FETAL GROWTH MEASUREMENT

A Thesis Submitted for the Degree of

Doctor of Philosophy of the Australian National University

by

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Declaration

I hereby declare that this thesis is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person except where due acknowledgment is made in the text of this thesis.

Signature 

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The role of fetal growth velocity in clinical practice

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Abstract

Ultrasound assessment of the fetus in pregnancy has become an integral part of antenatal care. For ultrasound practitioners and pregnant women alike, it is difficult to imagine pregnancy care without ultrasound. The assessment of fetal growth by evaluating changes in serial ultrasound measurements and haemodynamic assessment of the fetus with Doppler ultrasound have become valuable tools in obstetric management. Identification of pathologic fetal growth has become increasingly important as fetal growth restriction is associated with increased risk of adverse perinatal outcomes and undiagnosed fetal growth restriction is a risk factor for stillbirth. Large fetuses may also complicate pregnancies and confer an increased risk for birth trauma and neonatal morbidity.

With widespread adoption of ultrasound into obstetric practice, how to best discriminate between normal and pathological growth, which charts to reference these measurements to, and when to perform the measurements remain contentious issues. With increasing emphasis placed on ultrasound measures of fetal size and Doppler parameters to identify abnormal growth and guide clinical management, it has become imperative that charts used for these measures are reliable and used consistently. Continued lack of standardisation has the potential for misdiagnosis of abnormal fetal growth, and the suitability of reference charts derived from one population for use on a different population is an unresolved issue and problematic in multiethnic populations.

In this thesis I explore the origins of measurements used in ultrasound assessment of the fetus and how these are used to measure fetal growth and wellbeing. Ultrasound providers were surveyed to gain insights into current Australian practice in performing and reporting third trimester ultrasound. The performance of fetal reference charts currently used (now more than twenty-five years old) and recently published growth standards were evaluated in a prospective cross-sectional study of 1642 datasets. Lastly, methods to measure fetal growth velocity were assessed in a retrospective longitudinal study of 636 datasets.

The exploration of the emergence of measurements used in ultrasound assessment of the fetus consolidates many disparate sources and provides a single account of the origin of fetal measurements. Survey findings reveal inconsistent third trimester reporting practices persist in Australia, with at least four different population based reference charts in current use and lack of uniformity in fetal Doppler assessment. Evaluation of fetal reference charts currently recommended by the Australasian Society of Ultrasound in Medicine and recently published Intergrowth 21st growth standards reveal discrepancies in the proportion of measurements falling below the 10th centile and above the 90th centile, suggesting the Intergrowth 21st standards are not suitable for use in the Australian population. Assessment of fetal growth velocity between 20 and 36 weeks failed to demonstrate a strong relationship between reduced growth velocity and adverse neonatal outcome.

These findings have several implications for clinical practice. Inconsistent third trimester reporting practices not only raises the possibility of false-positive and false-negative diagnosis of fetal growth restriction but also has the potential for conflicting diagnoses based on the providers' choice of reference chart. A consensus on which reference charts should be used in Australia would help remedy this situation, however, evaluation of the recently published Intergrowth 21st growth standards indicates they are unsuitable for use in the Australian population. Adoption into clinical practice would result in a greater proportion of fetuses classified as large for gestational age, and fewer classified as small for gestational age. The absence of a strong relationship between reduced growth velocity between 20 and 36 weeks and adverse neonatal outcome implies formal reporting of fetal growth velocity is currently not warranted.

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Chapter One

Background

1.1 Introduction

An important aspect of antenatal care is the assessment of fetal growth. Suboptimal growth, and growth restriction in particular, increase the risk of perinatal mortality and morbidity[1, 2] and stillbirth[3]. An underlying assumption is that all fetuses have a pre-determined growth potential, which accounts for the normal variability in the birthweight of healthy infants[4]. Mechanisms which disrupt growth potential result in suboptimal growth.

Birthweights below or above certain thresholds are used to identify neonates at risk of short term complications. The World Health Organisation define low birthweight as below 2500g (irrespective of gestational age at birth growth) when collating global data[5]. In high resource countries with well-established and healthcare systems, birthweights are compared to population charts to determine the birthweight centile for gestational age at birth. Birthweights between the 10th and 90th centiles are considered appropriate for gestational age (AGA) and birthweights below the 10th centile are considered small for gestational age (SGA)[6]. Birthweights above the 90th centile for gestational age define large for gestational age (LGA) and birthweights above 4000g or 4500g are used to define macrosomia[7, 8].

1.2 Low birthweight and growth restriction

Globally, low birthweights are thought to account for 16.5% of all births with a higher incidence (25%) in low and middle income countries and an incidence of 3% - 9% in developed countries[9, 10]. Growth restricted neonates experience higher rates of respiratory distress, perinatal asphyxia, hypoglycaemia, hypocalcaemia, sepsis and immunological compromise[11]. The neonatal period may be further

compromised by complications associated with prematurity, including respiratory distress syndrome, necrotising enterocolitis, and intracranial haemorrhage. Long term health problems include an increased risk of cognitive delay, poor academic performance, behavioural problems and hyperactivity in childhood. Growth disorders such as failure to thrive and childhood obesity have also been reported, along with higher rates of adult onset diseases such as cardiovascular disease, diabetes mellitus, and renal disease[12].

Genetic syndromes are thought to account for up to 5% of cases of growth restriction, however, this may well be underestimated with the emergence of microarray analysis which is able to detect microdeletions and duplications[13]. Fetuses with structural anomalies are at increased risk for growth restriction[13] and fetal infection accounts for 5 – 10% of cases[10]. Maternal exposure to teratogens including radiation, environmental toxins, smoking, illicit drugs and alcohol confer an increased risk for growth restriction as does living at high altitudes. Other maternal factors include malnutrition, anaemia, chronic hypertension, and renal disease. Placental dysfunction and abnormal placentation in particular, is the most common cause of fetal growth restriction and often referred to as placental insufficiency[13].

1.3 High birthweight

In developed countries, there has been an increase of 15 – 20% of births with birthweights above the 90th centile for gestational age[8]. In pregnancies complicated by excessive fetal growth, neonates are at increased risk of hypoxia, hypoglycaemia and birth trauma[14], namely shoulder dystocia resulting in brachial plexus injury[15, 16]. Maternal complications include increased risks for genital tract trauma and postpartum haemorrhage, and higher rates of Caesarean section birth[14, 16]. For neonates with a high birthweight, there is an increased prevalence of childhood obesity, and cardiovascular disease, type 2 diabetes mellitus, hypertension and cancer later in life[8]. Several genetic syndromes are linked to fetal overgrowth, and maternal factors include race, high parity, maternal diabetes during pregnancy, maternal obesity, and weight gain during pregnancy[7, 8].

1.4 Antenatal detection of suboptimal growth

Antenatal detection of suboptimal growth is desirable as this allows targeted surveillance to help inform clinical decisions regarding timing of delivery to improve perinatal outcomes[17, 18]. Since the widespread adoption of ultrasound in antenatal care and the ability to measure the fetus, ultrasound measurements have been used to establish gestational age, fetal size, and fetal growth by evaluating changes in serial ultrasound measurements, and fetal haemodynamic state with Doppler ultrasound techniques.

Birthweight definitions for suboptimal growth have informed the definitions applied to ultrasound measurements of the fetus. Estimated fetal weight (EFW) is calculated using an equation incorporating the fetal measurements and then compared to a reference chart to determine the centile for gestational age. Additionally, the fetal abdominal circumference (AC) centile is considered an indicator of altered fetal growth as this measure reflects somatic growth[19] . The EFW and AC centiles are used to classify fetal size as appropriate for gestational age (AGA), small for gestational age (SGA), or large for gestational age (LGA). Typically, measurements between the 10th and 90th centile indicate appropriate growth, measurements below the 10th centile indicate SGA, and measurements above the 90th centile indicate LGA[20].

Size determined from a single ultrasound examination is not synonymous with growth, however, and fetal growth restriction (FGR) is suspected when SGA is identified. It is estimated that approximately 40% of fetuses diagnosed as SGA will have no underlying pathology and are constitutionally small, healthy fetuses[21]. Further criteria to assist in identification of FGR fetuses in the SGA cohort was proposed in a consensus based definition and includes EFW and AC centiles below the 3rd centile and abnormal Doppler assessment of blood flow in the umbilical, middle cerebral, and uterine arteries[22].

The gestational age at which FGR is diagnosed provides the additional classifications of early onset FGR (prior to 32 weeks) and late onset FGR (after 32 weeks). Early onset FGR is less common and confers greater risks of perinatal mortality and morbidity, the underlying cause for placental

dysfunction is frequently maternal vascular malperfusion, abnormal umbilical artery Doppler changes are common, and there is a strong association with pre-eclampsia[13]. Late onset FGR is generally a milder condition and can be more difficult to diagnose as the umbilical artery Doppler typically remains normal. Nonetheless, late onset FGR is still associated with adverse outcomes as sudden deterioration causes hypoxia and stillbirth[13, 23].

Several confounding factors limit the antenatal detection of suboptimal growth. Guidelines and recommendations from professional bodies do not have a consistent approach in definitions for LGA[14], SGA and FGR[17]. Most guidelines defining LGA, SGA and FGR stop short of recommending which chart should be used to define the 3rd, 10th, 90th and 97th centiles[13, 14].

While there may be an expectation that FGR fetuses will be identified exclusively amongst those identified as SGA, some growth restricted fetuses will have EFW and AC measurements above the 10th centile threshold depending on their individual growth potential[13]. Failure to identify these fetuses has significant implications as these fetuses are also at risk of antepartum death. It has been estimated that 74% of antepartum deaths occur in fetuses considered AGA in previous ultrasound examinations[24].

The ability of ultrasound measurements to reflect the true size of the fetus and potential measurement errors are a further consideration. Measurement error is the difference between a given measurement and the true value, however, when measuring the fetus the true value is seldom known[25]. Systematic measurement errors produce a consistent effect and in the case of ultrasound measurements may be associated with calibration of ultrasound equipment, and errors incurred when programming formulae used in calculation packages. An operator that consistently over or under measures, or consistently performs the measurement in the incorrect anatomical plane will also result in systematic error. The measurement method may also contribute to systematic error, for example, using an ellipse tool to measure a circumference the relevant chart methodology utilised a two diameter method[25]. Random errors are chance occurrences and may arise from image pixelation

errors related to digital image formation. The unpredictable nature of target misregistration where signals from anatomical structures imaged with ultrasound are not placed in the correct location in the image, may also be considered a source of random error[26]. Averaging multiple measurements can reduce random error, however, this approach may not be appropriate when some measurements are made on sub-optimal images[25]. Measurement errors are compounded when the BPD, HC, AC and FL are combined to estimate the fetal weight[25], and results in a reported estimation error of ± 15 - 20%[13, 27]. The calculated EFW may also vary according to the choice of formula, with some algorithms better suited to estimating weight in the small fetus, and others performing well in the large fetus[27, 28].

Centiles for a given measurement will vary depending on which chart the measurement is referenced to. A considerable number of reference charts have been published and differences in populations and chart methodologies mean that centiles for a given measurement may vary considerably. A study comparing different reference charts demonstrated up to a six-fold increase in measurements classified as below the 5th centile[29].

Most fetal reference charts are derived from local populations and are descriptive, depicting the distribution of fetal measurements for an unselected population[30]. Prescriptive charts by contrast, describe the distribution of fetal measurements in a selected low-risk or ideal population, and are therefore referred to as standards[30]. The EFW may be compared to one of several birthweight charts or an ultrasound based EFW chart, again with the potential for considerable differences in the assigned centile[31]. In an effort to discriminate SGA fetuses truly affected by pathological growth, individual customised EFW charts can be produced by correcting for maternal ethnicity, height, weight and parity and fetal sex to calculate the optimal birthweight at 40 weeks' gestation[32]. Using similar techniques, fetal weight charts can be customised to the population median birthweight at 40 weeks to produce a single fetal weight chart suitable for use by the local population[33].

While it is not unreasonable to expect national consistency in the choice of reference chart, a study in 2013 found there were at least eight fetal growth charts in clinical use in Australia[34]. This means it is

possible for a fetus to be diagnosed as growth restricted by one practitioner, and later that day found to be normally grown by a practitioner using a different reference chart. Despite this, the choice of fetal measurement reference chart remains a contentious issue in Australian ultrasound practices, with many raising concerns regarding the methodology used to construct the charts currently recommended by the Australasian Society for Ultrasound in Medicine[34].

Longitudinal assessment of fetal growth via serial measurements of size has been proposed as an alternative method to identify pathologic growth. How to best measure growth velocity and defining what constitutes a significant change in growth velocity is lacking in SGA guidelines[17]. Broadly speaking, there are two main approaches in assessing reduced growth velocity; the simplest is to assess the change in centile of a given parameter over time. Indeed, the consensus definition of FGR defines reduced growth velocity as measurements crossing centiles by two quartiles[22]. The second is to measure the incremental change in size of a given parameter over time, and compare this to a pre-determined threshold or reference chart[35].

Several confounding factors limit the application of growth velocity assessment in clinical practice. Firstly, guidelines and recommendations from professional bodies do not have a consistent approach in the definition for reduced growth velocity[17].

Secondly, comparison of measurement centiles may be affected by the use of different reference charts for the first and second ultrasound examination. The centiles assigned by different charts may vary greatly[29, 34], creating the potential for incorrect diagnoses of reduced, increased or stable growth velocity. Currently, there is no uniformity in the choice of fetal growth chart, and the charts used may even vary between ultrasound practices within the same region[34].

Thirdly, longitudinal assessment of fetal growth requires at least two ultrasound examinations performed at different time points in the pregnancy to assess the change in size. An additional ultrasound to screen for altered growth velocity would confer additional costs to pregnant women

and the healthcare system. In Australia, third trimester ultrasound is not routinely performed except when there are clinical concerns or known risk factors associated with abnormal growth[6, 36].

