 in the example); etc. The average cluster sizes (in the example, 22 at level two and 2.5 at level three) are not very important for the power of such tests. This implies that the sample size at the highest level is the main limiting characteristic of the design. Almost always, it will be more informative to have a sample of 60 schools with 3,300 pupils than one of 30 schools also with 3,300 pupils.

de Jong (de Jong K 2010) analysed three-level longitudinal models in psychotherapy research, particularly in therapist-effect or group-effect studies. Limited attention had been paid to power analysis in these models. His article demonstrated the effects of intraclass correlation, level of randomization, sample size, covariates and drop-out on power, using data from a routine outcome monitoring study. Results indicated that randomization at the patient level was the most
efficient, and that increasing the number of measurements did not increase power much. The results demonstrated that sufficient power can be reached with small sample sizes, but that larger sample sizes are needed to prevent estimation bias for the model parameters and standard errors.

1.13 Summary
This introduction has highlighted some of the difficulties in understanding normal fetal growth and defining abnormal growth.

The literature shows there are many determinants of fetal growth. Some of these (such as maternal ethnicity, parity, height and prepregnancy weight, or paternal factors) cannot be modified in pregnancy, and others (such as smoking and diet) can be modified during pregnancy. The maternal factors of ethnicity, parity, maternal height and prepregnancy weight are used in New Zealand to customise estimated fetal weight centile charts as well as to allocate a birthweight centile for the neonate. These factors were therefore chosen to investigate their effect on fetal biometry.

Many of the discussions of fetal biometry charts have highlighted that charts in different groups should be based on standards produced from that population.

A population reference is often established on the basis of a large sample size (ideally representing the underlying population), with a study population that includes both low-risk and high-risk pregnancies and both normal and abnormal perinatal outcomes. On the other hand, a standard usually is based on low-risk pregnancies with a normal outcome.

When the “population reference” and the “standard” are applied to an individual fetus or infant, interpretation of the findings differs. The use of a population reference will yield a relative fetal size in relation to the total population; a standard will assess a fetal size in comparison to normally grown fetuses. Thus, a standard may have more clinical utility than a population reference to detect deviation from normal (Zhang J 2010).

The CMDHB population is multi-ethnic and therefore this thesis investigated whether our ethnic groups did show a difference in growth compared to the population reference commonly used which is based on a European population. Socioeconomic data was not collected. This was because the participants were self-selected and may not be representative of the CMDHB population. The lower socio economic groups tend to present later in pregnancy than was needed for the study, as well as being outside the BMI range required for this study.

The literature highlights the importance of longitudinal data to create growth charts rather than size charts. The appropriate statistical technique to analyse these is multilevel modelling.
This thesis reports the investigation of the multilevel modelling of growth of individual fetuses in terms of novel fetal biometric measurements and relates these to maternal ethnicity, height, weight and ethnic BMI.
CHAPTER 2

METHODS

2.1 Introduction
This thesis describes a longitudinal study of ultrasound biometry of normal pregnancies in
different ethnic groups within the Counties Manukau District Health Board region of Auckland,
New Zealand.

Aim
The aim of this study was to evaluate the rate of growth of fetuses from different maternal ethnic
groups and to determine the influence of maternal characteristics on longitudinal fetal growth
parameters in normal pregnancy.

Hypotheses
The hypotheses are that
1. fetal growth in different ethnic groups is characterised by different growth patterns of
   skeletal and soft tissue biometry.
2. differences in fetal growth in these groups are due to maternal anthropomorphic
   characteristics.

It was postulated that the differences in mean birthweight between ethnic groups was due to a
difference in soft tissue, particularly in the arms and legs.

Measurement of fetal growth was performed using standard biometry as well as assessment of
soft tissue growth by analysis of 3D volume datasets, which were used to measure thigh and arm
volume and circumference.

Growth and growth velocity of the standard biometry and the novel soft tissue measurements
were graphed and analysed according to ethnicity and maternal characteristics with a view to
finding the best fit to perform a multilevel analysis of the longitudinal data.

2.1.1 Setting
Recruitment to this study occurred at Middlemore Hospital (a tertiary obstetric hospital) in
Auckland, New Zealand from June 2007 to December 2010. Not all the women recruited to the
study delivered in Middlemore Hospital. Because the women recruited were normal pregnant
women with no risk factors, they were eligible to deliver in one of three primary birthing units.
2.1.2 New Zealand Model of Maternity Care

The New Zealand model of maternity care is that the pregnant woman is cared for by a Lead Maternity Carer (LMC). This can be a Specialist Obstetrician, an Independent Midwife or a General Practitioner (GP).

In the Counties Manukau District Health Board (CMDHB) area there is a shortage of midwives as well as few GP’s delivering babies. CMDHB therefore has a maternity model that involves shared care between GP’s and community midwives. Care in labour is provided by staff on delivery suite. There are a small number of Case Loading Midwives, employed by CMDHB, who work in a similar way to Independent Midwives by following the woman through pregnancy and caring for her during labour.

2.1.3 Design

This was a prospective longitudinal observational study with retrospective analysis of data.

2.1.4 Ethics committee approval

Ethical approval for this study was given by the Northern Y Ethics committee Ref No: NTY/06/05/032

2.2 Recruitment

2.2.1 Recruitment

Potential participants were identified for recruitment from LMCs. Advertising brochures and posters were placed in hospital clinics as well as with community midwives, Independent Midwives and private scanning groups.

2.2.2. Inclusion criteria:

- Healthy pregnant women whose primary ethnicity was stated as European, New Zealand Māori, Pacific Island or Indian. Ethnicity was self-determined by the mother. Paternal ethnicity was not collected. Indian women are Asian Indian. Other Asian women were not included because the numbers that deliver at CMDHB were less than the numbers of Indian women.
- A singleton fetus with the dating scan in the first trimester.
- Gestational age at research scan of 18 +/- 2 weeks.
- BMI between 18.5 and an upper limit defined by ethnicity - 27.5 for Indian, 30 for European and 32 for Māori and Pacific Islander.
- Maternal age range – 18-36
- Parity 0-4
2.2.3 Exclusion Criteria:

2.2.3.1 Exclusion Criteria present at booking:

- Multiple pregnancy
- Maternal history of diabetes
- A history of maternal medical disorders that may alter fetal growth e.g. antiphospholipd syndrome, systemic lupus erythematosus. Such patients are referred to the Obstetric Medical Clinic. Recruitment was not sought from that clinic.
- A past history of early onset growth disorders defined as IUGR (birthweight <10\textsuperscript{th} customised centile) needing delivery before 34 weeks
- A past history of LGA (birthweight > 90\textsuperscript{th} customised centile)
- A history of substance abuse, alcohol intake (>2 standard drinks per week) and smoking cigarettes after 15 weeks gestation

2.2.3.2 Post recruitment exclusion.

Problems can develop or be detected during the pregnancy that may interfere with normal growth and therefore needed to be excluded. These include

- Major fetal abnormalities that would need delivery elsewhere or may be associated with growth disorders e.g.
  1. Chromosomal anomalies
  2. Surgical conditions, such as gastoschisis
  3. Major cardiac conditions, which are delivered elsewhere
  4. Skeletal dysplasia
- Development of diabetes, preeclampsia or gestational hypertension.
- Ante partum haemorrhage (vaginal bleeding after 20 weeks)
- Preterm birth defined as delivery before 37 completed weeks of pregnancy

Also excluded were those who were lost to follow up.

The study population does not reflect the hospital population, which is socioeconomically deprived. Therefore data on socioeconomic status was not collected.

Minor abnormalities that would not be associated with growth abnormalities were not excluded e.g.

1. Minor cardiac abnormalities
2. Isolated club foot
3. Unilateral cleft lip
2.2.3.3 Medical Disease Definitions

2.2.3.3.1 Hypertension

Hypertension in pregnancy in a previously normotensive woman was defined as:
1. Systolic blood pressure greater than or equal to 140 mm Hg and/or
2. Diastolic blood pressure greater than or equal to 90 mm Hg

a) Preeclampsia

A diagnosis of preeclampsia was made with hypertension after 20 weeks gestation and accompanied by dipstick proteinuria subsequently confirmed by spot urine protein/creatinine ratio ≥ 30mg/mmol - SOMANZ guidelines (Lowe SA 2008).

b) Gestational Hypertension (SOMANZ)

Gestational hypertension is characterised by the new onset of hypertension after 20 weeks gestation without any maternal or fetal features of preeclampsia, followed by return of blood pressure to normal within 3 months post-partum.

d) Pre-existing hypertension

This is defined by a blood pressure > 140 mm Hg systolic and/or > 90 mm diastolic confirmed before pregnancy or before 20 completed weeks gestation (Brown MA 2001).

2.2.3.3.2 Diabetes

Diabetes included women with either a pre-existing diagnosis of diabetes (Type 1 or Type 2 diabetes mellitus) or gestational diabetes mellitus (GDM). GDM was diagnosed by a 75 g oral glucose tolerance test (fasting) with a venous plasma glucose level at 0 hours of ≥5.5 mmol/L and/or at 2 hours of ≥9.0 mmol/L as per the Australasian Diabetes in Pregnancy Society (Hoffman L 1998).

2.3 Definitions

2.3.1 Ethnicity


2.3.2. BMI

BMI was classified using ethnic-specific BMI categories.
2.4 Maternal data

2.4.1 Demographic data
All women had baseline demographic details recorded, including past obstetric and medical histories. The data collected by the investigator at the first scan visit at 18 ± 2 weeks, included:

- ID - NHI (National Health Identifier). The patient name was included in the dataset and then replaced by a non-identifying number for data analysis and publication purposes
- Age at recruitment
- Ethnicity
- Parity was defined as the number of times a woman had given birth to liveborn infant(s) of any birthweight or gestation, or to a stillborn infant after 20 weeks of gestation or where the infant weighed 400g or more if gestation was unknown (Bai J. 2002)
- Maternal height in centimetres measured without shoes to the nearest millimetre using a stadiometer fixed to the wall (SECA, gmbh and co, Germany)
- Maternal weight, without shoes or outdoor clothing, in kg at booking with the midwife
- BMI was subsequently calculated and classified according to ethnic specific criteria

2.4.2 Pregnancy Dating
The estimated date of delivery (EDD) was calculated from the first day of last menstrual period (LMP) using a gestational age calculator wheel and confirmed by early scan before 12 weeks gestation. If the gestational age (GA) by Crown Rump Length (CRL) agreed with GA by LMP to within 7 days it was accepted. If there was a difference of more than 7 days the EDD calculated from the ultrasound was accepted (van de Velde EH 1980).

2.5 Equipment

2.5.1 Ultrasound
The Ultrasound equipment used was a Philips IU22 (Philips Ultrasound, Bothell, USA) with 3D capability. The ultrasound transducers used were Philips curvilinear array C5-2 or C5-1. The 3D transducer used was a mechanical curved-array 3D abdominal ultrasonic transducer (3D 6-2 Philips Ultrasound, Bothell, USA).

2.5.2 QLAB
Volume analysis were done off line on the Philips package QLAB™ version 6. QLAB is a software application package, designed to run in Microsoft Windows, which creates an environment for accessing images acquired on Philips ultrasound products and analysing the images using quantification tools known as plug-ins. Each plug-in provides tools and methods enabling clinicians to review and quantify the various data in ultrasound images and assess image content.
2.6 Scan procedures

2.6.1 Scan protocol

Each participant was scanned at 4 weekly intervals from between 18 +/- 2 weeks to delivery. Ultrasound data was stored on DVD as 3D Volume Data Sets for off line analysis. The stored datasets also were subsequently used to perform inter and intra observer correlation studies.

At each examination, all standard measurements were obtained three times from three separately generated ultrasound images and then averaged. The 3D volume measurements were obtained by averaging three measurements obtained by 3 manipulations of the one data set offline. A full morphological evaluation (anomaly scan) was arranged separately from the research scan by the participant’s LMC according to their normal practice.

2.6.2 Ultrasound Measurements

All scans were performed in the semi-recumbent position by the author or by one obstetric colleague with the Diploma of Diagnostic Ultrasound (DDU). Standard measurements were performed according to the protocols published by the Australasian Society for Ultrasound in Medicine. These measurements were Biparietal Diameter (BPD), Head Circumference (HC), Humerus Diaphyseal Length (HDL), Abdominal Circumference (AC) and Femur Diaphyseal Length (FL). The measurements were also used to calculate Estimated Fetal Weight (EFW) by the Hadlock equation (Hadlock FP 1985).

Measurements taken from the 3D volume dataset were Thigh Circumference (ThC), partial thigh volume (TVol), Arm circumference (ACirc) and partial Arm Volume (AVol) (see below). These measurements were as described by Lee (Lee W 2001; Lee W 2004) and were used to calculate a separate EFW from Lee’s equation (Lee W 2009).

Loss of integrity of data from the transfer and storage was checked by measuring the 3D volume dataset and comparing that measurement to those measured on the ultrasound machine. This was done for 10 femur lengths and 10 abdominal circumferences at 3 gestation ages (18, 28 and 34 weeks).

2.6.3 Measurement Protocols

The ultrasound images of BPD, HC, HDL, AC and FL were required to fill at least 2/3 of the monitor screen. The average of the three measurements of each parameter was used.
Biparietal diameter (BPD)

Anatomy.
- Cross-sectional view of the fetal head at the level of the thalami;
- angle of insonation is 90° to the midline echoes;
- symmetrical appearance of both hemispheres;
- continuous midline echo (falx cerebri) broken in middle by the cavum septi pellucidi and thalamus;
- no cerebellum visualized.

Caliper placement. The BPD was measured from the outer edge of the nearer parietal bone to the inner edge of the more distant parietal bone, at the widest part of the skull, using an angle that is perpendicular to the midline falx.

![BPD and Head Circumference](image)

Fig 2.1  BPD and Head Circumference

Head circumference (HC)

Anatomy. As described for the BPD.

Caliper placement. The HC was measured directly by placing the ellipse around the outside of the skull bone echoes.

Abdominal circumference (AC)

Anatomy.
- Transverse section of the fetal abdomen (as circular as possible);
- umbilical vein at the level of the portal sinus;
- stomach bubble visualized;
- ribs equal and symmetrical
- lung or kidneys should not be visible.
Calliper placement. The AC was measured at the outer surface of the skin line directly with ellipse callipers.

Fig 2.2  Abdominal circumference

Femur diaphysis length (FDL) and Humerus Diaphyseal Length (HDL)

Anatomy. The FDL or HDL was imaged optimally with both ends of the ossified metaphysis clearly visible. The longest axis of the ossified diaphysis was measured.

Calliper placement. Each calliper was placed at the ends of the ossified diaphysis without including the distal femoral epiphysis if it was visible. This measurement excluded the triangular spur artifacts that can falsely extend the diaphysis length.

Fig 2.3  Femur diaphysis length

Limb Circumference: This is a circumference measured with ellipse callipers at the midpoint of the limb (humerus or femur) diaphyseal length. This site was identified by the measurement on the 3D dataset using QLAB. The limb diaphyseal length was measured and then divided by 2 to get the midpoint. With the limb in the horizontal position, the circumference was measured from the orthogonal plane at right angles to the limb.
Fat and lean body-mass areas are evaluated on axial ultrasound images of the mid upper arm and mid upper leg. This is easily done in QLab using the same technique as for Limb Circumference.

The fat "mass" was measured by subtracting the central lean circumference (consisting of muscle and bone) from the total cross-sectional limb circumference (Fig 2.4). The same technique was used to measure partial limb volume fat.

This technique has been validated by comparison with fetal MR (Lee W 2009) Fractional limb volumes include fat, muscle and bone. Transverse views of a normal fetal thigh are demonstrated using T1 imaging sequences during the third trimester. Areas of high signal intensity (white arrows) represent the subcutaneous fat layer that surrounds muscle tissue and bone. Areas of intermediate signal intensity within the limb represent muscle tissue. Cross-sectional views of the femoral diaphysis are seen as low-intensity circular areas in the center of the limb muscle mass.

**Fig 2.4 Limb fat and lean mass**

**Fig 2.5. Fetal magnetic resonance images of the thigh** from two different pregnancies during the third trimester (28.0 weeks (a) and 34.5 weeks (b)) (Lee W 2009) reproduced with permission.
Partial limb volume: Each limb volume was acquired from a sagittal sweep, during maternal breath hold, which displayed both ends of the diaphysis and saved as a volume dataset onto a DVD and then measured using QLAB. Volume measurements were based on 50% of limb diaphyseal length. The diaphyseal length was measured with electronic callipers. The midpoint of the diaphysis was then located and a measurement of 50% around this midpoint was identified. This measurement was divided electronically by the software into 7 subsections of equal length centred on the midpoint of the limb diaphysis. Partial limb volumes were calculated by the software after each of the seven slices was manually traced from a transverse view of the extremity. Each slice is less than 5mm so that any volume measurement error as a cone rather than a cylinder is minimal.

