THE FETAL GROWTH STUDY –

A PROSPECTIVE COHORT STUDY OF FETAL GROWTH AND BODY COMPOSITION IN OVERWEIGHT AND OBESE PREGNANT WOMEN

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LIST OF ABBREVIATIONS

AC : abdominal circumference

AA : abdominal area

AFM : abdominal fat mass

BPD : biparietal diameter

BMI : body mass index

CS : caesarean section

EFW : estimated fetal weight

FL : femur length

GDM : gestational diabetes mellitus

GWG : gestational weight gain

HC : head circumference

IOL : induction of labour

IOM : Institute of Medicine

LGA : large for gestational age

LR : likelihood ratio

LR+ : positive likelihood ratio

LR- : negative likelihood ratio

MTFM : mid thigh fat mass

MTLM : mid thigh lean mass

MTTM : mid thigh total mass

NICU : neonatal intensive care

PCOS : polycystic ovarian syndrome

PEAPOD : air displacement plethysmography

ROC curve : receiver operating characteristic curves

SSFM : subscapular fat mass

TOBEC : total body electrical conductivity

WHO : World Health Organisation

ABSTRACT

Background

Maternal overweight and obesity pose significant risks both for the woman and her infant, including high infant birthweight. Gestational weight gain may also be an important factor in determining pregnancy outcomes. The effect of high maternal BMI and gestational weight gain on fetal growth and fetal body composition with reference to population standards has not been well described to date.

Aims

The aim of The Fetal Growth Study was to describe fetal growth and body composition prospectively in a large group of overweight and obese women during pregnancy and to examine the influence of maternal BMI and gestational weight gain on these measures.

Methods

Fetal biometric growth measures (biparietal diameter, head circumference, abdominal circumference, femur length and estimated fetal weight) and fetal body composition (mid thigh lean and fat mass, abdominal fat mass and subscapular fat mass) were assessed prospectively using ultrasound at 28 and 36 weeks' gestation. Important maternal and fetal outcomes were collected including gestational weight gain and infant birthweight.

Results

The findings of The Fetal Growth Study indicate that maternal overweight and obesity is significantly associated with increased fetal growth, an effect that is evident from 20 weeks' gestation when compared with published normal values. Additionally, when compared with population standards, the relative contributions of head and abdominal growth change throughout pregnancy with abdominal growth dominating in the second trimester and head growth in the third trimester. Both maternal BMI

category and gestational weight gain contribute to increased measures of fetal growth, predominantly through a modification of abdominal and overall growth. Gestational weight gain above current recommendations was associated with further increases in abdominal and overall growth. Maternal overweight and obesity is associated with a significant increase in fetal measures of both lean and fat mass. At 28 and 36 weeks, AC and EFW growth were associated with birthweight above 4500g, whilst HC was associated with birthweight above 4000g but not 4500g.

Furthermore, EFW, head and abdominal growth were associated with mode of birth, with measures above the 90th percentile increasing the likelihood of caesarean section for women. The only predictor of clinical outcomes with a moderately useful positive likelihood ratio was fetal AC above the 90th percentile at 28 weeks (LR+ 6.56 for birthweight above 4500g, LR- 0.37).

Conclusions

Maternal overweight or obesity and gestational weight gain above recommended ranges influence fetal growth and fetal body composition from mid pregnancy. Gestational weight gain above current recommended ranges is associated with a further increase in measures of fetal growth and fetal fat mass. In women who are overweight or obese, growth above the 90th percentile in the third trimester is associated with high infant birthweight and an increased likelihood of caesarean section. Further research from ongoing prospective intervention studies will provide important information regarding the effect of limiting weight gain on fetal growth and body composition and important maternal and infant outcomes.

DECLARATION

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution to Rosalie Mignon Grivell and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

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Rosalie Mignon Grivell

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AUTHOR'S CONTRIBUTION

I have been responsible for the development of the original fetal ultrasound protocols and methodology including the assessment of fetal body composition and obtaining research and ethics approval. I developed the ultrasound data collection sheets and coordinated the collection of all ultrasound data. I was responsible for training all research sonographers and for maintaining quality control. I personally performed 80% of the ultrasound examinations included in this thesis, including the assessment of interobserver variability. I have received statistical advice from Dr Helena Oakey regarding the analysis of interobserver variability. I conducted all other statistical analyses presented and accept responsibility for the veracity of the statistical analyses and their interpretation.

1. LITERATURE REVIEW

1.1 PURPOSE AND SCOPE

The purpose of this literature review is to provide the background for the prospective studies in this thesis which are examining the effect of overweight and obesity in pregnancy on fetal growth and fetal body composition. The problem of overweight and obesity, particularly in relation to pregnancy will be outlined and the risks for women and their infants summarised. Current knowledge about fetal growth and body composition in pregnant women who are overweight and obese will be examined and key research gaps identified. These research gaps will be highlighted throughout the literature review and the aims of The Fetal Growth Study will be identified and described.

When reviewing the literature, a systematic search strategy was applied using the following key words: fetal development, fetal growth, fetal programming, fetal organ maturity, fetal wellbeing, fetal growth restriction, fetal macrosomia, macrosomic, large for gestational age, obesity, overweight, obese, BMI, ultrasonography, prenatal, ultrasound. Studies were assessed and included in this literature review on the basis of study design, risk of bias, imprecision, inconsistency, indirectness, and magnitude of effect as described by the GRADE working group (Guyatt et al 2011).

1.2 OVERWEIGHT AND OBESITY

1.2(1) DEFINING OVERWEIGHT AND OBESITY

Overweight and obesity is defined by body mass index, body weight or waist circumference, the most commonly used measure being body mass index. Body mass index (BMI) is a measure of weight/height^2 where weight is measured in kilograms and height in metres**.** The World Health Organisation and the Australian Institute of Health and Welfare define normal weight as BMI of 18.5 to 24.9 kg/m^2, overweight as BMI of 25 to 29.9 kg/m^2 and obesity as BMI of 30 kg/m^2 or greater (AIHW

2001; WHO 2000) (Table 1.2(1)). Obesity may be further categorized into three subclasses; obese class I (BMI 30-34.9 kg/m^2), obese class II (BMI 35-39.9 kg/m^2), and obese class III (BMI ≥ 40.0 kg/m^2) (Table 1.2(1)) (WHO 2000).

Table 1.2(1) BMI categories as defined by The World Health Organisation (WHO 2000)

1.2(2) THE SCOPE OF THE PROBLEM

Obesity has been described as a worldwide epidemic (WHO 2000) and as such is a common and increasing problem in Australia and internationally (AIHW 2001; WHO 2000). The World Health Organisation reported that in 2005, approximately 1.6 billion adults around the globe were overweight and at least 400 million obese (WHO 2000). It is estimated that by 2015, 2.3 billion adults will be overweight and more than 700 million obese (WHO 2000). The National Health surveys of Australian adults have published measured BMI data, the most recent for 2007-8, in which 25% of adults were identified as obese and a further 37% overweight (AIHW 2001). When considering sex specific differences, 55% of females and 68% of males were either overweight or obese (AIHW 2001). Figures are similar in other developed countries, with 66% of adults in the United States (Flegal et al 2010), and almost 62% of adults in the United Kingdom either overweight or obese (Craig et al 2008).

National Australian data indicates rates of overweight and obesity to have increased from 1995 by 4% in males (64% to 68%) and 6% in females (49% to 55%) (AIHW 2001). In their Australian population survey from 2000, Cameron reported the prevalence of obesity to have doubled from the previous survey in 1980, from 7.4% to 18% (Cameron et al 2003), being particularly evident among women of reproductive age. Specifically, for women aged 25 to 44 years, 23.5% were overweight, with a further 15.5% obese (Cameron et al 2003). The Australian Longitudinal Study of Women's Health has indicated that young women (18-23 years) recruited in 1996 had gained on average 6.2kg over the following 8 years to 2004, the largest weight gain per age group (Adamson et al 2007). Furthermore, women gaining weight reported declining physical health compared with women whose weight remained stable (Adamson et al 2007).

1.2(3) OVERWEIGHT AND OBESITY AND WOMEN'S HEALTH

Overweight and obesity have important consequences for physical, mental and social health, with the WHO recognising obesity as the sixth most significant cause of ill health worldwide (WHO 2000). Adults who are obese report poorer health and lower quality of life than individuals of normal weight (AIHW 2001), including type 2 diabetes, ischaemic heart disease, hypertension, cerebrovascular disease, gall bladder disease and obstructive sleep apnoea (AIHW 2001; Haslam et al 2005). Obesity increases the risk of depression, osteoarthritis and many cancers, being cited as one of the most important preventable causes of malignancy (Haslam et al 2005).

While the common problems of overweight and obesity are associated with poor health for both women and men, the impact is more pronounced among obese women, who are more likely to report diabetes, high blood pressure and only poor or fair health, when compared with obese men (AIHW 2001).

When compared with women of normal BMI, women who are obese have an increased prevalence of diabetes (8.7% compared with 2.2%) (AIHW 2001), heart or circulatory conditions (38.8% compared with 23.8%) (AIHW 2001), high blood pressure (28.3% compared with 11.8%) (AIHW 2001) and high blood cholesterol (12.1% compared with 7.6%) (AIHW 2001). As BMI increases, so does the risk of all of these associated morbidities (AIHW 2001).

There is a well documented association between overweight and obesity and reduced fertility in women. When compared with women of normal BMI, overweight women experience a significantly longer time to conceive (Wise et al 2010), which persists even in the presence of a regular menstrual cycle (Gesink Law et al 2007). Obesity is strongly linked to polycystic ovarian syndrome (PCOS) and its associated endocrine disturbances including insulin resistance (Sam 2007). Furthermore obese women with PCOS who require fertility treatment have a reduction in cumulative pregnancy rates (Pettigrew et al 1997).

1.3 OVERWEIGHT AND OBESITY DURING PREGNANCY AND CHILDBIRTH

1.3(1) THE SCOPE OF THE PROBLEM

Studies published to date have used a range of methods to establish BMI in pregnancy, reliant on either documented pre-pregnancy weight, a self reported pre-pregnancy weight, or recorded weight in the first trimester of pregnancy. As there is very little reported change in maternal weight or BMI during the first trimester (Fattah et al 2010), calculation of BMI during pregnancy should use a recorded weight in the antenatal clinic, rather than relying on a self reported pre-pregnancy weight (RCOG March 2010).

In South Australia, since 2008, the calculation and recording of BMI (from an accurately measured height and weight) in early pregnancy is recommended in the local antenatal care guidelines (South Australian Perinatal Practice Workgroup 2010). Increased uptake of this practice should allow improved data collection and correlation with health outcomes (Chan et al 2011).

Estimates from an Australian tertiary hospital indicate that 34% of pregnant women are overweight or obese (Callaway et al 2006). More recent South Australian statewide data confirms that approximately 50% of pregnant women are overweight or obese (Chan et al 2011). These data are however limited, with an early pregnancy BMI reported for only 70% of confinements (Chan et al 2011).

Obesity in pregnancy increases a woman's risk of a range of pregnancy complications that impact on both maternal and fetal health (Table 1.3(1)). Pregnancy complications include those related to pre-existing disease processes that are associated with increased BMI, including diabetes, hypertension and high cholesterol (AIHW 2001).

The current trend for increasing maternal age and its concomitant health risks is also likely to significantly compound those associated with obesity, as older women are more likely to be overweight or obese (Adamson et al 2007; Cameron et al 2003).

There have been conflicting reports on the risk of spontaneous miscarriage in women who are overweight or obese (Hamilton-Fairley et al 1992; Turner et al 2010). While some authors suggest an increased risk of pregnancy loss (Hamilton-Fairley et al 1992), this is not universally reported. More recent prospective data indicates that in the presence of a sonographically confirmed viable gestation, the risk of early miscarriage is not increased with increasing BMI (Turner et al 2010).

The risks of adverse maternal and infant outcomes associated with high BMI in pregnancy have been consistently associated and directly related to BMI category, the risks increasing with increasing BMI (Abenhaim et al 2007; Callaway et al 2006; Cnattingius et al 1998 ; Dodd et al 2011a).

Table 1.3(1) Increased risk of adverse maternal outcomes in overweight and obese pregnant women compared with women of normal BMI

Outcome	Estimate of increased risk	Reference
Gestational diabetes	7.5 times	*(Callaway et al 2006; Dodd et al 2011a; LaCoursiere et al 2005; Sebire et al 2001)*
Hypertensive disorders	5.0 times	*(Athukorala et al 2010; Callaway et al 2006; Ness et al 1996; Sebire et al 2001; Sibai et al 1995; Wolfe 1998)*
Antenatal admission	2.0 times	*(Doherty et al 2006)*
Preterm birth	2.1 times	*(Callaway et al 2006; Cnattingius et al 1998; Dodd et al 2011a; Rosenberg et al 2003)*
Induction of labour	2.4 times	*(Athukorala et al 2010; Dodd et al 2011a; Doherty et al 2006; Sebire et al 2001; Usha Kiran et al 2005)*
Caesarean section	2.9 times	*(Athukorala et al 2010; Callaway et al 2006; Dodd et al 2011a; LaCoursiere et al 2005; Nohr et al 2005; Usha Kiran et al 2005)*
Instrumental birth	1.7 times	*(Dodd et al 2011a)*
Postpartum haemorrhage	1.7 times	*(Dodd et al 2011a; Doherty et al 2006)*
Maternal infection	2.0 times	*(Abenhaim et al 2007; Callaway et al 2006; Dodd et al 2011a)*

There is an increased risk of hypertensive disorders of pregnancy, including pre-existing hypertension, gestational hypertension and pre-eclampsia, (Athukorala et al 2010; Callaway et al 2006; Dodd et al 2011a; Doherty et al 2006), pre-eclampsia being up to five times more common in overweight and obese women (Abenhaim et al 2007; Athukorala et al 2010; Callaway et al 2006; Cedergren 2004; Dodd et al 2011a; Doherty et al 2006; Kabiru et al 2004; Rosenberg et al 2003; Sebire et al 2001). Women who are overweight or obese are more likely to require treatment and hospital admission in the antenatal period for hypertensive and other conditions (Callaway et al 2006; Doherty et al 2006).

Whilst already at increased risk of pre-existing diabetes, overweight and obese women have an increased risk of developing gestational diabetes (Abenhaim et al 2007; Kabiru et al 2004; Rosenberg et al 2003; Sebire et al 2001). Australian data consistently demonstrate an increased risk of gestational diabetes for women who have an increased pre-pregnancy or early pregnancy BMI, with an odds ratio of up to 7.0, increasing with BMI category, (Callaway et al 2006; Doherty et al 2006). Gestational diabetes itself is a risk factor for accelerated fetal growth and macrosomia (Crowther et al 2005), and will be discussed further subsequently.

Women who are overweight or obese have an increased risk of preterm birth (Callaway et al 2006). However, this predominantly reflects an increase in iatrogenic preterm birth rather than preterm birth due to spontaneous labour (Dodd et al 2011a; Torloni et al 2009).

In addition to the risk of medical complications, obesity and overweight are related to numerous practical difficulties during pregnancy. These include the challenges present during ultrasound scanning, performance of invasive prenatal testing and in the clinical assessment of fetal growth, fetal lie and presentation (Aagaard-Tillery et al 2010; Dashe et al 2009).

Women who are overweight or obese are more likely to require induction of labour (IOL) the risk increasing 1.2 fold for women who are overweight, and up to 1.7 times for women who are obese, when compared with women of normal BMI (Dodd et al 2011a; Doherty et al 2006). When compared with women of normal BMI, women who are overweight or obese are less likely to achieve spontaneous vaginal birth (Abenhaim et al 2007; Callaway et al 2006; Cedergren 2004; Dodd et al 2011a; Doherty et al 2006; Rosenberg et al 2003; Sebire et al 2001). In contrast, women of increasing BMI are more likely to require both instrumental vaginal birth and caesarean section (Cedergren 2004; Dodd et al 2011a). Women who are overweight have a 1.2 to 1.6 times increased risk of caesarean birth, increasing to 1.6 to 2 fold for women who are obese when compared with women of normal BMI (Athukorala et al 2010;

Dodd et al 2011a). Overweight and obesity are estimated to contribute to approximately one in every seven caesarean sections (LaCoursiere et al 2005).

Women who are overweight or obese are reported to be at increased risk of postpartum haemorrhage (Cedergren 2004; Doherty et al 2006; Sebire et al 2001), although this may in part reflect the increased risk of IOL, operative vaginal birth and caesarean section (Dodd et al 2011a). Other post partum complications, including wound infection, genital tract infection (Sebire et al 2001) and an increased length of postnatal stay (Callaway et al 2006; Doherty et al 2006) are more common among women who are overweight or obese. Women who are overweight or obese prior to pregnancy are less likely to successfully initiate or continue breastfeeding (Kehler et al 2009; Nohr et al 2009).

1.3(2) IMPLICATIONS FOR INFANT HEALTH AND BEYOND

Infants born to women who are overweight or obese are at increased risk of adverse health outcomes, (Table 1.3(2)), compared with infants born to women of normal weight. The risk of perinatal death including stillbirth and neonatal death is increased by up to three times (Cedergren 2004; Cnattingius et al 1998; Kristensen et al 2005; Nohr et al 2005; Sebire et al 2001). Other risks include the presence of congenital anomalies, particularly congenital heart disease and neural tube defects, neonatal hypoglycemia and admission to neonatal intensive care (Abenhaim et al 2007; Callaway et al 2006; Doherty et al 2006; Rosenberg et al 2003; Sebire et al 2001).

The spectrum of adverse birth outcomes in infants born to women who are obese or overweight in pregnancy is similar to that seen in infants of women with pre-pregnancy diabetes. It has been proposed that the mechanisms of complications such as congenital anomalies may be similar to that thought to be acting in pregnancies affected by diabetes and include impaired glucose tolerance, folate and other nutrient deficiencies and an altered inflammatory state (Huda et al 2010). Large for gestational age (LGA) infants are commonly reported to be associated with maternal overweight and obesity (Abenhaim

et al 2007; Cedergren 2004; Rosenberg et al 2003; Sebire et al 2001). Infants of women who are overweight are 1.3 to 1.5 times more likely to be LGA, the risk increasing further to 1.6 to 2.1 times for women who are obese (Dodd et al 2011a). Infants who are LGA or macrosomic have an increased risk of shoulder dystocia and its subsequent complications, in addition to neonatal hypoglycemia (Henriksen 2008).

Table 1.3(2): Increased risk of adverse infant outcomes in overweight and obese pregnant women compared with women of normal BMI

Outcome	Estimate of increased risk	Reference
Congenital anomaly	3.4 times	*(Callaway et al 2006; Cnattingius et al 1998; Rosenberg et al 2003)*
Perinatal loss	3.0 times	*(Callaway et al 2006; Nohr et al 2005; Sebire et al 2001; Usha Kiran et al 2005)*
Macrosomia	2.4 times	*(Abenhaim et al 2007; Athukorala et al 2010; Cedergren 2004; Cnattingius et al 1998; Dodd et al 2011a; Rosenberg et al 2003)*
NICU admission	2.8 times	*(Callaway et al 2006; Cnattingius et al 1998; Dodd et al 2011a; Rosenberg et al 2003)*
Neonatal hypoglycaemia	2.0 times	*(Callaway et al 2006; Doherty et al 2006)*

The effect of increasing maternal BMI on fetal growth restriction is less clear. The majority of studies reported to date do not suggest an increase in the risk of impaired fetal growth or small for gestational age (SGA) infants among women who are overweight or obese (Abenhaim et al 2007; Cnattingius et al 1998; Dodd et al 2011a; Sebire et al 2001). Inadequate fetal growth, resulting in fetal growth restriction is a significant contributor to perinatal mortality and morbidity (Baschat et al 2001; Gardosi et al 1998) with further implications for longer term child and adult health (Barker 2007).

The concept that in-utero events may determine subsequent health has been termed the "early origins of health and disease" or "Barker Hypothesis", after Professor David Barker and colleagues who conducted the initial underpinning epidemiological research. Under this hypothesis (Hales et al 2001), the fetus responds to an adverse intrauterine environment by reducing its growth, which subsequently allows preservation of energy for essential development. The adaptations to a nutritionally poor environment (Gluckman et al 2005; Gluckman et al 2004a; Hales et al 2001; 2001) are associated with an increased risk of a group of related conditions termed the metabolic syndrome, including hypertension, insulin resistance and diabetes, central obesity and dyslipidaemia (Haller 1977; Phillips 1978).

The effect of infant birthweight on the subsequent development of diabetes is evident not only in individuals of low birthweight, but it is increasingly recognized that the relationship between birthweight and insulin resistance is in fact U-shaped (Armitage et al 2005; Gluckman et al 2004a, 2004b; Osmond et al 2000). Thus high infant birthweight is linked to childhood obesity, adult insulin resistance and type 2 diabetes, an effect possibly mediated by gestational diabetes (Armitage et al 2005; Gluckman et al 2004a, 2004b; Osmond et al 2000), in addition to other factors.

1.3(3) THE EFFECT OF GESTATIONAL WEIGHT GAIN IN WOMEN WHO ARE OVERWEIGHT OR OBESE ON MATERNAL AND INFANT HEALTH

Generally, the reported risks of adverse maternal and infant health outcomes in the literature have not been adjusted for maternal weight gain during pregnancy. Gestational weight gain exerts an effect that is independent of maternal BMI (Cedergren 2006; Kiel et al 2007; Oken et al 2009). Gestational weight gain contributes to post partum weight retention, which in turn has significant implications for maternal health, including future pregnancies (Villamor et al 2006).

The Institute of Medicine (IOM) report on nutrition in pregnancy (IOM 2009) notes that most observational studies of weight gain in pregnancy report average gains of 10 to 15 kg (Edwards et al 1996; Kiel et al 2007). However, gestational weight gain appears to be more variable among women who are overweight or obese when compared with women of normal BMI (Health. 2007; Pettigrew et al 1997). In contrast, some studies have shown reduced gestational weight gain in women of higher BMI categories when compared with women with a normal BMI (Cedergren 2006), extending even to weight loss (Edwards et al 1996).

The IOM guidelines for optimal gestational weight gain were initially published in 1990, and have focused primarily on the prevention of preeclampsia and low birthweight infants (IOM 1990). The updated IOM recommendations, released in 2009, have incorporated an upper limit for gestational weight gain in women who are overweight or obese, and utilised World Health Organisation BMI categories (NRC 2007; WHO 2000) (Table 1.3(3)). While the risk of adverse maternal and infant health outcomes have been considered in the preparation of the IOM recommendations (IOM 2009), they are limited to the examination of outcomes as they relate to maternal BMI in population based cohort studies.

Table1.3(3) Updated IOM Recommendations for Total Weight Gain Range During Pregnancy, by Pre-pregnancy BMI (IOM 2009)

There is a clear association between gestational weight gain and health outcomes during pregnancy and childbirth. Cedergren and colleagues utilized Swedish population–based data to evaluate the effect of gestational weight gain on pregnancy outcomes for over 200,000 women of all BMI categories (Cedergren 2006, 2007). For women who were overweight or obese, gestational weight gain above 16 kg was associated with an increased risk of pre-eclampsia, gestational diabetes, operative birth and high infant birthweight. While restricting weight gain to less than 8 kg was associated with a reduction in both pregnancy complications and large for gestational age infants, it occurred at the expense of an increase in growth restriction and small for gestational age infants (Cedergren 2006, 2007).