Lastly, the heterogeneity in published methods for measuring fetal growth velocity add an additional layer of complexity for the clinician, as there is no standardised definition or formula to assess fetal growth velocity[35].

1.5 Research aims

This aims of this research are:

- to examine the historical development of ultrasound as a tool to measure the fetus
- to investigate current practice in performing and reporting third trimester ultrasound in Australia
- to assess the suitability of the recently published Intergrowth 21st growth standards for use in the Australian population
- to examine methods of measuring fetal growth velocity and whether this measure can be incorporated into clinical practice

This thesis begins with a narrative review of the history of fetal measurement in Chapter Two, exploring the circumstances that led to the standardised measurements we use today. The development of reference charts and differences in chart methodologies charts are examined, together with ultrasound methods for assessment of fetal wellbeing and how this has influenced contemporary practice.

Current trends in performing and reporting third trimester ultrasound are examined in Chapter Three, with particular reference to consistency in chart choice and reporting practice. A previous study published in 2013 found there were at least eight fetal growth charts in clinical use in Australia[34]. The potential for misdiagnosis of growth restriction leading to additional interventions and patient anxiety cannot be underestimated and unfortunately, inconsistencies in the choice of reference chart remain

problematic. A shortcoming of the previous study was that participants did not include radiologists from medical imaging practices where the majority of obstetric ultrasound services in Australia are provided[37]. Therefore, a more inclusive survey was proposed to investigate reasons why ultrasound providers have chosen to use particular reference charts. A web-based survey instrument was developed, utilising drop-down menus for responses where possible, and conditional questioning via skip and/or display logic. Two rating scale questions investigated factors influencing the choice of reference chart, and one open text question invited comment on how third trimester ultrasound is performed and reported. Semi-structured interviews were conducted with general radiologists to gain further insight into third trimester ultrasound reporting practices. The survey was approved by the Australian National University human research ethics committee (ANU HREC 2017/418 and the RANZCOG continuing professional development committee.

The performance of Intergrowth 21st (IG21) in Australian clinical practice is examined in Chapter Four. Arguably one of the most rigorously designed charts of fetal biometry, these charts were published in 2014[38]. Data from a selected low risk population from eight countries were used to create prescriptive longitudinal charts and may be well suited for use in Australia's multiethnic population but are yet to be validated. An observational, prospective, cross-sectional multicentre study was conducted to assess fetal biometry in pregnant women in the second and third trimester for the purpose of assessing the performance of the IG21 charts in the Australian population. The research was approved by the ACT Health Human Research Ethics Committee 2018.ETH.00222/ETH02432, ANU Human Research Ethics Committee 2019/497, Western NSW Local Health District Human Research Ethics Committee 2020-074, Sydney Local Health District Human Research Ethics Committee 2020/PID02715, and Western Health Office for Research 67092.

Lastly, how to best incorporate measurement of growth velocity in third trimester ultrasound is discussed in Chapter Five. This chapter includes a systematic literature review of publications describing methods to measure growth velocity and discusses relationships between altered growth

velocity and clinical outcome. This is followed by a retrospective study of longitudinal fetal growth where methods of measuring growth velocity are compared in order to define thresholds for suboptimal growth relevant to clinical practice. As all pregnant women are offered a routine ultrasound examination in the mid trimester (usually performed at 18 – 20 weeks), and many will have a third trimester ultrasound (often at 35 – 36 weeks) the study assessed growth velocity between these gestational ages. The relationship between neonatal outcomes and reduced growth rate was examined from birth outcome data. The study protocol was approved by ACT Health Human Research Ethics Committee 2021/ETH11858.

Chapter Two

The history of fetal measurement

2.1 Introduction

Ultrasound assessment of the fetus in pregnancy has become an integral part of antenatal care. For ultrasound practitioners and pregnant women alike, it is difficult to imagine pregnancy care without ultrasound[39, 40]. The assessment of fetal growth by evaluating changes in serial ultrasound measurements and haemodynamic assessment of the fetus with Doppler ultrasound have become increasingly important in obstetric management[6, 20, 36, 41]. Ultrasound measurements used in contemporary practice to assess fetal size include the biparietal diameter, head circumference, abdominal circumference and femur length, with the crown rump length the measurement of choice in the first trimester[20, 42]. Amniotic fluid around the fetus is measured to provide a semi-quantitative assessment of amniotic fluid volume, a marker of fetal wellbeing[43]. Additionally, Doppler ultrasound techniques are used to measure the blood flow in the umbilical artery, middle cerebral artery, ductus venosus and uterine arteries as a way to assess the haemodynamic state of the fetus[44]. Circumstances that led to the use of these particular measurements becoming standard in obstetric ultrasound and the evolution of fetal measurement charts are explored in this chapter.

Fundamental to assessing fetal growth is a reliable method to date the pregnancy. Traditional methods incorporated menstrual history and physical milestones, including the onset of pregnancy symptoms (usually 1-3 weeks after conception), first fetal movement (usually by 20 weeks), palpation of uterine size, and detection of fetal heart sounds by stethoscope (usually at 20 weeks) Several conditions impacted the reliability of this method: an irregular menstrual cycle or poor recollection of dates, variability in the onset and severity of pregnancy symptoms, appreciation of fetal movements and detection of fetal heart sounds, and suboptimal assessment of uterine size due to multiple pregnancy, oligohydramnios, polyhydramnios, uterine fibroids, adnexal masses and patient obesity[45].

Fetal growth was assessed by observing serial changes in maternal weight, girth, and uterine size or height[46]. Serial measurement of the uterine height from public symphysis to uterine fundus (SF height) was proposed as a method to monitor fetal growth and screen for abnormal growth[46, 47], and standardised SF measurement still remains an important element of antenatal care[48].

Identification of abnormal fetal growth and growth restriction in particular was confounded by the use of birth weight to define thresholds of maturity. Typically, infants weighing less than 2500g were considered premature regardless of the gestational age at birth [45, 47], and infants weighing more than 2500g were considered term births[45]. This problem was highlighted by William Rumbolz in his 1953 publication *Placental Insufficiency and the Small Undernourished Full-Term Infant*[47] where he described the relationship between poor uterine growth, fetal growth restriction, placental pathology and perinatal morbidity. In JS Wigglesworth's 1968 publication *Disorders of Fetal Growth*[49] he commented:

"fetal growth in late pregnancy is limited by the inability of the maternal environment fully to meet the nutritional needs of the fetus, rather than by any lack of fetal growth potential".

Studies have since shown growth restriction is a factor in half of preterm perinatal deaths and 20% of term perinatal deaths, and is associated with fetal distress in labour, metabolic acidosis leading to cerebral palsy[50], and stillbirth[3]. Recent studies of large population cohorts have also demonstrated fetal growth restriction is associated with increased risk of cardiovascular disease in adulthood[51]. Prenatal identification of the growth restricted fetus seemed elusive without a better way to measure the fetus.

The use of ultrasound in medicine and especially obstetrics began in earnest following Ian Donald's seminal publication *Investigation of Abdominal Masses by Pulsed Ultrasound* in 1958[52]. Donald recognised the potential of ultrasound as a medical imaging modality and acknowledged the importance of reproducibility and reliability, commenting:

"To be of any use at all to the clinician, the echo patterns obtained by pulsed ultrasound must be not only intelligible but also consistently reproducible at the same level in the same case."

Donald's paper described a technique to generate a recognisable image of the anatomy under investigation (known as B-scope or B-mode). Up to this point, ultrasound 'images' consisted of lines representing the returning echoes with the amplitude of the echo along the y – axis and time along the x – axis. This was known as A-scope or A-mode, and the stronger the returning echo, the higher the peak of the graph. Donald's B-mode images produced by early ultrasound equipment were unsophisticated; echo signals were displayed as bright dots on a storage tube oscilloscope as the operator moved the transducer to collect returning echo signals, building up a static image. All echoes over a certain amplitude threshold were displayed with the same brightness, forming a crude two dimensional image that was essentially the white outline of the anatomy under investigation on a black background, giving rise to the term 'bistable' (figure 2.1). The B-mode appearance of several obstetric and gynaecologic cases were described in this paper, and key amongst Donald's observations were that fluid filled structures could be easily identified due to the lack of returning echoes. This made the amniotic cavity of the pregnant uterus an ideal candidate for the application of ultrasound imaging where the fetal head could be reliably identified due to strong reflections from the skull.

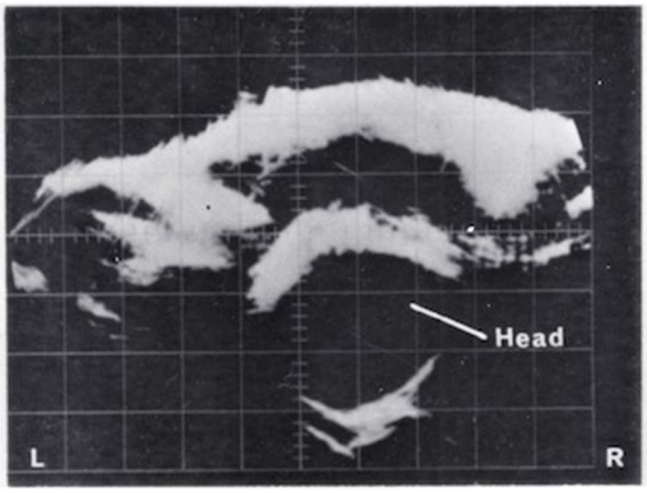

Figure 2.1 *Bistable obstetric echogram (ultrasound image) of the fetal head from 1963. Image reproduced with permission from the Australasian Society of Ultrasound in Medicine.*

2.2 Fetal measurement

2.2.1 The biparietal diameter

The technique of using ultrasound to measure the fetal head was described in 1962 as "ultrasonic cephalometry"[53]. Measurements of the head, or cephalometry, were an important element of anthropometry, the "systematic collection and correlation of measurements of the human body"[54]. Basic cephalometric measurements included the length of the head (occipital frontal diameter), the width of the head (biparietal diameter) and the ratio of these measurements (cephalic index)[55].

Measurements of the width of the fetal head were performed using A-mode ultrasound, where the strong reflections of the fetal skull were displayed on the oscilloscope produced high amplitude peaks (figure 2.2). By measuring the distance between the leading edges of the peaks, and assuming a constant speed of sound through tissue, the distance between the surfaces of the skull could be calculated.

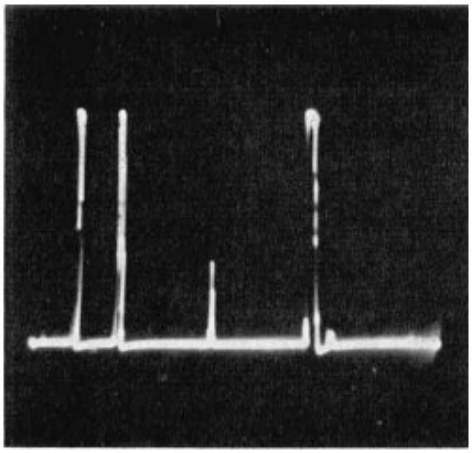

Figure 2.2 *Typical A-mode display demonstrating high amplitude signals from the fetal skull. The first peak represents the strong echo from the maternal abdominal wall. The following high amplitude peaks represent echoes from the parietal bones, with a low amplitude peak representing the interhemispheric fissure positioned midway between these (from Campbell S. An improved method of fetal cephalometry by ultrasound. The Journal of obstetrics and gynaecology of the British Commonwealth. 1968;75(5):568-76. Reproduced with permission Copyright © 2005 John Wiley & Sons Ltd. All rights reserved.)*

While the strongly reflective surfaces of the parietal bones of the skull were ideal to measure the width of the head, the orientation of the fetal head could only be established by external palpation; variability in fetal position meant measurements were not reproducible. To address this issue, Campbell[56] refined the measurement technique by first identifying the orientation of the fetal head using B-mode imaging, then switching to A-mode to record the amplitude peaks of echoes returning from the parietal bones. Measurements between the peaks were made using the innovation of electronic cursors on the oscilloscope, removing a potential source of measurement error that existed when measurements were made by placing a ruler against the oscilloscope screen, or on a photograph of the screen. Identification of a lower amplitude peak midway between the peaks from the parietal bones, representing the interhemispheric fissure (falx cerebri), was key to image reproducibility, and indicated the correct imaging plane for the biparietal diameter (BPD).

Campbell went on to demonstrate the accuracy of this technique by comparing ultrasound BPD measurements made prior to elective caesarean section, with BPD measurements made of each newborn with mechanical callipers. Similarly, Cohen[57] demonstrated good correlation of BPD measurements in the early second trimester with mechanical calliper measurements performed post hysterotomy. He and others[58] noted that ultrasound measurements could be measured consistently using electronic callipers directly on the B-mode image, an observation that paved the way for the integration of measurement callipers into ultrasound equipment[59].

More than 50 years on, identification of the interhemispheric fissure remains a landmark indicating the correct plane for the BPD, and the BPD is still measured from the leading edge of one parietal bone (the outer edge) to the leading edge of the other (the inner edge) by ultrasound practitioners in many countries, including Australia. By demonstrating it was possible to achieve reproducible ultrasound measurements that correlated with direct measurement of the fetal head, Campbell's work launched the development of fetal reference charts.

2.2.2 Impact of new ultrasound technologies

Prototype ultrasound equipment was bulky, and had been developed along the principles of contact scanning, where a transducer attached to a gantry was placed in contact with the patient's skin, or water-bath scanning, where a water bag lay between the transducer and the patient's skin. Both techniques produced static images, meaning an image was produced by combining returning echo signals as the transducer moved across the abdomen, and took several seconds to acquire[59, 60]. Fetal movements during image acquisition impaired image quality and anatomic assessment of the rapidly moving fetal heart was not possible[60].