Fig 2.6 Partial thigh volume theory (Lee W 2009) reproduced with permission

The above diagram demonstrates the theory of the partial (fractional) limb volume. Because the limb folds upon the adjacent parts of the body, the ends of the limb are difficult to image, so imaging has been described in the middle of the limb (Lee W 2009). “Based on our qualitative experiences, the central portion of the fetal limb appeared to give us the clearest views of the soft tissue borders - and a sub-volume based on 50% of the diaphysis length seemed to provide the best balance. When I tried 80%, it was less likely that the soft tissue borders would be clearly seen because of the problem of ill-defined soft tissue borders near the knee or hip joints” (Personal communication W Lee.)
The above screenshot illustrate the technique that was used for partial limb volume. Image optimisation was achieved by:-

1. Minimal abdominal transducer pressure. Excessive pressure can obliterate the small fluid layer that helps to differentiate soft tissue borders from the adjacent fetal limb and uterine wall.
2. Increasing the sweep angle and checking that the complete volume has been acquired after the sweep. An inadequate sweep angle or suboptimally centred placement of the volume probe on the maternal abdomen can lead to an incomplete scan of the fetal limb.
3. Maternal breath holding. Movement artifacts can occur from maternal respiration during volume acquisition.
4. Improved acquisition was attempted after fetal movement or trans abdominal manipulation of the fetus if there was compression by adjacent structures.
5. Careful checking of the anatomy. Upper and lower limbs can have very similar sonographic appearances. As early as 18 weeks, a characteristic indentation can be seen that separates the deltoid and triceps muscles of the fetal arm.

2.7 Neonatal data

2.7.1 Neonatal data collected
The following neonatal data was collected by the midwife within 30 minutes of delivery.

- Gestational age at delivery
- Birthweight (g, accuracy to within 5 g)
- Gender,
• Crown Heel Length (CHL), measured to the nearest mm
• Head Circumference (HC), measured to the nearest mm
• Thigh Circumference (ThC), measured the nearest mm
• Customised birthweight centile was calculated using the centile calculator v5.15_NZ for New Zealand. This calculator is downloaded free from [www.gestation.net](http://www.gestation.net). Birthweight details (birthweight, gender, gestational age) as well as maternal details (ethnicity, parity, maternal height and weight) are entered and a customised birthweight centile is produced
• Date of delivery
• Apgar scores
• Admission to Neonatal Unit (NNU)
• Any hypoglycaemia (<2.6 mmol/L) recorded (Harris DL 2010).
• Any abnormalities noted on neonatal examination were recorded

2.7.2 **Neonatal measurement protocol**

• Birthweight was measured electronically (Salter Australia PTL Ltd, Australia) and reported in g. The scales were regularly checked by the Biomedical Department and are accurate to within 5 g
• Crown Heel Length (CHL): This measurement was taken using a paper tape measure. The baby was supine and the legs stretched out by pressure on the knees to ensure legs were not flexed. The measurement was taken from the crown of the head to the heel. Measurements are in centimetres to nearest mm.

![Fig 2.8 Neonatal Crown Heel Length](image)
• Head Circumference (HC): The maximum occipito-parietal circumference was measured with a disposable tape measure to within the nearest mm.

• Neonatal thigh circumference was measured at a point located midway between the superior margin of the patella and the anterior superior iliac spine (Moyer-Mileur LJ 2009) with the lower leg at approximately 90 degrees with respect to the thigh. Deter and
Warda (Warda A 1986) found that postnatal thigh circumference measurements were affected by leg position.

Fig 2.11 Neonatal Thigh Circumference

2.8 Statistical Analysis

2.8.1 Sample size.
Sample size in longitudinal studies is difficult to compute, especially where a multilevel analysis is to be performed (Twisk 2006) (section 1.12.4).

To date, precise sample size formulae are unavailable for the longitudinally derived equations and so we must be guided by pragmatic considerations, such as feasibility and resource requirements, and what has been previously employed in the literature (personal communication A Stewart, statistician).

2.8.2 Missing data
Imputation methods can be used to replace missing data in longitudinal studies. The ‘mean or median of series’ imputation method involves calculation of the average value of the available data. This average value is imputed for the missing values. Because of its simplicity, it is by far the most frequently used imputation method in practice (Twisk J 2003).

This was the technique used for this study. The difference between two adjacent values was calculated and then a value calculated as a proportion of the difference of the time points. There
were only a few occasions when this was required because the 3D images were stored incorrectly.

Non-attendance of patients for appointments was rare and they were usually able to be given another appointment within a week. This made no difference to their data inclusion because multilevel data analysis does not require visits at exact intervals.

2.8.3 Inter and Intra observer measurement

Intra observer studies of all biometry measurements were performed - see chapter 3.
Intra and Interobserver studies of neonatal measurements were performed - see chapter 4.

A measurement of agreement was tested to investigate intra- and inter observer differences and reproducibility. The differences of all the measurements were plotted against their mean, to determine the distribution and to find any consistent differences (bias) from the mean within or between the observers. These graphs are the Bland and Altman plots in Chapters 3 and 4.

A check for normal distribution of the differences was made using D’Agostino and Pearson omnibus normality test as recommended by GraphPad Prism 5 software. If the differences are normally distributed, 95% of the differences will lie between the mean +/- 2 SD limits. These are the limits of agreement, and the measures between and among observers can be assumed to be interchangeable within these limits.

Intra Class Correlation (ICC) statistics were calculated. The ICC is defined as the ratio of the variance between subjects to total variance. ICC measures the strength of the agreement of the variables, independent of the dimension of the variable considered.

Additionally, the coefficient of variation (CV) was calculated for all fetal measurements, which, expressed as a percentage, is the ratio of the standard deviation (SD) of the measurement error and the overall mean (Bland JM 1996).

Fetal biometry is reproducible and valid in case of Intra Class Correlation (ICC) over 0.80, a CV under 10% and the limits of agreement from differences of measurement error to be within 95% (Bland JM 1996).

2.8.3.1 Ultrasound measurement data validation

Thirty datasets were selected, with 10 each at 18, 28 and 34 weeks (± 2weeks at each interval). The datasets were randomly selected by blindly removing the DVD storage disk from the box containing the disks (Chapter 3).
The BPD, HC, AC and FL biometry were selected to enable linear and elliptical measurements to be compared.
Three measurements were made offline, blind to the reported value and the average compared with that value. Bland–Altman plots (difference vs. average) were used to determine 95% limits of agreement (LOA) and bias for a measurement made on the ultrasound machine and those made by the same examiner off line (Chapter 3).

Statistical analysis and generation of the Bland-Altman plots and measures of agreement were performed using GraphPad software.

2.8.3.2 Volume measurements
After removal of subject identifiers, 10 arm and 10 thigh volume datasets were reviewed to investigate the reproducibility of these measurements. These datasets were selected to represent a broad range of menstrual ages (16-18, 26-30 and 32-36) (Chapter 3). Bland–Altman plots (difference vs. average) were used to determine 95% limits of agreement (LOA) and bias for a single examiner.

2.8.3.3 Neonatal measurements
The inter- and intra-observer neonatal measurements were performed by 2 midwives measuring 20 neonates, separate from the study group - (Chapter 4). The crown heel length by tape measure was compared to the value obtained using a Harpenden neonatometer (Holtain Ltd, Dyfed, UK). This comparison was made because the majority of the normal deliveries occurred in the primary units where there was no neonatometer.

Bland–Altman plots (difference vs. average) were used to determine 95% limits of agreement (LOA) and bias for a single examiner and between examiners for the neonatal measurements. The measurement differences for each examiner were averaged and the mean values compared to by t-test.

Bland Altman (Bland MJ 1999) plots were used to determine limits of agreement between a single examiner and between examiners for the crown heel measurement as measured by tape measure and by neonatometer.

2.8.4 Data Analysis
Because the present charts in use are based on a European population all graphs and analyses were performed using New Zealand European as the reference population. This allowed analysis of difference between ethnic groups compared to the reference population. Overall differences can also be analysed.

Univariate linear regression analysis was used to study the maternal characteristics. P-values less than 0.05 were considered statistically significant.

Distribution of measurements was assessed graphically and numerically, using standard tests for normality (i.e. Shapiro–Wilks, Kolmogorov–Smirnov, and Anderson–Darling tests).
Continuous variables were analysed by t test compared to the reference (European) group and by ANOVA for overall comparison across all groups. Mann-U-Whitney tests were used for variables that did not have a normal distribution.

Univariate linear regression analysis was used to study the associations of ethnic background with birth weight. P-values less than 0.05 were considered statistically significant.

The biometry was plotted against gestational age by maternal characteristic groups (ethnic group, height tertile, weight tertile, ethnic BMI tertile) as well as by customised birthweight centile.

The biometry was modelled as a linear mixed effects model to allow for the fact that repeated measurements will be correlated. Ethnicity and maternal characteristics and the measurements of gestational age were modelled as the fixed effects. Gestational age and patient ID were modelled as the random effects of the longitudinal data.

Multilevel modelling, random effect model, was used in order to construct mean curves of the fitted model to compare growth between the different ethnic groups. When necessary the transformation was up to a cubic function. Because the biometry curves tended to change at about 28 weeks a spline was fitted at the cubic level at 28 weeks.

Stepwise regression was performed to determine the best fitting model. Only independent variables with a significant improvement in the goodness-of-fit to the model as assessed by the AIC (Akaike Information Criterion) statistics \( p \leq 0.05 \) were included in the final regression models.

With each model, the residuals at both level 1 (observation) and level 2 (subject) were available and the distributions were inspected by scatterplots.

Growth velocity was modelled as the first derivative of the growth model. The growth velocity centiles were graphed and compared using ethnicity and maternal characteristics.

Software used for analysis was ‘R’ version 2.12.2, and GraphPad Prism 5 (GraphPad Software, San Diego, CA, USA). Multilevel modelling was performed with the Linear Mixed Effects (LME4) package in “R” statistical analysis program.
CHAPTER 3

REPRODUCIBILITY OF ULTRASOUND MEASUREMENTS

3.1. Introduction

The reproducibility of the ultrasound measurements is important in a longitudinal study to determine reliability, particularly because the results in a longitudinal study will be correlated. Reliability is the ability to repeat, reproduce or consistently obtain the same measurements under identical conditions. Reliable measurements are important for clinical usefulness as well as to be sure others can reproduce the study.

Because the volume measurements were made offline with proprietary software it was also important to determine the validity of these measurements compared to those made on the ultrasound equipment.

Validity is the degree to which a measurement measures what it purports to measure and reproducibility is the degree to which a measurement provides the same result each time it is performed on a given subject or specimen. Reproducibility is assessed using agreement analysis of within (intra) and between (inter) observer measurement comparison studies. Lack of agreement is inevitable, but the questions of interest are by how much do the measurements disagree and are these differences important? A common method of assessment was published by Bland and Altman (Bland JM 1986).

In its simplest form, the Bland-Altman limit of agreement approach compares unreplicated paired measurements between two methods over a number of subjects or specimens. A graphical depiction of differences between paired observations versus their average is presented in a scatter-plot. Superimposed on the scatter-plot is a horizontal line indicating bias (calculated as the mean difference between measurement pairs), and horizontal lines giving the 95% limits of agreement (calculated, assuming the differences are approximately normally distributed, using the standard deviation of the differences).

The limits of agreement define the range within which 95% of the differences between measurements by the two methods are predicted to lie. The scatter-plot is used to determine whether any patterns exist in the data, thereby potentially violating the method's assumptions, or revealing whether data transformation is necessary (Schluter PJ 2004).

3.2 Method

Statistical analysis was performed using the Bland Altman analysis in GraphPad Prism 5 software.
A measurement of agreement was tested to investigate intraobserver differences and reproducibility, because all the ultrasound measurements were performed by the author. The differences of all the biometry measurements performed in the study were plotted against their mean. The means were plotted and shown graphically. These are the Bland and Altman plots.

A check for normal distribution of the differences was made using D'Agostino and Pearson omnibus normality test as recommended by GraphPad Prism 5 software. If the differences are normally distributed, 95% of the differences will lie between the mean +/- 2 SD limits. These are the limits of agreement, and the measures among the observer can be assumed to be interchangeable within these limits.

The consensus and among the observer was analysed using the Intraclass Correlation Coefficient (ICC) for all fetal biometry measurements (Bland JM 1986). The ICC is defined as the ratio of the variance between subjects to total variance. ICC measures the strength of the agreement of the variables, independent of the dimension of the variable considered.

Additionally, the coefficient of variation (CV) was calculated for all fetal measurements, which, expressed as a percentage, is the ratio of the standard deviation (SD) of the measurement error and the overall mean (Bland JM 1996).

Fetal biometry is reproducible and valid in case of ICC over 0.80, a CV under 10% and measurements within the 95% limits of agreement (Bland JM 1996).

3.2.1 Ultrasound measurement data validation
Thirty datasets were selected, with 10 each at 18, 28 and 34 weeks (± 2 weeks at each interval). The datasets were randomly selected by blindly removing the DVD storage disk from the box containing the disks.

The BPD, HC, AC and FL biometry were selected to enable linear and elliptical measurements to be compared. Volume measurements were not assessed in this section because all the volume data measurements were made offline and not on the ultrasound machine. Three measurements were made offline, blind to the reported value and the average compared with that value. These measurements were made by the same observer. This reduced any interobserver measurement difference that may have produced a confounding bias.

Bland–Altman plots (difference vs. average) were used to determine 95% limits of agreement (LOA) and bias for a measurement made on the ultrasound machine (reference) and those made by the same examiner of line.
3.2.2 Intra observer offline 3D measurements
The 3D offline analyses for this thesis were performed by the author. Therefore only intra observer measurements were performed.

Because the offline measurements were limb circumference and limb volume other biometry measurements were not assessed for intra observer measurement agreement.

The DVDs for analysis were selected blindly from the storage box. The datasets on the DVD that were performed at the appropriate gestational age were then selected. Ten arm and 10 thigh volume datasets were reviewed to investigate the reproducibility of these measurements. These datasets were selected to represent a broad range of menstrual ages (16-20, 26-30 and 32-36).

Bland–Altman plots (difference vs. average) were used to determine 95% limits of agreement (LOA) and bias for a single observer.

Secondly, the consensus within the observer was analysed using the Intraclass Correlation Coefficient (ICC) for all fetal biometry measurements (Bland JM 1996)

3.3 Results

3.3.1 Ultrasound measurement data validation:
A representative Bland-Altman plot (fig 3.1) and computer output (table 3.1) for bias and limits are presented as an example. Not all plots are therefore shown but the analysis at each gestational age selected is summarised in the table 3.2.
The example presented is for Femur Length and is over the total range of gestational ages selected.

Fig 3.1 Bland-Altman plot of femur length measurements with 95% limits of agreement.
The Bland-Altman plot shows an increasing difference with increasing gestation. The p value and p value summary in Table 3.1 show that this is not statistically significant.
Number of values 30

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Std. Deviation</td>
<td>0.1474</td>
</tr>
<tr>
<td>Std. Error</td>
<td>0.02690</td>
</tr>
<tr>
<td>Lower 95% CI of mean</td>
<td>-0.01836</td>
</tr>
<tr>
<td>Upper 95% CI of mean</td>
<td>0.09169</td>
</tr>
<tr>
<td>D’Agostino &amp; Pearson omnibus normality test</td>
<td></td>
</tr>
<tr>
<td>K2</td>
<td>0.5565</td>
</tr>
<tr>
<td>P value</td>
<td>0.7571</td>
</tr>
<tr>
<td>Passed normality test (alpha=0.05)?</td>
<td>Yes</td>
</tr>
<tr>
<td>P value summary</td>
<td>ns</td>
</tr>
<tr>
<td>Sum</td>
<td>1.100</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bias</td>
<td>0.03667</td>
</tr>
<tr>
<td>SD of bias</td>
<td>0.1474</td>
</tr>
<tr>
<td>95% Limits of Agreement</td>
<td></td>
</tr>
<tr>
<td>From</td>
<td>-0.2521</td>
</tr>
<tr>
<td>To</td>
<td>0.3255</td>
</tr>
</tbody>
</table>

**Table 3.1 Femur length bias and 95% Limits of Agreement**

A correlation plot (Fig 3.2) was performed to determine the line of agreement between the online and offline measurements.