Keil and colleagues report similar findings from a US based population cohort of 120,000 overweight or obese pregnant women (Kiel et al 2007). In this study, the "optimal" amount of gestational weight gain varied by subclass of obesity, in terms of lowest observed risk of perinatal complications (Kiel et al 2007). Specifically, the lowest risk of complications occurred with gestational weight gain between 4.5 and 11.5 kg in women with BMI 30 to 34.9 kg/m^2; 0 to 4 kg for women with BMI 35 to 39.9 kg/m^2; and weight loss of up to 4kg for women with BMI $\geq$ 40kg/m^2 (Kiel et al 2007). While weight loss for women in obesity subclass III may be associated with reduced risks of perinatal complications, it appears to be at the expense of an increased risk of SGA (Cedergren 2006, 2007; Kiel et al 2007).

Gestational weight gain exerts a clear effect on longer term maternal and infant outcomes. Oken's report from the Project Viva cohort in the United States confirms that when considering adverse outcomes (including childhood obesity and maternal post partum weight retention) simultaneously, optimal gestational weight gain for women who are obese pre-pregnancy is lower than the currently recommended 0 to 6 kg range, with the lowest prevalence of adverse outcomes for obese women in their study occurring with gestational weight loss (Oken et al 2009).

The optimal amount of gestational weight gain for women who are overweight or obese is likely to represent a compromise between potential benefits and harms of both short term and long term maternal and infant outcomes. The effect of differing amounts of gestational weight gain on such outcomes should be evaluated in a randomised controlled trial.

1.4 EFFECT OF OVERWEIGHT AND OBESITY ON FETAL GROWTH

1.4(1)MECHANISMS FOR FETAL GROWTH IN MATERNAL OVERWEIGHT AND OBESITY

There are similarities between the metabolic disturbances associated with overweight and obesity in pregnancy, and diabetes in pregnancy (Heerwagen et al 2010). This likely reflects the complex relationship and shared pathophysiology of obesity and gestational diabetes. Both women with diabetes or overweight and obesity in pregnancy have similarly increased risks of large for gestational age infants and it has been reported that infants born to women with both conditions have abnormal metabolic profiles including insulin resistance (Catalano et al 2009). While fetal growth in the context of diabetes in pregnancy has been more commonly described in the literature, than in relation to overweight and obesity, it may be a reasonable model for the changes that occur with increasing maternal BMI.

There are a number of proposed mechanisms by which maternal overweight and obesity contribute to altered fetal growth and its consequences. In addition to the normal changes in glucose metabolism which occur during pregnancy, both maternal glucose intolerance and gestational diabetes are associated with further reductions in peripheral insulin sensitivity resulting in increased glucose availability to the fetus (Lain et al 2006). Both maternal glucose and insulin concentrations are positively associated with fetal size. Aside from direct fetal overnutrition, placental transport of nutrients is up-regulated, and the metabolic environment may influence tissue gene expression both in the placenta and the fetus (Freeman 2010). In addition to the changes that occur in lipid metabolism in normal

pregnancy, obesity in pregnancy is associated with a further increase in very low density lipoprotein cholesterol and triglyceride concentrations although low density lipoprotein cholesterol and total cholesterol concentrations are similar (Huda et al 2010).

Maternal gestational diabetes is also associated with increased lipid concentrations, fatty acid and triglyceride concentrations being correlated with fetal size (Lain et al 2006). The intrauterine environment in overweight and obesity is therefore similar to that described in association with diabetes, with evidence of abnormal lipid and carbohydrate metabolism and inflammatory status (Catalano et al 2009; Freeman 2010). From the limited literature available, body composition and insulin sensitivity appear similar in infants born to women with diabetes and obesity (Catalano et al 2009; Freeman 2010).

1.4(2) MATERNAL OVERWEIGHT AND OBESITY AND FETAL GROWTH TRAJECTORIES

To date, few studies have prospectively examined fetal growth with ultrasound in women who are overweight or obese. With a paucity of data describing the effect of maternal BMI on fetal growth, our current knowledge is derived from study populations with mixed BMI and varying levels of glucose intolerance. Although limited, the currently available literature suggests that maternal BMI has an important effect on fetal growth as early as 24 weeks, with the effect increasing with increasing BMI.

Ay and colleagues reported estimated fetal weight (EFW) Z-scores (standard deviation (SD) scores) throughout pregnancy from a prospective population based cohort study in the Netherlands (Ay et al 2009). The study included 8231 women, with the mean BMI of the population 24.5 kg/m^2 (SD 4.4). When compared with babies born to women of normal BMI, babies born to women with the highest BMI were noted to have significantly increased EFW Z-scores and EFW growth rates from as early as 24 weeks (Ay et al 2009).

Similarly in Schaefer–Graf's retrospective study including women of all BMI categories who were diagnosed with gestational diabetes or impaired glucose tolerance, maternal BMI exerted a significant influence on fetal growth, predominantly in the second trimester (Schaefer-Graf et al 2003). Whilst the significant effect of maternal obesity on growth was greatest in mid-pregnancy, maternal glycemia was a more significant influence in the late third trimester (Schaefer-Graf et al 2003).

In contrast, others have reported maternal overweight and obesity to have no significant effect on fetal growth trajectories (Hure et al 2011; Wong et al 2006). In a small study from an Australian tertiary maternity unit (Wong et al 2006), ultrasound was used to assess fetal growth from 18 weeks gestation in 174 women with diabetes (Wong et al 2006). The mean maternal BMI of the cohort was 27.8 kg/m^2 (SD 7.2) (Wong et al 2006). Fetal growth velocities for all fetal growth measures (biparietal diameter, abdominal area and femur length) were significantly higher than the reference normal values (Owen et al 1996) from 26 weeks onwards (Wong et al 2006). Maximal growth rates for women with diabetes for all parameters were seen at 32-34 weeks, with an accelerated growth rate when compared with the normal population evident until 38 weeks. While there was no demonstrated effect of maternal overweight or obesity on any of the biometric growth velocities (Wong et al 2006), the study is limited by the relatively small sample size.

Similar results have been reported from another Australian cohort (Hure et al 2011) of women from Newcastle, that examined pre-pregnancy weight and weight throughout pregnancy as predictors of fetal growth and fetal body composition in women of all BMI categories. Although a relatively small number of women with BMI ≥ 25 kg/m^2 were included (n=70), in this cohort pre-pregnancy weight was not found to be associated with fetal abdominal circumference (Hure et al 2011). However, GWG above the IOM recommended range was associated with increased BPD and AC growth, but not HC and FL growth at 36 weeks (Hure et al 2011).

As can be appreciated, very few women with high BMI or normal glucose tolerance have been included in existing prospective studies of fetal growth. It therefore remains unclear to what extent the differences in growth velocities observed to date reflect maternal diabetes, maternal BMI, or high gestational weight gain, acting alone or in combination.

The effects of high pre-pregnancy BMI on fetal growth as assessed by ultrasound have not been described in a large cohort of women in a prospective manner.

It is not clear how BMI category and gestational weight gain modify fetal growth parameters and growth velocities over the course of pregnancy.

1.5 ULTRASOUND PREDICTION OF MACROSOMIA AND CLINICAL OUTCOMES

Accelerated fetal growth may be defined using a weight threshold or a percentile threshold relative to gestational age. When defined relative to gestational age, the term large for gestational age (LGA) is used, referring to a fetus with an estimated weight above the 90th, 95th or 97th percentile (Hoffman et al 1974). Other authors may include in their definition an abdominal circumference greater than the 90th, 95th or 97th percentile for gestational age, as this measurement is thought to be a more sensitive marker of fetal growth (Hoffman et al 1974; Wong et al 2001). Macrosomia is often used synonymously to refer to an infant above a certain percentile or weight threshold. In the context of a pregnancy affected by diabetes it is used to refer specifically to the pattern of fetal overgrowth in the setting of fetal hyperglycemia, resulting in the stimulation of insulin, insulin-like growth factors, growth hormone, and other growth factors, which, in turn, stimulate fetal growth and deposition of fat and glycogen (Pedersen 1967). When used to refer to a fetus or neonate above a specific weight, thresholds range from 4000g

to 5000g (Boyd et al 1983). Infant macrosomia is more common in women with obesity (Dodd et al 2011a) and diabetes (Ju et al 2008; Sewell et al 2006).

In an effort to develop tools that may assist clinicians to reliably identify women at potential risk of adverse perinatal and maternal complications associated with infant macrosomia, various authors have evaluated the predictive value of ultrasound measures of fetal growth.

High infant birthweight, both in women with and without diabetes appears to be associated with a significant divergence from normal in fetal growth parameters and velocities from early in pregnancy. In a small study from Italy, infants were categorised by birthweight into three tertiles after undergoing serial ultrasounds from 12 to 40 weeks (Milani et al 2005). Both AC measures and AC growth velocity were significantly different between the lower and upper tertile from the second trimester (Milani et al 2005). Similarly, differences in fetal growth amongst infants whose mothers have pre-pregnancy diabetes have been documented to occur from early in the second trimester (Wong et al 2002). In this study, infants born large for gestational age (birthweight greater than the 90th percentile), recorded significantly greater AC Z-scores from 18-22 weeks, when compared with infants of normal birthweight, the difference increasing as pregnancy progressed, from 0.68 at 18-22 weeks to 1.96 at 34-38 weeks (Wong et al 2002). Although the mean BMI of this group of 100 women was in the overweight range, the small numbers of overweight and obese women included in both studies (Milani et al 2005; Wong et al 2002) highlight the lack of prospectively collected information evaluating associations between fetal growth and infant birthweight in this population of pregnant women.

The recognition of apparently altered fetal growth patterns in macrosomic or large for gestational age infants has led to the investigation of fetal growth parameters (both static measures and growth velocities) in the prediction of macrosomia and its associated adverse birth outcomes. Some authors have utilised likelihood ratios to evaluate the diagnostic accuracy of both EFW and AC measures in the

prediction of fetal macrosomia. Likelihood ratios are thought to be preferable to the commonly used concepts of sensitivity and specificity in the assessment of the clinical value of a test, as they assist in evaluating the likelihood of presence or absence of a condition when the test result is known to be positive or negative. A likelihood ratio indicates by how much a given test result will increase or decrease the probability of having the condition that the test is designed to predict. It is recommended that by utilising well accepted criteria for the usefulness of a test based on likelihood ratios, authors of studies evaluating diagnostic tests can more meaningfully and objectively summarise the findings of their research and minimise overstating their study findings and claiming conclusions that are not supported by their data (Jaeschke et al 1994; Khan et al 1999).

In 2005 Coomarasamy and colleagues reported results of their systematic review assessing the diagnostic accuracy of EFW and AC measures in the prediction of macrosomia (Coomarasamy et al 2005). Using a predefined protocol and Cochrane methodology, the authors identified and included 36 studies involving 19,117 women that met their inclusion criteria. Studies were included if accuracy of ultrasonographically determined EFW or AC was evaluated for predicting macrosomia. Summary likelihood ratios (LR) were calculated for each test threshold. If EFW was greater than the 90th percentile the positive LR for birthweight greater than the 90th percentile was 9.3 (95% CI 3.7–24.0) and the negative LR 0.37 (95% CI 0.14 – 0.93) (Coomarasamy et al 2005). For a fetal abdominal circumference measure of 36 cm, the positive LR for predicting a birthweight over 4000 g was 6.9 (95% CI 5.2 to 9.0) and the negative LR 0.37 (95% CI 0.30–0.45) (Coomarasamy et al 2005). The findings of this study suggest ultrasound derived EFW (above 4000g or the 90th percentile) is superior to that of AC in predicting high birthweight. It is unclear from Coomarasamy's report if the studies that contributed to their quantitative synthesis of the literature included a significant number of women with high BMI. High maternal BMI is likely to negatively influence the ability of ultrasound to accurately assess fetal weight and the relevance of Coomarasamy's findings to an overweight and obese population is uncertain.

Smaller studies published since the systematic review by Coomorasamy have provided conflicting information regarding the reliability of currently available methods of assessing fetal weight to predict infant birthweight. A small retrospective study of 350 term singleton fetuses from Germany reported EFW to correctly identify only 38% of infants with weight above 4000g (Hoopmann et al 2010). Furthermore, the sensitivity decreased with increasing birthweight to only 27% where birthweight was greater than 4500g (Hoopmann et al 2010). In contrast, the findings of Kernaghan and colleagues from the United Kingdom suggest that an ultrasound EFW Z-score of greater than 1.7 (equivalent to greater than the 95th percentile) had a sensitivity of 80% and specificity of 72% for predicting birthweight greater than the 95th percentile (Kernaghan et al 2007). The improved sensitivity for detecting high birthweight is promising but both studies may be of limited relevance to women with overweight and obesity as neither study report maternal BMI.

As can be appreciated, a single ultrasonographic estimate of fetal size may not be a sensitive measure for the detection of disturbances of fetal growth, these parameters providing little insight into fetal growth velocity. Fetal weight may be within the "normal" range for gestational age, and a fetus may still be growing at a rate above or below its growth potential.

Fetal growth velocity standards were first derived by Owen and colleagues from a population of 274 women with low risk pregnancies in Scotland (Owen et al 1996). Several authors have routinely compared growth velocities with this reference population (Kernaghan et al 2007; Wong et al 2006).

In Kernaghan's study of fetal growth in 242 women with varying degrees of impaired glucose tolerance, fetal growth velocities were examined to assess their value in predicting birthweight greater than 95th percentile (Kernaghan et al 2007). The optimum fetal growth velocity Z-score of greater than 1.7 revealed a sensitivity of 35% and specificity of 75% (Kernaghan et al 2007), again implying limited usefulness in predicting high birthweight.

As described previously, Kernaghan and colleagues evaluated the role of ultrasound EFW in prediction of infant birthweight above the 95th percentile, and additionally, constructed Receiver Operator Characteristic (ROC) curves to evaluate test characteristics for fetal growth velocity (Kernaghan et al 2007). Although EFW predicted high birthweight with a sensitivity of 80%, none of the antenatal growth characteristics identified were sufficiently sensitive or specific in their prediction of neonatal hypoglycaemia (Kernaghan et al 2007). No additional clinical outcomes were measured.

Other authors have used more complex equations and modelling to identify a useful predictor of abnormal fetal growth (Salomon et al 2005). Salomon's study of 356 unselected pregnant women, conducted in France, collected biometric data at three time points; 11-14 weeks', 20-24 weeks' and 30-34 weeks' gestation (Salomon et al 2005). The best test value cut off only yielded a sensitivity of 53% but a higher specificity of 89% in predicting birthweight above the 90th percentile (Salomon et al 2005).

As can be appreciated from the current literature, there is a clear need to not only describe fetal growth patterns in women who are overweight and obese in pregnancy but also assess the ability of third trimester ultrasound to predict high infant birthweight and important maternal and infant outcomes. When attempting to understand how ultrasound in the third trimester might assist in predicting clinical outcomes aside from birthweight, the literature is also sparse.

It is not clear how accurately ultrasound measures of fetal growth in late pregnancy are associated with or predict high infant birthweight in women who are overweight or obese.

1.6 FETAL AND NEONATAL BODY COMPOSITION.

Infant birthweight is routinely recorded in clinical practice, but provides only a gross estimate of body composition. Just as BMI and body weight in an adult population may not be sensitive markers of

adiposity, birthweight and ponderal index in the neonate do not provide information about the relative contribution of fat and lean mass to body composition which may be more important than birthweight in determining health and clinical outcomes, including childhood obesity.

Neonatal body composition has been examined in an attempt to characterise the relative contributions of fat and lean body mass, and has been utilised to gain insight into fetal growth. In simple terms, lean body mass is thought to be predominantly influenced by genetic factors, whilst the maternal environment is the main influence on fat mass (Sewell et al 2006; Sparks 1984). However, the relationship between fat and lean components of body mass and variations in the in-utero environment are likely to be far more complex.

The effect of maternal obesity on lifelong metabolism of the infant is thought to be mediated during fetal development, through alterations in insulin resistance, glucose and fatty acid metabolism. Skeletal muscle comprises up to 50% of total body mass in the fetus and infant, is an insulin responsive tissue and as such is a major site for glucose and fatty acid metabolism (Du et al 2010). After birth, there is no increase in muscle fibre numbers, and it has therefore been proposed that poor fetal skeletal muscle development may result in impaired fatty acid and glucose metabolism later in life (Du et al 2010). In fetal life, mesenchymal stem cells in fetal muscle are able to differentiate into adipocytes, fibroblasts and myocytes (Du et al 2010). It is postulated that maternal obesity mediates an increase in fetal inflammatory markers which contributes to enhanced adipogenesis (Du et al 2010), resulting in skeletal muscle becoming more insulin resistant in fetal and later life (Du et al 2010). Adipose tissue development in the fetus is influenced by nutrient supply, adipocytokines and other transcription factors. In turn, adipocytokines produced by adipose tissue including leptin and adiponectin exert effects on the metabolism and function of muscle and liver (Briana et al 2010).

Neonates with overgrowth secondary to maternal diabetes and with growth restriction have been shown to have increased adiposity (Catalano et al 2003; Galan et al 2001; Padoan et al 2004). In an attempt to better characterise early growth and their variants, various techniques have been developed to measure neonatal body composition. Catalano and colleagues established a method for assessing neonatal fat and lean mass using skin fold measurements (Catalano et al 1992). Their initial studies indicated that in normal healthy term neonates, fat constitutes only 12% to 14% of birthweight, but accounts for 46% of the variance in birth weight (Catalano et al 1992).

High maternal BMI is thought to be associated with an increase in fat mass of the neonate, resulting in the often observed increase in birthweight (Catalano et al 2003; Neggers et al 1995; Sewell et al 2006). In Sewell's study from the United States (Sewell et al 2006) neonatal anthropometry and total body electrical conductivity (TOBEC) estimates of body composition were obtained within 72 hours of birth in 220 term infants. Infants born to women who were overweight or obese were significantly more likely to be macrosomic, an effect likely mediated by the observed increase in fat mass and percentage body fat seen in these infants (Sewell et al 2006). Similarly, all skin fold measures were increased in neonates born to overweight and obese women, being significantly higher compared with the neonates of women with normal BMI (Sewell et al 2006). From this study, and other previous small studies (Catalano et al 2003; Neggers et al 1995) it is apparent that the increase in birthweight noted in women of high BMI is predominantly mediated by increased fat mass.

Even when birthweight remains unchanged, the relative contribution of fat and lean mass seems to be modified by increased maternal BMI. Hull and colleagues compared body composition (as measured by PEAPOD) in infants born to overweight and obese women with infants born to women with normal BMI (Hull et al 2008). Whilst the infants were of similar birthweight, those of overweight and obese women had significantly greater percentage of fat mass and total fat mass, and significantly less fat free mass (Hull et al 2008). The results of this study, suggest that in addition to, or independent of birthweight

differences, increases in fat mass are associated with maternal obesity and as such may be important mediators of later health. The contribution of maternal BMI to lean components of neonatal body composition is less clear. The need to further understand and characterise differences in fetal and neonatal growth, initially limited to studies of neonatal body composition led to the development of ultrasound techniques in this area. As an extension of many studies into neonatal body composition, mostly in relation to maternal diabetes (Catalano et al 2009; Catalano et al 2003; Catalano et al 1992), Bernstein and others developed techniques to characterise fetal body composition (Bernstein et al 1991; Gardeil et al 1999). The development of ultrasound technology with improvements in resolution has allowed ultrasonographic assessment of fetal body composition. It had been proposed that measuring fetal lean and fat mass would be a more sensitive marker of fetal growth and many of the initial studies focused on the accretion of fetal fat mass in women with diabetes during pregnancy (Bethune et al 2003; Greco et al 2003). More recently these measures have been investigated with the aim of improving the identification of not only large, but also small for gestational age infants (Gardeil et al 1999).

In subsequent studies of fetal body composition involving pregnancies in both low-risk and diabetic women, ultrasound measures of fetal body composition including fetal anterior abdominal wall thickness, “mid-femur fat area” and “mid-thigh lean area” were found to be well correlated with their neonatal equivalents of fat and lean mass respectively (Bernstein et al 1991; Bernstein et al 1997). Although still commonly reported in the literature, measures of humeral fat and lean mass do not seem to correlate well with neonatal body composition measures (Bernstein et al 1991; Bernstein et al 1997).

Fetal body composition measures that have been most frequently examined to date include subscapular fat mass (SSFM), abdominal wall fat mass (fetal abdominal fat layer) (AFM), mid thigh total mass (MTTM), mid thigh lean mass (MTLM) and mid thigh fat mass (MTFM) (Bernstein et al 1997; Gardeil et al 1999; Higgins et al 2008; Hill et al 1992; Larciprete et al 2008). Before ultrasound measures of fetal

adiposity are advocated for use in routine clinical practice, they should be rigorously assessed, firstly from the point of variability between assessors, and secondly in relation to their clinical value in the target population. In relation to inter-observer agreement, there is limited information published to date in the literature, with assessments involving a small number of women (Bernstein et al 1991; Hill et al 1992; Larciprete et al 2003). Further hampering this assessment of validity are the well recognised and reported technical difficulties that are associated with ultrasound imaging in pregnant women who are overweight or obese.

Inter-observer variability has not been evaluated for commonly used measures of fetal body composition.

Normal ranges for mid-arm fat mass and lean mass (MAFM, MALM), mid-thigh fat mass and lean mass (MTFM, MTLM), abdominal fat mass (AFM) and subscapular fat mass (SSFM), have been published from the prospective study of 218 healthy Italian women by Larciprete and colleagues (Larciprete et al 2003). In conjunction with their study of fetal body composition in healthy pregnant women, the same group of researchers (Larciprete et al 2003) assessed fetal body composition in 85 women with gestational diabetes. Fat mass measures recorded for the fetuses in the gestational diabetes group were significantly higher than in fetuses of women without GDM. Whilst BMI was higher in the group of women with gestational diabetes, it is difficult from this study to differentiate the effect of BMI and diabetes (Larciprete et al 2003).

Similarly, Greco and colleagues demonstrated that pre-gestational diabetes was associated with a significant increase in fetal fat mass measures (Greco et al 2003). In a small study (15 women with type 1 diabetes and 16 matched non-diabetic controls, with a mean BMI of both groups <25 kg/m^2), fetal abdominal wall fat mass and subscapular fat mass was significantly higher for fetuses of women with

diabetes at both 31 and 37 weeks, compared with fetuses of the matched controls. However, the relevance of these findings to obese pregnant women given the small sample size and near-normal BMI of the study groups is unclear (Greco et al 2003).

There is little information available regarding the effect of maternal BMI and gestational weight gain on fetal body composition. Hure and colleagues reported measures of fetal body composition in their recent prospective study of fetal growth amongst women of all BMI categories (Hure et al 2011). Whilst pre-pregnancy weight did not predict body composition (including measures of lean and fat mass), gestational weight gain was identified as a predictor of abdominal lean muscle mass (Hure et al 2011).

As can be appreciated, studies of fetal body composition to date have focused on women with diabetes in pregnancy, have involved only small sample sizes, and include very few women with high BMI. While maternal diabetes may be a reasonable model to describe the effects of high BMI there is limited information available specifically derived from pregnant women who are overweight or obese.

The effect of high maternal BMI on fetal body composition is unclear

As discussed previously, biometric measures of fetal growth may not predict large for gestational age infants or macrosomia. As body composition has been proposed to provide a more sensitive evaluation of nutritional status, measures of fetal fat mass have been proposed as potential predictors of macrosomia, particularly in women with diabetes (Bethune et al 2003; Higgins et al 2008). In Bethune's Australian study, 88 women with gestational diabetes were examined at 28 and 34 weeks gestation (Bethune et al 2003). Fetal AC measures were compared with fetal abdominal wall fat mass at various thresholds to predict birthweight greater than the 90th percentile (Bethune et al 2003). The test with the best positive likelihood ratio was a fetal abdominal wall fat mass of 5mm or above with a positive likelihood ratio of 9.75 (Bethune et al 2003). Despite this, the sensitivity was only 41%. In contrast, the

sensitivity of an AC measurement above the 90th percentile was 76%, with a positive likelihood ratio of 3.19 (Bethune et al 2003).