While new applications for ultrasound in obstetric imaging were explored by researchers, ultrasound technology evolved rapidly. Chroniclers of the history of obstetric ultrasound agree two of the most important developments were grey-scale imaging and real-time scanning[39, 61, 62]. Potentially useful diagnostic information was lost in the production of a bistable image, leading to development of grey-scale imaging by the team led by George Kossoff and William Garrett in 1972[63]. By using a conventional oscilloscope, where the brightness of the dot of light on the screen is proportional to the echo strength, images could be recorded on photographic film capturing up to ten shades of grey (figure 2.3). The grey-scale appearance of several fetal organs were described in this paper, notably the appearance of the liver, stomach and umbilical vein, which eventually became the landmarks for the measurement plane of the fetal abdomen[64].

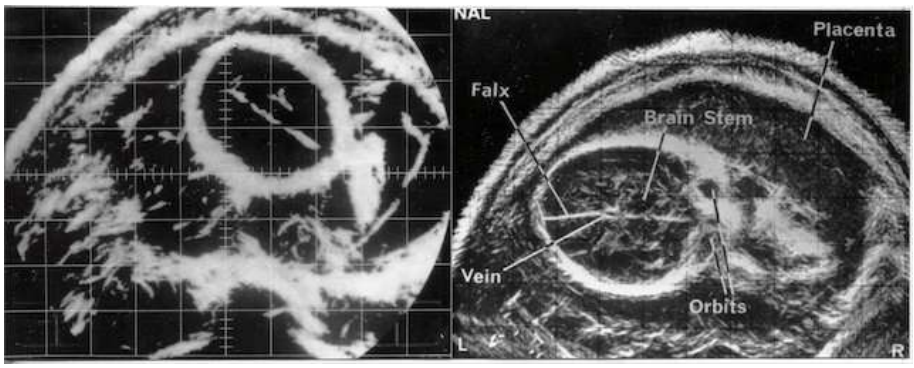

Figure 2.3 *Comparison of bistable and grey-scale images. A bistable image of the fetal head is on the left, and a comparable grey-scale image on the right. Image reproduced with permission from the Australasian Society of Ultrasound in Medicine.*

Following on from this work, Kossoff and Garrett further improved the quality of the grey-scale display with the development of scan converters capable of storing and processing a greater range of returning signal amplitudes. This also enabled images to be displayed on a standard television monitor where they could be scaled so that electronic cursors could be applied on screen, dramatically improving and simplifying methods for ultrasound measurements[61].

The development of real-time scanning made it possible to observe fetal movements with ultrasound, hence the term 'real-time'. Instead of one image taking several seconds to acquire, it was possible to acquire several images per second at sufficiently high frame rates to allow the image to update on the screen continuously as the transducer or fetus moved[62]. The reduced field-of-view images were a departure from the tomographic view static scanners provided, but the ability to reliably identify fetal anatomy without distortion caused by fetal movement more than compensated for this[61]. Ultrasound equipment became smaller, lighter, more portable, and simpler to use, enabling adoption of this technology into clinical practice[39, 65]. Importantly, grey-scale and real-time imaging together facilitated the emergent role of ultrasound in the diagnosis of fetal abnormalities and made reproducible identification of anatomical landmarks for fetal measurements possible[62].

2.2.3 The role of measurements in estimating gestational age

Campbell declared that measurement of the BPD could be used to "estimate fetal maturity" performed between 20 and 30 weeks gestational age and proposed the B-mode/A-mode measurement technique could be used as early as 16 weeks gestational age[66]. His reference charts on cephalometry were published in 1971[67], and this was soon followed by other researchers publishing cephalometry charts derived from their own patient populations[68-71]. It was observed, however, that the mean measurements for gestational age varied considerably between charts. This was attributed in part to measurement technique, whether gestational age was defined as completed weeks, and equipment calibration for the speed of sound, with some researchers calibrating equipment to 1600

m/s and others to 1529 m/s[72]. This led to the recommendation for reference charts to be developed by each institution performing ultrasound examinations, using defined parameters for reliable estimations of gestational age[45]. In 1975, consistency in calibration velocity for ultrasound equipment was recommended, eventually leading to the adoption of 1540 m/s, the average speed of sound in soft tissue[61]. Calibration and other technical issues aside, the accuracy of determining gestational age was impaired by biological variability, increasing from plus or minus one week in the mid trimester[66, 67] to more than plus or minus two weeks in the third trimester[73].

2.2.4 The crown-rump length

The obvious solution to estimating gestational age was that the earlier a measurement was performed (when there was less biological variability), the more reliable it would be. Donald had previously observed how the full bladder enabled visualisation of the uterus[74] and reported it was possible to identify the presence of the gestation sac as early as 5 weeks gestational age using this technique (figure 2.4), and described the ultrasound appearance and sequential changes in size and appearance of the gestation sac[75, 76].

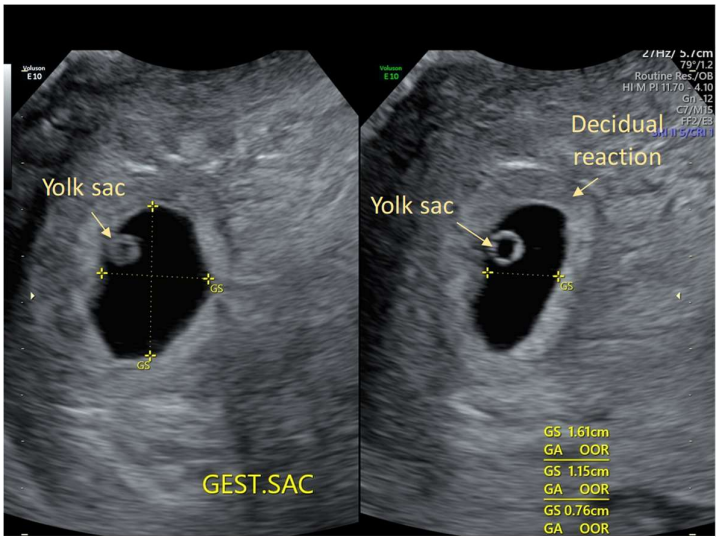

Figure 2.4 *Gestation sac at approximately 5 weeks imaged with contemporary ultrasound equipment measured in three planes. The yolk sac is identified within the gestational sac and its walls are thick and more echogenic than the myometrium due to the decidual reaction. Note electronic 'on screen' calipers and measurements displayed and averaged (bottom right corner). Image produced by D Paoletti.*

Ultrasound measurements of the uterus and gestation sac were evaluated as methods to evaluate gestational age, with mean gestation sac diameter charts published in 1969[77]. In 1973, Robinson[78] described a technique for measuring the size of the embryo/fetus by measuring the crown rump length (CRL) (figure 2.5), and demonstrated it was possible to predict the gestational age using this measurement to within 3 days when performed between 6 and 14 weeks. He validated these findings in a subset of fetuses that spontaneously miscarried, demonstrating good correlation between the ultrasound measurements and direct measurements (in 80% of cases the difference was 2mm or less).

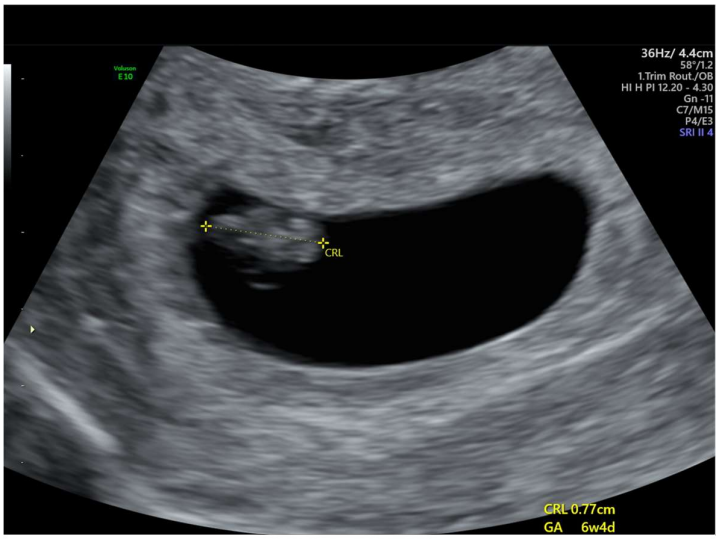

Figure 2.5 *Crown rump length (CRL) measured with contemporary ultrasound equipment. Note electronic 'on screen' calipers and measurements displayed (bottom right corner) with equivalent gestational age. Image produced by D Paoletti.*

2.2.5 The head circumference

Measurement of the head circumference (HC) was proposed by Hadlock in 1982 as a method to estimate gestational age[79], as variations in head shape had been shown to affect estimates based on BPD measurements[80]. The imaging plane for the HC was the same as that used for the BPD; in 1977 Campbell and Thoms described the anatomic landmarks for this plane as a horizontal section of the head including both biparietal diameter and occipitofrontal diameter, and visualisation of the midline echo from the interhemispheric fissure disrupted in the anterior third by echoes by what was initially thought to be the third ventricle[81], but later identified as the cavum septum pellucidum[82] (figure 2.6).

Using the imaging plane described by Campbell and Thoms[81], with new real-time ultrasound equipment, Hadlock found that fetal HC measurements correlated well with postnatal HC charts until 35 weeks' gestational age[79]. He attributed this finding to the difficulty in fitting larger fetal heads post 35 weeks into the field of view afforded by real-time scanners. Amongst his conclusions were that measurements performed with real-time scanners correlated well with measurements made by other researchers with static scanners, and that while the HC did not perform as well as the BPD for predicting gestational age, it should be the measurement of choice when the head shape was affected by extrinsic compression[79].

It should be noted that in the 1980s and 1990s, electronic callipers were limited to linear measurements. In order to measure a circumference, it was necessary to use an opisometer (map measurer or curvimeter), and make the measurement on a hard copy of the ultrasound image (typically a Polaroid® picture)[61, 79]. Alternatively, the head circumference could be derived from linear measurements of the BPD and occipitofrontal diameter[83].

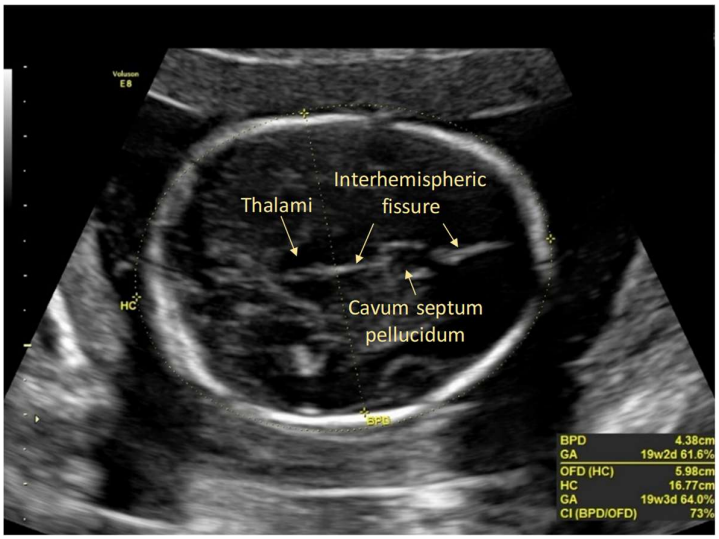

Figure 2.6 *Fetal head imaged with contemporary ultrasound equipment at the measurement plane for biparietal diameter and head circumference. Note electronic 'on-screen' callipers and measurements displayed (bottom right corner) with equivalent gestational age and centiles for known gestational age. Image produced by D Paoletti.*

2.2.6 The femur length

Measurement of the fetal long bones became the focus of other researchers with the advent of real-time scanning in the 1980s. A linear relationship with femur length and crown heel length (measured in neonatal anthropometry) had been described[84, 85]. Real time imaging allowed the length of the ossified portion of fetal long bones to be readily identified (figure 2.7). Measurement of the femur was proposed as an additional parameter for estimating gestational age, mainly to add reliability to the estimations based on the BPD measurement[86]. Keen to produce charts based on local populations, other researchers also published femur length charts and charts of other fetal long bones[86-88].

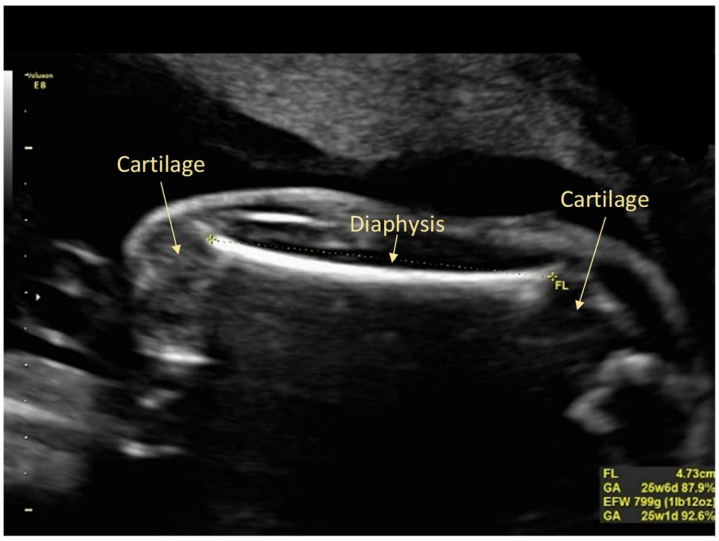

Figure 2.7 *Fetal thigh imaged with contemporary ultrasound equipment at the imaging plane for the femur length. Note electronic 'on-screen' callipers and measurements displayed (bottom right corner) with equivalent gestational age and centiles for known gestational age. Image produced by D Paoletti.*

2.2.7 Challenges in measuring fetal growth

Increasingly, research efforts centred on the identification abnormal fetal growth, and growth restriction in particular due to the association with perinatal morbidity and mortality. It was proposed fetal growth could be assessed by evaluating changes in serial measurements and it was shown that growth restriction could be identified by reduced BPD growth in the third trimester[73, 89].