![Fig 3.2](image)

**Fig 3.2. Scatterplot of offline measurement (Measure B) vs online measurement (reference data) of femur length at 18 weeks.**

The scatterplot shows an even distribution around the line of agreement suggesting there is no systematic bias between measurements made online or offline.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Week</th>
<th>Bias</th>
<th>SD of Bias</th>
<th>CV</th>
<th>Limits of agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower bound</td>
</tr>
<tr>
<td>BPD</td>
<td>18</td>
<td>0.04</td>
<td>0.08</td>
<td>1.67%</td>
<td>-0.13</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>-0.03</td>
<td>0.13</td>
<td>1.46%</td>
<td>-0.28</td>
</tr>
<tr>
<td></td>
<td>34</td>
<td>0.03</td>
<td>0.13</td>
<td>1.54%</td>
<td>-0.22</td>
</tr>
<tr>
<td>HC</td>
<td>18</td>
<td>0.1</td>
<td>0.17</td>
<td>1.26%</td>
<td>-0.23</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>0.05</td>
<td>0.32</td>
<td>1.0%</td>
<td>-0.59</td>
</tr>
<tr>
<td></td>
<td>34</td>
<td>-0.06</td>
<td>0.45</td>
<td>1.1%</td>
<td>-0.94</td>
</tr>
<tr>
<td>AC</td>
<td>18</td>
<td>-0.2</td>
<td>0.31</td>
<td>2.25%</td>
<td>-0.8</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>0.0</td>
<td>0.44</td>
<td>1.39%</td>
<td>-0.86</td>
</tr>
<tr>
<td></td>
<td>34</td>
<td>0.09</td>
<td>0.38</td>
<td>1.35%</td>
<td>-0.66</td>
</tr>
<tr>
<td>FL</td>
<td>18</td>
<td>0.04</td>
<td>0.11</td>
<td>3.95%</td>
<td>-0.17</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>-0.06</td>
<td>0.14</td>
<td>2.3%</td>
<td>-0.33</td>
</tr>
<tr>
<td></td>
<td>34</td>
<td>0.14</td>
<td>0.11</td>
<td>2.49%</td>
<td>-0.07</td>
</tr>
</tbody>
</table>

Table 3.2 Intra observer agreement statistics between online and offline measurements.

The IntraClass Correlation Coefficient was 0.83

All results are within the appropriate ranges as specified by Bland for fetal biometry (Bland JM 1996)

3.3.2 Intraobserver Measurement Agreement

An example is shown of the Bland-Altman plot and its table of results for Arm Circumference. The complete analysis is shown in Table 3.4

Bland-Altman of Arm Circumference:Difference vs average

Fig 3.3 Bland-Altman Plot of Arm Circumference 95% limits of agreement lines.
Number of values 30

Mean 0.01000
Std. Deviation 0.2264
Std. Error 0.04134

D’Agostino & Pearson omnibus normality test
K2 2.613
P value 0.2708
Passed normality test (alpha=0.05)? Yes
P value summary ns

Sum 0.3000

Bias 0.01000
SD of bias 0.2264
95% Limits of Agreement
From -0.4338
To 0.4538

Table 3.3 Bland-Altman data analysis for Arm Circumference.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Week</th>
<th>Bias</th>
<th>SD Bias</th>
<th>CV</th>
<th>Limits of agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower bound Upper Bound</td>
</tr>
<tr>
<td>Arm Circ</td>
<td>18</td>
<td>-0.03</td>
<td>0.17</td>
<td>5.52%</td>
<td>-0.38 0.32</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>-0.1</td>
<td>0.15</td>
<td>2.26%</td>
<td>-0.39 0.19</td>
</tr>
<tr>
<td></td>
<td>34</td>
<td>0.1</td>
<td>0.13</td>
<td>2.26%</td>
<td>-0.16 0.36</td>
</tr>
<tr>
<td>Thigh Circ</td>
<td>18</td>
<td>0.01</td>
<td>0.2</td>
<td>2.79%</td>
<td>-0.4 0.4</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>-0.1</td>
<td>0.37</td>
<td>3.8%</td>
<td>-0.82 0.62</td>
</tr>
<tr>
<td></td>
<td>34</td>
<td>-0.08</td>
<td>0.44</td>
<td>2.58%</td>
<td>-0.94 0.78</td>
</tr>
<tr>
<td>Arm Vol</td>
<td>18</td>
<td>0.01</td>
<td>0.15</td>
<td>4.44%</td>
<td>-0.29 0.31</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>-0.12</td>
<td>0.2</td>
<td>2.36%</td>
<td>-0.51 0.27</td>
</tr>
<tr>
<td></td>
<td>34</td>
<td>0.04</td>
<td>0.43</td>
<td>1.46%</td>
<td>-0.8 0.88</td>
</tr>
<tr>
<td>Thigh Vol</td>
<td>18</td>
<td>-0.1</td>
<td>0.2</td>
<td>8.82%</td>
<td>-0.49 0.29</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>0.03</td>
<td>0.5</td>
<td>2.36%</td>
<td>-1.0 1.1</td>
</tr>
<tr>
<td></td>
<td>34</td>
<td>-0.85</td>
<td>1.36</td>
<td>3.09%</td>
<td>-3.5 1.8</td>
</tr>
</tbody>
</table>

Table 3.4 Intra observer agreement analysis.

The IntraClass Correlation Coefficient was 0.9
3.4 Discussion

All results from the limits of agreement analysis are within accepted limits.

There is potential for images to be degraded when being transferred electronically. Because the ultrasound equipment did not have the software (QLAB) to measure 3D volumes installed, these measurements had to be performed offline. This involved transfer of images from the ultrasound to a DVD and from the DVD onto a computer. These steps all have the potential to degrade the image for measurement. Measurements which could be compared (linear and circumference) from the ultrasound and computer analysis were therefore compared. Because the agreement between the online and offline measurement was acceptable the volume measurements were considered acceptable as well. The volume calculations involved automatic computer calculation from linear and circumference measurements.

When dealing with intraobserver variation using the same method of measurement or where the repeated observations are made by the same observer on the same subject, there should not be any systemic bias. There is no consistent bias shown in the analyses.

3.5 Conclusion.

Ultrasound measurements obtained in this study have been shown to be within acceptable limits of agreement for offline analysis as well as for intraobserver measurements. Fetal biometry is reproducible and valid in case of ICC over 0.80, a CV under 10% and the measurements within the 95% limits of agreement (Bland JM 1996).
CHAPTER 4

REPRODUCIBILITY OF NEONATAL MEASUREMENTS

4.1 Introduction
The crown heel length was measured by tape measure because the majority of the babies were born in one of our primary birthing units. It was therefore important to determine the reliability of these measurements compared to those made in a neonatometer, which is the gold standard for such measurements.

Some lack of agreement between different methods of measurement is inevitable. What matters is the amount by which measurements differ.

There may be a consistent tendency for one method to exceed the other. This difference between measurements by the two methods is the bias and is estimated it by the mean difference. There will also be variation about this mean, which is estimated by the standard deviation of the differences. These estimates are meaningful only if we can assume bias and variability are uniform throughout the range of measurement, assumptions which can be checked graphically with a line of equality.

4.2 Methods
Statistical analysis was performed using the Bland Altman analysis in GraphPad Prism 5 software. The computer output tables for this chapter have been placed in the appendix with the tables of raw data.

Inter and Intra observer measurements
The inter- and intra-observer neonatal measurements were performed by 2 midwives measuring 20 neonates, separate from the study group.

Three measurements each of crown heel length, head circumference, and thigh circumference were made by each midwife using a paper tape, which was then creased at the measurement mark and recorded, blind to the measurer, by the author. These measurements were averaged for the purposes of the comparisons.

The average crown heel length by tape measure was compared to the value obtained using a Harpenden neonatometer

Bland–Altman plots (difference vs. average) were used to determine 95% limits of agreement (LOA) and bias for a single examiner and between examiners for the neonatal measurements.
Bland Altman plots were used to determine limits of agreement between a single examiner and between examiners for the Crown Heel measurement as measured by tape measure and by neonatometer.

4.3. Results

4.3.1. Interobserver CHL Tape

The Bland-Altman plot shows that there is no significant bias between the observers and all measurements are within acceptable limits of agreement.

4.3.2 Interobserver CHL Neonatometer

The Bland-Altman plot shows that there is no significant bias between the observers and all measurements are within acceptable limits of agreement.
4.3.3 Neonatal Head Circumference (HCN)

The Bland-Altman plot shows that there is no significant bias between the observers and most measurements are within acceptable limits of agreement.

4.3.4 Neonatal Thigh Circumference (ThCN)

The Bland-Altman plot shows that there is no significant bias between the observers and all measurements are within acceptable limits of agreement.
4.3.5 Intraobserver Tape vs Neonatometer

Midwife A

Bland-Altman of CHL:Neo,MW A :Difference vs average

The Bland-Altman plot shows that there is no significant bias between the observers and all measurements are within acceptable limits of agreement.

Midwife B

Bland-Altman of CHL:Neo, MW B:Difference vs average

The Bland-Altman plot shows that there is no bias between the observers and all measurements are within acceptable limits of agreement.
These results are all summarised in Table 4.1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Bias</th>
<th>SD Bias</th>
<th>CV</th>
<th>Limits of agreement</th>
<th>Lower bound</th>
<th>Upper Bound</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Midwife Interobserver</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHL Tape</td>
<td>0.08</td>
<td>0.72</td>
<td>4.9%</td>
<td></td>
<td>-1.32</td>
<td>1.48</td>
</tr>
<tr>
<td>Neonatometer</td>
<td>0.035</td>
<td>0.4</td>
<td>4.74%</td>
<td></td>
<td>-0.7</td>
<td>0.8</td>
</tr>
<tr>
<td>HCN</td>
<td>0.05</td>
<td>0.47</td>
<td>3.01%</td>
<td></td>
<td>-0.87</td>
<td>0.97</td>
</tr>
<tr>
<td>THCN</td>
<td>-0.08</td>
<td>0.36</td>
<td>9.93%</td>
<td></td>
<td>-0.77</td>
<td>0.62</td>
</tr>
<tr>
<td></td>
<td>Intraobserver</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHL:Neonatometer</td>
<td>A</td>
<td>0.08</td>
<td>4.94%</td>
<td></td>
<td>-0.44</td>
<td>0.59</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>-0.03</td>
<td>4.89%</td>
<td></td>
<td>-1.18</td>
<td>1.24</td>
</tr>
</tbody>
</table>

Table 4.1 Summary of midwives inter and intra observer neonatal measurements

ICC = 0.9

4.5. Summary

The limits of agreement are within the appropriate range

4.6 Conclusion

Neonatal measurements have been shown to be within acceptable limits of agreement for Interobserver as well as intraobserver measurements.

The conclusion is that the measurements can be replicated by the same and different observers.
CHAPTER 5

RESULTS

5.1 Introduction

The results are presented with the recruitment process and exclusions in the introduction. Recruitment and demographic data are tabulated to show that the study sample represents a healthy population. Socio economic factors are not included as the healthy population self-selected and were not representative of the poorer socio economic group who tend to present late and not access maternity services.

Measurement of fetal growth was performed using standard biometry as well as assessment of soft tissue growth by analysis of 3D volume datasets, which were used to measure thigh and arm volume and circumference.

Growth and growth velocity of the standard biometry and the novel soft tissue measurements were graphed and analysed according to ethnicity and maternal characteristics with a view to finding the best fit to perform a multilevel analysis of the longitudinal data.

The Software used for analysis was ‘R’ version 2.12.2, Microsoft Excel 2010, and Minitab vs 15.

Recruitment

Recruitment (n= 127)

Lost to follow up (n= 14)

Exclusion due to medical disease
Diabetes (n= 7)
Hypertension (n= 11)

Exclusion due to preterm delivery. (n= 6)

Study population (n= 89)

Fig 5.1 Recruitment flow chart
Patients excluded were 29.5% of the total. The reasons for exclusion in each ethnic group are shown in table 5.1, with the percentage of each group excluded.

<table>
<thead>
<tr>
<th>Ethnic Group</th>
<th>NZE</th>
<th>PI</th>
<th>Māori</th>
<th>Indian</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recruited</td>
<td>46</td>
<td>38</td>
<td>22</td>
<td>21</td>
<td>127</td>
</tr>
<tr>
<td>Lost to follow up</td>
<td>5</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>Preterm</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Total Excluded</td>
<td>15 (32.6%)</td>
<td>12 (31.5%)</td>
<td>8 (36.4%)</td>
<td>3 (14.3%)</td>
<td>38 (29.5%)</td>
</tr>
<tr>
<td>Total for analysis</td>
<td>31</td>
<td>26</td>
<td>14</td>
<td>18</td>
<td>89</td>
</tr>
</tbody>
</table>

Table 5.1 Patients excluded after recruitment.

Lost to follow up includes those who left the district and those who delivered elsewhere and for whom no postnatal data was available.

The study population was reduced further after delivery by exclusion of LGA (11) and SGA (4) resulting in a final AGA study population of 74. This allowed analysis of normal growth velocity. The numbers were too small to allow further analysis of LGA and SGA growth velocity.

The distribution of SGA, AGA and LGA by ethnicity is shown in (table 5.2).

<table>
<thead>
<tr>
<th>Ethnic Group</th>
<th>SGA &lt;10th centile customised</th>
<th>AGA</th>
<th>LGA &gt; 90th centile customised</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI</td>
<td></td>
<td>23</td>
<td>3</td>
</tr>
<tr>
<td>Māori</td>
<td>1</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>NZE</td>
<td>2</td>
<td>24</td>
<td>5</td>
</tr>
<tr>
<td>Indian</td>
<td>1</td>
<td>15</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 5.2 SGA, AGA and LGA according to maternal ethnicity

Data analysis

A data analysis plan (fig 5.2) outlines the recruitment process which selected normal mothers and fetuses and normal birthweight.

The factors used in multilevel analysis are outlined in the plan.
Recruitment

Mother

Exclude Medical Disease

Fetus

Exclude fetal abnormality

Normal maternal characteristics

Neonatal anthropomorphology
Exclude LGA and SGA

Ultrasound Biometry - standard and soft tissue

Multilevel analysis by – Maternal Ethnic group
- Maternal Height tertile
- Maternal Weight tertile
- Ethnic BMI

Model of fetal growth in normal pregnancy

Fig 5.2 Analysis Plan
5.2 Exploratory data analysis

5.2.1 Maternal characteristics

The maternal characteristics were analysed with ethnic groups compared to the referent group (NZE). Table 5.3 shows the results with the p values by student t-test for each group compared to NZE below the mean standard deviation (sd). Overall p values are shown in the total column.

The Indian women were shorter and lighter than the reference group (NZE) and the Pacific Island women were heavier. This can also be seen in the greater percentage of Indian women in ethnic BMI tertile A and the greater percentage of Pacific Island women in ethnic BMI tertile C. The Māori women were heavier and more likely to be multiparous compared with NZE (table 5.3).

<table>
<thead>
<tr>
<th></th>
<th>NZE n=31</th>
<th>Pacific Island n=26</th>
<th>Māori n=14</th>
<th>Indian n=18</th>
<th>Total n= 89</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>30.3 (5.73)</td>
<td>27 (4.35 (0.07)</td>
<td>28.1 (6.14 (0.7)</td>
<td>27.3 (4.73 (0.27)</td>
<td>0.24</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>166.1 (6.83)</td>
<td>166.8 (6.96 (0.62)</td>
<td>166.8 (5.45 (0.42)</td>
<td>159.3 (6.43 (0.001)</td>
<td>0.002</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>65.2 (9.34)</td>
<td>80.4 (11.38 (&lt;0.001)</td>
<td>70.4 (7.97 (0.05)</td>
<td>54.5 (7.84 (&lt;0.001)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI</td>
<td>23.6 (2.59)</td>
<td>28.8 (3.46 (0.1)</td>
<td>25.3 (2.55 (0.06)</td>
<td>21.4 (2.72 (0.013)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ethnic BMI Tertile (%)</td>
<td>A = 38.7</td>
<td>A = 15.4</td>
<td>A = 21.4</td>
<td>A = 55.6</td>
<td>A = 55.6</td>
</tr>
<tr>
<td></td>
<td>B = 48.4</td>
<td>B = 15.4</td>
<td>B = 50</td>
<td>B = 22.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C = 12.9</td>
<td>C = 69.2</td>
<td>C = 28.6</td>
<td>C = 22.2</td>
<td></td>
</tr>
<tr>
<td>Nullparity (%) (p)</td>
<td>0.45</td>
<td>0.31 (0.1)</td>
<td>0.21 (0.05)</td>
<td>0.61 (0.6)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Table 5.3 Mean maternal characteristics for the whole study population.

When the non AGA babies were removed from the analysis the Indian women were younger compared with the reference group (table 5.4). There was no significant difference between the ethnic groups for height, but the Pacific Island women remained heavier and Indian women lighter. There also was a difference in parity, especially in the Māori.

There remained a significant difference in BMI which was reflected in the ethnic BMI tertile percentages.
<table>
<thead>
<tr>
<th></th>
<th>NZE n=24</th>
<th>Pacific Island n=23</th>
<th>Māori n=11</th>
<th>Indian n=15</th>
<th>Total n= 74</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mat Age</td>
<td>29.2</td>
<td>27.4</td>
<td>27.8</td>
<td>27.1</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>4.58</td>
<td>(0.21)</td>
<td>4.7</td>
<td>4.49</td>
<td>(0.035)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>164.6</td>
<td>167.4</td>
<td>166.3</td>
<td>159.5</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>6.91</td>
<td>(0.16)</td>
<td>5.81</td>
<td>6.5</td>
<td>(0.06)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>64.1</td>
<td>81.4</td>
<td>69.1</td>
<td>55.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>8.89</td>
<td>(10.03)</td>
<td>7.44</td>
<td>7.97</td>
<td>(0.003)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(&lt;0.0001)</td>
<td>(0.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>23.4</td>
<td>28.9</td>
<td>25.1</td>
<td>21.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>(2.46)</td>
<td>(3.36)</td>
<td>(2.54)</td>
<td>2.63</td>
<td>(0.017)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(&lt;0.0001)</td>
<td>(0.09)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnic BMI tertile (%)</td>
<td>A = 41.6</td>
<td>A = 8.7</td>
<td>A = 27.3</td>
<td>A = 60</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>B = 50</td>
<td>B = 17.4</td>
<td>B = 45.5</td>
<td>B = 20</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C = 8.3</td>
<td>C = 69.2</td>
<td>C = 27.3</td>
<td>C = 20</td>
<td></td>
</tr>
<tr>
<td>Nulliparity (%) (p)</td>
<td>0.54</td>
<td>0.3 (0.1)</td>
<td>0.17 (0.017)</td>
<td>0.6 (1)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Table 5.4 Mean characteristics of mothers with AGA infants.