The utility of the fetal abdominal wall fat mass in predicting fetal weight has been confirmed by the work of Higgins and colleagues who examined fetal abdominal wall fat mass in 125 women with diabetes (Higgins et al 2008). In this study, the use of a raised abdominal wall fat mass measurement (above 3.5 mm at 30 weeks gestation, 4.5 mm at 33 weeks gestation and 5.5 mm at 36 weeks gestation) improved the prediction of birthweight greater than the 90th percentile when compared with use of the AC measurement alone (Higgins et al 2008).

In addition to improving the prediction of high birthweight, the clinical utility of assessing fetal body composition may be enhanced by considering not only sensitivity and positive likelihood ratios but also negative predictive values, which are seldom reported. In their study of fetal abdominal wall thickness in women of all risk profiles, Petrikovsky report that although sensitivity was limited at the majority of cut-off points examined, negative predictive value was high (Petrikovsky et al 1997). The potential value of fetal body composition in excluding a diagnosis of macrosomia or high infant birthweight should therefore be considered.

Maternal and infant outcomes are rarely reported in the currently available literature relating to fetal body composition. In a small cross sectional study of 137 healthy pregnant Irish women, a composite marker of neonatal morbidity (meconium aspiration, hypoglycaemia, hypothermia, poor feeding or jaundice) was significantly associated with measures of fetal subcutaneous fat (Gardeil et al 1999). There is potential for measures of fetal body composition to improve our ability to identify fetuses destined to be macrosomic at birth and subsequent morbidity.

There is a lack of information available regarding the use of fetal body composition for the prediction of birthweight, macrosomia and other maternal and infant outcomes in women who are overweight or obese.

1.7 RESEARCH GAPS IDENTIFIED AND AIMS OF THE FETAL GROWTH STUDY

1.7(1) GAPS IN OUR CURRENT KNOWLEDGE IDENTIFIED FROM THIS LITERATURE REVIEW

- The effects of high pre-pregnancy BMI on fetal growth as assessed by ultrasound have not been described in a large prospective cohort of women.
- It is unclear how BMI category and gestational weight gain modify fetal growth parameters and growth velocities over the course of pregnancy.
- It is unclear how accurately ultrasound measures of fetal growth in late pregnancy are associated with or predict high infant birthweight in women who are overweight or obese.
- Inter-observer variability has not been evaluated for commonly used measures of fetal body composition.
- The effect of high pre-pregnancy maternal BMI on fetal body composition has not been clearly described.
- There is a lack of information available regarding the use of fetal body composition for the prediction of birthweight, macrosomia and other maternal and infant outcomes in women who are overweight or obese.

These identified research gaps led to the design of the studies for this thesis:

The Fetal Growth Study – a prospective cohort study of fetal growth and body composition in overweight and obese pregnant women.

1.7(2) AIMS OF THE FETAL GROWTH STUDY

The aims of The Fetal Growth Study are to assess fetal growth trajectories and body composition in a large prospective cohort of overweight and obese pregnant women.

The Specific Aims of The Fetal Growth Study are:

- To prospectively assess fetal growth, including growth velocities, with standard biometric ultrasound measures in a cohort of overweight and obese women at 20, 28 and 36 weeks' gestation.
- To compare fetal growth in women who are overweight or obese in pregnancy with normal population standards for fetal growth.
- To examine the effect of maternal BMI category and gestational weight gain on fetal biometry and fetal growth velocities.
- To describe the association between and any predictive value of third trimester fetal growth measures and fetal macrosomia in women who are overweight or obese during pregnancy.
- To describe the association between and any predictive value of third trimester fetal growth measures and important clinical maternal and infant outcomes.
- To assess the interobserver variability of measures of fetal body composition.
- To describe fetal body composition prospectively in a large group of overweight and obese women using ultrasound at 28 and 36 weeks of pregnancy and to compare fetal body composition in women who are overweight and obese in pregnancy with normal population standards.
- To describe the effect of BMI category and gestational weight gain on measures of fetal body composition.
- To assess any correlation between measures of fetal body composition and maternal and infant outcomes including infant birthweight.

2. METHODS FOR THE FETAL GROWTH STUDY

2.1 THE LIMIT RANDOMISED TRIAL

The Fetal Growth Study was a prospective cohort study nested within the LIMIT multicentre randomised controlled trial.

The LIMIT trial is an ongoing multi-centre randomised trial, recruiting women from three metropolitan maternity hospitals in Adelaide, South Australia evaluating the effect of limiting gestational weight gain in women who are overweight or obese on maternal and infant health outcomes (Dodd et al 2011b). The protocol for the LIMIT randomised trial has been previously reported (Dodd et al 2011b). Briefly, women with a live, singleton pregnancy who have a BMI ≥ 25 kg/m^2 are recruited between 10^{+0} and 20^{+0} weeks gestation, and randomised to receive either a comprehensive dietary and lifestyle intervention, or to standard care. Exclusion criteria include women with a multiple pregnancy and type 1 or 2 diabetes diagnosed prior to pregnancy. The primary outcome of the LIMIT trial is the occurrence of large for gestational age infants.

Potentially eligible women are identified at the antenatal clinic of participating hospitals (The Women's and Children's Hospital, The Lyell McEwin Hospital and Flinders Medical Centre). A patient information sheet is provided and an explanation of the study given by a research officer. All women are counseled by a research officer and written informed consent obtained. Research and ethics approval was obtained at all three participating hospitals. Women who give informed written consent are randomised to one of two treatment groups of the LIMIT trial by the central telephone randomisation service of the Australian Research Centre for Health of Women and Babies, Discipline of Obstetrics and Gynaecology, The University of Adelaide. Eligible women are randomised and allocated a study number corresponding to either the 'Dietary and Lifestyle Advice Group' or the 'Standard Care Group'.

2.2 SPECIFIC METHODOLOGY FOR THE FETAL GROWTH STUDY

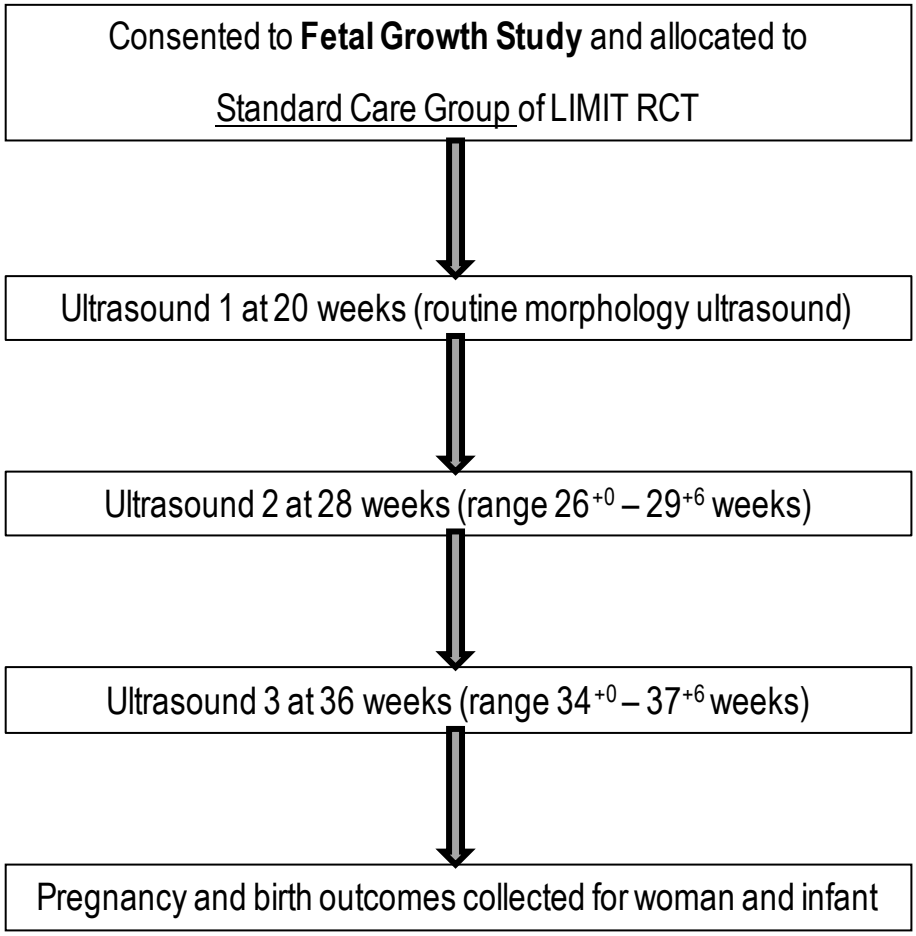
2.2(1) ELIGIBILITY AND STUDY ENTRY

As part of the LIMIT trial protocol, all women were asked to attend for fetal growth ultrasounds. Women were eligible for The Fetal Growth Study if they were allocated to the 'Standard Care Group' of the LIMIT trial. Following recruitment to the LIMIT trial, additional written consent was obtained for the performance of research ultrasounds for The Fetal Growth Study.

At trial entry, maternal booking height, weight and BMI were recorded, in addition to ethnicity, smoking status, parity, public or private health insurance status, details of previous obstetric history, and gestational age at trial entry. Collected data and subject information was entered into a password protected database by a research assistant and indexed through allocated study numbers.

Women who agreed to participate in The Fetal Growth Study were invited to attend for a research ultrasound at approximately 28 (range 26^{+0} – 29^{+6}) weeks and 36 (range 34^{+0} – 37^{+6}) weeks at the hospital providing their antenatal care. Information regarding an accurate estimated date of confinement was confirmed at the time of the woman's first research ultrasound. In addition, where possible, information was collected regarding fetal biometry at the time of routine morphology ultrasound (performed by external providers). If the woman was scheduled for a clinically indicated fetal growth ultrasound within two weeks of the planned Fetal Growth Study research scan, she was encouraged to attend the clinically indicated ultrasound and fetal growth parameters from that ultrasound were extracted from the medical record for use in The Fetal Growth Study. All research ultrasounds were performed by five medical practitioners with specialist or subspecialist level training in obstetric ultrasound. When the woman attended for the research ultrasound scan printed information outlining the fetal growth parameters was provided to her and her caregivers for use in clinical care. Ultrasound measurements were collected from August 2008 to December 2010.

Figure 2.1 (1) Ultrasound measurement time points for The Fetal Growth Study



All women continued to have their clinical care provided by clinicians at their planned hospital of birth. After birth, information was obtained relating to birth and infant outcomes from the case notes by a research assistant. Postnatal and neonatal data forms were completed for each live born infant after discharge from hospital. Outcomes were collected at the time of primary hospital discharge postnatally or at 6 weeks post-partum, whichever was greater.

2.2(2) ULTRASOUND MEASUREMENTS - BIOMETRY

Fetal biometry measurements taken at the routine fetal morphology ultrasound and any clinically indicated ultrasounds were collected from the woman's medical record where possible, including biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC) and femur length (FL). EFW was calculated if not included in the report using the Hadlock formula (Hadlock et al 1984). In some cases due to morphology ultrasounds being performed at private radiology practices, it was not possible to obtain the original measurements for those examinations.

At the 28 week and 36 week research ultrasound the following parameters were collected according to the Australasian Society for Ultrasound in Medicine Statement D7 - Statement On Normal Ultrasonic Fetal Measurements (ASUM 2001)

- **BPD** – biparietal diameter
- **HC** – head circumference
- **AC** – abdominal circumference
- **FL** – femur length
- **EFW** – estimated fetal weight – calculated by the included ultrasound software utilising the Hadlock 4 formula (Hadlock et al 1984).

2.2(3) ULTRASOUND MEASUREMENTS – FETAL BODY COMPOSITION

2.2(3)(i) Mid thigh total, lean and fat mass

The technique described by Bernstein and Larciprete was utilised (Bernstein et al 1991; Bernstein et al 1997; Larciprete et al 2003) to obtain mid thigh fat and lean mass. A longitudinal view of the femur was obtained, and used to identify the midpoint of the bone with an angle of 0 degrees to the transducer. The transducer was then rotated 90 degrees to obtain the cross sectional view of the mid thigh. **Mid thigh fat mass** (**MTFM**) was measured by taking the total cross sectional limb area **(MTTM, mid thigh**

total mass) and subtracting the **MTLM** (**mid thigh lean mass**) which is measured as the central lean area consisting of muscle and bone. Two measurements of each were made at each observation from two separate images and the mean value of each set of observations used in the analysis.

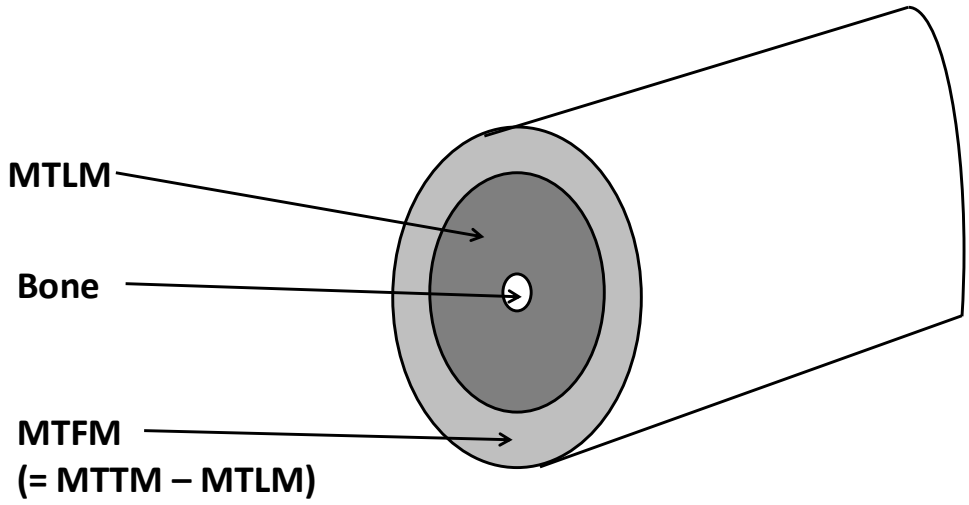
2.2(3)(ii) Anterior abdominal wall thickness/abdominal fat mass (AFM)

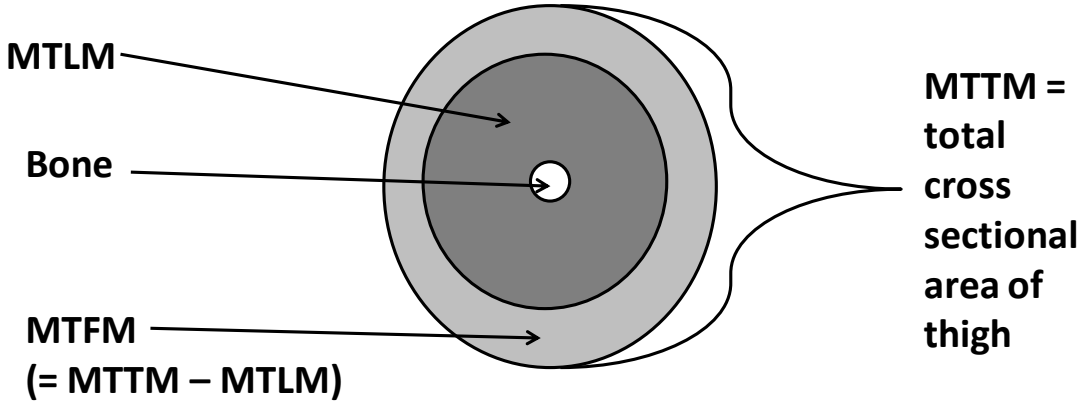
The technique described by Gardeil (1999) and Larciprete (2003) was utilised (Gardeil et al 1999; Larciprete et al 2003) to obtain the abdominal fat mass. The abdominal wall fat mass (**AFM**) was measured at the level of the abdominal circumference between the midaxillary lines and anterior to the margins of the ribs. The subcutaneous fat of the AFM was identified as the echogenic envelope surrounding the abdomen and most clearly identified anteriorly. The AFM was measured in millimetres on the anterior abdominal wall, using magnification. Four measurements were obtained from 1 or 2 separate images, and the mean used in the analysis.

2.2(3)(iii) Subscapular fat mass (SSFM)

The technique described by Larciprete (2003) was utilized (Larciprete et al 2003) to obtain the subscapular fat mass. The SSFM was evaluated longitudinally on the fetal trunk with a sagittal view, visualising the entire longitudinal section of the scapula between the skin surface and the subcutaneous tissue at the interface with the super-spinous and infra-spinous muscles. The measurement was taken at the end of the bone, taking the shoulder skin width. Two measurements were made and the mean value used in the analysis.

Figure 2.2(3)(i) Diagrammatic representation and ultrasound example of longitudinal and cross sectional view of the femur used to measure MTTM and MTLM





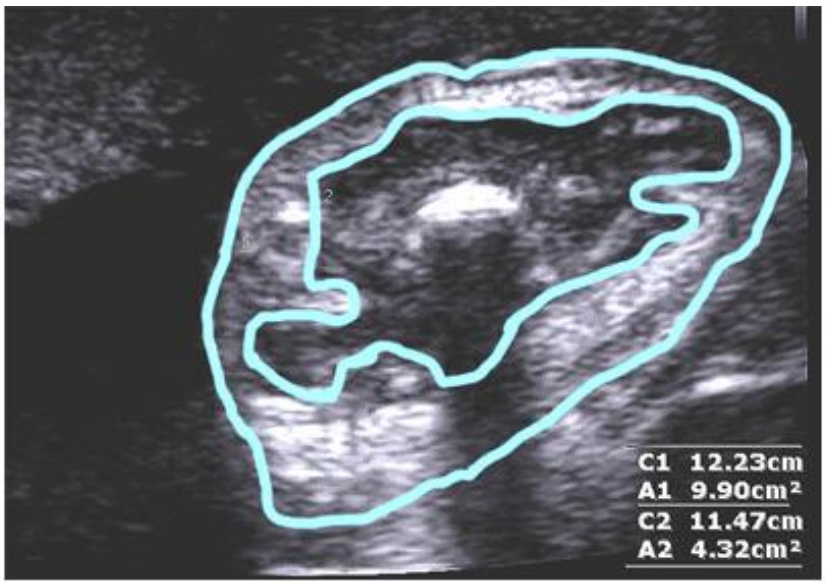
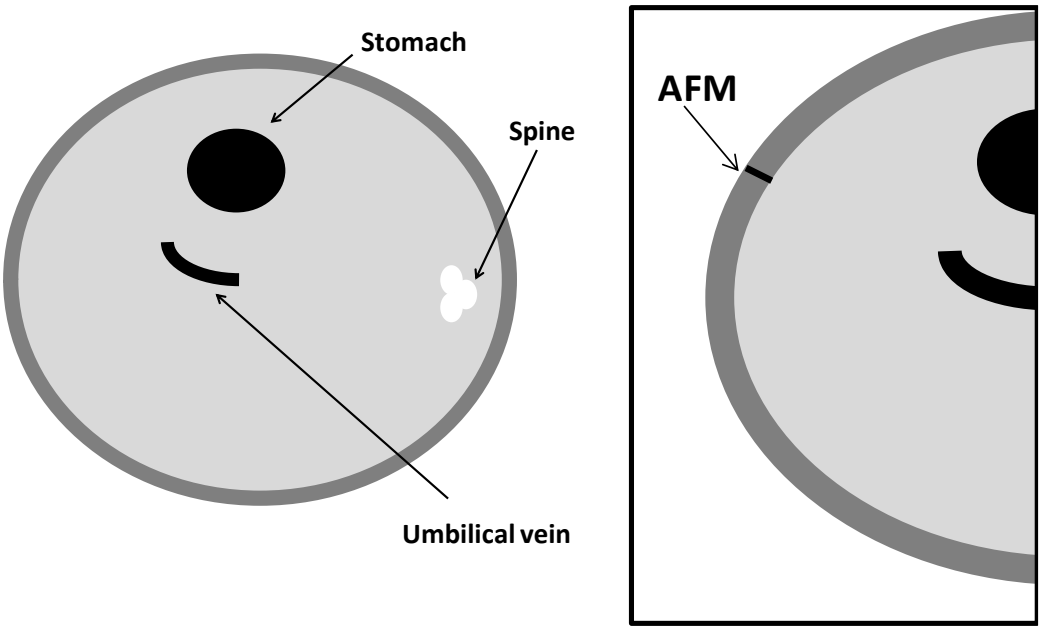


Figure 2.2(3)(ii) Diagrammatic representation of the abdominal circumference view used to obtain the AFM measurement and subsequent magnification view used to measure the AFM with ultrasound example.



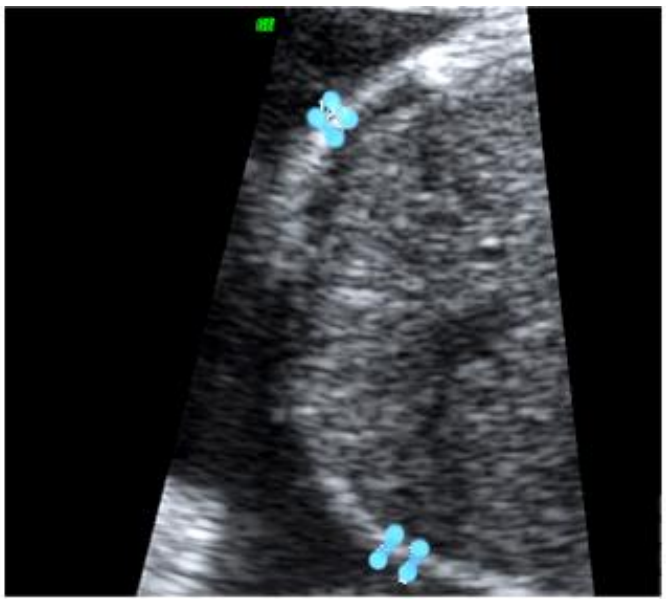
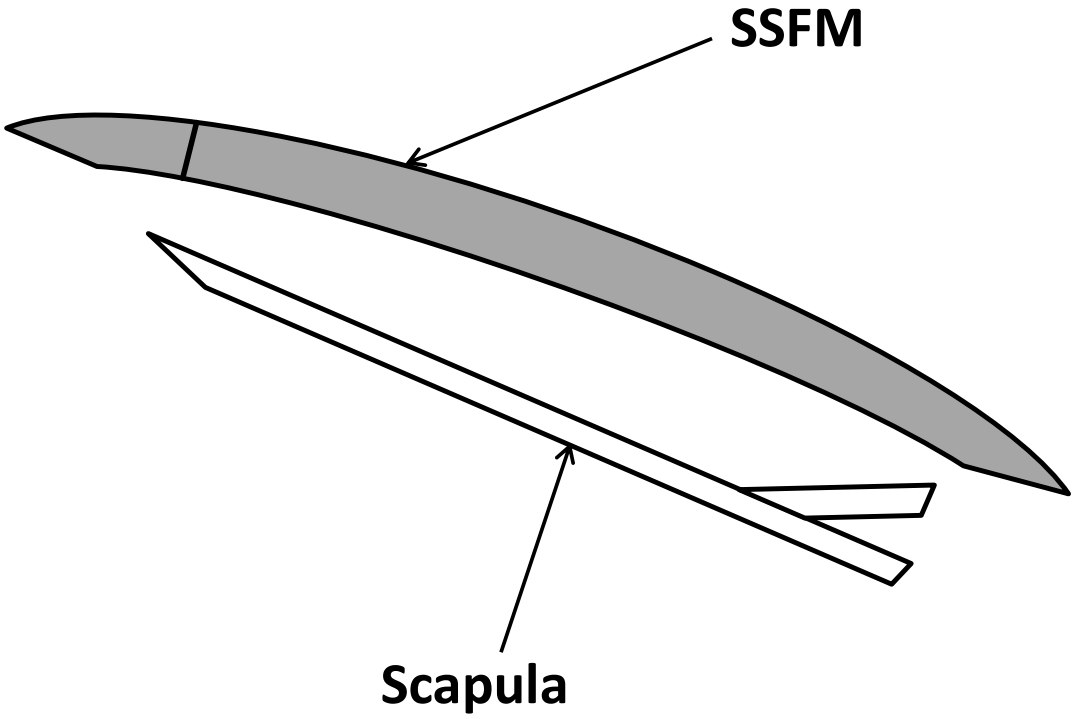
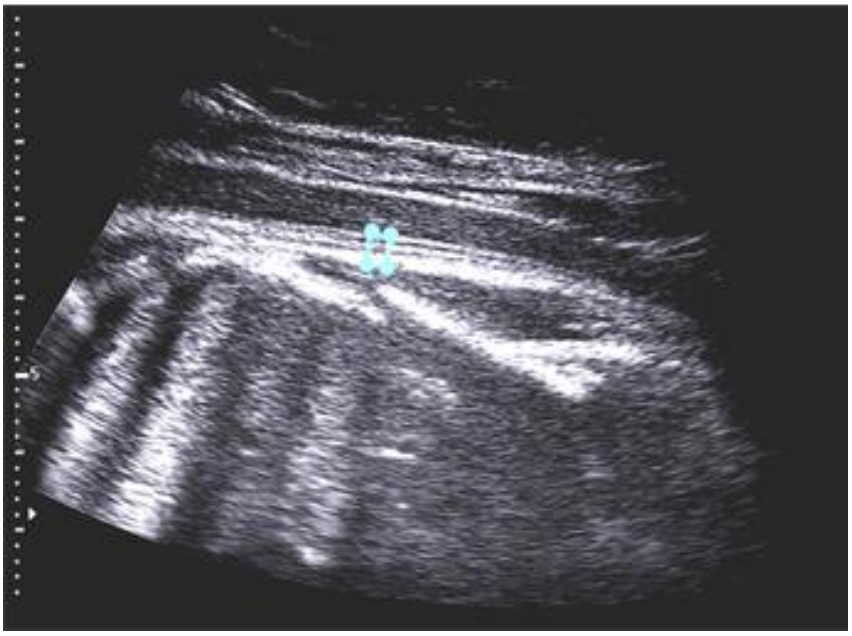


Figure 2.2(3)(iii) Diagrammatic representation and ultrasound example of the view used to measure the subscapular fat mass.