The first challenge for clinicians was to decide whether fetal size was appropriate for gestational age, and for this, a reliable method to date the pregnancy was required. Using the patient's menstrual history, the estimated due date is calculated as 280 days from the first day of the last menstrual period[90]. This method assumes mid-cycle ovulation and conception in a regular 28 day cycle, and requires the accurate recollection of menstrual dates. In 45% of pregnant women, menstrual history is unreliable, attributed to poor recall of the first day of the last menstrual period and factors such as irregular cycles or oral contraceptive use within two months of conception[91]. Even when the menstrual history is considered reliable, the timing of ovulation, conception and implantation is variable. More recently, it has been estimated that the median ovulation-implantation interval is 11 days[92]. The work of Robinson and Campbell helped establish the concept of an ultrasonic due date based on measurement of the CRL in the first trimester, and the BPD in the second trimester.

The second challenge was the growing realisation that head size may not be significantly affected in cases of growth restriction due to fetal circulatory adjustments conserving brain growth[93]. Therefore, to diagnose fetal growth restriction, an additional fetal biometric measurement was needed.

2.2.8 The abdominal circumference

Attention turned to fetal trunk measurements as a way to identify the growth restricted fetus, the premise being alterations in somatic growth would be better reflected in a trunk measurement. Thompson and Makowski demonstrated measurement of the BPD and antero-posterior thoracic diameter in neonates correlated with gestational age at birth and birthweight, and proposed that measurement of the thoracic diameter was incorporated into ultrasound assessment of the fetus[94].

Translation of thoracic diameter to fetal ultrasound had poor reproducibility, attributed in part to the lack of an easily identifiable and reproducible anatomic landmark. Publications variously described the measurement plane as "above the level of the fetal kidneys and below the level of the fetal heart"[95], at "its largest dimension with still visible cardiac apical action"[19], and "orthogonal to the long axis of the fetus and passed through the entrance of the umbilical vein in the ductus venosus"[96].

With the advent of grey scale imaging, reliable landmarks for the measurement of the abdominal circumference (AC) were reported[64] (figure 2.8), and furthermore, this measurement was shown to be useful for predicting birthweight[64, 84, 97]. Similar to head circumference measurements, it was initially necessary to use a map-measurer on a hard copy of the ultrasound image (typically a Polaroid® picture). The AC could also be derived from measurement of the transverse and antero-posterior diameters using formulae that approximate the circumference of an ellipse[98, 99], and later, incorporation of electronic digitisers into static ultrasound scanners and the development of real-time equipment with digital scan converters allowed on-screen tracing for circumference measurements[61].

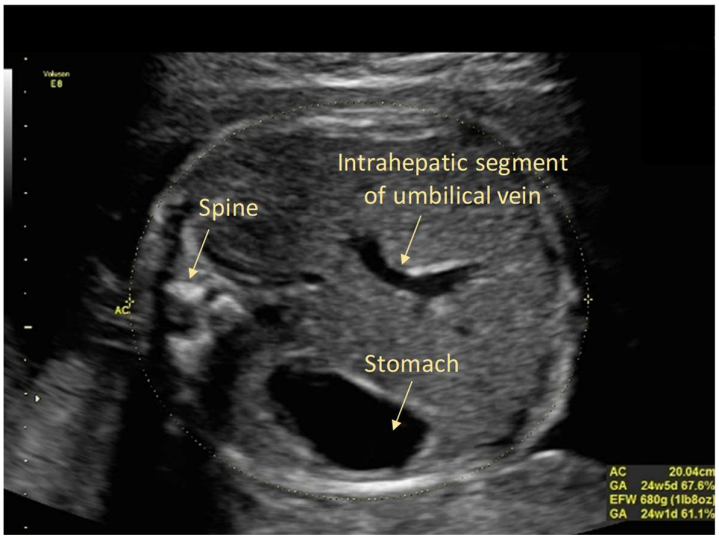

Figure 2.8 *Fetal abdomen imaged with contemporary ultrasound equipment at the measurement plane for the abdominal circumference. Note electronic 'on-screen' callipers and measurements displayed (bottom right corner) with equivalent gestational age and centiles for known gestational age. Image produced by D Paoletti.*

By the mid-1980s, standard ultrasound measurements of fetal size were established that were described by identifiable landmarks and shown to be reproducible. The BPD and HC reflected brain size[72], the AC was a measure of somatic growth, primarily through liver size[100], and the FL a proxy for fetal length[85].

2.2.9 Estimating fetal weight

The remaining challenge was how to relate measurements of fetal size to birthweight. A reliable method for estimating weight had been problematic with attempts to correlate the BPD with estimated fetal weight (EFW) having limited success[45]. A multi-parameter approach to EFW gained momentum with several studies reporting improved accuracy in EFW with the addition of the thoracic circumference to BPD measurements[97], despite methodological difficulties in measuring the fetal thoracic circumference.

As computers became widely accessible, more sophisticated methods to determine the relationship between ultrasound measurements and birthweight were explored. Using the method of AC measurement described by Campbell, in 1977 Warsof [101] described regression models using BPD, HC and AC measurements to predict birthweight, suggesting the BPD - AC model had the best performance. This was found to be reproducible by other researchers, albeit with variable random errors in different birthweight ranges[85]. Hadlock[85] reported no difference between EFW regression models based on BPD-AC and HC-AC, but recommended the addition of the femur length (FL) to the EFW equation. In 1985 he published a landmark paper describing four equations for estimating fetal weight[102]. Despite a modest sample size of 276 in his prospective study, the HC-AC-FL equation provides the most accurate prediction of birthweight to this day[27].

To evaluate in utero growth, especially in the third trimester of pregnancy, the EFW became increasingly important. The EFW was initially referenced to local birthweight charts developed from the recorded birthweights and gestations at birth for a given population[103]. Across all gestational ages there was good correlation between EFW when measured a few days before birth and the birthweight, however, the median birthweight in the preterm cohort was found to be lower than the median EFW. This difference was attributed to various methodological limitations, but one important realisation was that infants born prematurely were more likely to be growth restricted[104, 105]. This led to the

development of fetal weight charts based on the EFW derived from ultrasound measurements. Notably, the chart published by Hadlock and colleagues[104] remains in widespread use to this day.

2.3 Fetal growth and wellbeing

2.3.1 Measuring proportionality

Patterns of fetal growth restriction were reported by Campbell in 1971[89]. When examining BPD measurements of individual cases, he reported two patterns of fetal growth restriction when serial measurements were plotted; the first demonstrated a flattened curve in the third trimester, and the second demonstrated a reduced growth rate from the second trimester[72].

The latter was attributed to phenotype (i.e. normal small) at best case, or to an early disruptive process such as a fetal genetic abnormality or infection as the worst case[106]. The former was thought to occur in response to placental insufficiency, where fetal circulatory adjustments allowed conservation of blood supply to the brain at the expense of other structures[93] resulting in 'head sparing' or 'brain sparing'[72]. This theory was supported by animal studies where placental vessels were ligated to induce growth restriction. This caused asymmetric fetal growth patterns, with relative preservation of brain weight and a 50% reduction in liver weight[72]. Meanwhile, in human subjects, asymmetry between BPD and thoracic circumference was reported in some growth restricted fetuses[39]. With publications describing reliable landmarks for AC measurement and corresponding measurement charts available, assessment of proportionality using the ratio of the HC to the AC (HC/AC ratio) was proposed as a way to identify whether growth restriction was due to fetal abnormality or placental insufficiency [81]. Initial studies reported a relationship between an increased HC/AC ratio (greater than the 95th centile), growth restriction, and adverse pregnancy outcomes[81, 107]. A later study disputed these findings by reporting the HC/AC demonstrated poor correlation with ponderal index (a neonatal measure of wasting calculated by birthweight/length^3) and should not be adopted[108]. However, as discussed by Quinton et al in 2015, this conclusion is questionable as HC and AC measurements were made on the neonate and not the fetus[109]. Of note, measurements were made 24 – 48 hours after birth when

newborns are known to lose weight and the measurement plane of the neonatal AC was not the same as that measured in the fetus[109]. Other studies reported a considerable overlap in the phenotype of symmetrically and asymmetrically growth restricted fetuses, challenging the original assumptions of the underlying cause of growth restriction where a symmetric pattern was due to fetal abnormality, and an asymmetric pattern due to placental insufficiency [110, 111]. The ratio between the FL and AC (FL/AC ratio) was proposed as another way to detect fetal growth restriction as this remains relatively constant from mid trimester onwards and abnormal values were associated with growth restriction[112]. However, similar to the HC/AC ratio, the predictive accuracy was considered too low for routine clinical application[111]. As measurements of size, growth and proportionality were insufficiently sensitive to detect the growth restricted and potentially compromised fetus, research into measuring fetal well-being commenced.

2.3.2 Biophysical profile

A consequence of placental insufficiency is fetal hypoxia, and researchers postulated that the fetus would conserve oxygen consumption by modifying activity. It had been observed that decreased fetal movements preceded fetal demise, and counting fetal movements was proposed as a method to identify those fetuses at risk[113]. A formalised fetal biophysical profile to measure fetal well-being was proposed by Manning in 1980[114], consisting of an ultrasound assessment of fetal tone, gross body movement, breathing movements and amniotic fluid volume, and a non-stress test (cardiotocography) to measure fetal heart rate and reactivity. Each element scored 2 (maximum score of 10), however, interpretation was weighted according to the amniotic fluid score. For example, when amniotic fluid scored 2, 8/10 was considered normal, but 8/10 was abnormal when amniotic fluid scored 0. Ultrasound measurement of amniotic fluid volume was a semi-quantitative assessment using the deepest vertical pocket and a normal volume was indicated by measurements greater than 2cm and less than 8cm[115]. Later, an alternate method was proposed whereby measurements of the deepest vertical pockets in four quadrants of the uterus were summed to produce the amniotic fluid index (AFI). Initially, a normal volume was considered to be greater than 8cm and less than 18cm,

although several different thresholds have been reported[115]. A modified biophysical profile using ultrasound elements for scoring (maximum score of 8) was also proposed and gained popularity. Despite widespread adoption of the biophysical profile, a Cochrane review in 2008 concluded there was little evidence to support this as an assessment of fetal wellbeing[116].

2.3.3 Assessment of fetal and utero-placental circulation

Abnormal development of the utero-placental vessels had been proposed as the primary cause of impaired placental function and fetal growth restriction[49], and researchers began to explore the emerging Doppler ultrasound technology to measure blood flow to the placenta and uterus and within the fetus. Blood flow measurement using ultrasound had been an area of research since the 1950s and was based on the Doppler effect, "the apparent difference between the frequency at which sound or light waves leave a source and that at which they reach an observer, caused by relative motion of the observer and the wave source"[117]. Because red blood cells act as point source reflectors it is possible to detect the Doppler shift of moving blood. Received Doppler signals can be plotted as a function of time (X-axis) and frequency shift (Y-axis) providing a visual display and enabling measurements of the resulting spectral waveform and calculation of blood flow velocity through application of the Doppler equation (equation 2.1).

$$v = \frac{f_D c}{2 f \cos\theta} \qquad 2.1$$

where v = the velocity of the moving interface, f_D = the frequency shift, c = the velocity of sound in tissue, f = the frequency of the transducer, θ = the angle of incidence (angle of insonation)

Continuous wave Doppler equipment was developed in the 1960s and initial research was directed toward application in functional assessment of the heart and peripheral blood vessels in adults. Continuous wave Doppler, as the name implies, employed a technique of continuous ultrasound emission and reception of all returning echoes from the interrogating beam to detect the Doppler shift

of moving blood. The Doppler shift is in the order of 2kHz, within audible hearing range, and, this serendipitous discovery led to the first obstetric applications of Doppler ultrasound in fetal heart monitoring[118].

A limitation of continuous wave Doppler is that it does not provide information about the distance from the transducer to the moving target and this made it difficult to identify which structure was the source of the Doppler signal[119]. This was problematic in obstetric applications where the variability and mobility of fetal position made it difficult to determine which vessel was the source of the signal[61]. Nonetheless, detection of blood flow in the umbilical artery was reported in the late 1960s, and the technique of using B-mode ultrasound to identify where to place the continuous wave Doppler transducer was described in 1977 by Fitzgerald and Drumm, along with the characteristic appearance of spectral waveforms of the umbilical vein and artery [40]. Research into placental, uterine and fetal circulation began in earnest to identify vascular patterns indicative of fetal growth restriction.

Various methods to measure flow velocities and volumes in both the umbilical vein and artery were investigated but accurate measurements proved challenging. Exact measurement of the diameter of small fetal vessels needed for volume analysis was difficult, if not impossible, and it was not always possible to measure the angle of intersection between the ultrasound beam and the vessel (angle of insonation) required for velocity calculations[61, 120, 121]. Combined with the additional variables of fetal position, fetal movement, and operator skill, Doppler quantification seemed impractical. However, it became apparent that various indices could express systolic velocities *relative* to diastolic velocities and overcome some of these limitations[61].

The pulsatility index (PI) had been proposed as a parameter to quantify haemodynamic characteristics by researchers investigating peripheral arterial disease in adults[122]. Because it was possible to calculate an index when the diastolic velocity was zero or negative, the PI was favoured by those studying fetal circulation[123] (equation 2.2)[124]. However, the technique required digitisation of the waveform and computational analysis, deferring clinical adoption until technology 'catch up'

occurred. The resistive index (RI) was simpler to calculate (equation 2.3)[124], and the systolic/diastolic ratio (SD ratio) even simpler (equation 2.4)[124].

$$PI = \frac{maximum\ systolic\ velocity - minimum\ diastolic\ velocity}{mean\ velocity} \quad 2.2$$

$$RI = \frac{maximum\ systolic\ velocity - minimum\ diastolic\ velocity}{systolic\ velocity} \quad 2.3$$

$$SD\ ratio = \frac{maximum\ systolic\ velocity}{minimum\ diastolic\ velocity} \quad 2.4$$

where PI = pulsatility index, RI = resistive index, SD = systolic diastolic

2.3.4 Umbilical artery Doppler

When applied to the umbilical artery, it was found that there was no difference in the ability of these indices to predict fetal compromise, and that they outperformed other even more complex waveform analyses[125]. However, calculating indices such as the PI and RI required computational analysis not generally available outside of research settings, and this limited adoption into clinical practice.