5.2.2 Biometry
The fetal biometry of the AGA infants is presented individually in a graphical form. The significance of the biometry is presented at the end of this section. The biometry was graphed according to ethnic group, height tertile, weight tertile and ethnic BMI, as well as customised birthweight centile. Biometry scatterplot lines are the quadratic regression lines for each group compared. Individual points have been removed for illustrative purposes, but are shown in the raw data scatterplots in the appendix.

The complete set of graphs used for analysis is shown to allow comparison by juxtaposition.

5.2.2.1 Standard Biometry
The usual biometry report is presented as biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), and femur length (FL).

Biometry for this thesis has been grouped for presentation into skeletal then soft tissue. Skeletal includes BPD, HC, FL and humerus diaphyseal length (HDL). The soft tissue standard biometry is the AC.
Biparietal Diameter

Ethnic group

E = New Zealand European, Indian = Indian, M = Māori, PI = Pacific Islander.

Fig 5.3 BPD vs GA according to ethnic group

The graph illustrates the increasing difference in BPD with after 30 weeks gestation between the groups. In particular there is a slowing of the Indian BPD compared to the other groups.

Height Tertile

A = lower height tertile, B = medium height tertile, C = higher height tertile.

Fig 5.4 BPD vs GA according to height tertile.

The graph regression lines show a slowing of the BPD measurement in the fetus of shorter (lower height tertile) mothers, from 30 weeks onwards.
Weight tertile

A = lower weight tertile, B = medium weight tertile, C = higher weight tertile.

**Fig 5.5 BPD vs GA according to weight tertile**

The graph shows a slowing of the BPD regression line, particularly from about 34 weeks in the lighter (lower weight tertile) women.

Ethnic BMI tertile

A = lower ethnic BMI tertile, B = medium ethnic BMI tertile, C = higher ethnic BMI tertile.

**Fig 5.6 BPD vs GA according to ethnic BMI tertile.**
The graph shows a slowing of the BPD regression line, particularly from about 32 weeks in the lighter (lower ethnic BMI tertile) women.

**Customised birthweight centile tertile**

A = lower customised birthweight tertile, B = medium customised birthweight tertile, C = higher customised birthweight tertile.

**Fig 5.7 BPD vs GA according to customised birthweight centile tertile**

There was minimal difference in the BPD vs gestation when plotted according to customised birthweight centile tertile.

**Summary**

There was slowing of the BPD in Indian, shorter and lighter women. This was reflected in the ethnic BMI tertiles. The Indian women had a higher proportion in the lower ethnic BMI tertile A. There was no difference in BPD growth according to customised birthweight centiles. This suggests that there are parameters other than BPD which have a more important role in birthweight.
Head Circumference

Ethnic group

![Graph showing head circumference vs gestational age for different ethnic groups.](image)

**Fig 5.8 HC vs GA according to ethnic group**

The graph illustrates the differences in head circumference between the groups, particularly the increasing difference in the Indian HC after 30 weeks. This is comparable to the slowing of BPD in the Indian babies compared to the other ethnic groups.

Height tertile

![Graph showing head circumference vs gestational age for different height tertiles.](image)

**Fig 5.9 HC vs GA according to height tertile**
Weight tertile

Fig 5.10 HC vs GA according to weight tertile

Ethnic BMI tertile

Fig 5.11 HC vs GA according to ethnic BMI tertile
Fig 5.12 HC vs GA according to customised centile tertile

The graphs are comparable to the BPD graphs in that they show slowing of the HC in shorter and lighter women. This was reflected in the ethnic BMI tertiles. There was no difference in HC growth according to customised birthweight centiles, which suggested that customisation corrected for the maternal and ethnic variables.
Humerus Diaphyseal Length (HDL)

Ethnic group

![Graph](Image)

**Fig 5.13 HDL vs GA according to ethnic group**

The graph illustrates the difference in HDL with increasing gestation between the groups. Of interest was the slowing of the Indian group. This was a different pattern from the measurement of the FL.

**Height tertile**

![Graph](Image)

**Fig 5.14 HDL vs GA according to height tertile**
Weight tertile

Fig 5.15 HDL vs GA according to weight tertile

Ethnic BMI tertile

Fig 5.16 HDL vs GA according to ethnic BMI tertile
**Customised birthweight centile tertile**

**Fig 5.17 HDL vs GA according to customised centile tertile**

There is slowing of growth with the lower height tertile, lower weight tertile and ethnic BMI tertile as well as with the customised birthweight centile tertiles. This suggests that the slowing in this variable is not corrected by customisation and that Indian ethnicity is important.

**Femur Length**

There were no differences between the maternal characteristics plotted on the FL graphs.

**Ethnic Group**

**Fig 5.18 FL vs GA according to ethnic group**
Abdominal Circumference

Ethnic groups

Fig 5.19 AC vs GA according to ethnic group

The graph illustrates the differences in abdominal circumference between the groups and in particular there is a difference between the Indian and Pacific Island regression lines.

Height tertile

Fig 5.20 AC vs GA according to height tertile
There was a consistent difference in the regression lines between shorter women through all gestational ages.

**Weight tertile.**

The abdominal circumference continues to grow steadily in the heavier women (height tertile C), compared to the other two groups which slow from about 30 weeks.

**Ethnic BMI tertile**

**Fig 5.21 AC vs GA according to weight tertile**

**Fig 5.22 AC vs GA according to ethnic BMI tertile**
The AC in the lower ethnic BMI starts to slow at 32 weeks, the middle at 35 weeks and the higher tertile does not slow.

**Customised birthweight centile tertile**

![AC vs GA graph](image)

**Fig 5.23  AC vs GA according to customised birthweight tertile**

**Summary**

The graph illustrates the differences in abdominal circumference between the groups and in particular the difference between the Indian and Pacific Island regression lines, with the Pacific Island group showing no slowing in the regression line. There was a consistent difference in the regression lines between shorter women through all gestational ages. The abdominal circumference continues to grow steadily in the heavier women (weight tertile C), compared to the other two groups which slow from about 30 weeks. The heavier women were mostly from the Pacific Island women. The AC in the lower ethnic BMI tertile starts to slow at 32 weeks, the middle at 35 weeks and the higher tertile does not slow. There was no difference in the regression lines for the AC in customised birthweight centile tertiles.
5.2.2.2 Volume dataset measurements

Arm Circumference

Ethnic Group

![Arm Circumference vs GA](image)

**Fig 5.24 Arm Circumference vs GA according to ethnic group**

The graph shows slight divergence in arm circumference regression lines after 34 weeks between the groups. The divergence was not as marked as with abdominal circumference.

Height tertile

![Arm Circumference vs GA](image)

**Fig 5.25 Arm Circumference vs GA according to height tertile**
Weight tertile

Fig 5.26 Arm Circumference vs GA according to weight tertile

Ethnic BMI tertile

Fig 5.27 Arm Circumference vs GA according to ethnic BMI tertile
Customised birthweight centile tertile

Fig 5.28 Arm Circumference vs GA according to customised birthweight centile tertile

There was no difference in regression lines when plotted by height tertile, and only slight divergence when plotted by weight tertile, ethnic BMI tertile and customised birthweight tertile.

Arm Volume

Ethnic group

Fig 5.29 Arm volume vs GA according to ethnic group
The graph illustrates an increasing difference in arm volume with increasing gestation, between the groups. This difference was particularly marked between the Indian and Pacific Island and Māori patients after 34 weeks.

The difference can be explained by the shorter HDL seen in the different ethnic groups. Arm volume is calculated from 50% of the HDL. This is confirmed by graphing arm volume by HDL in the different ethnic groups (Fig 5.30).

**Arm vol vs HDL**

![Graph showing Arm volume vs HDL](image)

**Fig 5.30 Arm volume vs HDL**
Height tertile

Fig 5.31 Arm volume vs GA according to height tertile

Weight tertile

Fig 5.32 Arm volume vs GA according to weight tertile
**Ethnic BMI tertile**

**Fig 5.33 Arm volume vs GA according to ethnic BMI tertile**

**Customised Birthweight centile tertile**

**Fig 5.34 Arm volume vs GA according to customised birthweight tertile**

The graphs show a slowing of the arm volume after 26 weeks in the lower weight tertile. The graph of ethnic BMI tertile and customised birthweight centile tertile show similar slowing in the lower group.
Thigh Circumference (ThCirc)

Ethnic group

**Fig 5.35 Thigh circumference vs GA according to ethnic group**

The graph illustrates the increasing difference with gestational age from 34 weeks, in thigh circumference between the Māori and Pacific Island women compared to the European and Indian women.

Height tertile

**Fig 5.36 Thigh circumference vs GA according to height tertile**
Weight tertile

Fig 5.37 Thigh circumference vs GA according to weight tertile

Ethnic BMI tertile

Fig 5.38 Thigh circumference vs GA according to ethnic BMI tertile
Customised birthweight centile

![Graph showing Thigh Circumference vs GA]

Fig 5.39 Thigh circumference vs GA according to customised birthweight tertile

The thigh circumference regression lines show an increase from 34 weeks in the taller women and in the heavier and medium weight tertile women. This same increase was seen in the upper two ethnic BMI tertiles and customised birthweight centile tertiles.

Thigh Volume (TVol)

Ethnic group

![Graph showing Thigh volume vs GA]

Fig 5.40 Thigh volume vs GA according to ethnic group

The graph illustrates the increasing difference with gestational age in thigh volume, between the Pacific Island women after 32 weeks.
Height tertile

Fig 5.41 Thigh volume vs GA according to height tertile

Weight tertile

Fig 5.42 Thigh volume vs GA according to weight tertile
Ethnic BMI tertile

Fig 5.43 Thigh volume vs GA according to ethnic BMI tertile

Customised birthweight centile tertile

Fig 5.44 Thigh volume vs GA according to customised birthweight centile tertile

There was a similar increase in the taller height tertile, heavier weight tertile, heavier ethnic birthweight tertile and heavier customised birthweight centile tertile women.
5.2.2.3 EFW (Hadlock)

Ethnic group

Fig 5.45 EFW vs GA according to ethnic group

Height tertile

Fig 5.46 EFW vs GA according to height tertile
**Weight tertile**

![Graph of EFW vs GA according to weight tertile](image)

*Fig 5.47 EFW vs GA according to weight tertile*

**Ethnic BMI tertile**

![Graph of EFW vs GA according to ethnic BMI tertile](image)

*Fig 5.48 EFW vs GA according to ethnic BMI tertile*
Customised birthweight centile

**Fig 5.49 EFW vs GA according to customised birthweight tertile**

The ethnic group EFW graph reflects the difference in actual birthweights between the ethnic groups. These differences are seen particularly in the lower tertiles of the other maternal characteristics, but are less obvious after customisation.

**Summary**

There were differences in regression lines of the skeletal growth parameters – BPD, HC and HDL particularly with slower growth in the Indian ethnic group. There is no difference in the regression lines for the FL.

The soft tissue measurements – AC, Arm Circumference and volume, Thigh Circumference and volume all showed increasing differences from late second or early third trimester. All except abdominal circumference show an increasing regression line from this time, compared to skeletal graphs which show a slowing of the lines.

The increase in the regression lines for limb circumferences and volumes was greater in the heavier ethnic group (Pacific Island) as well as when displayed by height tertile, weight tertile, ethnic BMI tertile and customised birthweight centile tertile.

The difference is due to both an increase in muscle and fat, with a greater increase in fat after 35 weeks. There was an increasing velocity of fetal fat growth in the PI group compared to the velocity in the other groups (see Chapter 6).
5.2.3 Neonatal Outcomes

There were no intrauterine or neonatal deaths in the study group.
There were no fetal anomalies detected and no admissions to the neonatal unit.
No babies needed treatment for hypoglycaemia.

The neonatal outcomes in the different ethnic groups were compared to the referent group (NZE) (Table 5.5).

<table>
<thead>
<tr>
<th></th>
<th>NZE</th>
<th>PI n=26</th>
<th>Māori n=14</th>
<th>Indian n=18</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=31 sd</td>
<td>sd (p)</td>
<td>sd (p)</td>
<td>sd (p)</td>
</tr>
<tr>
<td>Birthweight (g)</td>
<td>3532 467</td>
<td>3791 433 (0.03)</td>
<td>3386 348 (0.31)</td>
<td>3214 482 (0.02)</td>
</tr>
<tr>
<td>Gestation at delivery</td>
<td>39.7 1.06</td>
<td>40.2 1.2 (0.4)</td>
<td>39.4 0.99 (0.8)</td>
<td>39.8 0.94 (0.9)</td>
</tr>
<tr>
<td>Customised birthweight centile</td>
<td>52.8 29.1</td>
<td>48.8 25.5 (0.9)</td>
<td>44.4 29.5 (0.8)</td>
<td>53 28.9 (1.0)</td>
</tr>
<tr>
<td>CHL (cm)</td>
<td>52.87 2.32</td>
<td>53.9 2.1 (0.02)</td>
<td>51.4 2.28 (0.2)</td>
<td>50.89 2.65 (0.03)</td>
</tr>
<tr>
<td>HCN (cm)</td>
<td>35.17 1.48</td>
<td>35.72 1.25 (0.13)</td>
<td>34.79 0.96 (0.31)</td>
<td>34.08 1.45 (0.007)</td>
</tr>
<tr>
<td>ThCN (cm)</td>
<td>15.71 2.0</td>
<td>17.65 1.23 (&lt;0.001)</td>
<td>16.3 1.28 (0.26)</td>
<td>15.47 1.71 (0.63)</td>
</tr>
</tbody>
</table>

CHL = Crown Heel Length.  HCN = Neonatal Head Circumference. ThCN = Neonatal Thigh Circumference.

Table 5.5 Mean neonatal outcomes by ethnicity for all babies (n=89).

There was a difference in birthweight of the Pacific Island and Indian babies compared to the New Zealand European babies. The mean Māori birthweight was smaller than the European mean birthweight, but this did not reach statistical significance.

There was no difference in the gestational age at delivery or the customised birthweight centiles between the ethnic groups.

The CHL was longer in the Pacific Island and was shorter in the Indian and Māori compared to the NZE babies, although that did not reach statistical significance for the Māori babies.
The neonatal head circumference was smaller in the Indian and the thigh circumference was larger in the Pacific Island compared to the NZE babies.

The neonatal outcomes were then compared to the referent group in AGA babies (table 5.6) (n=74).

<table>
<thead>
<tr>
<th></th>
<th>NZE n=24 sd</th>
<th>PI n= 23 sd (p)</th>
<th>Māori n=11 sd (p)</th>
<th>Indian n=15 sd (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birthweight (g)</td>
<td>3463</td>
<td>3698 (0.02)</td>
<td>3398 (0.6)</td>
<td>3171 (0.01)</td>
</tr>
<tr>
<td></td>
<td>323</td>
<td>328 (0.9)</td>
<td>317 (0.9)</td>
<td>408 (0.9)</td>
</tr>
<tr>
<td>Gestational age</td>
<td>40</td>
<td>40.1 (0.9)</td>
<td>39.5 (0.6)</td>
<td>39.8 (0.9)</td>
</tr>
<tr>
<td></td>
<td>1.01</td>
<td>1.18 (0.9)</td>
<td>1.11 (0.6)</td>
<td>0.94 (0.9)</td>
</tr>
<tr>
<td>Customised birth centile</td>
<td>48</td>
<td>43.2 (0.9)</td>
<td>45.7 (0.9)</td>
<td>50.5 (0.9)</td>
</tr>
<tr>
<td></td>
<td>21.5</td>
<td>21.3 (0.9)</td>
<td>26.2 (0.9)</td>
<td>24.2 (0.9)</td>
</tr>
<tr>
<td>CHL (cm)</td>
<td>51.86</td>
<td>53.43 (0.01)</td>
<td>51.45 (0.57)</td>
<td>50.78 (0.08)</td>
</tr>
<tr>
<td></td>
<td>1.94</td>
<td>1.62 (0.27)</td>
<td>2.34 (0.36)</td>
<td>2.53 (0.08)</td>
</tr>
<tr>
<td>HCN (cm)</td>
<td>35.1</td>
<td>35.5 (0.27)</td>
<td>34.62 (0.36)</td>
<td>34.03 (0.01)</td>
</tr>
<tr>
<td></td>
<td>1.5</td>
<td>1.08 (0.27)</td>
<td>0.79 (0.36)</td>
<td>1.39 (0.01)</td>
</tr>
<tr>
<td>ThCN (cm)</td>
<td>15.64</td>
<td>17.56 (0.0001)</td>
<td>16.49 (0.11)</td>
<td>15.35 (0.56)</td>
</tr>
<tr>
<td></td>
<td>1.56</td>
<td>1.2 (p&lt;0.0001)</td>
<td>1.29 (0.11)</td>
<td>1.73 (0.56)</td>
</tr>
</tbody>
</table>

Table 5.6 Neonatal outcomes by ethnicity in AGA infants,

The differences between the ethnic groups compared to the referent group remain the same whether the outcomes are for the all babies or the AGA babies.