2.2(4) PRIMARY STUDY ENDPOINTS FOR THE FETAL GROWTH STUDY

At 20 weeks' gestation:

1. Biparietal diameter (BPD)
2. Head circumference (HC)
3. Abdominal circumference (AC) – converted to abdominal area (AA) to allow calculation of fetal growth velocities
4. Femur length (FL)
5. Estimated fetal weight - calculated by utilising the Hadlock 4 formula (Hadlock et al 1984) with the biometric information provided in the external ultrasound report.

At 28 weeks' and 36 weeks' gestation:

1. Biparietal diameter (BPD)
2. Head circumference (HC)
3. Abdominal circumference (AC) - converted to abdominal area (AA) to allow calculation of fetal growth velocities
4. Femur length (FL)
5. Estimated fetal weight (EFW)
6. Mid thigh lean mass (MTLM)
7. Mid thigh fat mass (MTFM)
8. Abdominal fat mass (AFM)
9. Subscapular fat mass (SSFM)

2.2(5) CLINICAL OUTCOMES FOR THE FETAL GROWTH STUDY

1. Gestational weight gain (At approximately 36 weeks of pregnancy maternal weight was recorded and gestational weight gain calculated (= weight at 36 weeks – weight at study entry)).
2. Induction of labour
3. Caesarean section (any)
4. Caesarean section (emergency)
5. Caesarean section (elective)
6. Pregnancy induced hypertension (in accordance with recognised Australasian Society for the Study of Hypertension in Pregnancy criteria) (ASSHP 2000).
7. Preeclampsia (in accordance with recognised Australasian Society for the Study of Hypertension in Pregnancy criteria) (ASSHP 2000).
8. Gestational diabetes (defined as a positive oral glucose tolerance test with fasting blood glucose level ≥5.5mmol/L, or 2 hour blood glucose level ≥ 7.8mmol/L)
9. Shoulder dystocia
10. Admission to neonatal intensive care
11. Infant hypogylcaemia requiring intravenous treatment
12. Infant birthweight
13. Infant birthweight > 4000 grams
14. Infant birthweight > 4500 grams

2.2(6) SAMPLE SIZE FOR THE FETAL GROWTH STUDY

To detect a 5% difference in means when comparing the Fetal Growth Study cohort to published population standard for EFW growth velocity a minimum sample size of 400 women was required (from 19.9 g/day (+/- 3g/day) to 20.8 g/day at 28 weeks; power 80% and alpha = 0.05) (Owen et al 1996). This sample size would allow the detection of one standard deviation difference in means for biometric measures of growth (ASUM 2001) (power 80% and alpha = 0.05).

2.2(7) DATA ANALYSIS FOR THE FETAL GROWTH STUDY

2.2(7)(i) Study Entry, Pregnancy, Birth and Infant Outcomes.

Initial analysis involved the description of demographics, prior obstetric history, gestational age at trial entry, BMI at booking antenatal visit. Pregnancy (gestational weight gain, gestational diabetes, pre-eclampsia), birth (mode of birth) and infant (gestational age at birth, birthweight) outcomes were also examined. Normally distributed continuous variables were reported as means and standard deviations. Continuous variables, which were not normally distributed, were reported as medians and interquartile ranges. Categorical variables were reported as the number and percentage of women or infants in each category.

2.2(7)(ii) Fetal growth – calculation of Z-scores

Z-scores are used to describe and compare measures of growth independent of gestational age, and indicate how close to the gestational age-specific population mean a growth measurement lies. For example, an estimated fetal weight Z-score of minus two represents an estimated fetal weight that lies two standard deviations below the mean, whilst a Z-score of zero represents growth on the mean, and a Z-score of plus two represents growth two standard deviations above the mean. Z-scores were calculated for each fetal growth measurement by subtracting the population mean for the same

gestational age from the fetal growth measure and dividing this by the population standard deviation (*Quantitative Aspects of Psychological Assessment - Z-scores*).

$$\text{Z-score} = \frac{\text{observed measurement} - \text{mean gestation-specific measurement}}{\text{gestation-specific standard deviation}}$$

Z-scores were calculated for each fetus for BPD, HC, AC and FL at 28 and 36 weeks using the ASUM Ultrasonic Fetal Measurement Standards as compiled by Campbell-Westerway (ASUM 2001). Z-scores for EFW were calculated using the gestational age specific values as published by Hadlock (Hadlock et al 1991).

Comparison with expected ranges

The number of fetuses with BPD, HC, AC, FL and EFW below the 3rd, 5th and 10th percentile and above the 90th , 95th and 97th percentile respectively were calculated from the Z-score data. The following classifications were used for Z-scores:

- Z-score of -1.88 = 3rd percentile
- Z-score of -1.64 = 5th percentile
- Z-score of -1.28 = 10th percentile
- Z-score of 1.28 = 90th percentile
- Z-score of 1.64 = 95th percentile
- Z-score of 1.88 = 97th percentile

Chi–square tests for goodness of fit were used to test for any significant difference in the proportion of Z-scores falling in the respective percentile ranges.

2.2(7)(iii) Fetal growth velocities

Fetal growth velocities for BPD, FL, AA and EFW were calculated using pairs of measurements made at least 28 days apart (Owen et al 1996). Growth velocities were calculated for the 20 – 28 week period

using the measurements obtained from the routine morphology ultrasound and the 28 week research ultrasound. Growth velocities for the 28 – 36 week period were calculated using the measurements obtained from the 2 research scans. Published normal values for growth velocities report an abdominal area, therefore AC was converted to AA to allow calculation values that were able to be compared with published norms.

Abdominal circumference was converted to abdominal area using the formula:

$$\text{Area} = \frac{\text{circumference}^2}{4\pi}$$

Daily growth rates for each fetus were calculated by the following formula (Owen et al 1996):

$$\text{Daily growth rate} = \frac{\text{Observation 2} - \text{Observation 1}}{\text{number of days between Observations 1 and 2}}$$

Absolute daily increments for growth rates were reported using means and standard deviations for normally distributed values and medians and interquartile ranges for values which were not normally distributed. Z-scores for the mean daily growth rates for biparietal diameter, femur length, and fetal abdominal area were calculated based on the data published by Owen (Owen et al 1996). The number of fetuses with BPD, AA, FL and EFW growth velocities below the 3rd, 5th and 10th percentile and above the 90th, 95th and 97th percentile respectively were calculated from the Z-score data as described above.

2.2(7)(iv) Fetal body composition

In the initial phase of the study, two research sonographers established a technique for measuring fetal body composition based on the methods described by Gardeil, Larciprete and Bernstein (Bernstein et al 1997; Gardeil et al 1999; Larciprete et al 2003), which took place over a 3 month period, and involved

50 ultrasound scans. After establishment of appropriate technique, a process of inter-observer variability testing was undertaken. All measurements on individual women were performed on the same day using the same ultrasound equipment by two research sonographers blinded to the other's measurements and results. Two sonographers measured SSFM, AFM, MTTM, MTFM and MTLM at 28 weeks' (49 women) or 36 weeks' (28 women) gestation. Thigh measures (MTTM and MTLM) were made once for each woman by each sonographer and SSFM and AFM were made at least twice by each sonographer for each woman.

Inter-observer variability was tested by calculating the intra-class correlation (Shrout et al 1979). For the variables MTTM, MTLM, MTFM where each woman was measured once by each sonographer a variance component model was used with women and sonographers fitted as random effects. For the variables SSFM and AFM, where each woman was measured more than once by each sonographer, the variance component model also included a random effect for the interaction between woman and sonographer. The intra-class correlation was defined as the correlation between measurements taken from the same woman by different sonographers/observers.

Normally distributed measures of body composition were reported as means and standard deviations. Measures which were not normally distributed, were reported as medians and interquartile ranges. Using published normal ranges (Larciprete et al 2003), the proportion of body composition values below the 5th and above 95th percentile were calculated. Chi-square test for goodness of fit was used to test for any significant difference between the observed and expected number of measures in each of the 5th and 95th percentile ranges.

2.2(7)(v) Effect of BMI and gestational weight gain

To examine the association between fetal growth Z-scores and BMI and gestational weight gain (all non-normally distributed), BMI and gestational weight gain were converted to categorical variables.

Booking BMI was reclassified as overweight, obese class I, obese class II or obese class III (WHO 2000). Gestational weight gain was classified as below, within or above current IOM recommendations using BMI specific ranges (IOM 2009).

A Kruskal Wallis H test was conducted to test for differences in fetal growth (biometry and growth velocity) Z-scores and fetal body composition measures across BMI and gestational weight gain categories respectively. Post-hoc Mann Whitney U testing was used to test for differences between pairs of categories within the groups using adjusted P values to control for type I error. For BMI category, the overweight group was used as the reference group and for GWG, the within IOM group was used as the reference group. For BMI category $P < 0.017$ indicated statistical significance after Bonferroni adjustment (0.05 divided by 3). For GWG category $P < 0.025$ indicated statistical significance after Bonferroni adjustment (0.05 divided by 2).

2.2(7)(vi) Correlation with clinical outcomes

Fetal growth Z-scores and birthweight (all non-normally distributed), were converted to categorical variables to allow more reliable statistical analysis of the non-normal distributions. Each infant's birthweight was classified as below/equal to, or greater than 4000g and 4500g. Fetal growth Z-scores were classified by percentile equivalent; less than or equal to 1.28 (90^{th} percentile) or greater than 1.28 (90^{th} percentile). Chi-square tests for independence with Yates Continuity Correction were conducted to test for associations between categories of infant birthweight (above 4000g or 4500g versus equal to or below 4500g) and biometry and growth velocity Z-scores (above the 90^{th} percentile versus equal to or below the 90^{th} percentile). Chi-square tests for independence with Yates Continuity Correction were conducted to test for associations between fetal growth biometry Z-scores (above the 90^{th} percentile versus equal to or below the 90^{th} percentile) and categorical maternal and infant outcomes. For fetal body composition and correlation with the categorical clinical outcomes, body composition measures

were converted to a categorical variable (above the 95th percentile versus equal to or below the 95th percentile).

For all statistical tests, unless otherwise specified, an alpha (P) value of less than 0.05 was taken to represent statistical significance.

2.2(7)(vii) Prediction of clinical outcomes

For assessment of potential predictors of adverse maternal and infant outcomes, 2x2 tables were constructed for growth and fetal body composition measures that were noted to be significantly associated with maternal and infant outcomes. Sensitivity, specificity, positive likelihood ratio (LR+), negative likelihood ratio (LR-), positive predictive value and negative predictive value were calculated for pairs of outcomes and growth measures. Likelihood ratios were classified into levels of "usefulness" as follows (Jaeschke et al 1994; Khan et al 1999):

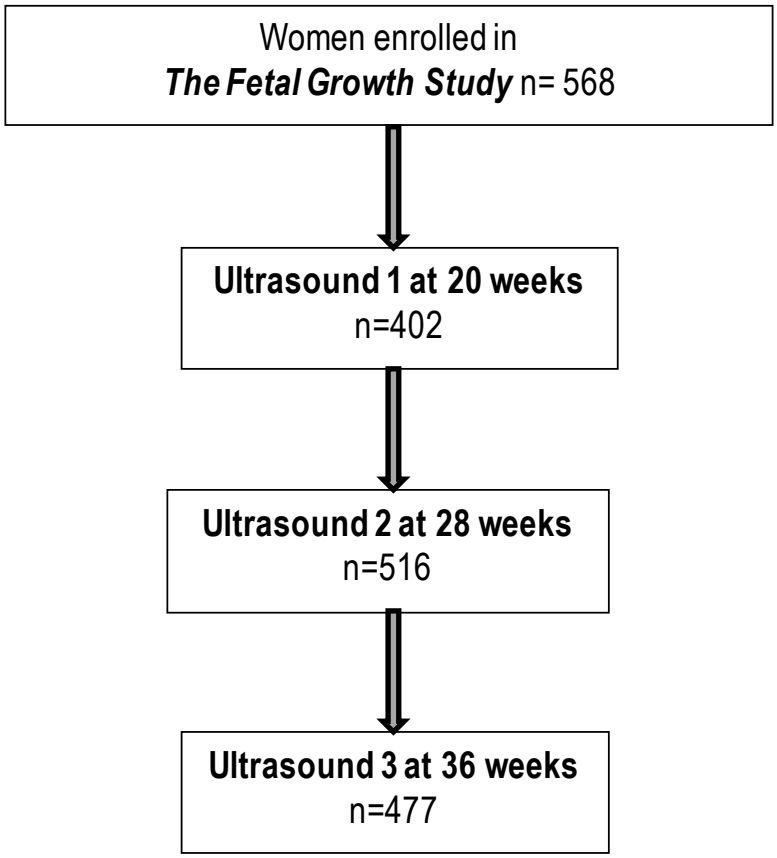
- LR + >10 = definitely useful
- LR + 5 to 10 = moderately useful
- LR + 2 to 5 = slightly useful
- LR + 1 to 2 = not at all useful
- LR - <0.1 = definitely useful
- LR - 0.1 to 0.2 = moderately useful
- LR - 0.2 to 0.5 = slightly useful
- LR - 0.5 to 1 = not at all useful.

3. RESULTS OF THE FETAL GROWTH STUDY 1: FETAL GROWTH, THE EFFECT OF BMI AND GESTATIONAL WEIGHT GAIN AND CORRELATION WITH CLINICAL OUTCOMES

3.1 DESCRIPTION OF THE FETAL GROWTH STUDY COHORT .

A total of 568 women consented to participate in The Fetal Growth Study**,** with 557 (98%) women attending for a research ultrasound at either 28 or 36 weeks gestation or both. At 28 weeks, 516 (91%) women attended for an ultrasound, with clinical outcome data available for 500 (97%) women. At 36 weeks, 477 (84%) women attended for an ultrasound, with clinical outcome data available for 448 (95%) women. A total of 450 (80%) women attended for an ultrasound at both time points with clinical outcome data available for 440 (98%) women.

Figure 3.1(1) Fetal Growth Study flow chart



Baseline characteristics of women in The Fetal Growth Study were comparable with the demographics published by the South Australian Pregnancy Outcome Unit which reports outcomes from all births in South Australia (Chan et al 2011). For women in The Fetal Growth Study, 38% of women were in their first ongoing pregnancy, 90% were of Caucasian ethnicity, and 13.3% were smokers. Of women participating in the study, 97% were public patients, 40% were overweight at pregnancy booking, and 60% were obese (30.0% obese class I, 16.5% obese class II and 13.5% obese class III) (Table 3.1(1)).

Table 3.1(1) Maternal Study Entry Characteristics for The Fetal Growth Study.

Mean gestational weight gain for women in the Fetal Growth Study was 9kg (+/- 7.6), with over half of women gaining weight in excess of the Institute of Medicine recommendation for their BMI category. The incidence of induction of labour, hypertensive disease and gestational diabetes, were lower than noted in the most recent South Australian Pregnancy Outcome Unit report, which described outcomes from all births in South Australia (Chan et al 2011). Of women participating in the study, 21.5% experienced caesarean birth, with a similar proportion of women requiring induction of labour. Consistent with large cohort studies reporting outcomes of women with high BMI, infants born to women in The Fetal Growth Study were heavier than the mean birthweight reported in the South Australian Pregnancy Outcome unit report (Chan et al 2011).

Table 3.1(2) Maternal and infant outcomes for The Fetal Growth Study.

3.2 FETAL GROWTH TRAJECTORIES.

Overall, for each of the growth parameters studied (BPD, HC, AC, FL and EFW) at each gestational age (20, 28 and 36 weeks' gestation), measured median Z-scores did not deviate appreciably from the reported standard population means (Table 3.2(1)).

Specifically, fetal biometry Z-scores for BPD, HC, AC, FL and EFW at 20 weeks were -0.22, 0.28, 0.33, 0.09 and -0.05 respectively (Table 3.2(1)). Fetal biometry Z-scores for BPD, HC, AC, FL and EFW at 28 weeks were 0.16, 0.37, 0.03, -0.21 and 0.24, respectively (Table 3.2(1)). Fetal biometry Z-scores for BPD, HC, FL, AC and EFW at 36 weeks were -0.09, 0.47, 0.15, -0.09 and 0.24 respectively (Table 3.2(1)). Fewer HC, AC and EFW Z-score measures than expected fell into the lower percentile ranges; whilst more measures than expected fell into the higher percentile ranges (Table 3.2(1)).

There was evidence of an upward shift in growth parameters, when considering the proportion of Z-score values falling within each percentile range (Table 3.2(1)). This information is presented graphically, where the black bars indicate the expected proportions, with the observed proportions at 20 weeks gestation represented in red, at 28 weeks' gestation in blue, and at 36 weeks' gestation in green (Figure 3.2(1), Figure 3.2(2), Figure 3.2(3), Figure 3.2(4), Figure 3.2(5)).

Specifically, at 20 weeks' gestation, there was a significantly greater proportion of EFW and AC Z-scores within the upper percentile ranges than expected. There was a significantly greater proportion of BPD Z-scores and fewer HC Z-scores in the lower centile ranges than expected, reflecting the contribution of BPD to an assessment of head shape, while HC is more representative of head size. At both 28 and 36 weeks' gestation, there was a significantly greater proportion of HC, AC and EFW Z-scores in the upper centile ranges than expected. The findings in relation to FL were not consistent, with

greater than expected proportions at both ends of the centile spectrum occurring at 28 weeks' gestation, while lower than expected proportions were evident at 36 weeks' gestation.

Growth velocities for abdominal area, femur length and estimated fetal weight were similar to or greater than the published normal ranges for both 20 to 28 and 28 to 36 weeks gestation (Table 3.2(2)). Specifically, median Z-scores for BPD, AA, FL and EFW growth velocities were -0.14, 0.36, 0.53 and -0.92 respectively (Table 3.2(2)). For growth velocities from 28 to 36 weeks gestation, median Z-scores for BPD, AA, FL and EFW growth rates were 0.96, 0.49, 0.71 and 0.59 respectively (Table 3.2(2)). When comparing median measures of growth with previously published values, the non-parametric distribution of the majority of measures of fetal growth seen in The Fetal Growth Study prevent useful and robust statistical comparisons being performed.