A landmark publication by Brian Trudinger et al in 1985 described the relationship between umbilical artery waveforms and placental resistance through calculation of the ratio of the peak systolic to least diastolic velocity[121]. He demonstrated the SD ratio progressively decreased with gestation in normal pregnancies, and importantly, high SD ratios were associated with growth restriction, perinatal hypoxia and maternal hypertension.

Echoing Campbell's B-mode/A-mode method for BPD measurements, Trudinger's technique used a real-time scanner to identify the umbilical cord to guide placement of a hand held continuous wave Doppler transducer. Audible assessment was used to discriminate between maternal and fetal vessels, the Doppler shift being in the order of 2 kHz and within audible hearing range, and simultaneous detection of flow from the umbilical vein in the opposite direction was used to confirm the arterial waveform originated from the umbilical artery.

Other researchers confirmed that abnormal umbilical artery waveform measurements were able to discriminate between distressed growth restricted fetuses and healthy small for gestational age fetuses[126]. Mean values of umbilical artery Doppler indices were described for different gestational ages with measurements greater that two standard deviations from the mean considered abnormal[123]. The SD ratio was relatively easy to calculate, and when a threshold of 3 was used to identify an abnormal SD ratio after 30 weeks[127], Doppler assessment of the umbilical artery became widely adopted (figure 2.9).

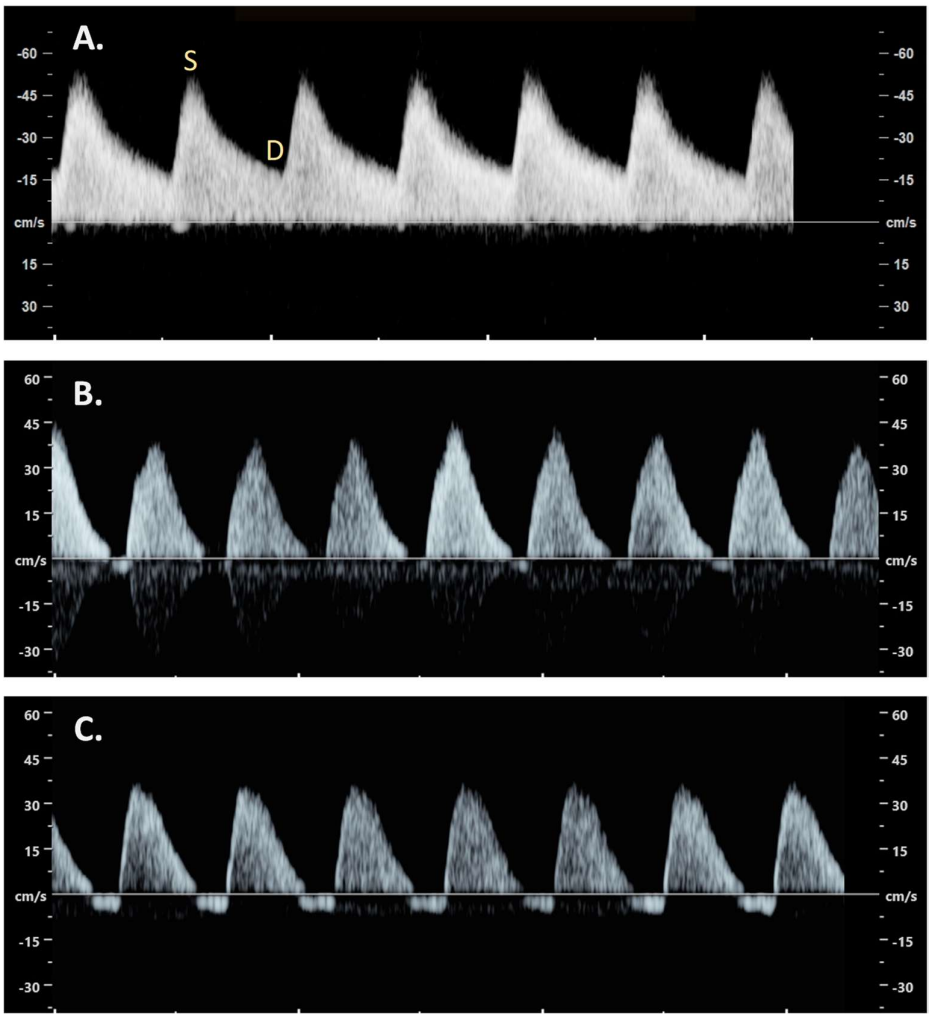

Figure 2.9 A. *Normal Doppler waveform of the umbilical artery imaged with contemporary ultrasound equipment. S is the peak systolic velocity and D is the least diastolic velocity.* ***B.*** *Umbilical artery Doppler waveform depicting absent diastolic flow* ***C.*** *Umbilical artery Doppler waveform depicting reversal of diastolic flow. Images produced by D Paoletti.*

2.3.5 Impact of new Doppler technologies

Two important developments in Doppler ultrasound technology were pulsed Doppler techniques and colour flow mapping. Both techniques were first reported in the 1970s but widespread clinical use in obstetrics was limited by technical shortcomings of transducer design and the signal processing ability[128, 129]. Incorporation of digital electronics and the progression to entirely digital signal processing over the next two decades saw vast improvements in this area[129].

Pulsed Doppler, as the name implies, involves the transmission of short pulses of ultrasound and analysis of echoes received after a pre-set time delay[124]. When incorporated with real-time ultrasound equipment, this enabled the operator to define the area for Doppler interrogation on the grey scale image on the monitor. This had the benefit of making acquisition of the Doppler signal a simpler process, increasing confidence that the source of the Doppler signal had been correctly identified[126, 130]. Colour flow mapping using multi-gated pulsed Doppler allowed superimposition of colour coded

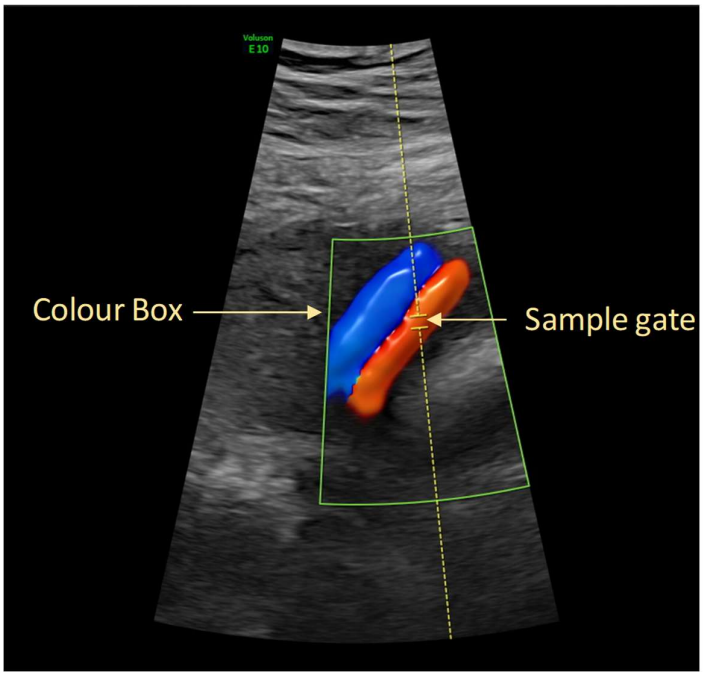

Figure 2.10 *Colour flow mapping and positioning of pulsed Doppler sample gate with contemporary ultrasound equipment. The user defined colour box allows superimposition of colour coded Doppler signals over the grey scale image. The colour denotes the direction of Doppler shift relative to the transducer; red is generally toward the transducer and blue is away. This enables the user to accurately define the area for analysis of received echoes by placement of the sample gate. Image produced by D Paoletti.*

Doppler signals over the grey-scale image[124] (figure 2.10). This improved identification of fetal central and peripheral vessels, and enabled researchers to expand on conventional understanding of fetal haemodynamics based on animal models by studying fetal circulation in-utero[120, 126, 131].

Inevitably technological improvements saw development of duplex ultrasound equipment incorporating real-time, pulsed Doppler[132] and ultimately colour flow mapping[133], which greatly improved the clinical utility of fetal Doppler assessment and saw these techniques transition from the research setting into mainstream clinical practice for assessment of fetal wellbeing.

2.3.6 Uterine artery Doppler

Investigators studied maternal blood supply to the uterus with both continuous wave and pulsed Doppler in the 1980s, reporting low pulsatility/high diastolic waveforms were characteristic of normal pregnancies after 20-24 weeks (figure 2.11 A), and high pulsatility/low diastolic waveforms were seen in pregnancies complicated by maternal hypertension, suboptimal fetal growth and fetal hypoxia[134, 135]. The presence of a pre-diastolic notch in the waveform was also reported to be a strong predictor of adverse outcomes[136] (figure 2.11 B).

However, reported sensitivities and predictive values for growth restriction and pre-eclampsia varied, due in part to inconsistent ultrasound techniques that assessed different segments of the utero-placental circulation [137]. Techniques included the identification and Doppler assessment of large (3mm) vessels in the uterine wall, presumed to be arcuate arteries, [93, 134] and interrogation of sub-placental vessels with continuous wave Doppler[135]. The advent of colour Doppler improved visualisation of the main uterine artery and allowed for the identification of a reliable landmark (where the uterine artery crosses the external iliac artery) to standardise measurements[137] (figure 2.12).

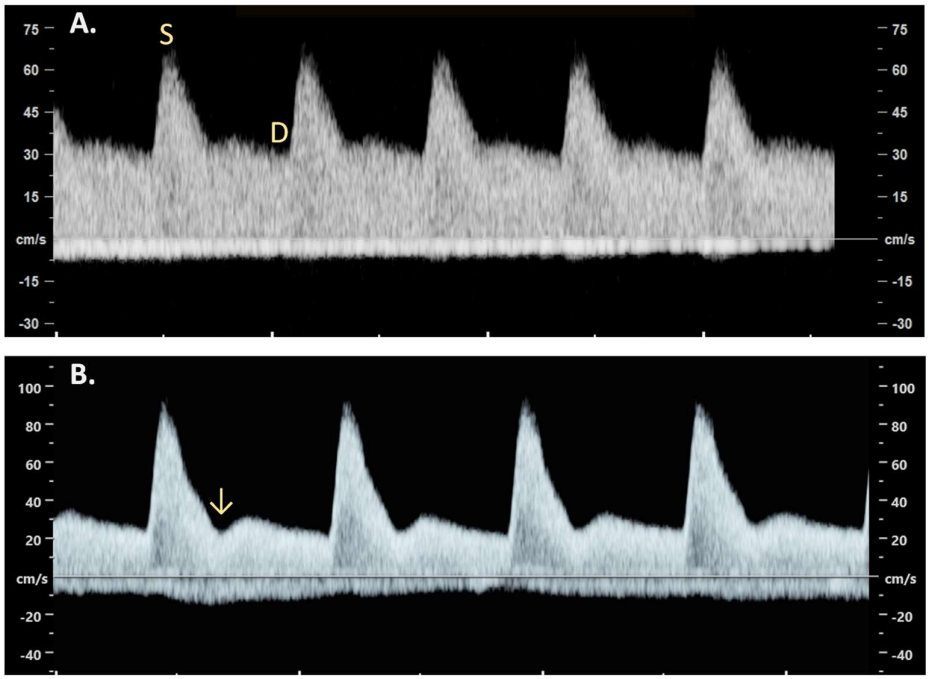

Figure 2.11 A. *Normal Doppler waveform of the uterine artery imaged with contemporary ultrasound equipment. S is the peak systolic velocity and D is the least diastolic velocity.* ***B.*** *Uterine artery Doppler waveform depicting high resistance and a pre-diastolic notch (arrow). Images produced by D Paoletti.*

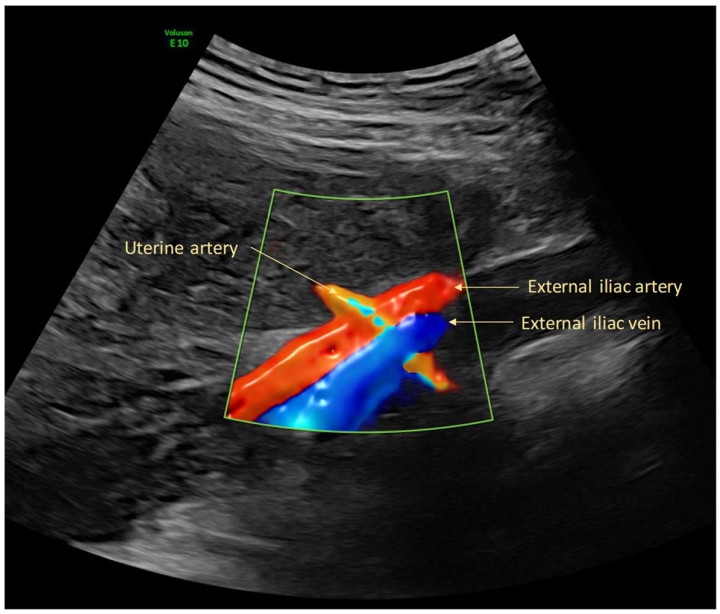

Figure 2.12 *Colour flow mapping with contemporary ultrasound equipment demonstrating the uterine artery crossing the external iliac vessels. Image produced by D Paoletti.*

While these initial observations suggested evaluation of uterine arteries may be a suitable method to screen for growth restriction and preeclampsia, in practice, the positive predictive value has proved too low for widespread clinical implementation[138].

2.3.7 Middle cerebral artery Doppler

During the 1980s Doppler assessment of fetal vessels became the subject of research and with the advent of colour flow mapping, included investigation of the aorta, renal arteries, iliac arteries, common carotid arteries, cerebral arteries and the ductus venosus[126].