There was no difference in the gestational age at delivery, but there is a significant difference in birthweight.

Indian babies and Pacific Island babies show the biggest difference in birthweight. This difference was reflected in all neonatal measurements (CHL, HC and Th Circ), suggesting that Indian babies have smaller skeletal structure (length and head circumference) as well as soft tissue (thigh circumference). The converse was shown for the Pacific Island babies.

**Neonatal outcome in relation to other characteristics**

Neonatal outcomes were compared according to infant gender and maternal parity.
<table>
<thead>
<tr>
<th></th>
<th>Male infants sd</th>
<th>Female infants sd</th>
<th>P value</th>
<th>Nulliparity sd</th>
<th>Multiparity sd</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birthweight (g)</td>
<td>3628</td>
<td>3432</td>
<td>0.06</td>
<td>3408</td>
<td>3598</td>
<td>0.07</td>
</tr>
<tr>
<td>(g)</td>
<td>548</td>
<td>433</td>
<td></td>
<td>451</td>
<td>513</td>
<td></td>
</tr>
<tr>
<td>Gestational age</td>
<td>39.94</td>
<td>39.86</td>
<td>0.8</td>
<td>40.14</td>
<td>39.73</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>0.94</td>
<td>1.16</td>
<td></td>
<td>1.0</td>
<td>1.09</td>
<td></td>
</tr>
<tr>
<td>Customised</td>
<td>41.65</td>
<td>50.33</td>
<td>0.1</td>
<td>49.8</td>
<td>44.44</td>
<td>0.09</td>
</tr>
<tr>
<td>birthweight</td>
<td>21.45</td>
<td>22.67</td>
<td></td>
<td>22.54</td>
<td>22.34</td>
<td></td>
</tr>
<tr>
<td>centile</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHL (cm)</td>
<td>53</td>
<td>51.9</td>
<td>0.06</td>
<td>51.57</td>
<td>52.94</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>2.8</td>
<td>2.27</td>
<td></td>
<td>2.35</td>
<td>2.55</td>
<td></td>
</tr>
<tr>
<td>HCN (cm)</td>
<td>35.29</td>
<td>34.7</td>
<td>0.05</td>
<td>34.49</td>
<td>35.29</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>1.05</td>
<td>1.5</td>
<td></td>
<td>1.15</td>
<td>1.39</td>
<td></td>
</tr>
<tr>
<td>ThCN (cm)</td>
<td>16.59</td>
<td>16.1</td>
<td>0.19</td>
<td>16.17</td>
<td>16.42</td>
<td>0.51</td>
</tr>
<tr>
<td></td>
<td>1.9</td>
<td>1.45</td>
<td></td>
<td>1.46</td>
<td>1.82</td>
<td></td>
</tr>
</tbody>
</table>

Table 5.7 Mean neonatal outcomes in relation to gender and parity

There was no statistically significant difference between the means with respect to gender, although males tend to be heavier and longer with bigger heads.

There was a statistically significant difference in crown heel length and head circumference between nulliparous and multiparous women. There was a trend towards larger babies in the multiparous women.

The trends that were seen have been shown to be significant in the literature and may have become significant in this series with greater numbers.

Neonatal outcomes related to other maternal characteristics

A scatterplot matrix (Fig 5.50) of the neonatal measurements (CHL, HCN and ThCN) against the maternal characteristics of height and weight show a positive correlation between all neonatal and all maternal parameters.
Fig 5.50 Scatterplot matrix of neonatal measurements and maternal characteristics.

The significance of these measurements in the ethnic groups compared to the referent NZE group is shown in table 5.8. Compared to the referent group the CHL is significant in the Indian maternal weight group, HCN is significant in the Pacific Island maternal weight group and there is no significant difference in the ThCN groups.

<table>
<thead>
<tr>
<th></th>
<th>PI (maternal)</th>
<th>Māori (maternal)</th>
<th>Indian (maternal)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Height</td>
<td>Weight</td>
<td>Height</td>
</tr>
<tr>
<td>CHL</td>
<td>0.4</td>
<td>0.6</td>
<td>0.3</td>
</tr>
<tr>
<td>HCN</td>
<td>0.56</td>
<td>0.02</td>
<td>0.22</td>
</tr>
<tr>
<td>ThCN</td>
<td>0.72</td>
<td>0.8</td>
<td>0.54</td>
</tr>
</tbody>
</table>

Table 5.8 Significant (p values) of neonatal measurements.
5.3 Data analysis and modelling

5.3.1 Multilevel modelling

Each biometry parameter was modelled using a linear mixed model, including fixed and random effects, up to a cubic polynomial and using a knot for a spline at 28 weeks. An equation including all maternal characteristics (ethnic BMI tertile, height or height tertile, weight or weight tertile, ethnic group and GA and the GA polynomial terms were used in the fixed effects part of the model. GA and ID were included in the random effects part of the model. The best model was then chosen using AIC (Akaike Information Criterion) after checking the residual plots to determine if further transformation of the parameters were needed.

This equation was subsequently modelled as a growth velocity, which mathematically is the first derivative of that equation. Results are summarised below and graphically illustrated by using head circumference and thigh volume.

Standard Biometry

BPD
The equation with the best fit was \( \text{BPD} \sim \text{GA} \times \text{Eth.Grp} + \text{GA}^2 + \text{GA}^3 + \text{GA}^3K + (1 + \text{GA} \mid \text{ID}) \), where \( \text{GA}^2 \) is \( \text{GA}^2 \), \( \text{GA}^3 \) is \( \text{GA}^3 \) and \( \text{GA}^3K \) is the cubic spline that has been fitted at gestational age of 28 weeks. \((1 + \text{GA} \mid \text{ID})\) is the random effects part of the mixed model equation. The fixed effects of \( \text{GA}^2 \), \( \text{GA}^3 \) were statistically significant components of the model (p= 0.0009 and 0.0002 respectively), as was the interaction of GA:Indian ethnic group compared to NZE (p=0.004).

Pairwise comparisons of the ethnic groups showed a statistically significant difference in BPD growth between Indian and European, Pacific Island and European, Indian and Māori as well as between Indian and PI.

- European==Indian, p= 0.006
- European==Māori, p= 0.18
- European==PI, p= 0.015
- Indian==Māori, p=0.00017
- Indian==PI, p<0.0001
- Māori==PI, p = 0.2

HC
The equation with the best fit was \( \text{HC} \sim \text{GA} \times \text{Eth.Grp} + \text{GA}^2 + \text{GA}^3 + \text{GA}^3K + (1 + \text{GA} \mid \text{ID}) \). The fixed effects of \( \text{GA}^2 \), \( \text{GA}^3 \) were statistically significant components of the model (p= 0.008 and 0.001 respectively), as was the interaction of GA:Indian ethnic group compared to NZE (p=0.03).
Pairwise comparisons of the ethnic groups showed that there was no statistically significant difference in HC growth between Māori and the referent NZE, as well as Māori and PI. There were significant differences when comparing other ethnic groups.

European==Indian, p = 0.049  
European==Māori, p = 0.72  
European==PI, p = 0.009  
Indian==Māori, p = 0.023  
Indian==PI, p < 0.0001  
Māori==PI, p = 0.09

**FL**

There were no significant effects other than GA with multilevel modelling of FL. The best fit equation was \(\text{FL} \sim \text{GA} + \text{GA}^2 + \text{GA}^3 + \text{Eth.Grp} + (1 + \text{GA} | \text{ID})\).

Pairwise comparisons of ethnic groups showed no significant difference between any of the ethnic groups.

European==Indian, p = 0.13  
European==Māori, p = 0.25  
European==PI, p = 0.2  
Indian==Māori, p = 0.13  
Indian==PI, p = 0.054  
Māori==PI, p = 0.25

**HDL**

The equation with the best fit was \(\text{HDL} \sim \text{GA} + \text{GA}^2 + \text{GA}^3 + \text{Eth.Grp} + (1 + \text{GA} | \text{ID})\).

The fixed effects of GA was a statistically significant component of the model (p= 0.005), as was Indian ethnic group compared to NZE (p=0.02).

Pairwise comparisons of ethnic groups showed a significant difference between European and Indian as well as Indian compared to PI or Māori.

European==Indian, p = 0.019  
European==Māori, p = 0.09  
European==PI, p = 0.15  
Indian==Māori, p = 0.003  
Indian==PI, p = 0.009  
Māori==PI, p = 0.13
AC
The equation with the best fit was \( AC \sim GA^{Eth.Grp} + GA2 + GA3 + GA3K + (1 + GA | ID) \). The fixed effects of GA was a statistically significant component of the model \( (p=0.01) \), as was the interaction of GA:Pacific Island ethnic group compared to NZE \( (p=0.03) \).

Pairwise comparisons of ethnic groups showed no difference in Māori compared to NZE, but did show a significant difference between all the other pairwise comparisons of ethnic groups.

- European==Indian, \( p=0.002 \)
- European==Māori, \( p=0.064 \)
- European==PI, \( p=0.01 \)
- Indian==Māori, \( p=0.016 \)
- Indian==PI, \( p<0.0001 \)
- Māori==PI, \( p=0.013 \)

Volume biometry

Arm Circumference
The equation with the best fit was \( ArmCirc \sim GA + GA2 + GA3 + GA3K + Eth.Grp + (1 + GA | ID) \). The fixed effects of GA, GA2, GA3 and GA3K were statistically significant components of the model \( (p=0.001, 0.007, 0.006 \) and 0.03 respectively).

Pairwise comparisons of ethnic groups showed no significant difference between any group.

- European==Indian, \( p=0.19 \)
- European==Māori, \( p=0.18 \)
- European==PI, \( p=0.12 \)
- Indian==Māori, \( p=0.11 \)
- Indian==PI, \( p=0.06 \)
- Māori==PI, \( p=0.23 \)

Arm volume
The equation with the best fit was \( Arm Volume \sim GA + GA2 + GA3 + GA3K + Eth.Grp + (1 + GA | ID) \). The fixed effects of GA, GA2, and GA3 were statistically significant components of the model \( (p=0.04, 0.03 \) and 0.04 respectively).

Pairwise comparisons of ethnic groups show a significant difference in the comparison between Indian and PI.
European==Indian, p= 0.12
European==Māori, p= 0.24
European==PI, p= 0.15
Indian==Māori, p= 0.15
Indian==PI, p= 0.03
Māori==PI, p= 0.17

**Thigh circumference**

The equation with the best fit was Thigh Circumference ~ GA + GA2 + GA3 + GA3K + Eth.Grp + (1 + GA | ID). The fixed effect of GA was a statistically significant component of the model (p=0.02), as was Indian ethnic group compared to NZE (p=0.009).

Pairwise comparisons of ethnic groups show a significant difference between the Indian and PI groups.

European==Indian, p= 0.09
European==Māori, p= 0.39
European==PI, p= 0.53
Indian==Māori, p= 0.5
Indian==PI, p= 0.02
Māori==PI, p= 0.2

**Thigh volume**

The equation with the best fit was Thigh volume ~ GA*Eth,Grp + GA2 + GA3 + GA3K + (1 + GA | ID). The fixed effect of GA3 was a statistically significant component of the model (p=0.02). The fixed effect of Pacific Island (p=0.02) and the interactive term of GA:Pacific Island (p=0.008) were significant components of the model compared to NZE.

Pairwise comparisons of ethnic groups show a significant difference in PI compared to the other groups.

European==Indian, p= 0.37
European==Māori, p= 0.87
European==PI, p= 0.01
Indian==Māori, p= 0.6
Indian==PI, p= 0.017
Māori==PI, p= 0.04
The above equations are the best fit models. If a model using height or weight is used and also used with an interactive term with ethnic group there were some significant findings even though they may not be the best fit.

For thigh volume there was a significant effect of height (p = 0.03) as well as height and gestational age (p = 0.02).

In the same equation using weight instead of height significance with GA was p = 0.04 and with weight p = 0.02.

If height and ethnic group were used as an interactive term then the height significance is lost.

When weight and ethnic group are used as an interactive term there is only a significant (p = 0.03) interaction between gestational age, weight and Indian ethnic group.

**Graphs of fitted model and Ethnic groups**

**HC**

![Graph](image)

**Fig 5.51 Fitted curve HC vs GA - Māori**
Blue is the mean and confidence intervals for PI. Black is the mean and confidence intervals for Indian.

**Fig 5.52 Fitted curve HC vs GA – Indian compared to PI.**

The curves (Fig 5.52) illustrate the different slope of the curves for the Pacific Island and the Indian fetuses. This difference correlates well with the difference in head circumference seen in the neonatal measurements.

These graphs are representative. To overlay Māori and New Zealand European makes a graph that are difficult to read. These examples are used to illustrate the differences in biometry as can be seen from the fitted equations.
Thigh volume

Blue is the mean and confidence intervals for PI. Black is the mean and confidence intervals for Indian.

**Fig 5.53 Fitted curve thigh volume – Indian compared to PI**

The difference in the fitted graph of the Indian and the Pacific Island fetuses can be seen from 20 weeks GA.
Thigh volume and head circumference fitted equation

Blue is the mean and confidence intervals for thigh volume. Black is the mean and confidence intervals for head circumference.

**Fig 5.54 Thigh volume and head circumference fitted equation comparison**

The graph illustrates the difference in the slope of the fitted equations using head circumference as the skeletal parameter and thigh volume as the soft tissue parameter.
5.3.2 Velocity

Velocity of fitted model

HC

Blue is the mean and confidence intervals for PI. Black is the mean and confidence intervals for Indian

Fig 5.55 Velocity fitted curve HC vs GA – Indian compared to PI

The graph demonstrates the peak of head circumference growth velocity at about 20 weeks. The Indian HC growth velocity is always less than that of the Pacific Island fetus.
Thigh volume

![Velocity Fitted Curve Indian and PI](image)

Blue is the mean and confidence intervals for PI. Black is the mean and confidence intervals for Indian.

**Fig 5.56 Velocity fitted curve Thigh volume vs GA – Indian compared to PI**

The graph demonstrates the continual increase in growth velocity of the soft tissue as illustrated by thigh volume. Pacific Island growth velocity is greater than Indian fetuses throughout the pregnancy.
Blue is the mean and confidence intervals for thigh volume. Black is the mean and confidence intervals for head circumference.

**Fig 5.57 Velocity fitted curve HC compared to Thigh volume**

The velocity reflects the growth difference shown in the fitted model. This curve is for the referent NZE group and demonstrates the difference in growth velocity between skeletal growth (HC) and soft tissue growth (thigh volume). Skeletal growth velocity slows with gestational age whereas soft tissue velocity accelerates.
### 5.3.3 Ratios

The ratios of skeletal neonatal measurements (CHL and HCN) to soft tissue measurement (ThCN) were compared between the ethnic groups and the referent group (NZE) (Tables 5.9 and 5.10).

<table>
<thead>
<tr>
<th></th>
<th>NZE</th>
<th>PI</th>
<th>Māori</th>
<th>Indian</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHL/HCN</td>
<td>1.49</td>
<td>1.51</td>
<td>1.48</td>
<td>1.49</td>
</tr>
<tr>
<td></td>
<td>0.069</td>
<td>0.049</td>
<td>0.059</td>
<td>0.065</td>
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<tr>
<td></td>
<td>(0.26)</td>
<td>(0.026)</td>
<td>(0.55)</td>
<td>(0.86)</td>
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<tr>
<td>CHL/ThCN</td>
<td>3.38</td>
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<td>3.17</td>
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<td>0.44</td>
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<td>(0.0003)</td>
<td>(0.003)</td>
<td>(0.04)</td>
<td>(0.46)</td>
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<tr>
<td>CHL/HCN/ThCN</td>
<td>0.096</td>
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<td></td>
<td>(0.0002)</td>
<td>(0.002)</td>
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<td>(0.7)</td>
</tr>
<tr>
<td>HCN/ThCN</td>
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<td>2.23</td>
</tr>
<tr>
<td></td>
<td>0.32</td>
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<td>0.15</td>
<td>0.24</td>
</tr>
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<td>(0.0002)</td>
<td>(0.002)</td>
<td>(0.08)</td>
<td>(0.47)</td>
</tr>
<tr>
<td>BW/CHL</td>
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</tr>
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<td>6.9</td>
</tr>
<tr>
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<td>(0.3)</td>
<td>(0.3)</td>
<td>(0.8)</td>
<td>(0.1)</td>
</tr>
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</table>

Table 5.9 Neonatal ratios for total study population.