Table 3.2(1) Ultrasound biometry Z-scores and distribution across percentile ranges from 20 to 36 weeks

	BPD			HC			AC			FL			EFW		
Weeks of gestation	20	28	36	20	28	36	20	28	36	20	28	36	20	28	36
Z-score: *Median*	-0.22	0.16	-0.09*	0.28*	0.37	0.47	0.33	0.03	0.15	0.09	-0.21	-0.09	-.05	0.24	0.24
Interquartile range	1.31	1.71	1.21	0.79	1.25	1.17	1.70	1.26	1.25	0.40	1.37	0.70	1.62	1.25	1.16
% Z-scores <3rd centile#	**5.74**	**9.04**	**6.02**	**0.50**	2.21	**1.16**	2.24	**1.00**	3.46	**0.40**	**5.63**	1.39	3.53	**0.60**	1.62
P value	**<0.01**	**<0.01**	**<0.01**	**<0.01**	0.30	**0.02**	0.37	**<0.01**	0.57	**<0.01**	**<0.01**	0.05	0.57	**<0.01**	0.09
% Z-scores <5th centile#	**8.73**	**11.65**	**8.80**	**1.00**	**2.61**	**2.08**	3.49	3.21	4.61	**0.60**	**8.84**	**1.62**	5.59	**0.80**	**2.31**
P value	**<0.01**	**<0.01**	**<0.01**	**0.00**	**0.01**	**<0.01**	0.17	0.07	0.72	**<0.01**	**<0.01**	**<0.01**	0.61	**<0.01**	**0.01**
% Z-scores <10th centile#	**14.46**	**16.87**	**13.89**	**1.75**	**5.02**	**3.47**	7.98	8.43	7.85	**1.00**	**13.88**	**3.00**	**15.00**	**4.02**	**5.08**
P value	**<0.01**	**<0.01**	**<0.01**	**<0.01**	**<0.01**	**<0.01**	0.18	0.19	0.18	**<0.01**	**<0.01**	**<0.01**	**<0.01**	**<0.01**	**<0.01**
% Z-scores >90th centile#	**6.73**	**17.27**	12.09	9.23	**16.67**	**19.90**	**23.24**	12.45	11.55	**0.75**	8.45	**0.69**	**16.21**	**15.86**	**15.70**
P value	**0.03**	**<0.01**	0.12	0.61	**<0.01**	**<0.01**	**0.00**	0.07	0.28	**<0.01**	0.25	**<0.01**	**<0.01**	**<0.01**	**<0.01**
% Z-scores >95th centile#	3.74	**12.45**	**7.64**	4.24	**11.65**	**10.80**	**13.97**	**7.03**	**7.16**	**0.25**	5.03	**0.46**	**10.00**	**10.64**	**8.08**
P value	0.25	**<0.01**	**<0.01**	0.49	**<0.01**	**<0.01**	**0.00**	**0.04**	**0.04**	**<0.01**	0.98	**<0.01**	**<0.01**	**<0.01**	**<0.01**
% Z-scores >97thth centile#	1.50	**9.04**	4.40	2.49	**7.23**	**7.41**	**7.48**	**4.62**	4.62	**0.00**	3.22	**0.23**	**8.82**	**8.43**	**5.31**
P value	0.08	**<0.01**	0.05	0.55	**<0.01**	**<0.01**	**0.00**	**0.03**	0.05	**<0.01**	0.77	**<0.01**	**<0.01**	**<0.01**	**<0.01**

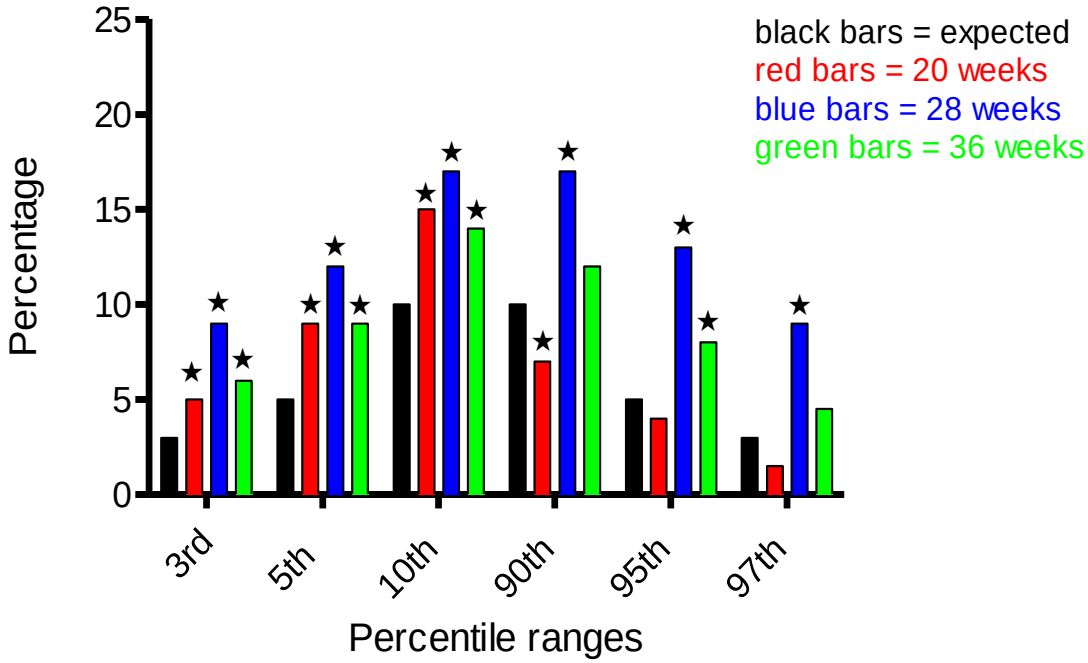
Figures are Z-scores median and interquartile range or * Z-score mean and SD or # percentages
BPD = biparietal diameter
HC = head circumference
AC = abdominal circumference
FL = femur length
EFW = estimated fetal weight
Statistically significant results in bold text with shaded box

Table 3.2(2) Growth velocities for biometric measures for The Fetal Growth Study compared with normal ranges

	BPD growth velocity		HC growth velocity		AA growth velocity		FL growth velocity		EFW growth velocity	
Weeks of gestation	**20 to 28**	**28 to36**	**20 to 28**	**28 to36**	**20 to 28**	**28 to 36**	**20 to 28**	**28 to 36**	**20 to 28**	**28 to 36**
Growth velocity ***Median***	0.45 mm/day	0.32 mm/day	1.69 mm/day	1.02 mm/day	0.52 cm^2/day	0.68 cm^2/day	0.37 mm/day	0.29 mm/day	17.84 g/day	29.66 g/day
Interquartile range	0.08	0.08	0.25	0.27	0.11	0.16	0.04	0.06	3.9	6.49
Published Normal Ranges for growth velocity (Owen et al 1996)	0.47 mm/day	0.26 mm/day	None available		0.48 cm^2/day	0.60 cm^2/day	0.34 mm/day	0.25 mm/day	18.30 g/day	26.90 g/day
Growth Velocity Z-score ***Median***	-0.14	0.96	Unable to calculate		0.36	0.49	0.53	0.71	-0.92	0.59
Interquartile range	0.88	1.30			1.20	1.12	0.77	1.23	1.62	1.38

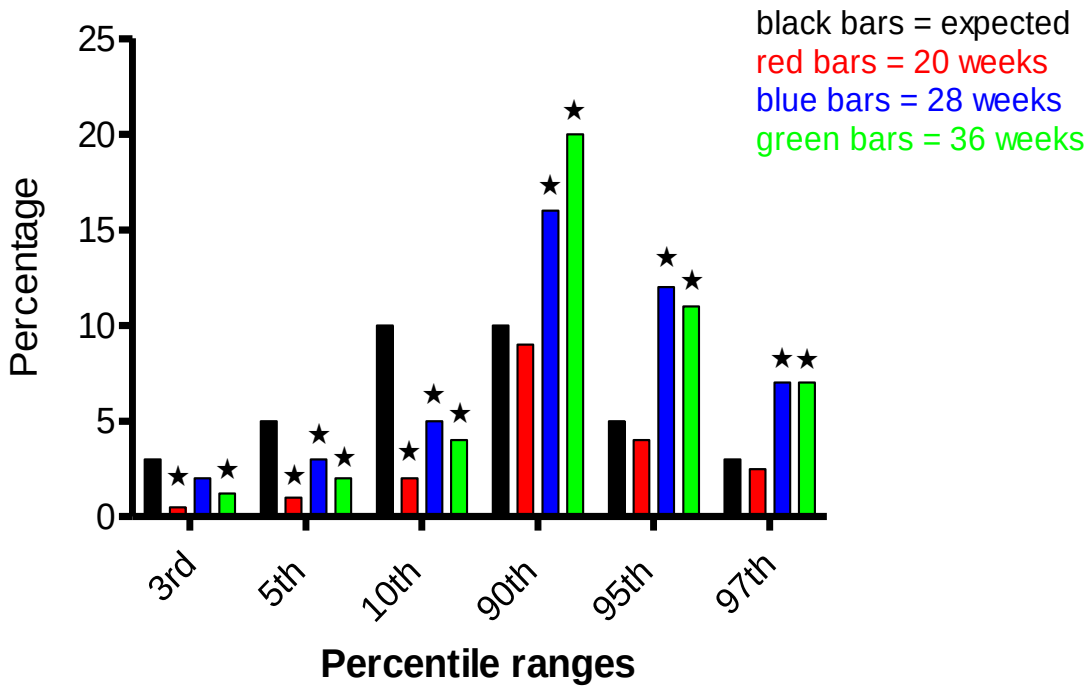
Figures are median and interquartile range
BPD = biparietal diameter
HC = head circumference
AC = abdominal circumference
FL = femur length
EFW = estimated fetal weight
Normal ranges from Owen et al (Owen et al 1996)

Figure 3.2(1) Biparietal diameter Z-score distribution by percentile ranges



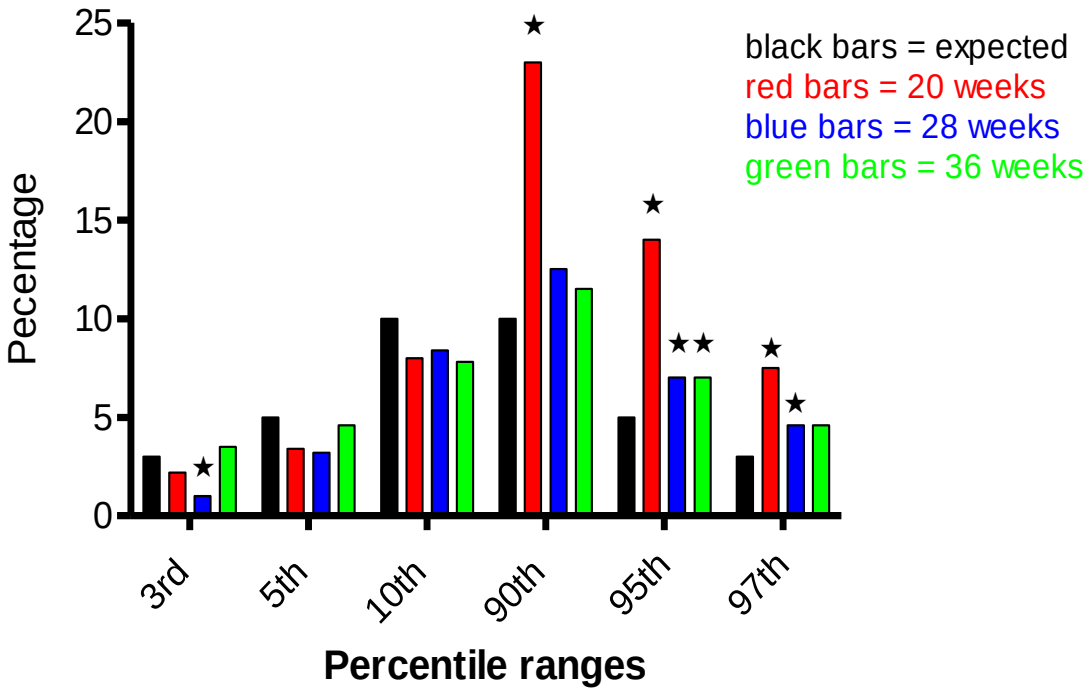
★ indicates statistically significant difference between proportions in expected and observed at each gestational age.

Figure 3.2(2) Head circumference Z-score distribution by percentile ranges



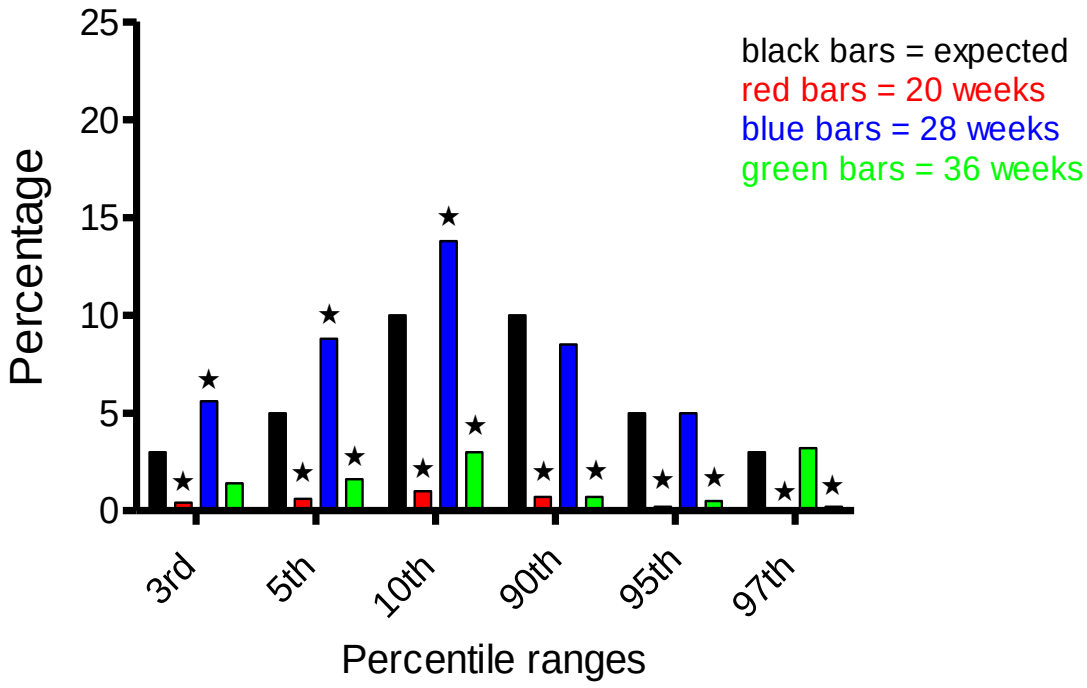
★ indicates statistically significant difference between proportions in expected and observed at each gestational age.

Figure 3.2(3) Abdominal circumference Z-score distribution by percentile ranges



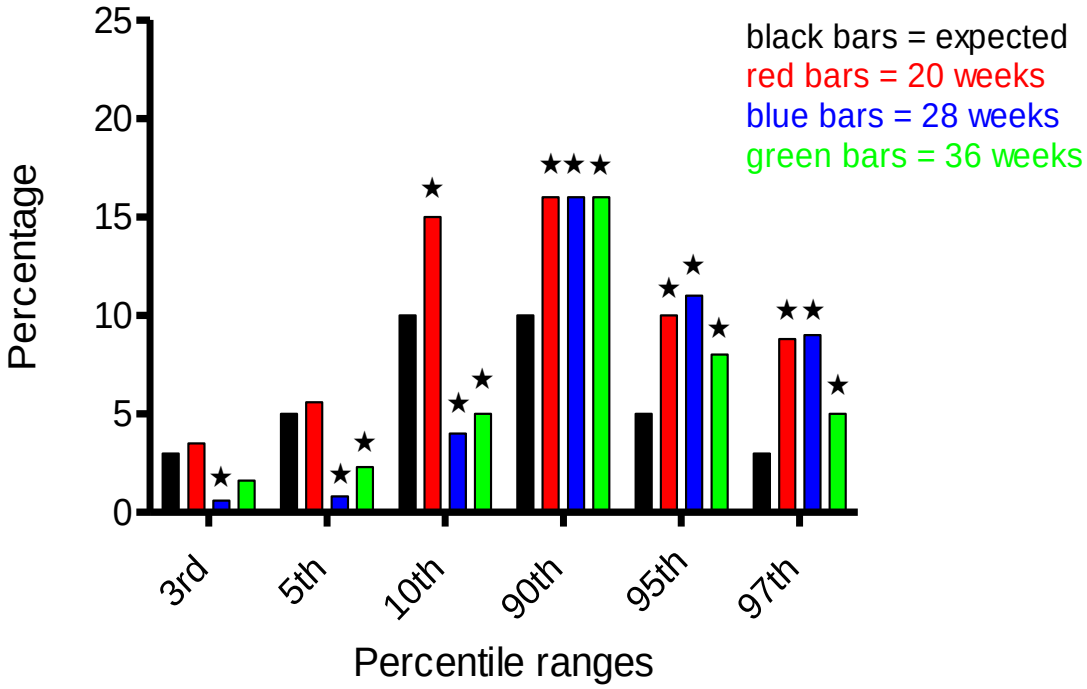
★ indicates statistically significant difference between proportions in expected and observed at each gestational age.

Figure 3.2(4) Femur length Z-score distribution by percentile ranges



★ indicates statistically significant difference between proportions in expected and observed at each gestational age.

Figure 3.2(5) Estimated fetal weight Z-score distribution by percentile ranges



★ indicates statistically significant difference between proportions in expected and observed at each gestational age

3.3 THE EFFECT OF MATERNAL BMI AND GESTATIONAL WEIGHT GAIN

At 20 weeks' gestation and 36 weeks' gestation, maternal BMI category did not significantly influence fetal growth Z-scores. However at 28 weeks' gestation, when compared with women who were overweight, women in obesity class I and obesity class III were noted to have significantly higher median EFW Z-scores and AC Z-scores respectively ($p<0.017$). There was no effect identified between maternal BMI category for fetal growth velocities between 20 and 28 weeks' gestation, or 28 and 36 weeks' gestation (Table 3.3(1)).

In contrast, gestational weight gain category (below, within or above Institute of Medicine recommendations, for specific BMI category) did influence fetal growth parameters (Table 3.3(2)). At 28 weeks' gestation, when compared with women who gained within the IoM recommendations, higher gestational weight gain was significantly associated with higher BPD and HC Z-scores. At 28 and 36 weeks', gestational weight gain category significantly influenced both AC and EFW Z-scores. Gestational weight gain category did not influence growth velocity Z-scores between 20 and 28 weeks' gestation. However, when compared with women who gained within the IoM recommendations, higher gestational weight gain was associated with a significant increase in AA and EFW growth velocity Z-scores between 28 and 36 weeks' gestation (Table 3.3(2)).

Table 3.3(1) Effect of BMI category on fetal growth biometry and growth velocity Z-scores

	BPD			BPD growth velocity		HC			AC			AA growth velocity		FL			FL growth velocity		EFW			EFW growth velocity	
Weeks gestation	**20**	**28**	**36**	**20 to 28**	**28 to 36**	**20**	**28**	**36**	**20**	**28**	**36**	**20 to 28**	**28 to 36**	**20**	**28**	**36**	**20 to 28**	**28 to 36**	**20**	**28**	**36**	**20 to 28**	**28 to 36**
Overweight	-0.28	0.26	-0.10	-0.11	0.92	0.25	0.32	0.40	0.28	-0.07	0.03	0.20	0.43	0.09	-0.26	-0.08	0.52	0.80	-1.08	0.12	0.19	-0.92	0.51
Obese class I	-0.28	0.03	-0.24	-0.20	0.89	0.22	0.34	0.49	0.50	0.17	0.26	0.52	0.41	0.09	-0.14	-0.11	0.55	0.63	-0.98	**0.40***	0.31	-0.90	0.61
Obese class II	-0.35	0.01	-0.05	-0.16	1.04	0.17	0.45	0.45	0.00	-0.25	0.29	0.31	0.68	0.03	-0.14	-0.07	0.51	0.75	-1.10	0.11	0.19	-1.0	0.64
Obese class III	0.06	0.34	0.14	-0.13	1.04	0.50	0.72	0.74	0.40	**0.33***	0.18	0.68	0.50	0.09	0.06	-0.19	0.67	0.87	-0.9	0.32	0.41	-0.82	0.69
P value (effect across BMI categories)	0.09	0.10	0.28	0.16	0.44	0.14	0.07	0.05	0.08	**0.02**	0.12	0.33	0.78	0.28	0.20	0.81	0.93	0.35	0.50	**0.02**	0.31	0.90	0.77

Figures are median Z scores for each BMI category
Bold/shaded = statistically significant
* = significantly different to reference group (overweight) on post-hoc testing
BPD = biparietal diameter
HC = head circumference
AC = abdominal circumference
AA = abdominal area
P value = effect across BMI categories with Kruskal- Wallis testing

Table 3.3(2) Effect of Gestational weight gain on fetal growth biometry and growth velocity Z-scores

	BPD			BPD growth velocity		HC			AC			AA growth velocity		FL			FL growth velocity		EFW			EFW growth velocity	
Weeks	**20**	**28**	**36**	**20 to 28**	**28 to 36**	**20**	**28**	**36**	**20**	**28**	**36**	**20 to 28**	**28 to 36**	**20**	**28**	**36**	**20 to 28**	**28 to 36**	**20**	**28**	**36**	**20 to 28**	**28 to 36**
GWG below IOM	#	-0.18	-0.32	-0.16	1.16	#	0.24	0.39	#	-0.07	-0.08	0.30	0.43	#	-0.42	-0.14	0.55	0.97	#	0.04	-0.04	-0.67	0.64
GWG within IOM		0.01	-0.12	-0.19	0.93		0.37	0.40		-0.11	0.08	0.33	0.32		-0.23	-0.06	0.53	0.68		0.24	0.19	-0.87	0.40
GWG above IOM		**0.38^**	0.05	-0.10	0.89		**0.52^**	0.52		0.22	0.23	0.36	**0.70^**		-0.10	-0.07	0.53	0.65		0.39	0.37	-1.15	**0.72^**
P value (effect across GWG categories)		**<0.01**	0.05	0.52	0.16		**0.01**	0.05		**0.01**	**<0.01**	0.86	<0.01		**0.04**	0.20	0.97	0.29		**<0.01**	**<0.01**	0.12	**<0.01**

Figures are median Z scores for each GWG category
Bold/shaded = statistically significant
^ = significantly different to reference group (GWG within IOM) on post-hoc testing
BPD = biparietal diameter
HC = head circumference
AC = abdominal circumference
AA = abdominal area
EFW = estimated fetal weight
P = effect across BMI categories with Kruskal- Wallis testing

3.4 CORRELATION WITH CLINICAL OUTCOMES

There was a significant relationship between fetal growth at 28 weeks and infant birthweight. Fetuses with higher HC, AC, FL and EFW fetal growth Z-scores (greater than the 90th percentile) at 28 weeks were significantly more likely to weigh more than 4000g at birth, whilst fetuses with higher fetal growth Z-scores (greater than the 90th percentile) for AC and EFW were significantly more likely to have birthweight greater than 4500g (Table 3.4(1)).

Similarly, fetal growth Z-scores at 36 weeks were significantly associated with infant birthweight. Fetuses with HC, AC and EFW greater than the 90th percentile were significantly more likely to weigh more than 4000g at birth, whilst fetuses with AC and EFW greater than the 90th percentile were significantly more likely to weigh more than 4500g at birth (Table 3.4(1)).

A significant association was found between fetal growth velocity Z-scores at 20-28 weeks and infant birthweight. Fetuses with AA growth velocity greater than the 90th percentile were significantly more likely to weigh above 4000g and above 4500g at birth. Fetal growth velocity Z-scores for 28-36 weeks were also significantly associated with infant birthweight, with fetuses recording AA and EFW growth greater than the 90th percentile significantly more likely to weigh more than 4000g at birth. Additionally, those fetuses with EFW fetal growth velocity greater than the 90th percentile were significantly more likely to have a birthweight greater than 4500g (Table 3.4(1)).

Fetal growth at 28 weeks was significantly associated with a woman's mode of birth; when HC, AC or EFW measures were reported above the 90th percentile, a woman was significantly more likely to birth by caesarean section. Women were significantly more likely to experience an elective caesarean section if EFW at 28 weeks was noted to be above the 90th percentile, whilst HC above the 90th

percentile was significantly associated with a woman's chance of emergency caesarean section. Maternal gestational diabetes was associated with HC growth above the 90th percentile at 28 weeks, while infants who were noted to have EFW or HC above the 90th percentile at 28 weeks were significantly more likely to be hypoglycemic after birth.

Fetal growth at 36 weeks was significantly associated with mode of birth, with women more likely to birth by caesarean section if HC or BPD had been recorded above the 90th percentile. Women were significantly more likely to experience an elective caesarean section if BPD, HC or EFW at 36 weeks was noted to be above the 90th percentile. There was a significant relationship between HC measures above the 90th percentile and a woman's chance of developing pregnancy induced hypertension and gestational diabetes.

Table 3.4(1) Association between fetal growth and growth velocity Z-scores (above 90th percentile) and birthweight

	BPD				HC		AC		AA		FL				EFW			
Weeks of gestation	28	36	20 to 28 GV	28 to 36 GV	28	36	28	36	20 to 28 GV	28 to36 GV	28	36	20 to 28 GV	28 to 36 GV	28	36	20 to 28 GV	28 to 36 GV
Birthweight > 4000g	**0.04**	0.17	0.36	0.42	**<0.01**	**<0.01**	**<0.01**	**<0.01**	**<0.01**	**<0.01**	**<0.01**	0.32	0.31	1.00	**<0.01**	**<0.01**	0.70	**<0.01**
Birthweight > 4500g	0.46	0.36	0.61	1.00	0.46	0.94	**<0.01**	**<0.01**	**<0.01**	0.09	0.28	1.00	0.44	0.49	**<0.01**	**<0.01**	0.82	**<0.01**

Figures are P values for Chi-square test for independence
BPD = biparietal diameter
HC = head circumference
AC = abdominal circumference
AA = abdominal area
EFW = estimated fetal weight
Bold/shaded = statistically significant
GV = growth velocity

Table 3.4(2) Association between fetal growth Z-scores (above 90th percentile) and clinical outcomes

	BPD		HC		AC		FL		EFW	
Weeks of gestation	28	36	28	36	28	36	28	36	28	36
Association with maternal outcomes										
Induction of labour	0.31	0.86	0.96	0.49	0.36	0.13	1.00	1.00	0.21	0.12
Caesarean section	0.11	**0.03**	**<0.01**	**<0.01**	**0.04**	0.10	0.20	0.10	**0.02**	0.21
Elective	0.65	**0.01**	0.18	**0.04**	0.10	**0.04**	0.62	1.00	**0.04**	**0.00**
Emergency	0.14	1.00	**<0.01**	0.09	0.41	0.75	0.37	0.10	0.35	0.34
Pregnancy induced hypertension	0.13	0.44	0.10	**<0.01**	0.59	0.80	0.74	0.87	0.40	1.00
Pre-eclampsia	0.53	0.55	1.00	0.82	1.00	1.00	1.00	0.29	1.00	0.84
Gestational diabetes	1.00	0.95	**<0.01**	**0.03**	0.26	0.99	0.78	**0.04**	0.35	0.69
Association with infant outcomes										
Shoulder dystocia	0.40	0.77	0.37	0.69	0.53	1.00	1.00	1.00	0.08	0.42
NICU admission	0.61	0.57	0.58	0.86	0.76	0.55	1.00	1.00	0.54	0.72
Hypoglycemia	0.19	0.81	0.01	0.58	0.11	0.76	0.27	1.00	0.03	1.00

Figures are P values for Chi-square test for independence
BPD = biparietal diameter
HC = head circumference
AC = abdominal circumference
AA = abdominal area
EFW = estimated fetal weight
NICU = neonatal intensive care unit
Bold/shaded = statistically significant

3.5 PERFORMANCE OF FETAL GROWTH MEASURES IN THE PREDICTION OF MATERNAL AND INFANT OUTCOMES

To assess the potential role of ultrasound measures in prediction of infant birthweight and clinical outcomes, the performance of fetal growth measures in the prediction of infant birthweight and various outcomes was expressed in terms of sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, positive predictive value and negative predictive value (Table 3.5(1)). The only predictor with a moderately useful positive likelihood ratio was AC above the 90th percentile at 28 weeks, with a LR+ of 6.56 for birthweight above 4500g. The majority of likelihood ratios were only slightly useful or not useful at all (Khan et al 1999). The sensitivity of most measures for predicting birthweight was less than 50%, however specificity was greater than 80% in most cases.