Doppler waveforms of the abdominal arteries demonstrated a similar pattern to that observed in the umbilical artery, namely pulsatility normally decreasing with increasing gestation, and high pulsatility in cases of growth restriction. A wide normal range for aortic Doppler indices and poor reproducibility due to suboptimal angles of insonation made assessment of the fetal aorta unsuitable for clinical practice[139].The pattern observed in the fetal cerebral arteries was different to that of the umbilical

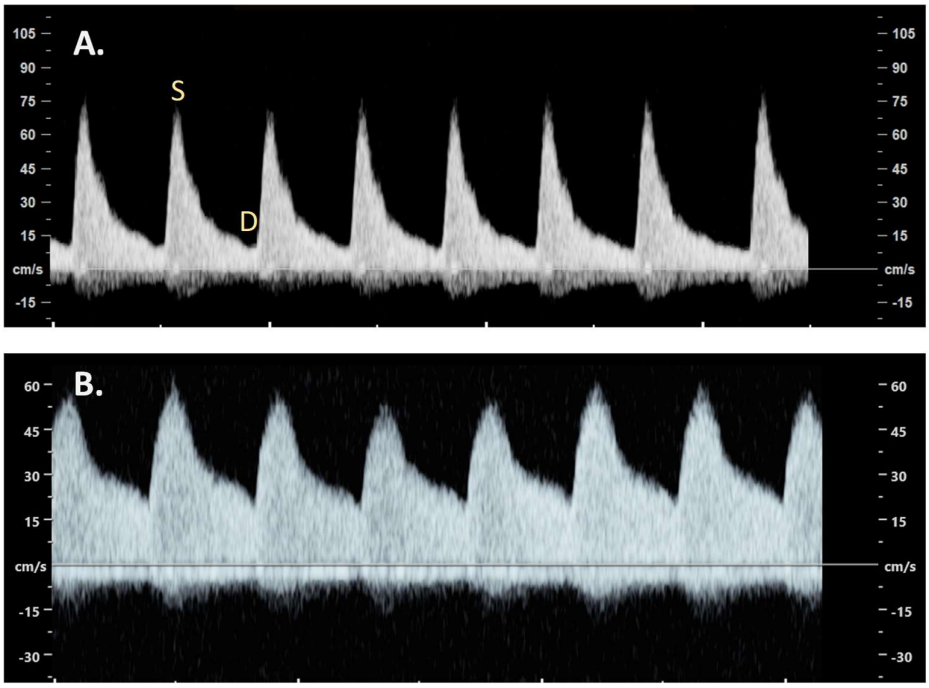

Figure 2.13 A. *Normal Doppler waveform of the middle cerebral artery imaged with contemporary ultrasound equipment. S is the peak systolic velocity and D is the least diastolic velocity.* ***B.*** *Doppler waveform of the middle cerebral artery demonstrating increased end diastolic velocity. Images produced by D Paoletti.*

artery – in normally grown fetuses the pulsatility was high (figure 2.13 A). In cases of growth restriction the pulsatility was reduced reflecting decreased vascular resistance in the brain, the vascular manifestation of the 'brain sparing effect'[140] (figure 2.13 B).

This was observed in both the internal carotid artery and middle cerebral artery. Doppler signals from the internal carotid artery were typically obtained as it entered the Circle of Willis or at the level of bifurcation into the middle and anterior cerebral artery[141]. Doppler signals from the middle cerebral artery could be obtained placing the sample gate parallel to the sphenoid bone[142]. Ultimately, colour flow mapping enabled the cerebral vasculature to be readily identified (figure 2.14) and provided an easily reproducible landmark for placement of the sample gate at insonation angles close to 0°.

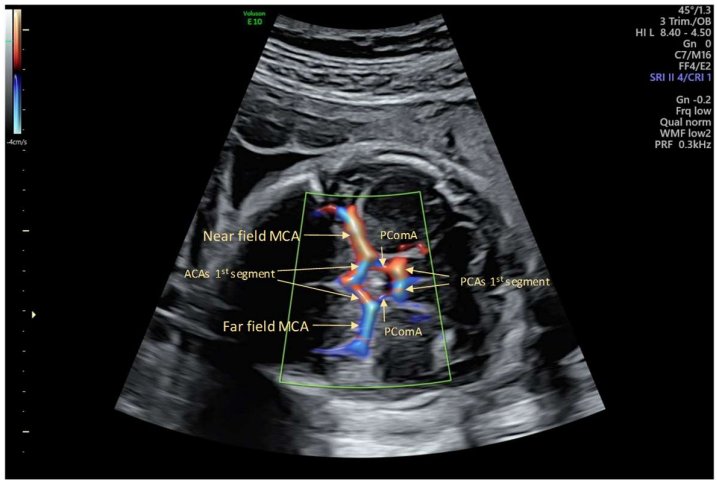

Figure 2.14 *Colour Doppler image of cerebral arteries imaged with contemporary ultrasound equipment. The orientation of the middle cerebral arteries (MCA) enables these vessels to be readily identified at an optimal angle of insonation for reproducible measurements. The first segment of the anterior cerebral arteries (ACAs), posterior cerebral arteries (PCAs) and posterior communication arteries (PComA) complete the Circle of Willis. Image produced by D Paoletti.*

Concurrently, researchers investigating fetal anaemia observed the peak systolic velocity of the middle cerebral artery was high in anaemic fetuses pre-transfusion and was low when measured post-transfusion. The use of middle cerebral artery velocity became transformational in the management of suspected fetal anaemia. Not only were measurements reproducible, due to the favourable angle

of insonation, but fewer fetuses required invasive testing to diagnose anaemia[142]. By consensus, the middle cerebral artery became the vessel of choice for fetal arterial assessment due to the dual role of the assessment of fetal growth restriction and the assessment of fetal anaemia[139].

2.3.8 Ductus venosus Doppler

The ductus venosus is a small physiological shunt present in fetal life between the umbilical vein and the systemic circulation via the thoracic inferior vena cava (figure 2.15). Understanding of its function had been based on post-mortem and animal models and although the mechanisms are unclear, the ductus venosus performs a regulatory function by directing oxygenated blood from the umbilical vein into the right atrium, across the foramen ovale to the left heart and ultimately to the fetal brain[124].

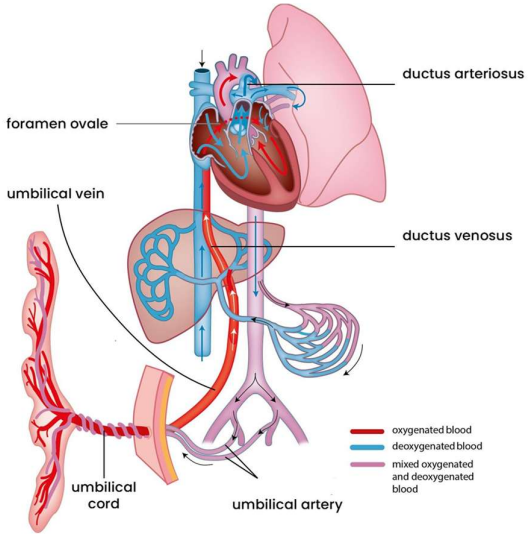

Figure 2.15 *Diagram of fetal circulation indicating the position of the ductus venosus. Based on "Slagter - Drawing Fetal circulation - Latin and English labels" at AnatomyTOOL.org by Ron Slagter and O. Paul Gobée, LUMC, license: Creative Commons Attribution-NonCommercial-ShareAlike. Note Latin labels have been removed.*

Doppler ultrasound together with colour flow mapping enabled research into its role in human fetal haemodynamics during the 1990s. At less than 2mm in diameter, it is difficult to identify the short vessel with standard real time imaging, however, colour flow mapping greatly facilitates identification

of the vessel and optimisation of the angle of insonation for Doppler acquisition (figure 2.16). It was found that in normally grown fetuses, the ductus venosus shunts approximately 30% of blood from the umbilical vein to the systemic circulation at mid-gestation, reducing to approximately 20% at term[143].

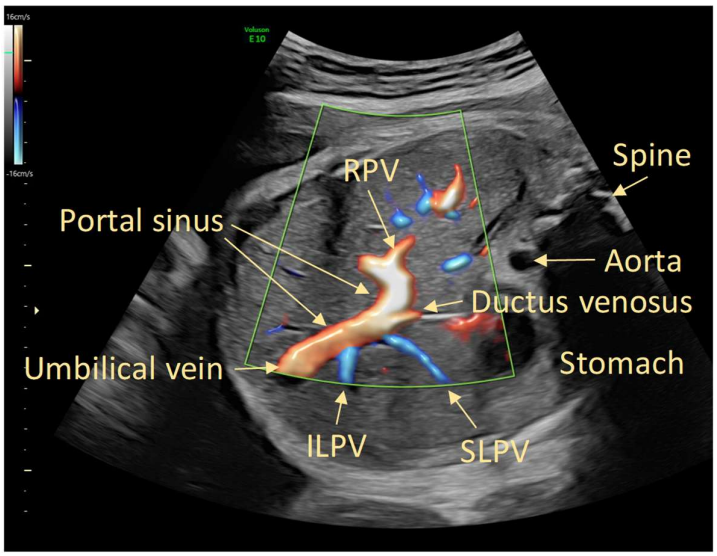

Figure 2.16 *Ductus venosus imaged with contemporary ultrasound equipment in a transverse oblique section of the fetal abdomen. The ductus venosus is identified by colour flow mapping as a short vessel arising from the portal sinus opposite the umbilical vein enabling optimal positioning of the Doppler sample gate. ILPV inferior left portal vein, SLPV superior left portal vein, RPV right portal vein. Image produced by D Paoletti.*

The Doppler waveform of the ductus venosus demonstrates a characteristic pattern reflecting ventricular systole (S-wave), ventricular relaxation or late systole (v-wave), ventricular diastole (D-wave), and atrial systole (a-wave)[144] (figure 2.17 A).

Key amongst initial observations was that in normal fetuses, positive flow through the ductus venosus was maintained during atrial systole. However, in growth restricted fetuses, greater shunting occurs with resultant increased pulsatility of the ductus venosus. Reversal of the a-wave occurs when compensatory mechanisms can no longer be maintained and fetal acidosis and hypoxaemia occurs as a result[145] (fig 2.17 B). Abnormal ductus venosus waveforms were also noted to be a feature of cardiac disease, including valvular disease, arrhythmias, cardiomyopathies and cardiac tumours[143, 144].

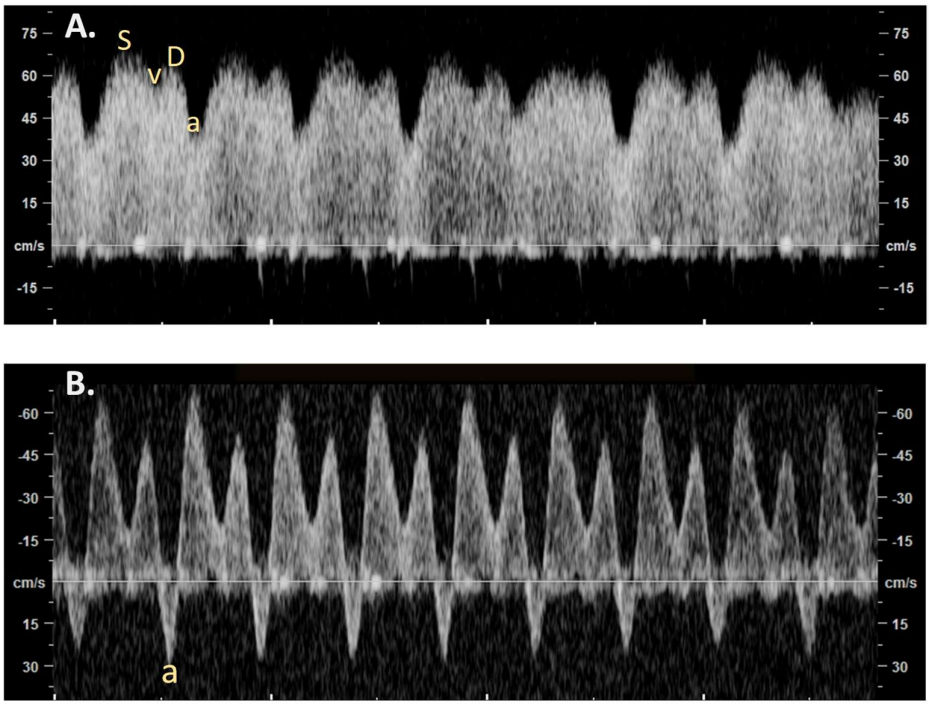

***Figure 2.17 A**. Components of the ductus venosus waveform. Ventricular systolic ejection corresponds to S. Ascent of the closed atrioventricular valves in late systole corresponds to v, the v-trough (v-descent) that precedes passive diastolic ventricular flow D. Contraction of the atria during atrial systole produces the readily recognizable a-wave (a) that corresponds to active diastolic ventricular filling. **B.** Ductus venosus waveform demonstrating increased pulsatility and negative a-wave. Images produced by D Paoletti.*

New indices to measure the pulsatile ductus venosus waveform were proposed to take into account the triphasic shape of the waveform by measuring the maximum velocity at the S-wave and the minimum velocity at the a-wave, and included the pulsatility index for veins (PIV) (equation 2.5) and peak velocity index for veins (PVIV) (equation 2.6)[146].

$$PIV = \frac{maximum\ velocity\ ventricular\ systole(S) - minimum\ velocity\ atrial\ contraction(a)}{time\ averaged\ maximum\ velocity} \quad 2.5$$

$$PVIV = \frac{maximum\ velocity\ ventricular\ systole(S) - minimum\ velocity\ atrial\ contraction(a)}{mean\ velocity\ early\ diastole\ (D)} \quad 2.6$$

where PIV = pulsatility index for veins, PVIV = peak velocity index for veins

The PVIV is able to reflect more aspects of cardiac function by inclusion of the D-wave in the formula, however, the PIV is the index most widely utilized[44, 147].