<table>
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<tr>
<th></th>
<th>NZE</th>
<th>PI</th>
<th>Māori</th>
<th>Indian</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHL/HCN</td>
<td>1.48</td>
<td>1.51</td>
<td>1.48</td>
<td>1.49</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td></td>
<td>(0.16)</td>
<td>(0.16)</td>
<td>(0.85)</td>
<td>(0.6)</td>
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<tr>
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<td>0.32</td>
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<td>0.3</td>
</tr>
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<td></td>
<td>(0.004)</td>
<td>(0.004)</td>
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<td>(0.003)</td>
<td>(0.003)</td>
<td>(0.11)</td>
<td>(0.35)</td>
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<tr>
<td>HCN/ThCN</td>
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<td>2.11</td>
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</tr>
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<td></td>
<td>0.25</td>
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</tr>
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<td>(0.002)</td>
<td>(0.002)</td>
<td>(0.04)</td>
<td>(0.72)</td>
</tr>
<tr>
<td>BW/CHL</td>
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<td>69.71</td>
<td>65.94</td>
<td>62.42</td>
</tr>
<tr>
<td></td>
<td>5.38</td>
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<td>3.74</td>
<td>5.88</td>
</tr>
<tr>
<td></td>
<td>(0.3)</td>
<td>(0.3)</td>
<td>(0.9)</td>
<td>(0.07)</td>
</tr>
</tbody>
</table>

Table 5.10 Neonatal ratios for AGA babies
The results showed no difference between the ethnic groups in the skeletal ratio (CHL/HCN). There were significant differences in the Pacific Island and Māori groups when the skeletal to soft tissue ratio was examined. This suggested that in these ethnic groups it was the soft tissue that has a greater contribution to birthweight.

Antenatal AGA biometry ratios were graphed according to Ethnic group, height tertile, weight tertile and ethnic BMI tertile. These antenatal soft tissue/skeletal ratios were illustrated using thigh volume and head circumference.

The antenatal ratios show an increase with increasing gestational age for ethnic group, height tertile, weight tertile, ethnic BMI tertile and customised birthweight centile. The increase was greater in the Pacific Island fetus, the fetus of the taller and heavier woman, and the heavier customised birthweight centile tertile.

The soft tissue/skeletal ratio is illustrated with the different maternal variables as has been done for the biometry.

**Ethnic Group**

![Fig 5.58 Thigh volume/head circumference ratio by ethnic group.](image-url)
**Height tertile**

Fig 5.59 Thigh volume/head circumference ratio by maternal height tertile.

**Weight tertile**

Fig 5.60 Thigh volume/head circumference ratio by maternal weight tertile.
Ethnic BMI tertile

![Graph showing Tvol/HC vs GA by Ethnic BMI tertile.]

Fig 5.61 Thigh volume/head circumference ratio by ethnic BMI tertile.

Customised birthweight centile

![Graph showing Tvol/HC vs GA by Customised birthweight centile.]

Fig 5.62 Thigh volume/head circumference ratio by customised birthweight centile.
As can be seen in all the graphs the ratio increases more rapidly in the heavier taller Pacific Island women. This is still apparent after customisation and therefore the graphs at the moment could not be used to determine rapid growth or slowing of growth. Appropriate graphs still need to be derived for these situations.

The velocity ratios also show an increase as would be expected with increasing soft tissue velocity and decreasing velocity in skeletal growth. These have not been illustrated.

5.4 Summary – Fetal Growth

Summary table

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<tr>
<th>Skeletal</th>
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<td>Indian</td>
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<td>All</td>
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<table>
<thead>
<tr>
<th>New Soft tissue</th>
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<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GA Change</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Eth Grp = pairwise comparisons as in section 5.3.1. L = lower tertile. H = high tertile.

Table 5.11 Summary growth table

Skeletal growth is characterised by a slowing of growth with increasing gestation. Soft tissue is characterised by an acceleration of growth with increasing gestation.

A model of normal growth that encompasses all these factors either needs to look at each parameter separately or combine them all together into an EFW equation.

5.4.1 Growth as EFW
Clinically fetal growth is compared using estimated fetal weight, which is calculated from an equation that has been developed from a combination of measured ultrasound parameters.
As discussed in section 1.7 there are a number of studies comparing EFW formulae, with no consistently superior method to estimate fetal weight (Dudley N 2005).

Three EFW equations from the thesis population were compared graphically. Measurements for the thesis population were taken usually more than a week before delivery and therefore the accuracy compared to birthweight cannot be compared.

**Fig 5.63 EFW Hadlock vs GA**

The Hadlock 4 equation is the commonly used equation within the community. Lee (Lee W 2009) has suggested that addition of thigh volume can improve the estimation.

**Fig 5.64 EFW Lee vs GA**
The addition of thigh volume changes the y axis on the graph and gives lower estimates than the Hadlock 4 graph. Another formula that is used in Scandinavia is the Combs equation, which has modelled EFW on theoretical body volumes.

![Graph](image)

**Fig 5.65 EFW Combs vs GA**

When comparing these three graphs it can be seen that they have different slopes, especially in the Pacific Island population. The Lee equation has different values on the y axis compared to the other two. The Combs slope is flatter than the other two between 20 and 30 weeks. This could be important when assessing EFW in preterm labour at that gestation. The Combs equation is closer than Lee in values of the y axis to the Hadlock equation.

All the graphs show the trend of heavier babies in the Pacific Island population.

Extrapolation of the graphs to the mean birthweights shows Hadlock equation is closest to NZE and Māori, Hadlock and Combs equations are closest to PI and Māori. This study was, however, not designed to check accuracy of EFW. Such a study needs equation validation within 4 days of delivery.

Recently three-dimensional ultrasound measurements of fetal limb volumes have been reported as the best parameters to estimate fetal weights as well as fetal fat mass when compared with abdominal circumference and traditional estimation of fetal weight (Khoury FR 2009; Lee W 2009).
Conclusions

Bennini (Bennini JR 2010) stated "that the greatest sources of discrepancy in estimation of birth weight are the phenotypic differences among patients used to create each of the formulae". Their data suggested the need for customized birth-weight prediction formulae, regardless of whether 2D or 3D measurements were employed.

The above graphs show a difference in EFW by the use of various equations. This suggests that with the widespread clinical use of EFW to assess fetal growth it would be appropriate to develop EFW equations for the local ethnic groups.
CHAPTER 6

FETAL FAT MEASUREMENT

6a PREVIOUS STUDY

6.1 Introduction

A previous study by the author (Parry G 2007) has measured fat mass in fetuses on the day of induction of labour or the morning of caesarean section.

It has been shown that ultrasound soft tissue measurements in normal fetuses have a unique exponential growth profile during the second half of gestation, both in lean mass and in fat mass, suggesting that the measurement of fetal fat could provide a more sensitive and specific marker of abnormal fetal growth than standard biometry (Schild. 2009).

Buhling (Buhling KA 2011) has shown that sonography of subcutaneous tissue is a reliable method for a non-invasive intrauterine measurement of fetal soft tissue that correlates well with postnatal measurements.

Partial limb volume is a soft tissue parameter that has also been described for the evaluation of fetal nutritional status (Lee W 2009). Lee performed longitudinal growth studies that demonstrated accelerated soft tissue accretion of the fetal limbs after approximately 28 weeks in pregnancies with normal growth outcome.

There have been a number of studies looking at fetal soft tissue with 3D Ultrasound in the assessment of fetal growth (Matsumoto M 2000; Schild RL 2000; Lee W 2001; Lee W 2004; Chang CH 2002; Chang CH 2005).

Schild in an editorial (Schild RL 2009) commented that ultrasound-generated estimates of fetal fat may be useful in the evaluation of fetal growth abnormalities. Fat and lean body mass have long been used in the postnatal nutritional assessment of an individual. In fetal life, weight correlates better with soft tissue thickness than it does with two-dimensional (2D) measurements.

6.2 Methods of the author’s fetal fat study.

One hundred and twenty women were scanned prior to induction of labour or caesarean section. The scanning measurement protocols were identical to those for this thesis. From the 3D volume datasets additional measurements were made of the muscle circumference or volume to subtract from the total to give a measurement of fetal fat.

Birthweights were classified as LGA with birthweight >90th customised centile, AGA between 10th and 90th customised centile and SGA <10th customised centile.
Fetal soft tissue includes fat and muscle tissue. The fetal fat mass can be assessed by subtracting muscle and bone measurements from the total (fig 2.4, page 75). These measurements can be the differences between a circumference, an area or a volume. The results are presented for a circumference. The circumference is a measurement that can be made without 3D capability. The results are also presented for a volume. A volume is more representative of mass. Because the measurement is made from 50% of the limb length, it has an approximate relationship to skeletal size and proportion.

6.3 Results

Soft tissue measurements

The measurements are presented with the p values of LGA and SGA compared to the AGA babies.

<table>
<thead>
<tr>
<th>AGA</th>
<th>LGA</th>
<th>P value</th>
<th>SGA</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=61</td>
<td>N=37</td>
<td></td>
<td>N=22</td>
<td></td>
</tr>
<tr>
<td>Birthweight</td>
<td>3690</td>
<td>4530</td>
<td>&lt;0.0001</td>
<td>2680</td>
</tr>
<tr>
<td>GA</td>
<td>39.8</td>
<td>39</td>
<td>38.7</td>
<td></td>
</tr>
<tr>
<td>HC/FL</td>
<td>9.48</td>
<td>9.4</td>
<td>0.37</td>
<td>9.38</td>
</tr>
<tr>
<td>AC/FL</td>
<td>33.9</td>
<td>34.3</td>
<td>0.2</td>
<td>32.0</td>
</tr>
<tr>
<td>Th Circ</td>
<td>15.39</td>
<td>16.89</td>
<td>0.0006</td>
<td>14.35</td>
</tr>
<tr>
<td>ThC/HC</td>
<td>0.45</td>
<td>0.49</td>
<td>0.002</td>
<td>0.45</td>
</tr>
<tr>
<td>ThVol</td>
<td>57.63</td>
<td>72.78</td>
<td>0.001</td>
<td>44.63</td>
</tr>
<tr>
<td>TVol/HC</td>
<td>1.69</td>
<td>2.12</td>
<td>0.0001</td>
<td>1.38</td>
</tr>
<tr>
<td>TVol/FL</td>
<td>7.85</td>
<td>9.82</td>
<td>0.0001</td>
<td>6.43</td>
</tr>
</tbody>
</table>

Table 6.1 Soft tissue ratios fetal fat study

There was a significant difference in the birthweights in this study. There was no difference in the skeletal ratio (HC/FL), but there were significant differences in soft tissue/skeletal parameter ratios especially with the LGA babies. The thigh circumference ratios were not significant in the SGA babies, but the thigh volume ratios were significant in the SGA as was the standard biometry ratio of AC/FL.

The fetal fat mass measurements were more useful in the LGA babies (Table 6.2).
<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>LGA</th>
<th>P value</th>
<th>SGA</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hum fat circ</td>
<td>3.35</td>
<td>4.5</td>
<td>0.002</td>
<td>3.3</td>
<td>0.9</td>
</tr>
<tr>
<td>Thigh fat circ</td>
<td>3.62</td>
<td>3.73</td>
<td>0.9</td>
<td>3.33</td>
<td>0.8</td>
</tr>
<tr>
<td>Hum fat vol</td>
<td>18.03</td>
<td>23.72</td>
<td>0.03</td>
<td>16.03</td>
<td>0.7</td>
</tr>
<tr>
<td>Thigh fat vol</td>
<td>26.49</td>
<td>35.44</td>
<td>0.02</td>
<td>21.33</td>
<td>0.54</td>
</tr>
</tbody>
</table>

Table 6.2 Fetal fat measurements

This suggests that measuring soft tissue in this way may be more useful in the LGA fetuses rather than SGA fetuses. This may be because with less fat the measurements become more difficult. In the particular sample that was used for this birthweight study there were a number of morbidly obese women and scanning is technically more challenging.

6b Present study

Using the techniques described in the first part of this chapter (nd in chapter 2), measurements of the total and muscle volumes and circumferences were made from the 3D datasets. The muscle measurements were subtracted from the total to give the fat measurements. These were graphed from 30 weeks onwards, because of the rapid soft tissue growth from this time.

Graphs Fat mass growth

Thigh volume

Fig 6.1 Thigh volume vs GA by ethnic group from 30 weeks
Thigh volume velocity

The graphs of thigh volume and thigh volume velocity show a marked increase from 30 weeks onwards, especially in the Pacific Island group.

Thigh volume muscle velocity

FF = Fat Free, which equates to the muscle mass.

Fig 6.2 Thigh volume velocity vs GA by ethnic group

Fig 6.3 Thigh volume muscle vs GA by ethnic group from 30 weeks

This graph shows that the muscle mass of the Pacific Island fetus is greater than the other groups. After 34 weeks the muscle mass in the Māori population seems to catch up.
Thigh volume fetal fat

**Fig 6.4 Thigh volume fetal fat vs GA by ethnic group from 30 weeks**

This graph shows that fetal fat increases more in the Pacific Island population. Thus the increased volume in this group is contributed to by both muscle and fat. The velocity graph below shows that only in the Pacific Island group is fetal fat velocity increasing after 35 weeks.

Thigh volume fetal fat velocity

**Fig 6.5 Thigh volume fetal fat velocity vs GA by ethnic group from 30 weeks**
6.4 Conclusion

Soft tissue measurements are useful techniques for assessment of fetal growth. They may be particularly useful in the assessment of adequate fetal nutrition, although further work needs to be done with respect to ethnic differences.
CHAPTER 7

DISCUSSION

7.1 Introduction
This thesis reports a longitudinal study of the growth of individual fetuses in terms of various fetal novel biometric measurements and relates these to maternal ethnicity, height, weight and BMI.

Hypotheses
The hypotheses are that

1. fetal growth in different ethnic groups is characterised by different growth patterns of skeletal and soft tissue biometry.
2. differences in fetal growth in these groups are due to maternal anthropomorphic characteristics.

It was postulated that the differences in mean birthweight between ethnic groups was due to a difference in soft tissue, particularly in the arms and legs.

Measurement of fetal growth was performed using standard biometry as well as assessment of soft tissue growth, by analysis of 3D volume datasets, which were used to measure thigh and arm volume and circumference.

Growth and growth velocity of the standard biometry and the novel soft tissue measurements were graphed and analysed according to ethnicity and maternal characteristics with a view to finding the best fit to perform a multilevel analysis of the longitudinal data.

A strength of the study is that the patients were selected to reduce as many of the variables that have a pathological impact on fetal growth as possible. Thus they were not obese, they did not smoke, they had no history of medical disease that may alter growth or if they developed such medical disease they were excluded from the study. As such they are likely to reflect a group with optimum fetal growth. The patients self-selected as being interested in the study and did not come from a lower socio-economic group, which could also be a co-confounder of an adverse variable on fetal growth. Low socio-economic groups tend to be obese, smoke and are poor attenders.

The participants were enthusiastic about seeing their baby and so lack of data due to missed appointments was rare. Complete data is important in a longitudinal study.
The strength of the study might be seen as a weakness in that it did not represent the population of CMDHB, because this population has a high incidence of obesity. However such an inclusion would have added a confounding influence to the study (see comment section 7.2).

Another strength of the study is the prospective longitudinal design and multilevel analysis that takes into account both the increasing variation with gestational age and the hierarchical structure of the data.

A limitation of the study is the small number of women recruited, although the number is comparable to other studies (section 1.6.7). The difficulty with recruitment reflects our socioeconomically disadvantaged population with transport difficulties, language differences and difficult access to antenatal care. Many of our women book late in pregnancy (after 28 weeks) or present in labour. Recruitment of our Indian women is also determined by the ability of the husband to attend any appointments with them.

Despite the small numbers there were significant differences seen between the different ethnic groups, particularly in the pairwise correlation in the fitted equations (section 5.3.1).

7.2 Maternal Characteristics

The thesis was proposed because of the number of patients being referred for scanning because of possible growth abnormalities. Many of these were from different ethnic groups and they were being assessed on biometry that had been developed from a Caucasian population. Customising of estimated fetal weight in this population showed that many were in the normal range. It was then suggested that biometry may be able to be customised. To do that a study needed to be done that related fetal biometry to maternal characteristics in our population.

The study sample showed differences between maternal anthropomorphic characteristics of the different ethnic groups (section 5.2.1). The study sample does not completely represent the CMDHB population which has a high incidence of obesity and a high incidence of gestational diabetes, particularly in our Pacific Island Women. Both of these have been shown to influence fetal growth and therefore would have had a confounding influence on the study. The thesis results do provide a baseline to expand the sample in Indian and Māori and allow further study of fetal growth in maternal diabetes and the higher BMI patients in our population.