When assessing the performance of growth measures above the 90th percentile in predicting clinically important outcomes including mode of birth and infant hypoglycemia all positive likelihood ratios were slightly useful or not at all useful. Sensitivity of all measures was less than 40%, however specificity was high at over 80% for all measures.

Table 3.5(1) Performance of fetal biometry and growth velocity (above the 90th percentile) in the prediction of macrosomia

	Fetal growth parameter	Birthweight	Sens	Spec	LR+	LR-	PPV	NPV
28 weeks	BPD	>4000g	25.88	84.56	1.68 (1.08 – 2.61)	0.88 (0.77 – 1.00)	30.68	66.02
	HC	>4000g	29.41	85.49	**2.03 * (1.33 – 3.09)**	0.83 (0.72 – 0.95)	34.72	82.20
	AC	>4000g	32.91	92.28	**4.27 * (2.63 – 6.92)**	0.73 (0.62 – 0.85)	52.83	83.99
		>4500g	71.43	89.11	**6.56 # (4.25 – 10.14)**	**0.32 * (0.14 – 0.74)**	18.87	98.88
	FL	>4000g	17.65	92.59	**2.38 * (1.31 – 4.34)**	0.89 (0.80 – 0.99)	38.46	81.08
	EFW	>4000g	41.18	89.81	**4.04 * (2.68 – 6.10)**	0.65 (0.55 – 0.78)	51.47	85.34
		>4500g	71.43	85.32	**4.86 * (3.24 – 7.31)**	**0.33 * (0.15 – 0.77)**	14.71	98.83
36 weeks	HC	>4000g	35.53	81.72	1.94 (1.32 – 2.87)	0.79 (0.66 – 0.94)	33.75	82.87
	AC	>4000g	34.21	93.10	**4.96 * (2.93 – 8.39)**	0.70 (0.59 – 0.83)	56.52	84.38
		>4500g	45.45	88.45	**3.94 * (1.94 – 7.99)**	0.62 (0.36 – 1.06)	10.87	98.13
	EFW	>4000g	46.05	89.66	**4.45 * (2.99 – 6.76)**	0.60 (0.49 – 0.74)	53.85	86.38
		>4500g	54.55	83.38	**3.28 * (1.82 – 5.90)**	0.55 (0.29 – 1.04)	9.23	98.34
20-28 weeks	AA growth velocity	>4000g	23.03	88.61	**2.02 * (1.02 – 3.99)**	0.87 (0.77 – 0.98)	79.55	37.43
		>4500g	4.61	97.47	1.82 (0.39 – 8.55)	0.98 (0.93 – 1.03)	77.78	41.18
28-36 weeks	AA growth velocity	>4000g	23.38	89.38	**2.20 * (1.29 – 3.74)**	0.86 (0.75 – 0.98)	38.30	80.53
	EFW growth velocity	>4000g	54.55	78.02	**2.48 * (1.83 – 3.36)**	0.58 (0.45 – 0.75)	41.18	85.89
		>4500g	66.67	72.19	**2.40 * (1.55 – 3.71)**	**0.46 * (0.21 – 1.03)**	7.84	98.39

BPD = biparietal diameter
HC = head circumference
AC = abdominal circumference
AA = abdominal area
EFW = estimated fetal weight
# moderately useful likelihood ratio= dark shading
* slightly useful likelihood ratio = light shading
Sens = sensitivity
Spec = specificity
LR+ = positive likelihood ratio with 95% confidence interval in brackets
LR- = negative likelihood ratio with 95% confidence interval in brackets
PPV = positive predictive value
NPV = negative predictive value

Table 3.5(2) Performance of fetal biometry (above the 90th percentile) in the prediction of clinical outcomes.

	Fetal growth parameter	Outcome	Sens	Spec	LR+	LR-	PPV	NPV
28 weeks	HC	CS (any)	28.28	86.22	**2.05 * (1.38 - 3.06)**	0.83 (0.73 – 0.95)	33.73	82.89
		CS (emergency)	32.61	85.18	**2.20 * (1.36 – 3.48)**	0.79 (0.65 – 0.97)	18.07	92.77
		Infant hypoglycemia	37.50	84.39	**2.40 * (1.38 – 4.19)**	0.74 (0.54 – 1.01)	10.84	96.39
	AC	CS (any)	24.05	89.22	**2.23 * (1.38 – 3.62)**	0.85 (0.75 – 0.97)	30.65	81.84
	EFW	CS (any)	24.24	86.22	1.76 (1.15 – 2.69)	0.88 (0.78 – 0.99)	30.38	82.10
		CS (elective)	25.93	85.36	1.77 (1.07 – 2.93)	0.87 (0.74 – 1.02)	17.72	90.45
		Infant hypoglycemia	33.33	85.02	**2.23 * (1.15 – 3.87)**	0.78 (0.59 – 1.05)	10.13	96.18
36 weeks	BPD	CS (any)	19.54	89.83	1.92 (1.13 – 3.26)	0.90 (0.80 – 1.00)	32.69	81.53
		CS (elective)	26.09	89.61	**2.51 * (1.42 – 4.43)**	0.82 (0.69 – 0.98)	23.08	91.03
	HC	CS (any)	32.18	83.14	1.91 (1.30 – 2.80)	0.82 (0.70 – 2.95)	32.56	82.90
		CS (elective)	32.61	81.56	1.77 (1.11 – 2.82)	0.83 (0.67 – 1.02)	17.44	91.01
	EFW	CS (elective)	34.78	86.49	**2.58 * (1.61 – 4.12)**	0.75 (0.61 – 0.94)	23.53	91.74

BPD = biparietal diameter
HC = head circumference
AC = abdominal circumference
AA = abdominal area
EFW = estimated fetal weight
# moderately useful likelihood ratio
* slightly useful likelihood ratio
Sens = sensitivity
Spec = specificity
LR+ = positive likelihood ratio
LR- = negative likelihood ratio
PPV = positive predictive value
NPV = negative predictive value

3.6 DISCUSSION

3.6 (1) FETAL GROWTH AT 20, 28 AND 36 WEEKS

The Fetal Growth Study is the first study of substantial size to prospectively assess fetal growth, including growth velocities, with standard biometric ultrasound measures in a cohort of overweight and obese women throughout gestation and to compare these parameters with normal population standards.

The findings of The Fetal Growth Study indicate that maternal overweight and obesity is significantly associated with increased fetal growth, an effect that is evident from 20 weeks gestation when compared with published normal values. Additionally, when compared with population standards, the relative contributions of head and abdominal growth change throughout pregnancy with abdominal growth dominating in the second trimester and head growth in the third trimester.

Few studies have specifically examined the effect of maternal BMI on fetal growth over the course of pregnancy as assessed by ultrasound. The Generation R study in the Netherlands reported EFW Z-scores obtained at mid pregnancy (18-25 weeks) and late pregnancy (after 25 weeks) by BMI quintiles (Ay et al 2009). The 4th quintile group, with a BMI of 23.5-26.4 were noted to have a late pregnancy EFW Z-score of 0.14 and the 5th quintile group (BMI >26.4) an EFW Z-score of 0.33 (Ay et al 2009), suggesting that higher maternal BMI contributes to an increased EFW. Whilst the study populations are not directly comparable in terms of maternal BMI, Ay and colleague's report of higher EFW Z-score from 25 weeks for women with higher BMI, is consistent with the documented EFW Z-scores of 0.24 at 28 and 36 weeks in the Fetal Growth Study. Specifically, The Fetal Growth Study demonstrated an increase in the proportion of fetuses with EFW measures recorded in the higher percentile ranges, reflecting the skewed distribution observed across the population studied.

Consistent with the documented increased static measures of growth, The Fetal Growth Study demonstrated an increase in daily incremental growth velocities for all parameters, evident from 20 weeks' gestation and persisting to 36 weeks' gestation. Although direct comparison with the work of others is hampered by different populations under investigation, this is in keeping with the available literature. Ay and colleagues have also reported increasing EFW growth rates with increasing pre-pregnancy BMI, using the first quintile of BMI as the reference group (Ay et al 2009). With each successive quintile, significantly higher EFW growth rates were observed in the third trimester, increasing from an additional 1.99 g/week (95% CI 1.10 – 2.88) in the second quintile BMI group, to an additional 4.39 g/week (95% CI 3.48 – 5.29) for the 5th BMI quintile group (Ay et al 2009).

The findings of The Fetal Growth Study allow the contribution of various growth parameters to accelerated growth, in the context of high maternal BMI, to be ascertained. Whilst it has been consistently reported that excess fetal growth associated with maternal diabetes is related to increased abdominal growth (Kernaghan et al 2007; Wong et al 2002; Wong et al 2006), findings from The Fetal Growth Study suggest that in women with high BMI, head and abdominal growth both contribute to the noted increase in EFW at different time points in gestation. Specifically, abdominal growth appears the dominant contributor to increased fetal weight at 20 weeks' gestation, whilst from 28 weeks onwards, head growth is the more significant contributor to the overall increase in fetal weight. AC Z-scores were highest at 20 weeks and subsequently decreased over the course of pregnancy, with 23% of fetuses recording an AC above the 90th percentile at 20 weeks, decreasing to 12% at 28 and 36 weeks. In contrast, head circumference Z-scores continued to increase throughout gestation with 20% of fetuses recording a HC above the 90th percentile at 36 weeks' compared with 16% at 28 weeks and 9% at 20 weeks gestation.

Similar findings have been reported in a retrospective study of fetal growth in women with gestational diabetes and impaired glucose tolerance, involving women of all BMI categories (Schaefer-Graf et al 2003). A range of maternal characteristics were examined for their impact on the risk of AC above the 90th percentile from 24 weeks to birth (Schaefer-Graf et al 2003). At 24 weeks, but not in the third trimester, maternal obesity was significantly associated with AC growth suggesting an isolated early influence of BMI on abdominal growth (Schaefer-Graf et al 2003).

When comparing fetal growth velocity in the Fetal Growth Study with the low-risk reference population, all growth velocity Z-scores were greater (Owen et al 1996). Specifically, BPD and FL growth velocity Z-scores were higher than AA growth velocity Z-scores, again suggesting that head growth may contribute more than abdominal growth to the observed increase in EFW.

This is in contrast to the report of Wong and colleagues who published growth velocities in a population of 174 pregnant women with pre-existing diabetes (Wong et al 2006), where ultrasound assessment of growth occurred at approximately 4 weekly intervals from 18 weeks' gestation. The mean BMI of the study population was 27.8 (+/- 7.2) kg/m^2 with 65% of women overweight or obese (BMI ≥ 25 kg/m^2). Growth velocities for BPD, FL and AA were calculated and compared with the population standard to derive growth velocity Z-scores (Owen et al 1996). Fetal growth velocities for all parameters were increased from 26 weeks' gestation, the greatest effect evident in AA growth velocity (Z-score = 1.44) (Wong et al 2006).

When comparing fetal growth parameters with published population standards, potential limitations should be considered. Whilst the commonly utilised EFW formulae including those published by Hadlock, have been validated by numerous authors, most have been performed in later pregnancy, with very few pregnancies of less than 24 weeks (Coomarasamy et al 2005; Dudley 2005). This

raises questions about the validity of calculating EFW at earlier gestational ages as has been performed in The Fetal Growth Study. Although EFW is not routinely reported at early gestational ages, the calculation of EFW using externally collected data in this study has allowed calculation of growth velocities and limited comparison with normal values. Comparison with population growth parameters and velocities is limited not only by potential sources of bias but also by the quality and generalisability of the population standards. Although widely accepted and recommended by the ASUM, the data is derived from a cross sectional study that at later gestations included less than 100 pregnancies at each week of gestational age (Westerway et al 2000) and included women of unknown BMI categories. Similarly, the growth velocities published by Owen and colleagues have been derived from a small study of 274 low-risk pregnancies in the early 1990s (Owen et al 1996) in Scotland. Whilst an alternative comparator for The Fetal Growth Study might be women from a similar population with normal BMI, the comparison with charts in current clinical use enabled the ultrasound data to be provided to care providers in the same format as a clinically indicated ultrasound.

It would appear that the growth trajectories and contributions to fetal growth that exist in the presence of high maternal BMI differ from those described in the context of diabetes. Specifically, in women who are overweight or obese, abdominal growth is the more significant contributor to fetal weight up until 28 weeks gestation, after which time head growth becomes the more dominant parameter.

The association between maternal BMI and fetal head growth in late pregnancy has been described previously, albeit in populations with largely normal or low BMI (Goldenberg et al 1997; Wills et al 2010). It has been suggested that in these populations, improved maternal nutrition is associated with maternal BMI, which in turn promotes placental growth and development in early pregnancy,

thus enhancing increased fetal growth in late pregnancy (Wills et al 2010). Supporting this hypothesis, higher maternal BMI has been documented to be associated with increased placental volume in early – mid pregnancy (Wills et al 2010). A larger placenta, whilst requiring more energy itself, has a larger surface area, which allows increased nutrient transfer to the fetus (Wills et al 2010). While beyond the scope of the aims of this thesis, it will be possible in the future to determine placental to birthweight ratios for a subset of study participants to evaluate this further.

It is clear from many studies examining the fetal programming hypothesis that size at birth is related to outcomes in later life, with nutritional influences at different times during pregnancy and early infant development influencing clinical and health outcomes (Barker 2007; Barker et al 2002; Hanson et al 2008; Harding 2001). To date, very few studies have examined fetal growth and its components in relation to later infant and childhood outcomes.

The Generation R study has followed a large population of women and their infants from early pregnancy into childhood, evaluating the relationship between ultrasound derived fetal growth parameters in early pregnancy and infant development (Henrichs et al 2010). In their follow up study of infant neurodevelopment at 6 to 18 months, higher HC and EFW growth at mid- and late - pregnancy was associated with a lower risk of delayed infant development, independent of postnatal growth (Henrichs et al 2010). It has been suggested that head circumference growth is associated with brain volume (Cooke et al 1977). Therefore more optimal brain development, as reflected by head circumference growth may result in more optimal infant development, an effect seen to be operating from as early as mid-pregnancy. The ongoing follow up of women and their infants recruited to the LIMIT randomised trial, within which the Fetal Growth Study is nested, will provide the opportunity to evaluate such potential effects in a population of women who are overweight or obese in pregnancy.

3.6 (2) THE EFFECT OF BMI AND GESTATIONAL WEIGHT GAIN

The Fetal Growth Study has examined the effect of maternal BMI category and gestational weight gain on fetal biometry and fetal growth velocities. The results of The Fetal Growth Study indicate that in a population of women who are overweight or obese, both maternal BMI category and gestational weight gain modify fetal growth, predominantly through a modification of abdominal and overall growth. When fetal growth biometry Z-scores were compared between women who were overweight and those who were obese, BMI category was noted to significantly influence AC and EFW measures at 28 weeks, but not at 36 weeks' gestation. These results are consistent with the findings of Schaefer- Graf (Schaefer-Graf et al 2003), who reported that while maternal obesity was strongly correlated with AC growth at 24 weeks' this effect was not seen later in pregnancy. In contrast, the findings recently reported by Hure and colleagues in their prospective study of fetal growth, suggest that maternal pre-pregnancy weight is not positively associated with fetal size as assessed by abdominal circumference (Hure et al 2011). Prior reports have included a total of less than 200 women with high BMI and may have been underpowered to detect a clinically relevant difference in fetal growth for women with high BMI (Hure et al 2011; Schaefer-Graf et al 2003).

The Fetal Growth Study did not demonstrate an association between BMI category and fetal growth velocities from either 20-28 weeks' or 28-36 weeks' gestation. These findings are consistent with those of Wong et al (Wong et al 2006), whose study population included 65% of women who were overweight or obese (BMI > 25 kg/m^2). While the reported growth rates for biparietal diameter, femur length, and fetal abdominal area were comparable between obese and non-obese women (Wong et al 2006), the power of the study to detect any differences based on maternal BMI is limited.

Women in the Fetal Growth Study gained an average of 9 kg throughout pregnancy, with over half gaining weight above Institute of Medicine recommendations for their BMI category. When gestational weight gain was above IOM guidelines, estimated fetal weight, head and abdominal growth measures were increased, as compared with gestational weight gain within IOM guidelines. These results are consistent with the only other Australian data reported to date in this area from Hure and colleagues (Hure et al 2011). In their population of women across all BMI categories, over half of women gained weight above Institute of Medicine recommendations for their BMI category, being associated with increased head and abdominal growth (Hure et al 2011).

While there is extensive literature outlining the association of gestational weight gain with maternal and infant outcomes, to date the influence of gestational weight gain on fetal growth throughout pregnancy has not been well described. The Fetal Growth Study contributes new information. Although maternal early pregnancy BMI contributes significantly to accelerated fetal growth from as early as the second trimester, gestational weight gain is an important modifier, and limiting gestational weight gain is likely to modify fetal growth and therefore infant birthweight. It is yet to be determined the optimal gestational weight gain for improved maternal and infant outcomes, and whether gestational weight gain lower than that recommended by the IOM is beneficial for women and their infants.

3.6 (3) CORRELATION WITH AND PREDICTION OF CLINICAL OUTCOMES

The findings of The Fetal growth Study indicate a significant association between a range of ultrasound derived fetal growth measures at 28 and 36 weeks' gestation with high infant birthweight. Furthermore, EFW, head and abdominal growth were associated with mode of birth with measures above the 90th percentile increasing the likelihood of caesarean section for women.

At 28 and 36 weeks, AC and EFW growth was associated with birthweight above 4500g, whilst HC was associated with birthweight above 4000g but not 4500g. A similar association was noted in Schafer-Graf's study of fetal growth in 368 women with diabetes or impaired glucose tolerance diagnosed in pregnancy (Schaefer-Graf et al 2003). Ultrasound biometry data was examined retrospectively and outcomes compared for fetuses with AC ≥ 90th percentile at 28 weeks with fetuses with AC < 90th percentile at the same time point (Schaefer-Graf et al 2003). Identification of an AC measurement above the 90th percentile at 28 weeks was significantly associated with the infant being LGA at birth (OR 1.04; 95% CI 1.01–1.08) (Schaefer-Graf et al 2003).

The Fetal Growth Study identified the only predictor of clinical outcomes with a moderately useful positive likelihood ratio to be AC above the 90th percentile at 28 weeks (LR+ 6.56 for birthweight above 4500g, LR- 0.37). The calculated likelihood ratio for EFW to predict birthweight above 4500g was slightly lower at 4.86 with a negative likelihood ratio of 0.33, both in the slightly useful range. These findings are consistent with those of the systematic review published by Coomarasamy and colleagues, which is to date the most comprehensive assessment of the diagnostic accuracy of EFW and AC measures in the prediction of macrosomia (Coomarasamy et al 2005). When summarising results across studies, EFW greater than the 90th percentile resulted in a positive LR of 9.3 (95% CI 3.7–24) and a negative LR 0.37 (95% CI 0.14 – 0.93) for birthweight greater than the 90th percentile (Coomarasamy et al 2005).

Fetal abdominal circumference did not perform as well as EFW for the prediction of birthweight, when considering five studies that examined abdominal circumference. Furthermore, four of the studies included utilised a threshold for AC of 36cm at term (equivalent to the 90th percentile) (Coomarasamy et al 2005). For this threshold, the positive LR for predicting a birthweight over 4000g was 6.9 (95% CI 5.2 to 9.0) and the negative LR 0.37 (95% CI 0.30–0.45) (Coomarasamy et al 2005). In The Fetal Growth Study, fetal AC measures above the 90th percentile performed better at

28 weeks, than 36 weeks, with positive likelihood ratios of 6.56 and 3.94 and negative likelihood ratios of 0.32 and 0.62 respectively. In contrast to the findings of the systematic review, AC rather than EFW provided superior positive likelihood ratios at both 28 and 36 weeks in The Fetal Growth Study.

In addition to static measures of growth being associated with high infant birthweight, high AA and EFW growth velocity Z-scores were associated with birthweight above 4000 and 4500g, suggesting an additional potential predictor for macrosomia/large for gestational age. However neither are likely to be clinically useful with likelihood ratios only in the slightly useful range. Although very few studies have utilized growth velocities in the prediction of macrosomia or high birthweight, these findings are consistent with previous reports. In Kernaghan's study of fetal growth in women with varying degrees of impaired glucose tolerance, the best predictor of birthweight above the 95th percentile was a fetal growth velocity Z-score of greater than 1.7 with a sensitivity of 35% and specificity of 75%, implying limited usefulness in predicting high birthweight (Kernaghan et al 2007). Outside a research setting, static measures of fetal growth are more likely to be clinically applicable and relevant to clinicians as growth velocities are not routinely reported, although accelerated growth may be able to be appreciated from a growth trajectory which crosses increasing percentile lines.

In The Fetal Growth Study, EFW and AC parameters above the 90th percentile in the third trimester, in addition to high growth rates of the same parameters were both associated with high infant birthweight. Future work should focus on determining which aspect of fetal growth is the best predictor of high birthweight and what measures are most useful for application in the clinical setting.

HC, AC and EFW growth Z-scores above the 90th percentile were significantly associated with a woman's chance of requiring both an elective and emergency caesarean section. In particular, fetal

growth Z-scores above the 90th percentile for EFW at 28 and 36 weeks were significantly associated with a woman's chance of elective caesarean section, raising the possibility that the provision of ultrasound results to clinicians may have contributed to in an increase in elective CS. These results are consistent with those of the Cochrane systematic review by Bricker and colleagues (Bricker et al 2008) assessing the effects on pregnancy outcome of routine late pregnancy ultrasound (after 24 weeks gestation) in women with low risk pregnancies. Randomised and quasi-randomised studies were considered with 8 trials (27,024 women) included. The authors noted a slightly increased risk of caesarean section for women in the screened group, although this did not reach statistical significance (Bricker et al 2008).

Whilst it may appear from the findings of The Fetal Growth Study that suspicion of a large for gestational age fetus is associated with an increase in caesarean section, there is little evidence to suggest that this is associated with improved health outcomes for either the woman or her infant. Management of the suspected large for gestational age fetus at term is aimed at reducing the inherent risks, namely birth trauma and neonatal treatment for the infant and operative birth and perineal trauma for the woman.