Measurement of ductus venosus Doppler in contemporary practice is used in the management of the growth restricted fetus prior to 32 weeks gestation. Low pulsatility indices and waveforms suggest fetal adaptation to placental insufficiency and high pulsatility indices and waveforms indicate a deterioration in fetal condition[148].

2.4 Charts of fetal size and growth

With widespread adoption of ultrasound into obstetric practice, the questions of how to discriminate between normal and pathological growth, which charts to reference the ultrasound measurements to, and when to perform the measurements remains controversial to this day. Reliable identification of abnormal fetal growth is at the centre of the debate because of the association with increased perinatal morbidity and mortality. Importantly, it has been shown that prenatal identification of fetal growth restriction allows targeted surveillance and timely delivery, and can reduce the stillbirth rate[18].

The terms *size* and *growth* tend to be used interchangeably, indeed ultrasound examinations performed after the routine 18 - 20 weeks' gestation fetal abnormality screen are referred to as 'growth scans'. The tendency to confuse terminology may well stem from early publications when charts of fetal size were referred to as 'growth curves'. However, charts to assess fetal size are not necessarily designed to assess fetal growth, as highlighted by Altman and Chitty[149]. They identified the purpose of charts of fetal measurements as follows:

> "*(1) To compare the size of a fetus (of known gestational age) on a single occasion with reference data;*
>
> *(2) To estimate gestational age from fetal size;*
>
> *(3) To compare the growth of a fetus between two occasions with reference data."*

They argued the chart's intent should be reflected in the methodology used to collect and analyse data and that statistical analysis differed for each approach.

The first published fetal reference charts were based on measurements derived from a local population in the way that infant and child growth charts are constructed[150]. This descriptive approach depicts the distribution of fetal measurements for an unselected population[30]. However minimal selection criteria were generally applied [151], and while excluding fetal abnormalities and maternal conditions known to affect fetal growth was considered reasonable, excluding measurement outliers was not recommended[152]. For example, the population for Campbell's 1971 BPD chart comprised of Caucasian women with uncomplicated singleton pregnancies that laboured spontaneously, and excluded infants with a birthweight below the 5th centile for 40 weeks gestation [67].

Prescriptive charts by contrast, describe the distribution of fetal measurements in a selected low-risk or ideal population, and are therefore referred to as standards[30, 151]. For example, charts produced by the Intergrowth-21st project were generated from multiethnic populations from diverse geographical regions including Brazil, China, India, Italy, Kenya, Oman, United Kingdom and United States, with the aim to produce charts suitable for international use[153]. Additionally, extensive exclusion criteria relating to obstetric history, sociodemographic and clinical factors were applied to ensure measurement data were sourced from a low-risk population[153].

Data collected for charts of fetal size may be cross-sectional, that is, each participant contributes only one set of measurements during the pregnancy, or longitudinal, where participants contribute several sets of measurements at different time points in the pregnancy. Most charts in current use are based on a cross-sectional design[154], perhaps due to the strong recommendations by Altman and Chitty[149, 152]. They argued a cross-sectional design reduces bias because a fetus with abnormal growth will only contribute measurements at a single time point instead of several time points in the pregnancy. Cross-sectional designs have the additional advantage of being less demanding on participant time and more cost effective than designs requiring multiple ultrasound examinations, which may have contributed

to their popularity[151]. It should be noted that according to Altman and Chitty's definitions, cross-sectional charts are suitable for comparing size to a reference for known gestational age, and estimating gestational age from size, but strictly speaking, unsuitable for evaluating growth[149]. To assess growth, it is argued, charts based on longitudinal data, where each fetus is measured at several time points in the pregnancy, should be used[72, 149, 151].

It is generally accepted that fetal measurement data for a given gestational age are normally distributed and increase as the pregnancy progresses, therefore parametric methods are suitable to estimate the mean, standard deviation, and centiles at each gestational age[152]. This approach is suitable for cross-sectional studies, but longitudinal studies require a different approach because serial measurements from a single fetus are highly correlated, making the number of participants in the study (rather than number of observations) an important factor[149, 152].

The sample size required to construct a reference chart is typically described as requiring "several hundred observations"[152] in order to achieve a degree of precision in estimating the centiles. Calculations may be based on parametric or non-parametric approaches, a method for estimating the sample size for reference ranges of normally distributed data published by Royston in 1991[155]. This approach is suitable for cross-sectional studies, however, sample size calculation for longitudinal studies is complex[151].

Data used for chart construction may be collected prospectively or retrospectively, and taken from routine or indicated ultrasound examinations or from examinations performed for research purposes. Prospective data collection allows measurements to be collected explicitly for the purpose of chart construction[149], and additionally allows quality control processes to be implemented, such as standardisation of fetal measurements and image quality, and accurate collection of maternal demographic data[151]. Retrospective data collection permits large sample sizes for analysis, however, the underlying assumption is that data is accurately recorded[151]. In modern clinical practice, ultrasound data is stored electronically, with the advantage of making very large samples available for

retrospective analysis. The disadvantage is that in modern obstetric practice ultrasound examinations are performed for an increasing number of clinical indications, limiting the ability of researchers to assess effects of bias due to clinical confounders[154]. The suitability of a reference chart derived from one population for use on a different population has been questioned as differences in fetal measurements between populations led to the conclusion that fetal size is influenced by racial characteristics[156]. This resulted in the publication of scores of different reference charts over the years developed for different populations, and heterogeneity in study designs and chart methodologies meant centiles for a given measurement could vary considerably[154]. Indeed, comparison of three fetal measurement reference charts has demonstrated a six-fold increase in measurements classified as being below the 5th centile[29]. For clinicians practising in multiethnic populations or where no fetal charts based on the local population are available, this variability makes it difficult to assess which chart should be adopted.

2.4.1 Fetal weight charts

Thresholds for defining birthweights that are too low and too high can be traced to works by Battaglia and Lubchenco in 1967. They proposed using both the gestational age at birth and the birthweight centile to help identify a high risk group of neonates (previously, infants weighing less than 2500g were considered premature regardless of the gestational age at birth [45, 47]). Birthweights below the 10th centile were referred to as small for gestational age (SGA), those above the 90th centile large for gestational age (LGA), and those between the 10th and 90th centiles appropriate for gestational age (AGA)[157]. Although these definitions were intended to be applied after birth, they have been co-opted into terminology used to describe prenatal estimates of fetal weight based on ultrasound measurements, and form the basis of many national guidelines for the management of suspected fetal growth restriction[17]. In the cohort of fetuses with an estimated weight below the 10th centile, many will be constitutionally small, and the number that are pathologically small will depend on the population prevalence. Therefore, other thresholds for defining abnormal fetal weight (such as the 3rd and 97th centile) in some populations have been proposed, and indeed may be more appropriate

when prescriptive fetal growth charts are used, as these charts are based on measurements of fetuses in healthy pregnancies[110].

The calculated EFW can vary according to the choice of formula, with some models better suited to estimating weight in the small fetus and other models performing better in the large fetus[27, 28]. Once calculated, the EFW may be compared to one of several birthweight charts or ultrasound based EFW charts, again with the potential for considerable differences in the assigned centile[31]. Measurements less than the 10th centile for gestational age or greater than the 90th centile for gestational age tend to be triggers to change clinical management[17], however, these thresholds have high false positive and negative rates; a significant proportions of fetuses defined at SGA will be healthy or 'constitutionally small' and similarly, some fetuses that are growth restricted may have an estimated weight above the 10th centile threshold.

Fetal growth restriction (FGR) as defined by the International Federation of Gynaecology and Obstetrics (FIGO), is "the failure of the fetus to meet its growth potential due to a pathological factor, most commonly, placental dysfunction"[41]. The term 'fetal growth potential' recognises the normal variation in the birthweight of healthy infants attributed to several physiological factors[4]. In an effort to better identify those fetuses truly affected by pathological growth, Gardosi and colleagues proposed personalising fetal growth charts by correcting for maternal ethnicity, height, weight and parity and fetal sex to calculate the optimal birthweight at 40 weeks' gestation[32]. Using this optimal birthweight as the endpoint and applying Hadlock's in-utero fetal weight model[104], an individually customised fetal weight chart can be produced. This approach assumes all fetuses have the same pattern of intrauterine growth and that the maternal characteristics influencing optimal fetal weight are constant across gestational ages. Initial studies demonstrated customised charts were able to better identify fetuses at risk for adverse outcomes, but later studies contradicted this finding and a subsequent meta-analysis was inconclusive[158].

An alternative approach to individual customisation of fetal weight charts is population customised charts as proposed by Mikolajczyk and colleagues[33]. This method applies Hadlock's in-utero fetal weight model[104] to the population median birthweight at 40 weeks to produce a single fetal weight chart suitable for use by the local population.

2.5 Screening for abnormal growth

Whether or not to implement universal third trimester ultrasound to screen for abnormal fetal growth remains a vexed question. A Cochrane review in 2008[159] found routine third trimester ultrasound was not associated with an improvement in perinatal mortality and the 2008 National Institute for Health and Care Excellence (NICE) guideline on antenatal care (United Kingdom) recommended against routine third trimester ultrasound[160], echoed in the guidelines of several other countries including Australia, New Zealand, and Canada. However, other countries include third trimester ultrasound as an integral part of antenatal care, namely, France, Germany and Belgium[161]. A study from France in 2014 found routine third trimester ultrasound was not a good predictor of FGR and that neonatal outcome was not improved when FGR was suspected prenatally[162]. In 2015, the Pregnancy Outcome Prediction (POP) trial found an improvement in the detection of SGA fetuses with routine ultrasound (57%) compared to targeted ultrasound (20%), however the false positive rate for SGA meant that for every SGA fetus detected, two were falsely identified as SGA[163]. This finding supports the observation that the majority of SGA fetuses are 'constitutionally small' evidenced by no increased risk in neonatal morbidly in SGA fetuses with normal AC growth velocity, and an increased risk when AC growth velocity was below the 10th centile[163].

Detection for LGA was also found to be improved in the POP trial from 27% with targeted ultrasound to 38% with routine ultrasound, and increased AC growth velocity was associated with an increased risk for adverse neonatal outcomes [164].

In Australia targeted third trimester ultrasound is recommended based on the presence of maternal or fetal conditions associated with abnormal growth[165]. Even so, there has been a steady increase in

the number of third trimester ultrasound examinations performed in Australia (figure 2.18), suggesting that most, if not all singleton pregnancies in Australia will have at least one ultrasound examination in the third trimester.

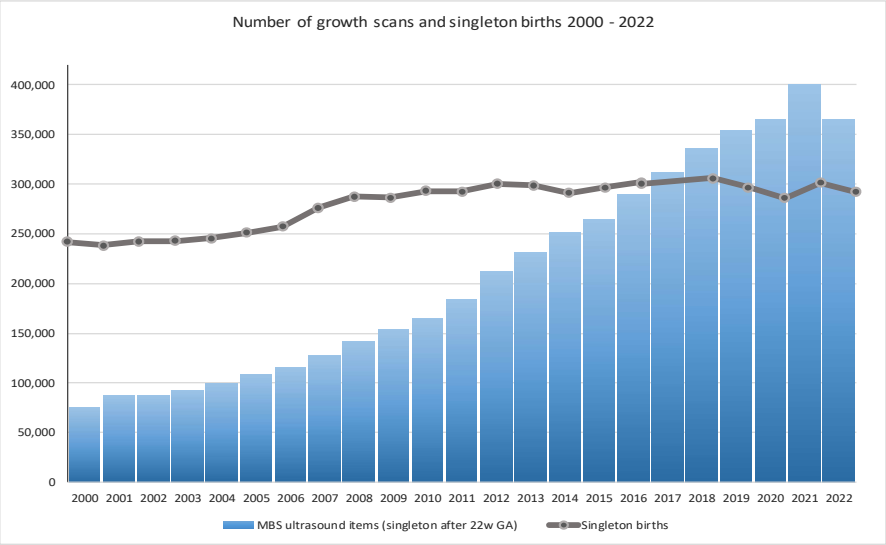

Figure 2.18 *Number of singleton growth scans and singleton births 2000 – 2022. Data compiled by D. Paoletti from MBS claims for ultrasounds performed after 22 weeks' gestation on singleton pregnancies, available from http://medicarestatistics.humanservices.gov.au/statistics/mbs_item.jsp and singleton births, available from https://www.abs.gov.au/statistics/people/population/births-australia*

2.6 Chapter summary

This chapter describes the evolution of the ultrasound parameters that are used to measure fetal size, gestational age, estimate fetal weight, and evaluate fetal wellbeing. Pioneers of fetal ultrasound diligently ensured measurements were reproducible and could be related to neonatal measurements. Fetal ultrasound measurement was a key factor in the concept of an ultrasonic estimated due date, reinforcing the importance of accurate dating when assessing fetal growth. Rapid advances in technology over the next few decades played a critical role in the ability of ultrasound practitioners to recognise anatomical landmarks for fetal measurements and to measure fetal and uteroplacental blood flow, enhancing the ability to perform accurate and reproducible measurements. For each parameter of fetal measurement, a chart relating the measurements to gestational age was developed for the purposes of establishing gestational age, assessing growth, and fetal wellbeing. However,

methodologies of chart design vary considerably raising the question of which chart is most suitable to use on a given population. These differences mean that centiles for a given measurement may vary considerably; indeed, the choice of reference chart may result in up to a six-fold increase in measurements classified as below the 5th centile[29]. Uniform adoption of fetal measurement charts is required to address these inconsistencies, but despite recommendations of the Australasian Society of Ultrasound in Medicine (ASUM)[166] dating from 2001, a survey conducted in 2013 of members of the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) revealed there were at least eight fetal growth charts in clinical use in Australia[34].