Although many studies use WHO BMI classification, in this thesis an ethnic based BMI classification has been used. This allowed a better comparison of BMI across the groups. For example an Indian mother with a BMI of 23.5 is in the overweight range, whereas this would be considered normal for the other groups. Similarly an Indian woman with a BMI of 28 is considered obese, whereas in the other groups this is overweight.
The four ethnic groups studied had very different proportions of participants in the ethnic BMI tertiles – the referent NZE group were mostly in tertile A (42.6%) and B (50%), whereas the Pacific Island group were mostly in tertile C (69.2%), Māori in tertile B (45.5%) and Indian in tertile A (60%).

The significant differences between the groups with the AGA fetuses compared to the reference group were in weight (PI and Indian), maternal age (Indian), BMI (PI and Indian), and parity (Māori). These characteristics have all been discussed in the introduction to have clinically important influences on mean birthweights. When birthweights are customised by customised centiles the differences in birthweight are no longer significant (section 5.2.3).

7.3 Biometry

Standard Biometry

Skeletal

There were differences in skeletal growth – BPD, HC and HDL particularly in the Indian ethnic group. There was no difference between ethnic groups in FL growth (section 5.2.2.1).

These findings support Hadlock’s (Hadlock FP 1990) study which failed to demonstrate significant differences in femur diaphyseal length (FDL), in 300 Black and Hispanic fetuses from 20 to 41 weeks compared to their White middleclass group. However it does not agree with the other findings from that study which showed no difference in biparietal diameter (BPD) or head circumference (HC).

Johnsen (Johnsen SL 2004) demonstrated that only maternal age and fetal gender affected GA estimation when using HC. Therefore HC was suggested as the more robust method to estimate GA. This would not apply in our multi-ethnic population.

The study from Raman (Raman S 1996) showed differences in both humeral and femoral length whereas this thesis only showed differences in humeral length.

This means that the femur length chart that is used can therefore be used in all ethnic groups for assessment of gestational age. Slowing of FL growth on these charts therefore is more likely to be pathological rather than due to constitutional causes. Care, however, needs to be taken in interpreting changes in BPD and HC measurements in different ethnic groups. Slowing of growth in an Indian fetus may be constitutional as may be acceleration or growth along 90th centile in a Pacific Island fetus.

AC

The abdominal circumference shows slowing over GA in a similar way to skeletal biometry, except for Pacific Island fetuses, which continues to grow after 34 weeks. The Indian AC is less than the other ethnic groups at all gestations.
3D Measurements

Soft tissue
The soft tissue measurements – arm circumference and volume, thigh circumference and volume all showed increasing an increasing growth from early third trimester, compared to skeletal growth which showed a slowing (section 5.2.2.2).

The increase in the soft tissue growth, especially thigh volume, was greater in the heavier ethnic group (Pacific Island) as well as when seen by height tertile, weight tertile and ethnic BMI. The Indian group showed a lower increase in arm volume compared to the other groups.

These soft tissue increases are consistent with other findings from the literature, which demonstrate accelerated soft tissue accretion of the fetal limbs after approximately 28 weeks in pregnancies with normal growth outcome (Lee W 2009; Bernstein IM 1997; Larciprete G 2003).

7.4 Neonatal
There was no difference in the gestational age at delivery between ethnic groups, but there was a significant difference in birthweight (section 5.2.3).

Indian babies and Pacific Island babies showed the biggest difference in birthweight, compared to European. This difference was in all other neonatal measurements (CHL, HC and Th Circ), suggesting that Indian babies have smaller skeletal structure (length and head circumference) as well as soft tissue (thigh circumference).

If the skeletal measurements are examined as a ratio there was no difference between the ethnic groups section 5.3.3). This suggests the fetuses in the different ethnic groups are in proportion. This is supported by the lack of any difference between the ethnic groups in the birthweight/CHL ratio.

If soft tissue is then examined ratios becomes significant, especially in relation to Pacific Island Group. This significance is shown for HCN/ThCN (p=0.0004) and CHL/ThCN (p=0.0002), suggesting that any difference in birthweight between the Pacific Island babies and the NZE babies may be due to greater proportion of soft tissue in the Pacific Island babies. The application of such ratios may have a use in determining nutritional status in the neonates of different ethnic groups.

It is well described that the firstborn infant is smaller than the second or third. However in this sample birthweight showed there was no difference in parity (p=0.07) or with gender (p=0.06). This is likely to be a reflection of the sample size. Parity and gender were excluded, therefore, from further comparisons of biometry. These were included in the multilevel equations, but were removed during the stepwise selection of the best fit.
My findings of neonatal differences between ethnicities are not consistent with the literature. Leary (Leary S 2006 (b)) compared several studies of body proportions in newborns of at least 37 weeks from several different geographic areas (UK, India, China, Africa and Asia).

In the Leary study neonates in Europe were the largest, followed by Jamaica, East Asia (China), then Africa and South Asia. Birthweight varied widely between countries (mean values 2730 gms to 3570gms), but in contrast, head circumference was similar in all except China (markedly smaller). The main difference in body proportions between populations was the head to length ratio, with small heads relative to length in China and large heads relative to length in South Asia and Africa. This thesis did not show any difference in head to length in the population studied.

This is the first time, to the author’s knowledge, that soft tissue/skeletal ratios have been examined in normal neonates in a New Zealand multiethnic society. The findings suggest that these factors should be taken into account when assessing the normality of growth and weight, particularly in our Pacific Island babies.

### 7.5 Maternal characteristics and neonatal measurements

The results in the study show a heavier Pacific Island group. This group demonstrated a larger thigh volume with acceleration in fetal fat compared to other ethnic groups (section 5.2.3).

Sletner (2011) described neonatal body composition, in relation to maternal body composition in South Asian, East Asian, Middle East and Somali neonates (mothers mostly 1 generation immigrants), with Scandinavians’ as reference, in a multi-ethnic population in Oslo, Norway. She found all ethnic minority women were shorter compared to Scandinavian women, BMI was lower in South and East Asians and higher in Somali compared to Scandinavians, but South Asian, Middle East and Somali women had larger subscapular skinfolds. South Asian neonates were smaller in all body measurements, most marked for AC, less so for length and skinfolds. East Asian also had lower birthweight and AC than Scandinavian but not as marked as South Asian.

Although all ethnic minorities were shorter and had relatively more subcutaneous fat, neonatal body composition varied substantially between ethnic minorities. They concluded that this may indicate that factors beyond maternal size and body composition influence ethnic differences in neonatal size and body composition.

The relationship between percent body fat and BMI has been demonstrated by Rush (Rush E 2009) to be different for European, Pacific Island, and Asian Indian women which may, at least in part, be due to differences in muscularity. Pacific women had the lowest central fat mass and highest limb muscle mass, whereas Asian Indian women had the highest central fat mass, but lowest limb muscle mass.
Whincup (Whincup P 2002) demonstrated that precursors to the metabolic syndrome, mean insulin concentrations, mean heart rate and triglyceride and fibrinogen concentrations were higher among South Asian compared to white children despite a lower ponderal index.

It would be interesting to compare the fetal fat in the different ethnic groups with the maternal fat content. The increase in fetal fat in the CMDHB population may give insights to the high incidence of obesity and diabetes in the Pacific Island group, despite the Rush results demonstrating a low central fat mass and high limb muscle mass in that group.

### 7.6 Multilevel Modelling

The results of this thesis (section 5.3.1) agrees with some of the findings in other studies such as Pang (Pang MW 2003).

Within Pang’s ethnic study it was demonstrated that increased fetal head size and abdominal circumference were significantly associated with extremes of maternal age. This thesis did not have a population with extremes of maternal age and therefore could not investigate this relationship.

The thesis did not confirm an effect of parity on fetal head and abdominal circumference, nor of fetal gender on head and femur measurements. It did confirm the minimal effects of maternal and pregnancy characteristics on the femur diaphysis length.

It was possible that the difference was due to Pang’s study having only one ethnic group because with the overall thesis study group there was a difference with BPD and maternal height. When multilevel modelling was employed ethnic group was the most important factor and maternal height was removed.

Pang decided to construct customized models of individual fetal biometric parameters rather than fetal weight. They argued that this approach eliminated the potential problem of erroneous estimation of fetal weight using formulae for its calculation. In addition Pang stated it allowed direct assessment of the characteristics of the growth aberration by comparison of the deviation of the individual fetal biometric parameters from the expected values.

Another major study in the literature on ethnicity and fetal growth is from Rotterdam (Drooger J 2005).

The conclusion from that study was that there are ethnic differences in fetal growth, which to a large extent may be attributed to differences in maternal weight, height, age and parity. For some ethnic groups, however, additional factors are involved, as differences remain significant after correction for fetal and maternal characteristics.
They did show that when adjusting for the most important maternal and fetal characteristics (i.e. maternal weight, height, age, parity and fetal gender) the differences with most ethnic groups became smaller but still remained. That is the effect that this thesis has found by multilevel modelling.

Despite these findings Drooger questioned whether developing subgroup specific standards for birth weight within countries was as useful as developing individual growth curves, which take into account different variables influencing prenatal growth. Individual growth curves may be derived taking into account prenatal ultrasound growth data. This may lead to a more accurate diagnosis of intrauterine growth restriction and the prevention of unnecessary obstetric interventions. It can be questioned whether it is useful to include ethnicity as a separate variable in the individualised growth curves.

Models that include ethnicity might be limited in use to the population in which they are developed, while a model that includes fetal and maternal characteristics might be useful in different populations.

This thesis would argue that in the multi-ethnic population of the CMDHB models that include ethnicity would be very useful in determining individualised growth curves.

With intermarriage between ethnic groups, maternal characteristics may become more significant. Maternal height and weight tertiles have shown different growth patterns in the longitudinal data for this thesis. To use these maternal characteristics would have wider application and therefore supports Drooger’s argument for customising biometry on those parameters.

**7.7 Velocity**

Bertino (Bertino E 1996) studied growth patterns for several one-dimensional morphometric traits and found that growth velocities peak at 18 weeks for biparietal diameter and head circumference, 20 weeks for femur length, and 22 weeks for abdomen circumference.

The results of this thesis (section 5.3.2) have shown that skeletal growth velocities are similar to those reported by Bertino. However there are differences in growth velocities between the different ethnic groups. There are also differences in growth velocity graphs between the height tertile, weight tertile and ethnic birthweight tertiles.

Soft tissue growth velocity accelerates after 30 weeks, which is the reverse to skeletal velocity. These velocities are also different between ethnic groups. There was a greater increase in the graph in the taller height tertile, heavier weight tertile, heavier ethnic birthweight tertile women and heavier customised birthweight centile tertile babies. This is in agreement with the AC velocity graph of Bertino that shows a different curve with lighter or heavier babies.
The study population was selected to represent a normal maternal phenotype and normal fetal growth and therefore could not determine whether these velocities would be useful in the detection of growth abnormalities.

A study of growth velocity in LGA and SGA would determine the usefulness of velocity in detection of growth abnormalities.

**7.8 Ratios**

Ratios of soft tissue to skeletal growth may be useful to determine growth abnormalities, but as with velocity the study was selected for normal growth and cannot determine whether they will be useful.

Without customising the biometry, ratios may help with the determination of soft tissue growth compared to skeletal growth in distinguishing fetal growth abnormality. The findings of the previous investigation suggest that they would be (Chapter 6). A larger longitudinal study of the population to include LGA and SGA would help answer this question.

**7.9 EFW**

As discussed in section 1.7 there are a number of studies comparing EFW formulae, with no consistently superior method to estimate fetal weight (Dudley N 2005).

Kehl (Kehl S 2011) concluded that the current accuracy of fetal weight estimation with conventional biometric parameters by two-dimensional ultrasound had reached its limits and further improvement would probably only be achieved through new approaches in ultrasound.

Schild (Schild RL 1999) confirmed a greater accuracy of estimated fetal weight by the use of his own formula compared to 2D biometry. However application of published 3D weight formulae (Chang FM 1997, Liang RI 1997) which were derived from East Asian populations to Schild’s predominantly Caucasian population led to gross overestimation of fetal weight stressing the need for population-specific weight formulae.

A number of authors have attempted to use soft tissue measurements to try to improve the reliability of estimated fetal weight determination. Lee (Lee W 2001) and others (Chang FM 1997) have used limb volumes to determine EFW. These authors have found different regression equations from their studies. This may be because these studies have been performed in completely different populations. Lee’s study was from Detroit, USA whereas Chang’s study was performed in a population from Taiwan and it is possible that these populations would have different soft tissue growth in their ethnic groups.
The study by Bennini (Bennini JR 2010) showed that there was no statistically significant difference in the prediction of birth weight by 2D and 3D formulae that were generated from the same set of patients. Conversely, it demonstrated that 2D and 3D equations that were created using different populations had significantly lower performances in the prediction of birth weight in their patients than the model they developed.

Although EFW was not designed as an assessment of fetal growth in this study, it is an important clinical tool. The graphs in the results (section 5.2.2.3) do show different slopes for the various ethnic groups, as well as between the graphs. This suggests that notice should be taken of Bennini’s statement that there is a lower performance of the prediction of birthweight using equations that were developed from other populations and this therefore needs to be investigated prospectively in the CMDHB multiethnic population.

### 7.10 Summary Discussion

The hypotheses are that

1. fetal growth in different ethnic groups is characterised by different growth patterns of skeletal and soft tissue biometry.
2. differences in fetal growth in these groups are due to maternal anthropomorphic characteristics

This thesis has demonstrated that fetal growth in normal pregnancy in different ethnic groups is characterised by different patterns of growth in skeletal and soft tissue biometry. The first hypothesis is therefore confirmed.

This thesis has demonstrated that these differences in fetal growth may be due to maternal characteristics, such as height and weight. The second hypothesis is therefore confirmed.

### Key Points

There are ethnic differences in biometry when measured in a longitudinal study. As growth is a change in a measurement at 2 different times, then these measurements show that growth is different in different ethnic groups. Growth is also different for skeletal and soft tissue parameters.

The concept of fetal growth velocity is a different way of looking at fetal growth. There are differences between ethnic groups as well as with maternal characteristics. A customised fetal growth velocity of soft tissue could lead to a new soft tissue definition of IUGR.

Statistical modelling has allowed appropriate assessment of longitudinal growth because these measurements are highly correlated.
The use of ethnic BMI has allowed better comparison of maternal height and weight in the different ethnic groups.

**Clinical application**

The thesis has confirmed differences in constitutional variation which affect fetal growth. These variations therefore will affect any clinical application of a growth standard, which is important in differentiating SGA due to constitutional cause from pathological causes. This means that any universal growth standard needs to be able to be customised.

To be able to develop such a universal growth standard requires longitudinal growth studies in different ethnic groups with normal growth to determine appropriate coefficients. These growth standards need to be applied to standard biometry as well as soft tissue biometry.

There is still a lot of work that needs to be done before these concepts can be incorporated into clinical practice.

**Future directions/research**

A larger study in normal pregnancies, including other ethnic groups such as Korean, Vietnamese and Chinese, as well as the ethnic groups in this study would confirm the findings of the thesis. Once normal standards have been established they would be used in studies of abnormal pregnancies.

These larger studies could be combined with biomarker analysis.

A longitudinal study in obese/diabetic patients may show a greater influence of maternal weight. A study in diabetic pregnancy in the ethnic groups also would be interesting to compare biometry of the fetal thigh and if it may reflect glycaemic control.

A longitudinal study of those at risk for SGA would also be useful to determine if soft tissue growth gave any more information for the management of such patients. Chapter 6 suggests that fetal fat could be useful.
CHAPTER 8

CONCLUSION

8.1 Introduction
The aim of this study was to evaluate the rate of growth of fetuses in different ethnic groups and to determine the influence of maternal characteristics on longitudinal fetal growth parameters in normal pregnancy in a multiethnic population.

Many factors are involved in growth and we have learnt a great deal more than when Kloosterman made the statement “How intrauterine growth processes during a normal pregnancy evolve and what regulates these processes in humans is practically unknown. The fact is that fetal growth velocity differs and that it is malpractice to use birth weight as a measure for maturity at birth. An early born giant and a late born dwarf with a similar birth weight can differ largely in maturity and development.” (Verburg 2007).

When the “population reference” and the “standard” are applied to an individual fetus or infant, interpretation of the findings differs. The use of a population reference will yield a relative fetal size in relation to the total population; a standard will assess a fetal size in comparison to normally grown fetuses. Thus, a standard may have more clinical utility than a population reference. (Zhang J 2010)

This thesis has addressed some of the basic issues identified by Zhang (Zhang J 2010) namely whether fetuses of different racial/ethnic groups have a similar growth pattern and therefore can be measured against one ethnic standard. It has also looked at whether differences in measurements between ethnic groups are related to skeletal growth and therefore readily measured with standard biometry, or is the difference related to soft tissue mass and therefore requires new methods of measurement?

8.2 Summary
This thesis has shown that there are differences in fetal growth in normal pregnancy between ethnic groups. Some of these differences can be related to maternal anthropomorphic characteristics. There are differences in body proportionality of each fetus at different gestational ages, with differences in the growth velocities of each parameter. In particular there are marked differences in soft tissue accretion in the latter stages of pregnancy which is particularly seen in the fetuses of the heavier Pacific Island women.
This thesis has shown that soft tissue measurements are feasible. Measurements can be performed offline and volume measurements and can be performed within 2 minutes.