Various approaches to management of suspected macrosomia have been evaluated in the literature. The Cochrane review of induction of labour for suspected macrosomia by Irion and colleagues included 3 studies (372 women) (Irion et al 2000). Compared with expectant management, induction of labour for suspected macrosomia was not shown to reduce the risk of caesarean section (relative risk (RR) 0.96, 95% confidence interval (CI) 0.67 to 1.38) or instrumental vaginal birth (RR 1.02, 95% CI 0.60 to 1.74)(Irion et al 2000). Whilst fetal growth in the current study was associated with an increase in caesarean section, there did not appear to be an association with induction of labour. Similar findings have been reported in the Cochrane systematic review evaluating elective birth in

diabetic pregnant women (Boulvain et al 2001). A single trial comparing a policy of active induction of labour at 38 completed weeks of pregnancy, with expectant management until 42 weeks was included. While the risk of caesarean section was not statistically different between treatment groups (relative risk (RR) 0.81, 95% confidence interval (CI) 0.52 - 1.26), the risk of macrosomia was reduced following active induction of labour (RR 0.56, 95% CI 0.32 - 0.98) (Boulvain et al 2001). Additionally, three cases of mild shoulder dystocia were reported in the expectant management group.

It may be that upon noting an estimated fetal weight above the 90th percentile at either 28 or 36 weeks, clinicians were more likely to offer or suggest a caesarean section as the most appropriate mode of birth, rather than offering induction of labour. In The Fetal Growth Study, all clinicians were provided with fetal growth information following any research ultrasound, in a similar format to a clinically indicated ultrasound. While it is not possible to conclude that provision of ultrasound reports increases interventions such as caesarean section, it warrants further evaluation, particularly recognising the clearly increased perioperative and postpartum risks following operative birth among women who are overweight or obese (Abenhaim et al 2007; Callaway et al 2006; Dodd et al 2011a; Doherty et al 2006).

When evaluating the performance of fetal growth measures in predicting maternal and infant outcomes, although significant associations were present as described above, all measures were poorly predictive of clinical outcomes with low likelihood ratios and sensitivity. Head circumference growth measures above the 90th percentile at 28 weeks but not 36 weeks were significantly associated with a woman's chance of emergency caesarean section, although the likelihood ratio was low (2.13) and the sensitivity poor (32.6%). Evaluation of the indication for emergency CS did not suggest specific trends.

Head circumference growth measures above the 90th percentile, but not overall estimated fetal weight measures, at 28 and 36 weeks were associated with maternal gestational diabetes. Whilst other authors have suggested maternal diabetes during pregnancy is associated predominantly with an increase in abdominal growth (Schaefer-Graf et al 2003; Wong et al 2006), the growth pattern identified in the Fetal Growth Study suggests that different metabolic and nutritional effects may be operational in an overweight and obese population. Further work should evaluate the contribution of not only BMI and gestational weight gain but also maternal glucose intolerance to all components of fetal growth.

Future research should focus on establishing which individual measures of fetal growth are most predictive of macrosomia and adverse maternal outcomes and establish likelihood ratios and sensitivity and specificity for each measure. It is important that any tool for predicting outcomes such as high birthweight, caesarean section or infant hypoglycemia be simple and easy to apply in the clinical setting. Although the ultrasound measurement of fetal weight in the third trimester may predict birthweight with acceptable accuracy, the impact of providing utlrasound results on clinical management and outcomes is not clear, although there is an apparent increase in CS when a fetus is suspected to be large for gestational age.

3.6 (4) WHAT THIS STUDY ADDS

Maternal overweight and obesity is associated with a significant increase in fetal growth Z-scores from 20 weeks, suggesting that high maternal BMI influences fetal growth from early in pregnancy with contribution from both head and abdominal growth.

Independent of maternal BMI, gestational weight gain has been identified as an important contributor to fetal growth, with weight gain above the IOM recommendations associated with increased fetal growth.

EFW above the 90th percentile in the third trimester is strongly and significantly associated with birthweight above 4000g and 4500g and a woman's chance of elective caesarean section.

3.6 (5) IMPLICATIONS FOR PRACTICE

In women who are overweight or obese in pregnancy, estimated fetal weight above the 90th percentile at 28 or 36 weeks, is associated with an increased risk of infant birthweight above 4000g and above 4500g.

Gestational weight gain is an important potential modifier of fetal growth, however until it is clear that intervening to limit weight gain in pregnancy is associated with improved outcomes for women and their infants caution is warranted.

3.6 (6) IMPLICATIONS FOR RESEARCH

Population norms for fetal biometry and body composition have limitations due to small samples and study design. Due to increasing overweight and obesity amongst pregnant women, generalisability is limited. Local researchers should consider creating an updated Australasian population ultrasound growth standard.

Future research should examine in more detail the significant predictors of abnormal fetal growth, including estimated fetal weight, abdominal circumference and measures of fetal adiposity.

The results of ongoing randomised trials, including the LIMIT trial are likely to provide important information regarding the effects of limiting weight gain in pregnancy.

The incidence of gestational diabetes in Fetal Growth Study cohort was similar to that documented in women with high BMI throughout South Australia. However, it was not possible to specifically examine the effect of gestational diabetes in a statistically robust manner due to relatively small numbers. Future studies should examine the additional effect of gestational diabetes on fetal growth in a population of women with high pre-pregnancy BMI. This may be possible through subsequent examination of entire LIMIT randomised trial cohort at the completion of recruitment.

3.6 (7) CONCLUSIONS

Maternal overweight and obesity is significantly associated with increased fetal growth, an effect that is evident from 20 weeks gestation when compared with published normal values. Additionally, when compared with population standards, the relative contributions of head and abdominal growth change throughout pregnancy with abdominal growth dominating in the second trimester and head growth in the third trimester. Gestational weight gain exerts an important effect on fetal growth, with weight gain above current IOM recommendations being associated with increased fetal growth.

Further research, including a comparison of fetal growth trajectories between treatment groups in the LIMIT randomised trial will provide important information regarding the effect of limiting weight gain in pregnancy on fetal growth.

4. RESULTS OF THE FETAL GROWTH STUDY 2: FETAL BODY COMPOSITION, THE EFFECT OF BMI AND GESTATIONAL WEIGHT GAIN AND CORRELATION WITH CLINICAL OUTCOMES

4.1 INTEROBSERVER VARIABILITY

Ultrasound fetal body composition measurements (SSFM, AFM, MTTM, MTFM and MTLM) were collected for 49 women at 28 weeks' and 28 women at 36 weeks' gestation for the assessment of inter-observer variability. Intra-class correlation coefficients were calculated for the measures of fetal body composition (Table 4.1). At 28 and 36 weeks' gestation, moderate agreement was demonstrated for the measures of SSFM, MTTM and MTFM, with only fair agreement for AFM and MTLM (Table 4.1).

Table 4.1 Intraclass correlation coefficients (ICC) for measures of fetal body composition at 28 and 36 weeks with corresponding level of agreement.

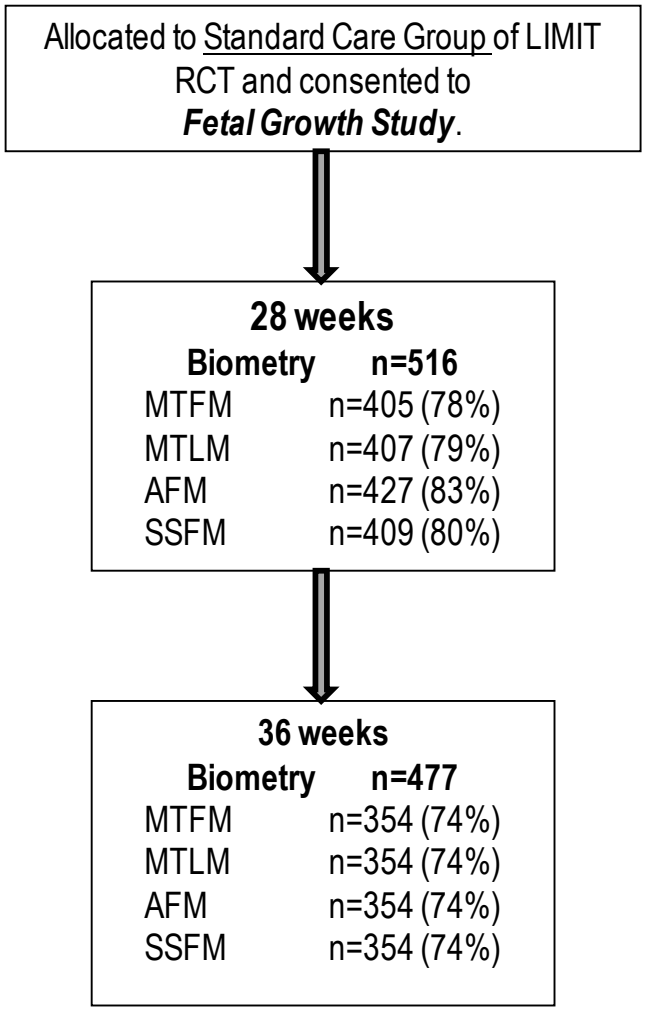
Variable	ICC 28 weeks	*Level of agreement	ICC 36 weeks	*Level of agreement
SSFM	0.58	Moderate	0.53	Moderate
AFM	0.29	Fair	0.20	Fair
MTTM	0.52	Moderate	0.40	Moderate
MTLM	0.33	Fair	0.26	Fair
MTFM	0.58	Moderate	0.47	Moderate

Figures are intraclass correlation coefficients
SSFM = subscapular fat mass
AFM = abdominal fat mass
MTTM = mid thigh total mass
MTFM = mid thigh fat mass
MTLM = mid thigh lean mass
* Reference for level of agreement: (Landis et al 1977)

4.2 FETAL BODY COMPOSITION

At 28 weeks, fetal body composition measures were obtained for approximately 80% of women who attended for a research ultrasound. At 36 weeks, fetal body composition measures were obtained for 74% of women who attended for a research ultrasound.

Figure 4.2 (1) Study flow chart – fetal body composition measures obtained



Overall, for each fetal body composition measure studied (MTFM, MTLM, AFM and SSFM) at each gestational age, 28 and 36 weeks' gestation, median measures were increased when compared with the published normal ranges (Table 4.2). At 28 weeks, fewer MTFM and MTLM measures were observed in the less than 5th percentile range; whilst more measures than expected were observed in the 95th percentile range. For SSFM, significantly fewer measures were observed in the less than 5th percentile range (Table 4.2). At 36 weeks gestation, fewer MTFM and SSFM measures fell into the less than 5th percentile range and more were observed in the 95th percentile range, whilst for MTLM, significantly more measures were observed in the greater than 95th percentile range (Table 4.2).

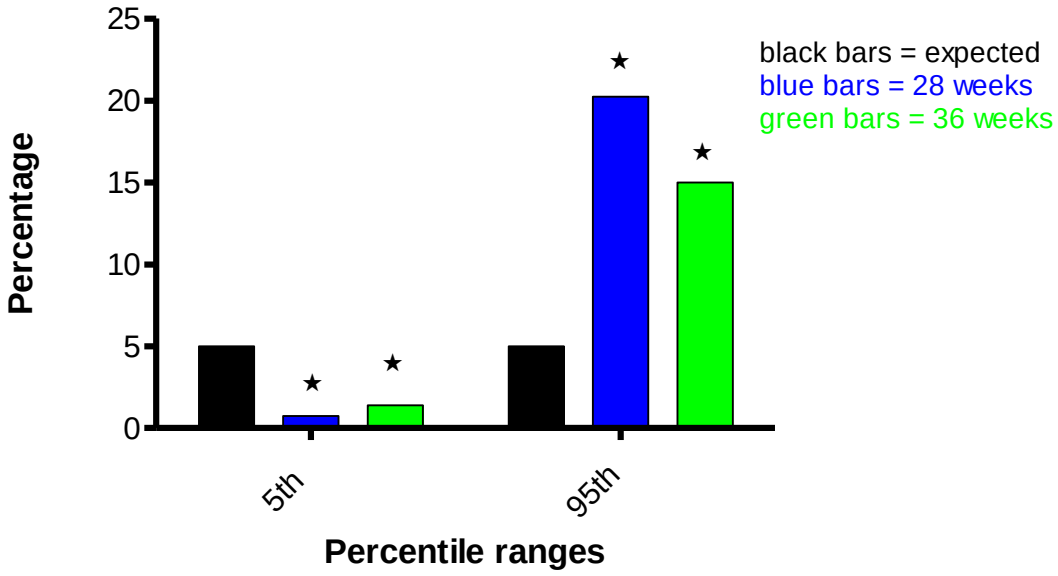
There was evidence of an upward shift of body composition measures at both 28 weeks' and 36 weeks' gestation, for MTFM, MTLM and SSFM, when considering the proportion of measures falling within the 5th and 95th percentile ranges (Table 4.2). This information is presented graphically, where the black bars indicate the expected proportions, with the observed proportions at 28 weeks' gestation in blue, and at 36 weeks' gestation in green (Figure 4.2(2), Figure 4.2(3), Figure 4.2(4), Figure 4.2(5).

Table 4.2 Fetal body composition measures and comparison with normal ranges

	MTFM (cm^2)		MTLM (cm^2)		AFM (mm)		SSFM (mm)	
Weeks of gestation	**28**	**36**	**28**	**36**	**28**	**36**	**28**	**36**
Median	4.50	11.32	4.93	8.82	3.63	5.99	3.17	5.32
Interquartile range	1.59	3.88	1.30	3.57	1.36	1.97	1.05	1.88
Published Normal Ranges* **Mean** **95%Confidence interval**	3.70 2.45 – 5.58	9.66 6.40 – 14.57	3.91 2.72 – 5.62	8.03 5.59 – 11.54	3.58 2.38 – 5.41	5.68 3.76 – 8.57	2.95 1.86 – 4.68	4.58 2.89 – 7.25
% BC measures <5th centile ##	**0.74**	**1.41**	**0.00**	4.24	6.32	3.63	**1.96**	**1.65**
P value	**<0.01**	**<0.01**	**<0.01**	0.52	0.20	0.24	**0.01**	**<0.01**
% BC measures >95th centile ##	**20.25**	**14.69**	**21.62**	**9.60**	5.85	3.91	6.85	**12.12**
P value	**<0.01**	**<0.01**	**<0.01**	**<0.01**	0.41	0.36	0.09	**<0.01**

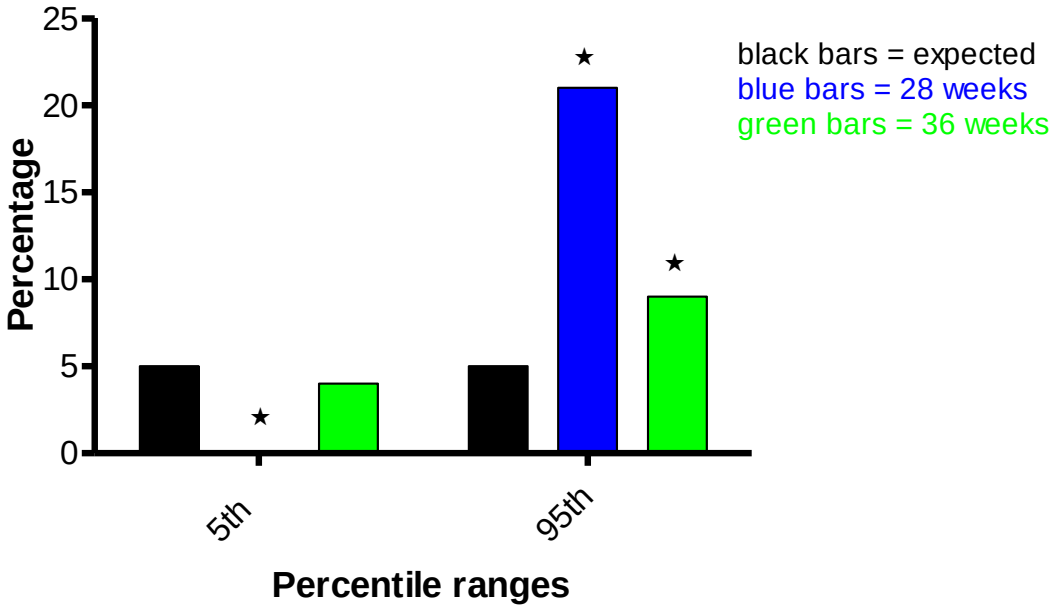
Figures are median and interquartile range or # Mean and 95%CI or ## percentages
* Published normal values derived from Larciprete and colleagues (Larciprete et al 2003)
MTFM = mid thigh fat mass
MTLM = mid thigh lean mass
AFM = abdominal fat mass
SSFM = subscapular fat mass
X^2 = Chi-square test for goodness of fit between expected and observed percentage of measures in percentile ranges
Statistically significant results in bold text with shaded box

Figure 4.2(2) Mid thigh fat mass distribution by percentile ranges



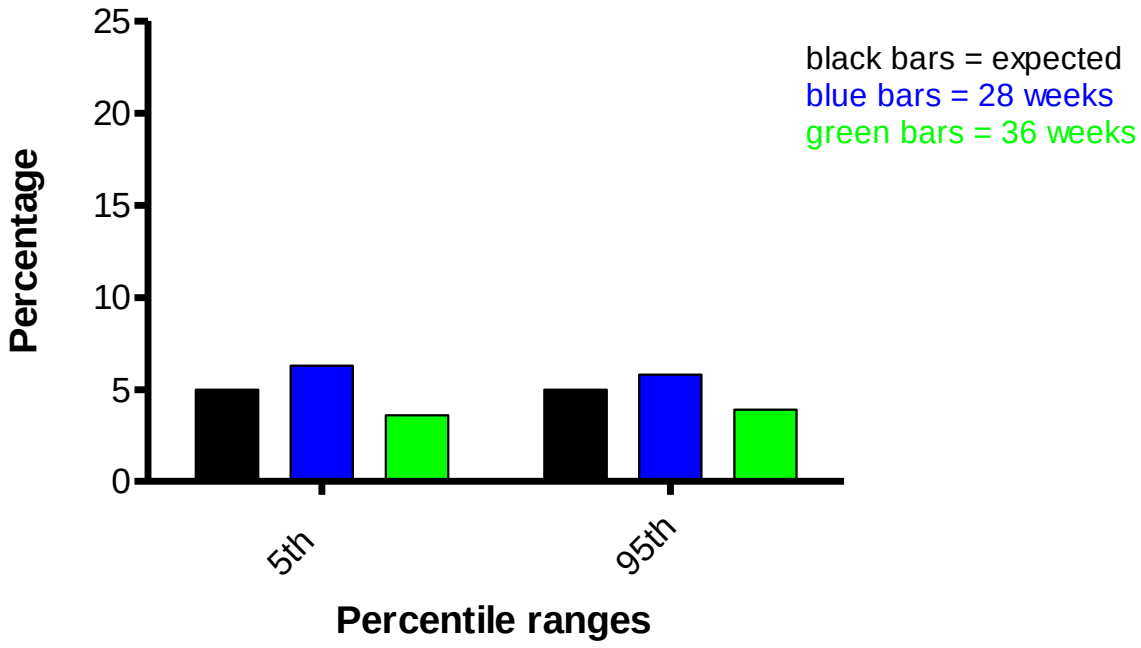
★ indicates statistically significant difference between proportions for expected and observed at each gestational age.

Figure 4.2(3) Mid thigh lean mass distribution by percentile ranges



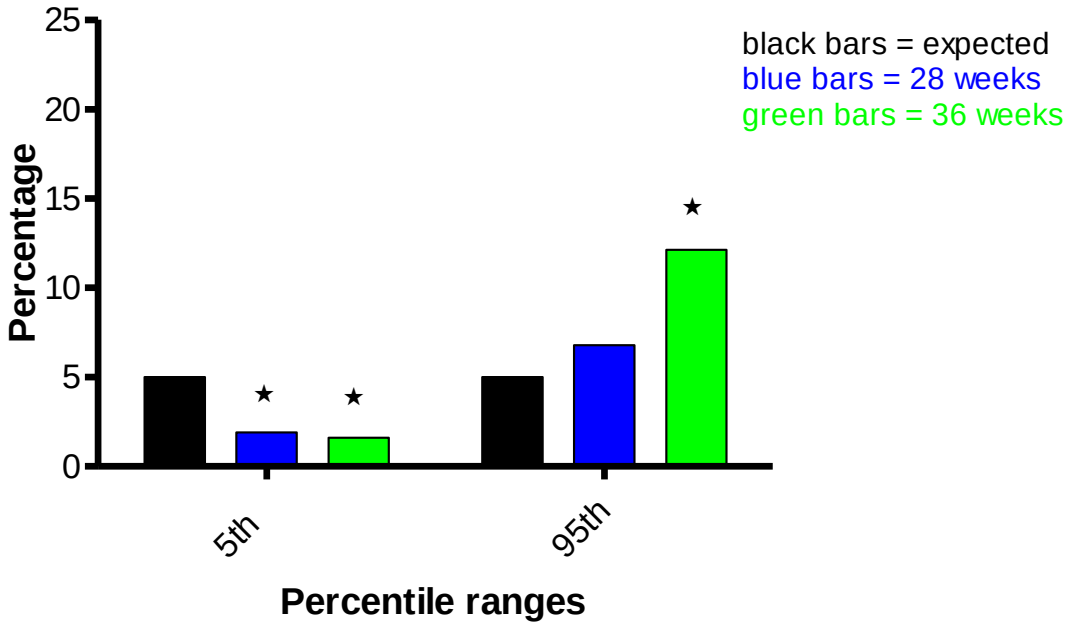
★ indicates statistically significant difference between proportions for expected and observed at each gestational age.

Figure 4.2(4) Abdominal fat mass distribution by percentile ranges



★ indicates statistically significant difference between proportions for expected and observed at each gestational age.

Figure 4.2(5) Subscapular fat mass distribution by percentile ranges



★ indicates statistically significant difference between proportions for expected and observed at each gestational age.

4.3 THE EFFECT OF BMI AND GESTATIONAL WEIGHT GAIN

At 28 weeks' and 36 weeks' gestation, maternal BMI category did not significantly influence fetal body composition measures (Table 4.3(1)). In contrast, gestational weight gain category (below, within or above Institute of Medicine recommendations for specific BMI category) did influence fetal body composition. At 28 weeks' gestation, gestational weight gain above IOM recommendations was significantly associated with higher AFM and SSFM measures (Table 4.3(2)). At 36 weeks, gestational weight gain above IOM recommendations was significantly associated with higher MTFM and SSFM measures (Table 4.3(2)).