These soft tissue measurements have the potential applicability to assess fetal nutrition. The velocity of soft tissue growth may have the potential to determine management plans in IUGR.

The standards for the novel measurements can be developed from this thesis in a larger population.

Standard and the novel biometry could be customised and growth assessed on an individual basis by other techniques such as conditional charts, growth velocity or assessment of soft tissue to define nutritional status. This may lead to a soft tissue definition of SGA or LGA instead of birthweight.

Growth is complex, as has been confirmed in the population for this study and each parameter grows with a different velocity. Estimated fetal weight is a composite of the different parameters so that a long skinny fetus may have the same EFW as a short fat fetus. Growth could be then classified as skeletal or soft tissue. Skeletal growth is important for skeletal dysplasia diagnosis and early onset uteroplacental vascular problems, whereas soft tissue growth is important for nutritional status and in the context of fetal wellbeing is the important assessment.

This thesis has only been able to address a few of the determinants of fetal growth in normal pregnancy which need to be validated on a larger study, but it provides a basis on which other determinants of fetal growth can be studied, such as nutrition and maternal medical conditions such as diabetes and hypertension.

The study is relevant to current practice in that it emphasises the difference in fetal growth within our multi-ethnic population. Until appropriate charts are developed or biometry customised biometry will continue to be plotted on the charts that are in common use, but the interpretation of these charts needs to take ethnic differences into account.

**Conclusions**

Appropriate ethnic characteristics should be included in customised biometry charts.

Growth velocity of soft tissue may be useful to determine growth abnormalities, especially after 34 weeks. Soft tissue growth may help distinguish fetal growth restriction or SGA or if macrosomia is pathological in Pacific Island diabetics.
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APPENDICES

APPENDIX A Tertile Classification and Definitions

Height tertiles (cm)
A 149 – 160
B 161 - 171
C 172 +

Weight tertiles (kg)
A 41-60
B 61-79
C 80+

Ethnic BMI tertiles

Indian
A 18.5 – 21.49
B 21.5 – 24.49
C 24.5 – 27.5

NZE
A 18.5 – 22.31
B 22.32 – 26.16
C 26.17 – 29.99

Māori/Pacific Island
A 18.5 – 22.89
B 22.9 – 27.4
C 27.41 – 31.9

Customised Birthweight centiles
A 10 - 36
B 37 - 63
C 64 - 90

EFW equations:
Lee: \(\ln BW = -0.8297 + 4.0344 \ln BPD - 0.7820 (\ln BPD)^2 + 0.7853 (\ln AC) + 0.0528 (\ln TVol)^2\)

Hadlock 4
\[
\log_{10} BW = 1.3596 - 0.00386 AC*FL + 0.0064*HC + 0.00061*BPD*AC + 0.0424*AC + 0.174*FL
\]

(Combs CA 1993) has used a theoretical volume calculation for his model. The Combs equation is commonly used in Scandinavia.

\( EFW = (0.23718*AC*AC*FL)+(0.03312*HC*HC*HC)\)
Definitions

Small for Gestational Age was defined as less than the 10th customised Birthweight centile adjusted for maternal weight, maternal height, ethnicity, parity, gestation at delivery and infant sex using the New Zealand Customised Birthweight Centile Calculator (McCowan LM 2004).

Large for Gestational Age was defined as greater than the 90th customised Birthweight centile adjusted for maternal weight, maternal height, ethnicity, parity, gestation at delivery and infant sex using the New Zealand Customised Birthweight Centile Calculator (McCowan LM 2004).

Customised Birth Weight Centiles:
Customised birth weight centiles adjust newborn weight for maternal height, weight, ethnicity and parity.

Appendix B: Raw data Biometry

Raw Ultrasound data of the study population
Raw data is shown as scatterplots with 10th, 50th and 90th centiles.

Standard biometry

BPD

Scatterplot of raw BPD data vs GA of total study population
Head Circumference

Scatterplot of raw Head Circumference data vs GA of total study population

Femur length

Scatterplot of raw Femur Length data vs GA of total study population
Humerus Length

Scatterplot of raw Humerus length data vs GA of total study population

Abdominal Circumference

Scatterplot of raw Abdominal Circumference data vs GA of total study population
Volume Biometry

Arm Circumference

Scatterplot of raw Arm Circumference data vs GA of total study population

Arm Volume

Scatterplot of raw Arm Volume data vs GA of total study population
Scatterplot of raw Thigh Circumference data vs GA of total study population

Scatterplot of raw Thigh Volume data vs GA of total study population
Scatterplot of EFW (Hadlock) vs GA of total study population
Appendix C Inter/Intra Observer data

Electronic data validation

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Data used to determine agreement between measurements made on the ultrasound machine and from the 3D dataset (section 3.2.1) These measurements were performed by the author (intra observer). The first second and third measurements are the measurements taken from the dataset and the mean then compared to the reported value which was the mean value from 3 measurements taken at the time of the scan on the ultrasound machine.
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Neonatal interobserver measurements used to determine measurement agreement between midwife A and B using paper tape measure (section 4.2)
### CHL Tape Interobserver statistics

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Pearson r correlation = 0.96

Statistical analysis of interobserver measurement between two midwives using a paper tape measure for neonatal measurements (section 4.2).
Neonatometer

CHL Neonatometer Interobserver

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Statistical analysis of interobserver measurement between two midwives using a neonatometer for crown heel measurement (section 4.2).
Intraobserver CHL:Neonatometer – Midwife A

Bias
0.08000
SD of bias
0.2628
95% Limits of Agreement
From -0.4350
To 0.5950

Number of values
20
20

Mean
52.21
52.13
Std. Deviation
2.579
2.427
Std. Error
0.5767
0.5428
Lower 95% CI of mean
51.00
50.99
Upper 95% CI of mean
53.41
53.26

D’Agostino & Pearson omnibus normality test
K2 0.8931
P value 0.6398
Passed normality test (alpha=0.05)?
Yes Yes
P value summary
ns ns

Sum
1044
1043

Paired t test
P value
0.1893
P value summary
ns
Are means signif. different? (P < 0.05)
No
One- or two-tailed P value?
Two-tailed
T, df
t=1.361 df=19
Number of pairs
20

Pearson r =0.99

Statistical analysis of intraobserver measurement of midwife A comparing a neonatometer and a paper tape measure for crown heel measurement (section 4.2).

Intraobserver CHL:Neonatometer – Midwife B

Bias
0.03000
SD of bias 0.6191
95% Limits of Agreement
From -1.183
To 1.243

Number of values
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Mean
52.06
52.03
Statistical analysis of intraobserver measurement of midwife B comparing a neonatometer and a paper tape measure for crown heel measurement (section 4.2).

**Interobserver HCN**

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Number of values 20 20

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D'Agostino & Pearson omnibus normality test

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Sum 701.7 700.7
Paired t test

- **P value**: 0.6402
- **P value summary**: ns
- **Are means signif. different? (P < 0.05)**: No
- **One- or two-tailed P value?**: Two-tailed
- **t, df**: t=0.4750 df=19
- **Number of pairs**: 20

*Pearson r = 0.89*

Statistical analysis of interobserver measurement between two midwives using a paper tape measure for neonatal head circumference measurement (section 4.2).

**THCN**

- **Bias**: -0.07500
- **SD of bias**: 0.3552
- **95% Limits of Agreement**
  - **From**: -0.7712
  - **To**: 0.6212
- **Number of values**: 20  20

- **Mean**: 16.32  16.39
- **Std. Deviation**: 1.619  1.449
- **Std. Error**: 0.3621  0.3240

- **Lower 95% CI of mean**: 15.56  15.71
- **Upper 95% CI of mean**: 17.07  17.07

D’Agostino & Pearson omnibus normality test

- **K2**: 1.081  1.495
- **P value**: 0.5823  0.4735
- **Passed normality test (alpha=0.05)?**: Yes  Yes
- **P value summary**: ns  ns

*Pearson r = 0.97*

Statistical analysis of interobserver measurement between two midwives using a paper tape measure for neonatal thigh circumference measurement (section 4.2).
Appendix D

Patient Clinical Information Forms
**MATERNITY REGISTRATION FORM – Section 2 – Clinical Information**

**Family Details:**
- Last Name: 
- Given Names: 
- Date of Birth: 
- Menstrual Cycle: 
- LMP: 
- Regular: 
- EDD by date: 
- Gravidity: 
- Irregular: 
- EDD by scan: 
- Parity: 
- Blood Group: 
- Height: 
- Weight: 

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<th>Antenatal tests</th>
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<th>Length of Labour</th>
<th>Induced?</th>
<th>Sex &amp; name of baby</th>
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**Women's Medical History:**

- **Medical History:**
  - Rheumatic Fever: 
  - Cardiac Disease: 
  - Hypertension: 
  - Epilepsy: 
  - Diabetes: 
  - Thyroid: 
  - Impotence: 
  - Impotence: C: 
  - Other/Surgery — state:

- **Significant Gynaec History:**
  - Ectopic pregnancy: 
  - Autoimmune: 
  - Molar pregnancy: 
  - Nystagmus: 
  - Tubal ligation: 

- **Family History:**
  - Adopted: 
  - INR: 
  - Hypertension: 
  - Malignancy: 
  - Diabetes: 
  - Other: state:

- **Sexual Health/HIV:**
  - HIV screening offered: 
  - HIV screening completed: 
  - STI: 
  - Treatment: 
  - Date: 

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**Completed by:**
- Name: 
- Designation: 

**Signature:** 
- Date: 

Please select one of the following options:
- [ ] I have chosen CMOH as my LMC to provide my maternity care.
- [ ] I have chosen another LMC to provide my maternity care.
- [ ] I certify that the information is correct. 

Birth Mother or Caregiver Signature: 
Date: 

Re-Order No: 0387/10 Revised October 2008
Participant Information and Consent Form

INDIVIDUALISED GROWTH ASSESSMENT IN DIFFERENT ETHNIC GROUPS - An Observational Study.

Investigator: Dr Graham Parry
Consultant Obstetrician
C/- Mother and Baby Assessment Unit
Middlemore Hospital
Private Bag 93311
Otahuhu
Auckland
Ph: (09) 276 0000

Study participant number:..........

Introduction
You are invited to take part in a research study into Individualised Growth Assessment in Different Ethnic Groups. Before you decide if you want to take part, it is important to know why this study is being done and what it will involve. Please take time to read this information carefully and feel free to discuss it with your family and support people. If anything is unclear or you want more information, your doctor will be happy to answer your questions or give you more information.

The study is being conducted by Dr Graham Parry at Middlemore Hospital.

What is the purpose of this study?
The purpose is to compare the growth of the fetus in different ethnic groups and to see if there is a difference compared to our standard measurements used at the moment, which are based on a European population.
Is taking part in this study voluntary?
Yes, taking part in this study is voluntary. If you decide to take part you will be asked to sign and date the consent form (the last page of this document) and keep a copy for your information.
If you decide to take part but later on wish to stop, this will be possible at any time. In this case contact the study doctor. He will explain what you should do.
If you decide not to take part, this will have no effect on your relationship with your doctor, or on your current or future medical care.

Problems associated with wrong assessment of baby's growth.
Abnormalities of fetal growth complicate 20% of all pregnancies and are the cause of significant illness for baby. When baby is a long way from the due date, expectant management is appropriate to allow baby to mature. When growth abnormalities complicate pregnancies closer to the due date, the risks of prematurity are lower and the risk to the fetus of stillbirth becomes of greater significance. It is therefore important that the diagnosis and assessment is correct. At the moment we compare the growth of the unborn baby to charts that were produced in a European population. This is not appropriate for our population with its many ethnic groups. If a small baby is wrongly diagnosed this will lead to an increase in investigations, Induction of labour, or Caesarean section as well as anxiety in the patient and her caregiver.

How the study will be carried out.
If you agree to participate in this study, you will be allocated follow up scanning appointments every four weeks until you deliver your baby.

Your obstetric and medical histories will be recorded.

Once your baby is born he or she will be examined and measured by a neonatal nurse specialist. This is to help us determine whether your baby has normal birth measurements.
Further information may need to be obtained from either your delivery record or your baby’s record of its first days of life.
What are the advantages of this study?
Your participation in this study will help us to determine how to compare the growth of an individual fetus in an individual pregnancy. This may not help you directly, but may help you in a future pregnancy.

Who is able to join the study?
If you have a single fetus and the fetal age has been confirmed by ultrasound before 18 weeks and no features in the history to suggest a potential growth problem.

If your baby has been found to have a problem, if you have twins or you have a medical disorder, as well as a past history of early onset growth disorders you would not be eligible for the study.

Your LMC will talk to you further about the study and make an appointment at MABAU if you wish to join or if you want to know more about the study. Once you have consented to be involved in the study, your entry details will be recorded on the study entry form and you will be given a follow up appointment time for your next scan.

Are their any risks?
The scan measurements are standard clinical ultrasound measurements apart from the 3D volume measurements of the arm and the leg. These number and types of scans have not been shown to be harmful to you or baby.
Neither you nor your baby will be at any increased risk by taking part in this trial.

What happens if other information becomes available?
The preliminary results will be assessed regularly.
If other information from other studies becomes available we will continue the study as each study is important to its own community.

How is confidentiality maintained?
This information will remain confidential and will only be used in the study in an anonymous manner.
All aspects of the study, including results, will be strictly confidential and only the investigators will have access to information on participants. A report of the study may be submitted for publication, but individual participants will not be identifiable in such a report.
Will I be compensated for any study related injury?
This study is being conducted as an Observational study in a normal clinical situation. Therefore you are covered under ACC regulations, as you would be in any other clinical situation. If you have any questions about ACC, contact your nearest ACC office or the investigator.

Ethics approval
This study has ethical approval from the Northern Y Ethics Committee.

What if I have any more questions?
If you have any queries or concerns regarding your rights as a participant in this study you may wish to contact a Health and Disability Advocate.
Advocacy Network Services Trust
0800 423 638
Free fax 0800 27827678
Email advocacy@hdc.org.nz

Please feel free to contact Dr Parry if you have any questions about this study.

Dr Graham Parry
Consultant Obstetrician
C/- Mother and Baby Assessment Unit
Middlemore Hospital
Private Bag 93311
Otahuhu
Auckland
Ph: (09) 276 0000

Other help and support can be obtained from the Māori Health Division
Te Matapuna Rauora
Middlemore Hospital
Private Bag 93311
Otahuhu
Auckland
Ph: (09) 276 0044 Extension 8138
Consent Form

INDIVIDUAL GROWTH ASSESSMENT IN DIFFERENT ETHNIC GROUPS - AN OBSERVATIONAL STUDY

Investigator: Dr Graham Parry
Consultant Obstetrician
C/- Mother and Baby Assessment Unit
Middlemore Hospital
Private Bag 93311
Otahuhu
Auckland
Ph: (09) 276 0000

Participant's Name:   Participant number:

I have read and understood the information sheet dated 16 October 2006 for volunteers taking part in the study designed to compare fetal growth in different ethnic groups. I have had the opportunity to discuss this study. I am satisfied with the answers I have been given.

I have had the opportunity to use whanau support or a friend to help me ask questions and understand the study.

I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time and this will in no way affect my continuing health care.

I understand that my participation in this study is confidential and that no material that could identify me will be used in any reports on this study.
I have been made aware of the procedures involved in the study, including any known or expected inconvenience, risk, discomfort or potential side effect and of their implications as far as they are currently known by the researchers.

I understand that participation in this study will allow the researchers to collect information about my pregnancy and on the birth of the baby from the hospital record and I agree to this.

I freely choose to participate in this study and understand that I can withdraw at any time and this will in no way affect my future health care.

I understand the compensation provisions for this study.

I have had time to consider whether to take part.

I know who to contact if I have any questions about the study.

I agree to my maternity caregiver being informed of the results of my participation in this study.

I wish to receive a copy of the results

I hereby agree to participate in this research study.

NAME: .........................................................................................................................

SIGNATURE: ................................................................................................................

DATE: ............................................................................................................................

NAME OF WITNESS: .....................................................................................................
**SIGNATURE OF WITNESS:** .................................................................

Date

Project explained by:

Project role

Signature

Date

Researcher: Dr Graham Parry
Ph 09 276 0044. Pager 93 8771

Request For Interpreter

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<thead>
<tr>
<th>Language</th>
<th>Request for Interpreter</th>
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<th>No</th>
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<td></td>
<td></td>
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<td>Ae</td>
<td>Kao</td>
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<td>Samoan</td>
<td>Ou te mana’o ia I ai se fa’amatala upu</td>
<td>Ioe</td>
<td>Leai</td>
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<tr>
<td>Tongan</td>
<td>Oku ou fiema’u ha fakatonulea</td>
<td>Io</td>
<td>Ikai</td>
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<td>Ae</td>
<td>Kare</td>
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<td>Io</td>
<td>Sega</td>
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<td>Haan</td>
<td>Nahin</td>
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