Table 4.3(1) Effect of BMI category on fetal body composition

	MTFM (cm^2)		MTLM (cm^2)		AFM (mm)		SSFM (mm)	
Weeks' gestation	**28**	**36**	**28**	**36**	**28**	**36**	**28**	**36**
Overweight	4.46	11.23	4.86	8.69	3.47	5.92	3.25	5.20
Obese class I	4.58	11.57	4.85	8.97	3.71	6.01	3.01	5.34
Obese class II	4.47	11.58	4.97	9.13	3.62	5.86	3.15	5.42
Obese class III	4.67	11.36	5.19	8.01	3.91	6.23	3.40	5.53
P value (effect across BMI categories)	0.74	0.72	0.21	0.15	0.25	0.57	0.23	0.87

Figures are median measures of body composition for each BMI category
MTFM = mid thigh fat mass
MTLM = mid thigh lean mass
AFM = abdominal fat mass
SSFM = subscapular fat mass
P value = effect across BMI categories with Kruskal- Wallis testing

Table 4.3(2) Effect of Gestational weight gain category on fetal body composition

	MTFM (cm^2)		MTLM (cm^2)		AFM (mm)		SSFM (mm)	
Weeks	**28**	**36**	**28**	**36**	**28**	**36**	**28**	**36**
GWG below IOM	4.29	11.13	4.92	8.80	3.35	5.52	2.99	4.90
GWG within IOM	4.53	10.92	4.77	8.67	3.58	6.00	3.10	5.29
GWG above IOM	4.58	11.84	4.95	8.84	3.83	6.10	3.34	5.45
P value (effect across GWG categories)	0.09	**0.04**	0.86	0.58	**0.01**	0.08	**0.01**	**0.04**

Figures are median measures of fetal body composition for each GWG category
MTFM = mid thigh fat mass
MTLM = mid thigh lean mass
AFM = abdominal fat mass
SSFM = subscapular fat mass
Bold/shaded= statistically significant
P value = effect across GWG categories with Kruskal- Wallis testing

4.4 FETAL BODY COMPOSITION AND CORRELATION WITH CLINICAL OUTCOMES

At 28 weeks gestation, there was a significant relationship between fetal body composition and infant birthweight. Fetuses with MTFM measures greater than the 95th percentile at 28 weeks were significantly more likely to weigh more than 4000g or 4500g at birth. Similarly, fetal body composition measures at 36 weeks were significantly associated with infant birthweight. Fetuses with MTFM or MTLM measures greater than the 95th percentile were significantly more likely to weigh more than 4000g or 4500g at birth (Table 4.4(1)).

Fetal body composition at 28 weeks was significantly associated with a woman's mode of birth; when SSFM was reported above the 95th percentile, a woman was significantly more likely to birth by emergency caesarean section (Table 4.4(2)).

At 36 weeks' gestation fetal body composition was significantly associated with mode of birth, with women more likely to require a caesarean section or emergency caesarean section if AFM was above the 95th percentile. If SSFM at 36 weeks was above the 95th percentile, women were significantly more likely to experience a caesarean section (Table 4.4(2)).

Table 4.4(1) Association between fetal body composition (above 95th percentile) and infant birthweight

	MTFM		MTLM		AFM		SSFM	
Weeks' gestation	**28**	**36**	**28**	**36**	**28**	**36**	**28**	**36**
Birthweight > 4000g	**0.01**	**0.01**	0.06	**<0.01**	0.87	0.25	0.20	0.51
Birthweight > 4500g	**<0.01**	**<0.01**	0.13	**0.04**	0.19	0.60	1.00	0.41

Figures are P values for Chi-square test for independence
MTFM = mid thigh fat mass
MTLM = mid thigh lean mass
AFM = abdominal fat mass
SSFM = subscapular fat mass
Bold/shaded = statistically significant

Table 4.4(2) Association between fetal body composition (above 95th percentile) and clinical outcomes

	MTFM		MTLM		AFM		SSFM	
Weeks' gestation	28	36	28	36	28	36	28	36
Association with maternal outcomes								
IOL	1.00	0.28	0.54	1.00	0.11	0.07	0.79	0.15
CS (any)	0.39	0.11	0.52	1.00	0.69	**0.01**	0.13	**0.04**
CS (elective)	0.71	0.16	1.00	0.28	1.00	0.26	0.41	0.46
CS (emergency)	0.21	0.92	0.53	0.56	0.39	**0.04**	**<0.01**	0.09
PIH	0.22	0.34	0.91	1.00	0.70	0.58	1.00	0.35
Pre-eclampsia	0.20	0.87	0.25	1.00	1.00	1.00	0.10	0.70
GDM	0.52	0.49	0.52	1.00	0.80	0.48	0.61	0.84
Association with infant outcomes								
Shoulder dystocia	0.31	0.18	0.35	1.00	0.12	0.69	1.00	0.49
NICU admission	0.56	0.68	0.53	1.00	1.00	1.00	1.00	1.00
Hypoglycemia	0.82	0.09	0.16	0.96	1.00	0.15	0.86	1.00

Figures are P values for Chi-square test for independence
Bold/shaded = statistically significant
MTFM = mid thigh fat mass
MTLM = mid thigh lean mass
AFM = abdominal fat mass
SSFM = subscapular fat mass
IOL = induction of labour
CS = caesarean section
PIH = pregnancy induced hypertension
GDM = gestational diabetes

4.5 PERFORMANCE OF FETAL BODY COMPOSITION MEASURES IN THE PREDICTION OF MATERNAL AND INFANT OUTCOMES

To assess the potential role of ultrasound measures in prediction of infant birthweight and clinical outcomes, sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, positive predictive value and negative predictive value were calculated (Table 4.5(1)). Three predictors produced a moderately useful positive likelihood ratio; MTFM above the 95th percentile at 28 weeks, with a LR+ of 11.29 for birthweight above 4500g, MTFM above the 95th percentile at 36 weeks with a LR + of 8.56 for birthweight above 4500g and MTLM above the 95th percentile at 36 weeks with a LR+ of 5.27 for birthweight above 4500g. The remainder of likelihood ratios were only slightly useful or not at all useful (Khan et al 1999). The sensitivity of most measures for predicting birthweight and clinical outcomes was less than 50%, however specificity was greater than 80% in most cases.

Table 4.5(1) Performance of fetal body composition (above the 90th percentile) in the prediction of macrosomia and clinical outcomes

		Outcome	Sens	Spec	LR+	LR-	PPV	NPV
28 weeks	MTFM	Birthweight >4000g	31.94	83.03	1.88 (1.23 – 2.89)	0.82 (0.69 – 0.97)	33.33	82.12
		Birthweight >4500g	8.33	99.26	**11.29# (2.33 – 54.78)**	0.92 (0.86 – 0.99)	75.00	80.30
	SSFM	CS (emergency)	28.57	91.58	**3.39* (1.73 – 6.65)**	0.78 (0.62 – 0.99)	20.00	94.57
36 weeks	MTFM	Birthweight >4000g	31.37	84.73	**2.05* (1.25 – 3.38)**	0.81 (0.67 – 0.98)	28.57	86.38
		Birthweight >4500g	9.80	98.85	**8.56# (2.11 – 34.71)**	0.91 (0.83 – 1.00)	62.50	84.92
	MTLM	Birthweight >4000g	40.63	84.70	2.65 (1.61 – 4.38)	0.70 (0.52 – 0.94)	23.21	92.61
		Birthweight >4500g	9.38	98.22	**5.27# (1.32 – 21.02)**	0.92 (0.82 – 1.03)	37.50	90.49
	AFM	CS (any)	9.72	97.91	**4.65* (1.61 – 13.41)**	0.92 (0.85 – 1.00)	53.85	81.21
		CS (emergency)	11.11	97.21	**3.99* (1.29 – 12.30)**	0.91 (0.81 – 1.03)	30.77	90.75

MTFM = mid thigh fat mass
MTLM = mid thigh lean mass
AFM = abdominal fat mass
SSFM = subscapular fat mass
# moderately useful likelihood ratio= dark shading
* slightly useful likelihood ratio = light shading
Sens = sensitivity
Spec = specificity
LR+ = positive likelihood ratio
LR- = negative likelihood ratio
PPV = positive predictive value
NPV = negative predictive value

4.6 DISCUSSION

4.6 (1) INTEROBSERVER VARIABILITY

The findings of The Fetal Growth Study indicate moderate inter-observer agreement for measures of SSFM, MTTM, and MTFM at both 28 and 36 weeks' gestation. The inter-observer agreement between AFM and MTLM were considered fair. The calculation of intra-class correlation coefficients as a measure of reliability has been advocated as a more robust method than assessing the coefficient of variation (Shrout et al 1979). The results described here are the first to demonstrate that measures of fetal body composition are reproducible between different observers using robust methodology in a population of pregnant women who are overweight or obese, thus supporting the use of fetal body composition measures in a research context.

While fetal body composition measures have been evaluated in the prediction of fetal macrosomia and growth restriction, there has been very little published on the reliability and reproducibility of these measurements. Three studies have reported inter-observer agreement using the coefficient of variation methodology (Galan et al 2001; Larciprete et al 2003; Parretti et al 2003). While these three studies assess inter-observer variability, their methods are not directly comparable with those used in The Fetal Growth Study.

Larciprete and colleagues measured fetal SSFM, AFM, MTFM and MTLM parameters on 20 women with low risk pregnancies across two observers (Larciprete et al 2003). In this study, the coefficient of variation was reported as an approximation for inter-observer correlation or agreement, and stated to be 7.0-10.9% for all measures (Larciprete et al 2003). Parretti and colleagues studied 66 non-obese women with abnormal glucose tolerance, and compared the ultrasound findings with 123 non-obese women with gestational diabetes (Parretti et al 2003). A subset of 20 images was reviewed to assess intra-observer variability using coefficients of variance. Inter-observer variability was reported to be 5.2%

for anterior abdominal wall thickness, 6.1% for subscapular thickness, and 5.9% for mean thigh fat mass, the authors recommending the incorporation of these measures into clinical assessments for women with impaired glucose tolerance (Parretti et al 2003). In contrast, Galan and colleagues reported a higher inter-observer coefficient of variation of 11.1% for anterior abdominal wall thickness, in their assessment of 20 images from women with a singleton pregnancy (Galan et al 2001).

A strength of The Fetal Growth Study is the larger sample size of women compared with all previous studies reported in the literature. Women who are overweight or obese during pregnancy have a well recognised increased risk of having an infant born large for gestational age (Dodd et al 2011a). Furthermore, high maternal BMI and the associated technical difficulties of ultrasound scanning (Aagaard-Tillery et al 2010; Dashe et al 2009) influences the reliability of antenatal detection of disordered fetal growth, even when using traditional fetal biometry assessments. The results of The Fetal Growth Study suggest that there is fair to moderate inter-observer agreement in the measurement of AFM, SSFM, MTTM, MTLM and MTFM, which in a research setting provides a tool that can be used to further evaluate clinical correlations between adiposity measures and health outcomes in a larger population

4.6 (2) FETAL BODY COMPOSITION AT 28 AND 36 WEEKS

The Fetal Growth Study has described fetal body composition prospectively in a large group of overweight and obese women using ultrasound at 28 and 36 weeks of pregnancy comparing with population reference standards (Larciprete et al 2003). Maternal overweight and obesity is associated with a significant increase in measures of both fetal lean and fat mass. When compared with a low-risk reference population, the relative contributions of fat and lean mass change throughout pregnancy. Thigh lean and fat mass are a more dominant contributor at 28 weeks and subscapular fat mass contributes more significantly at 36 weeks.

Very few studies have specifically examined fetal body composition throughout pregnancy in women with high BMI. Hure and colleagues have published the first prospective report detailing fetal growth and body composition throughout pregnancy in women of all BMI categories (Hure et al 2011). Body composition measures assessed included thigh lean and fat area and abdominal lean and fat area (Hure et al 2011). While the measures of thigh lean and fat area are directly comparable with those utilised in The Fetal Growth Study, the abdominal lean and fat measures are unique in the literature and may not be directly comparable with other reported studies. Despite differences in methodology, maternal pre-pregnancy weight does not appear to be significantly associated with abdominal lean mass area (Hure et al 2011).

Although there is limited information available describing fetal body composition in women who are overweight or obese, comparisons can be made with the literature describing neonatal body composition in various populations. A number of small retrospective studies have evaluated neonatal body composition in women with and without gestational diabetes (Catalano et al 2003; Sewell et al 2006). In general, when the effect of maternal overweight and obesity is considered, high maternal BMI appears to be associated with an increase in total and relative fat mass (Catalano et al 2003; Sewell et al 2006). The effect of BMI on lean mass is not consistent between studies, with some suggesting a decrease (Hull et al 2008), whilst others report there to be no significant effect of increasing BMI (Catalano et al 2003).

The results from previously described studies of both fetal and neonatal body composition are consistent with those of the Fetal Growth Study when considering the effect of maternal BMI on measures of fetal fat mass. While high maternal BMI was associated with increased fetal and neonatal fat mass, the effect of maternal BMI on fetal lean mass is less clear. Hure and colleagues reported no significant association between maternal pre-pregnancy weight and measures of lean mass (abdominal

lean mass area and thigh lean mass area) (Hure et al 2011). In contrast, The Fetal Growth Study demonstrated that high maternal BMI was associated with an increase thigh lean mass. Differences in methodology and the study populations may account for some of the variations observed.

4.6(3) THE EFFECT OF BMI AND GESTATIONAL WEIGHT GAIN

The Fetal Growth Study has evaluated the effect of BMI category and gestational weight gain on measures of fetal body composition. While measures of fetal body composition were increased among women with high BMI, BMI category did not modify fetal body composition. These findings are consistent with the limited available literature (Hure et al 2011; Sewell et al 2006), although the sample size of these studies is small. Furthermore, differences in methodology somewhat limit comparisons being made directly with The Fetal Growth Study.

In contrast, gestational weight gain was identified as a significant modifier of fetal fat mass, but not lean mass, an effect evident at both 28 weeks' and 36 weeks' gestation, findings which are consistent with a retrospective study of neonatal body composition in infants born to women with normal glucose tolerance (Sewell et al 2006). In contrast however, others report increasing gestational weight gain to be a significant predictor of abdominal lean area but not abdominal fat, lean thigh or thigh and fat area (Hure et al 2011), although the study population and methodology prevents direct comparisons. It is quite possible that the effect of gestational weight gain on body composition varies considerably between women of different BMI categories.

Strengths of the Fetal Growth Study include the prospective study design, the large sample of women with high BMI and the use of well validated fetal body composition measures. On the basis of the current study and previous reports, gestational weight gain appears an important modifier of fetal body composition. Fetal fat mass measures, which have been shown to be increased in an overweight and

obese population, are significantly modified by maternal gestational weight gain. These results are consistent with the findings previously reported from the Fetal Growth study where gestational weight gain was found to significantly modify fetal growth as assessed by biometry. Limiting gestational weight gain is likely to be an important means to modify the well documented outcome of large for gestational age amongst infants born to women who are overweight and obese in pregnancy.

4.6(4) CORRELATION WITH AND PREDICTION OF CLINICAL OUTCOMES

The Fetal Growth Study has assessed potential correlations between measures of fetal body composition and maternal and infant outcomes including infant birthweight, indicating a significant association between a number of ultrasound derived measures of fetal body composition and high infant birthweight and mode of birth. High fetal fat mass measures at 28 and 36 weeks' gestation were associated with an increased likelihood of caesarean section for women.

In the Fetal Growth Study, mid thigh fat mass above the 95th percentile at both 28 weeks' and 36 weeks' gestation was significantly associated with birthweight above 4000g and 4500g. Mid thigh lean mass was significantly associated with birthweight above 4000g and 4500g at 36 weeks' gestation. To date there has been limited reporting of clinical outcomes in existing studies of fetal body composition. Hure and colleagues reported all measures of fetal body composition to be significantly correlated with birthweight (Hure et al 2011). Additionally, lean measures of body composition were more strongly correlated with birthweight than were fat meaures (Hure et al 2011). Despite different methodologies and study populations, the results of the two studies are consistent.

The Fetal Growth study identified the only predictors of high infant birthweight with moderately useful positive likelihood ratios to be mid thigh fat mass above the 95th percentile at 28 weeks (LR+ 11.29 for

birthweight above 4500g), mid thigh fat mass above the 95th percentile at 36 weeks (LR+ 8.56 for birthweight above 4500g) and mid thigh lean mass above the 95th percentile at 36 weeks (LR+ 5.27 for birthweight above 4500g). The role of thigh lean and fat mass in predicting high infant birthweight has not been previously reported. Despite positive likelihood ratios in the moderately useful range, the clinical utility of such measures is likely to be limited by low sensitivity and negative likelihood ratios considered to be of low value.

The Fetal Growth Study did not identify abdominal fat mass to be significantly associated with infant birthweight, in contrast to previous reports by Bethune, Petrikovsky and Higgins (Bethune et al 2003; Higgins et al 2008; Petrikovsky et al 1997). All of these studies have reported improvements in the detection of macrosomia with the use of abdominal fat mass meaurements. The contrasting results with The Fetal Growth Study may in part be due to different population characteristics with Higgins and Bethune evaluating only women with diabetes in pregnancy (either pre-pregnancy or gestational) (Bethune et al 2003; Higgins et al 2008), and while Petrikovsky included women of all "risk" catgeories, maternal BMI was not reported (Petrikovsky et al 1997). A relatively small proportion of women in The Fetal Growth Study were diagnosed with gestational diabetes, although the rate is similar to that seen in women with high BMI throughout South Australia (Dodd et al 2011a). With increased available sample size at the completion of recruitment of the entire LIMIT cohort, further evaluation of the effects of gestational diabetes and high maternal BMI may be possible.

While the Fetal Growth Study did not demonstrate fetal abdominal fat mass to be associated with infant birthweight, fetal abdominal fat mass above the 95th percentile at 36 weeks was significantly associated with both caesarean section and emergency caesarean section, with positive likelihood ratios of 4.65 and 3.99 respectively. The association of fetal body composition with maternal outcomes has not been previously reported but are consistent with the findings reported in chapter three, where abdominal

circumference and estimated fetal weight above the 90th percentile were both associated with an increased chance of caesarean section. Future work should focus on which measures of fetal body composition are the best predictors of infant birthweight and maternal outcomes and also identify which measures are likely to be most useful in the clinical setting.

4.6 (5) WHAT THIS STUDY ADDS

The results described here are the first to demonstrate that measures of fetal body composition are reproducible between different observers using robust methodology in a population of pregnant women who are overweight or obese, supporting their use in a research context.

High maternal BMI is associated with a significant increase in measures of both fetal lean and fat mass. When compared with previous published measures of fetal body composition from a low-risk population, the relative contributions of fat and lean mass change throughout pregnancy. Thigh lean and fat mass are a more dominant contributor at 28 weeks and subscapular fat mass contributes more significantly at 36 weeks.

Whilst measures of fetal body composition are increased when compared with the normal low-risk population, maternal BMI category is not a significant modifier of fetal body composition.

Gestational weight gain category significantly modifies measures of fetal fat mass, but not lean mass at both 28 weeks' and 36 weeks' gestation.

A number of ultrasound derived measures of fetal body composition at 28 weeks' and 36 weeks' gestation are significantly associated with high infant birthweight and mode of birth, with high fetal fat mass measures increasing the likelihood of caesarean section for women.

4.6 (6) IMPLICATIONS FOR PRACTICE

Gestational weight gain is an important potential modifier of fetal growth and adiposity, however until it is clear that intervening to limit weight gain in pregnancy is associated with improved outcomes for women and their infants caution is warranted.

4.6 (7) IMPLICATIONS FOR RESEARCH

Measures of fetal body composition are reproducible between different observers using robust methodology, supporting their use in a research context.

Future work should focus on which measures of fetal body composition are the best predictors of infant birthweight and clinical outcomes and also identify which measures are likely to be most useful in the clinical setting.

4.6 (8) CONCLUSIONS

Maternal overweight and obesity are associated with a significant increase in measures of both fetal lean and fat mass, when compared with previously published values from a low-risk population. Gestational weight gain, but not maternal BMI category is a significant modifier of fetal adiposity, suggesting that limiting weight gain to current IOM recommendations may be an important potential intervention. Further research, including a comparison of fetal body composition between treatment groups in the LIMIT randomised trial will provide important information regarding the effect of limiting weight gain in pregnancy.

5. OVERALL CONCLUSIONS

5.1 FETAL GROWTH, THE EFFECT OF BMI AND GESTATIONAL WEIGHT GAIN AND CORRELATION WITH CLINICAL OUTCOMES

For each of the fetal growth parameters studied, at each gestational age, measured median Z-scores did not deviate appreciably from the reported standard population means. However, there was evidence of an upward shift in growth parameters, when considering the proportion of Z-score values falling within each percentile range. Growth velocities for all parameters were similar to or greater than the published normal ranges for both 20 to 28 and 28 to 36 weeks' gestation.

Maternal overweight and obesity was associated with increased fetal growth from 20 weeks' gestation, with abdominal growth the predominant contributor in the second trimester and head growth in the third trimester.

At 20 weeks' gestation and 36 weeks' gestation, maternal BMI category did not significantly influence fetal growth Z-scores, but did modify EFW and AC Z-scores at 28 weeks' gestation. Maternal BMI category did not significantly influence fetal growth velocities from 20 through to 36 weeks' gestation. In contrast, gestational weight gain category did influence fetal growth parameters, including both AC and EFW Z-scores at 28 and 36 weeks, and AA and EFW growth velocities from 28 to 36 weeks.

Maternal BMI category modified fetal abdominal and overall growth at 28 weeks. Gestational weight gain independently modified fetal growth from 28 weeks, with weight gain above current IOM recommendations associated with increased abdominal and overall fetal growth.

Increased fetal growth, particularly measures of abdominal growth and overall weight at 28 and 36 weeks were significantly associated with high infant birthweight. Fetal growth measures above the 90th percentile at 28 weeks, particularly for AC and EFW, were significantly associated with birth by caesarean section. Women were significantly more likely to experience an elective caesarean section if BPD, HC or EFW at 36 weeks had been noted to be above the 90th percentile.

Increased fetal growth measures at both 28 and 36 weeks were significantly associated with an increased chance of caesarean section for women who are overweight or obese

When considering associations between fetal growth measures and clinical outcomes using likelihood ratios, an AC measurement above the 90th percentile at 28 weeks predicted birthweight above 4500g, with a LR+ of 6.56, in the moderately useful range. The sensitivity of most measures for predicting birthweight was less than 50%. However specificity was greater than 80% in most cases.

Most measures of fetal growth do not perform well as clinical predictors, with the majority of likelihood ratios slightly useful at best.

5.2 FETAL BODY COMPOSITION, THE EFFECT OF BMI AND GESTATIONAL WEIGHT GAIN AND CORRELATION WITH CLINICAL OUTCOMES

Ultrasound fetal body composition measurements (SSFM, AFM, MTTM, MTFM and MTLM) were collected at 28 weeks' and 28 women at 36 weeks' gestation with moderate agreement between observers demonstrated for the measures of SSFM, MTTM and MTFM, but only fair agreement for AFM and MTLM.

Measures of fetal body composition were reproducible between different observers using robust methodology, supporting their use in a research context.

For each fetal body composition measure studied (MTFM, MTLM, AFM and SSFM) at each gestational age, 28 and 36 weeks' gestation, there was evidence of an upward shift in fetal body composition measures, when considering the proportion of measures falling within each percentile range.

Maternal overweight and obesity were associated with a significant increase in measures of both fetal lean and fat mass, when compared with previously published values from a low-risk population.

At 28 weeks' and 36 weeks' gestation, maternal BMI category did not significantly influence fetal body composition measures. In contrast, gestational weight gain category (below, within or above Institute of Medicine recommendations for specific BMI category) did influence fetal fat mass. Further research,

including a comparison of fetal body composition between treatment groups in the LIMIT randomised trial will provide important information regarding the effect of limiting weight gain in pregnancy.

Gestational weight gain, but not maternal BMI category was a significant modifier of fetal adiposity, suggesting that limiting weight gain to current IOM recommendations may be an important potential intervention for improving maternal and infant health outcomes.

A range of ultrasound derived measures of fetal body composition were significantly associated with high infant birthweight and mode of birth. High fetal fat mass measures at 28 and 36 weeks' gestation were associated with an increased likelihood of caesarean section for women. Despite positive likelihood ratios in the moderately useful range, the clinical utility of most measures is likely to be limited by low sensitivity and negative likelihood ratios considered to be of low value.

Whilst measures of fetal body composition are significantly associated with high infant birthweight and mode of birth, clinical utility is likely to be limited by low sensitivity and negative likelihood ratios in the "not useful" range.

The Fetal Growth Study presented in this thesis is the first study of substantial numbers of women and babies that has prospectively assessed fetal growth and body composition in overweight and obese pregnant women. The findings of The Fetal Growth Study have provided clinically relevant information and identified further areas requiring research that will contribute to improving the health of women and their babies.

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