Defining normal and pathological fetal growth and how to best screen for abnormal fetal growth remain much debated issues. Haemodynamic assessment of the fetus with Doppler ultrasound has become a feature of monitoring fetal well-being, and just like charts of fetal size, there are many reference charts for fetal Doppler indices. Similarly, heterogeneity in chart design of fetal Doppler charts has the potential misclassify the well-being of up to 50% of fetuses[167]. There are currently no recommended Doppler charts in Australia, although the Obstetric Doppler Guideline from the New Zealand Fetal Medicine Network[168] is endorsed by ASUM[169]. Therefore, it is probably unsurprising that more than half of the RANZCOG members surveyed in 2013 were unsure of which umbilical artery Doppler chart was used at their practice and demonstrated inconsistencies in the Doppler index reported[170].

Some fifteen years since these survey findings were published[34, 170], inconsistencies in the choice of reference chart remain problematic. A comprehensive survey of current practice in reporting third trimester fetal biometry and Doppler was undertaken and is discussed in the following chapter.

Chapter Three

Current practice in reporting third trimester fetal measurements

3.1 Introduction

As discussed previously, fetal biometry is an established part of ultrasound assessment in determining fetal size and growth. The diagnosis of abnormal growth is based on differences between the actual measurements and expected measurements for a given gestational age. As fetal growth restriction is associated with increased risk of adverse perinatal outcomes[3, 171], the ability to identify these fetuses allows for increased antenatal monitoring to inform clinical decisions regarding delivery and improve perinatal outcomes[18]. The estimated weight and/or abdominal circumference is typically used to classify fetal size as appropriate for gestational age (AGA), large for gestational age (LGA), small for gestational age (SGA), or as fetal growth restriction (FGR) with measurements less than the 10th centile for gestational age or greater than the 90th centile triggers to change clinical management[17]. The Perinatal Society of Australia and New Zealand and Centre of Research Excellence Stillbirth define an estimated fetal weight or abdominal circumference below the 10th centile as SGA, and measurements below the 3rd centile indicate FGR[6]. Acknowledging that not all SGA fetuses are growth restricted and that some AGA fetuses may be growth restricted, additional considerations in defining growth restriction include abnormal umbilical artery Doppler parameters (absent end diastolic flow or pulsatility index > 95th centile), abnormal ratio between the umbilical artery and middle cerebral artery pulsatility indices (< 5th centile) and growth velocity (crossing centile > 2 quartiles)[6, 22]. With increasing emphasis placed on ultrasound measures of fetal size and Doppler parameters to identify FGR and guide clinical management, it has become imperative that charts used for these measures are reliable and used consistently.

Many reference charts have been published and differences in populations and chart methodologies means that centiles for a given measurement may vary considerably. A study comparing the choice of

reference chart demonstrated up to a six-fold increase in measurements classified as below the 5th centile[29]. When examining three charts in common use in Australia[34], differences in assigned centile will classify the same fetus as growth restricted, small for gestational age and normally grown, as demonstrated in figure 3.1.

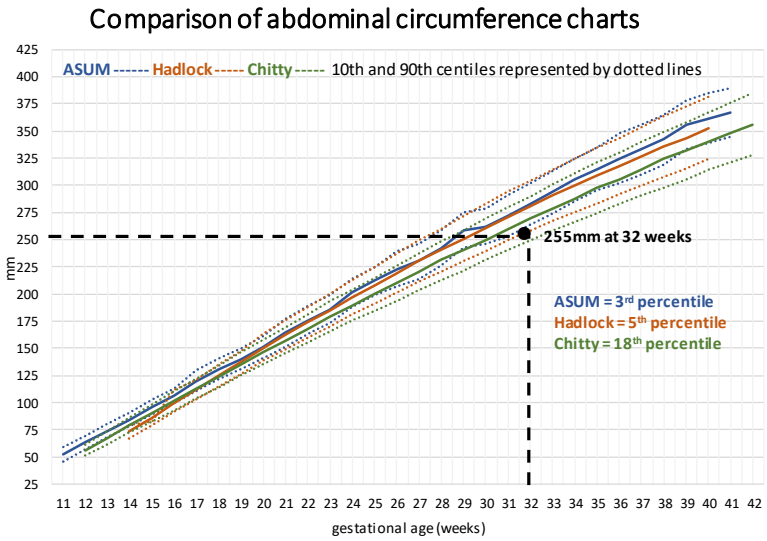

Figure 3.1 *Comparison of three commonly used charts in Australia demonstrating differences in assigned centile for the same abdominal circumference. Figure compiled by D Paoletti and previously published in a conference poster at the Australasian Society for Ultrasound in Medicine conference 2021*

Similarly, the calculated estimated fetal weight (EFW) can vary according to the choice of formula, with some algorithms better suited to estimating weight in the small fetus, and others performing well in the large fetus[27, 28]. Centiles for the calculated EFW may be derived from one of many population birthweight charts or from charts based on EFW calculated from fetal ultrasound measurements, again with the potential for considerable discrepancies in the assigned centile[31]. Heterogeneity also exists in charts of fetal Doppler measurements[167] and variations in which Doppler parameter is reported and which chart is used has also been reported[170].

Which fetal measurement reference chart to use has been a contentious issue in Australian ultrasound practices for the past two decades. In 2001 the Australasian Society of Ultrasound in Medicine (ASUM) recommended the use of the Campbell Westerway charts for fetal biometry which were formulated from an Australian population[172]. Despite this, a survey conducted in 2013 of members of the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) found there were at least eight fetal growth charts in clinical use in Australia[34]. The potential for misdiagnosis of growth restriction leading to additional interventions and patient anxiety cannot be underestimated. For example, it is possible for a fetus to be diagnosed as growth restricted by one practitioner, and later that day found to be normally grown by a practitioner using a different reference chart. Consistent use of reliable growth charts is necessary to recognise abnormal fetal growth and inconsistency in current Australian practice highlights issues in adherence to clinical practice guidelines.

Some fifteen years since those survey findings were published, inconsistencies in the choice of reference chart remain problematic. Obstetric ultrasound services in Australia are provided by radiologist led medical imaging private practices, obstetrician led private practices, medical imaging departments in public hospitals, and obstetric ultrasound departments in public hospitals. The majority of obstetric ultrasound examinations in Australia are performed by radiologist led medical imaging practices (both public and private)[37]. A shortcoming of the 2013 survey was that survey participants were RANZCOG members, therefore, a more inclusive survey to investigate reasons why ultrasound providers have chosen to use particular reference charts was proposed. Findings of this study were published as *A survey of current practice in reporting third trimester fetal biometry and Doppler in Australia and New Zealand* [173] in the Australasian Journal of Ultrasound in Medicine. Sections of this manuscript, including tables and figures, are reproduced in this chapter.

3.2 Methods

A survey instrument was developed for use on either a desk-top or mobile device, utilising drop-down menus for responses where possible, and conditional questioning via skip and/or display logic. Two

rating scale questions investigated factors influencing the choice of reference chart, and one open text question invited comment on how third trimester ultrasound is performed and reported. The survey was approved by the Australian National University human research ethics committee (ANU HREC 2017/418 and the RANZCOG continuing professional development committee.

3.2.1 Pilot study

A pilot study was undertaken in 2017 (prior to the final survey) to test the suitability of questions for the final larger survey of sonologists. In Australia, the vast majority of ultrasound examinations are performed by sonographers who are allied health professionals, and sonologists provide the written report. The term sonologist refers to medical specialists that report or perform diagnostic ultrasound, and includes radiologists (medical imaging specialists), obstetricians (often with additional ultrasound qualifications), and other medical specialists with specific ultrasound training and qualifications.

Response rates to email surveys have been reported as 25 - 30%[174] and it has been reported the response rate from medical specialists is declining[175]. Indeed, the response rate from the survey published by McCarthy and colleagues in 2013 was 26%[34]. Sonographers, being a similar group to the target population by virtue of their knowledge of fetal biometry measurements, were chosen to pilot the questionnaire. It was hoped this strategy would simplify distribution of the final web-based survey (i.e. pilot study participants would not require removal from the distribution list) and not further reduce an anticipated low response rate.

Survey questions (Appendix A) were developed from published questionnaire text[34] and informed by personal experience and current practice as a sonographer in a high risk obstetric ultrasound. Questions included three demographic questions, a question about what elements were included in a third trimester ultrasound, and a further eleven questions about the way measurements are reported, which charts are used, and when Doppler ultrasound is performed. Four questions exploring the choice of reference chart were assessed by five Likert items. The final question invited comment on how third trimester ultrasound is performed and reported.

When deciding the most appropriate questionnaire format, consideration was given to the fact that half of the sonographer workforce is part time and almost half work at multiple sites[176]. Access to a computer is typically through a shared work station, therefore, hard copy questionnaires were provided to each practice to collect data from sonographers in the workplace. It was estimated the questionnaire would take approximately 15 minutes to complete. A tamper-proof box was provided for completed questionnaires which were collected two weeks after initial distribution. This gave the many sonographers who work part time and at multiple sites the opportunity to complete the questionnaire.

A short semi-structured interview with a sonologist from each practice was conducted to gain further insight into choice of fetal biometry reference charts, opinions on chart methodologies, and potential barriers to adopting reference standards. Interview was chosen primarily for responder convenience as sonologists are typically time-poor and medical specialist response rates to questionnaires is known to be low[175].

Four ultrasound practices representative of obstetric ultrasound services in Australia (namely radiologist led medical imaging private practices, obstetrician led private practices, medical imaging departments in public hospitals, and obstetric ultrasound departments in public hospitals) were invited to participate in the pilot study. The hard-copy questionnaire (Appendix A) was distributed to sonographers to determine what measurements are included in a standard third trimester ultrasound, which fetal biometry reference charts are used, factors that may have influenced the choice of fetal biometry reference chart, and how fetal measurements are reported at their practice.

Responses were assessed for question suitability and comprehension in order to refine questions for the final survey. An interesting aspect of using hard copy questionnaires was that several respondents used this as an opportunity to write additional comments adjacent to certain questions and further assisted assessment of question clarity. A high proportion of responses to questions exploring factors influencing the choice of chart were marked neutral in the 5 point Likert response format. One

interpretation of this finding is that many in this cohort did not consider decisions on the choice of chart to be within their scope of practice. A summary of responses and analysis is provided in tables 3.1, 3.2 and 3.3.

The sonologist interview guide (Appendix A) included two demographic questions, eleven questions on reporting third trimester ultrasounds, three questions on adopting new reference charts, and a final question inviting comment on any other aspect of third trimester ultrasound. Responses to questions on adopting new charts and other aspects of third trimester ultrasound were evaluated for emerging themes to inform wording of these questions in the final survey. A summary is provided in table 3.4.

3.2.2 Refining questions for final survey

Questions were adapted for the target population of sonologists, and refined following analysis of the pilot survey. Additional questions on the use of Doppler assessment in third trimester ultrasound examinations were drafted and included in the final questionnaire. Questions were further assessed by expert panel review before using the Qualtrics platform (Qualtrics, Provo, UT) to create the on-line survey. Drop-down menus were utilised as much as possible for question responses, and features such as skip and display logic were employed when questions were not applicable based on previous responses. The survey layout was assessed for formatting inconsistencies for both desk top and mobile devices and pre-tested by the expert panel. Minor formatting adjustments were made to improve readability, such as using a bold font to highlight important elements in questions.

The final survey (Appendix A) comprised five sections with the first section including the participant information sheet and electronic consent. Section 2 comprised four demographic questions under the heading *About you & your Workplace* to determine the type of medical practice, its location, qualifications and experience of the respondents. Section 3 was titled *Reporting third trimester ultrasound* and included questions on how measurements are reported, which measurement charts are used, and thresholds for reporting growth restriction. Questions on the use of Doppler ultrasound

were in Section 4 headed *Third trimester Doppler* with an explanatory note *These questions relate to the use of Doppler in third trimester ultrasound for fetal growth*. The final section *Choice of reference chart* included two questions on chart choice with a Likert response format and an open question inviting comment on any aspect of third trimester ultrasound.

3.2.3 Survey Distribution

The intended survey recipients included obstetricians performing obstetric ultrasound as part of their clinical practice, obstetricians with ultrasound subspecialty qualifications, radiologists, and other medical specialists with ultrasound qualifications. The respective colleges and professional bodies of these groups were approached to distribute the survey link to their members, namely the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG), Royal Australian and New Zealand College of Radiologists (RANZCR) and Australasian Society for Ultrasound in Medicine (ASUM). While current Australian practices were the focus of this research, due to the binational membership of these organisations, Australian and New Zealand members were invited to participate in the survey.

Following college and professional body approval, letters inviting participation and links to the electronic survey were distributed to members of RANZCOG via email on 16/9/2019 with one reminder email two weeks later. Links were distributed to members of the RANZCR Obstetrics and Gynaecology Special Interest Group 15/8/2019 via social media and again on 24/2/2020 via email. Survey links were advertised in the ASUM member electronic newsletter on 7/11/2019 and the ASUM Diploma of Diagnostic Ultrasound (DDU) newsletter on 20/2/2020. Ideally, distribution emails would have been sent simultaneously, however, coordinating this aspect with the professional bodies proved to be challenging. Unfortunately, general radiologists were not included in the survey distribution as RANZCR did not wish to overly burden generalists with emails inviting survey participation.

Data were analysed using Microsoft Excel (2016) and IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, N.Y., USA).

Table 3.1 *Summary of Pilot Study responses*

Q5. Third trimester measurements are usually reported alongside:			
Response option:	N	Written comments	Notes
a. An equivalent number of weeks and days	0	'radiologist dependant, every radiologist different'	Responses indicate that option (b) may require rewording as it is would be unusual to report both centile and range. For clarity. examples for each response option will be included: a. an equivalent number of weeks and days e.g. AC 270.2mm 31w1d b. A reference range e.g. AC 270.2mm 30w3d – 32w0d c. the measurement and standard deviation e.g. AC 270.2mm +/- 2SD d. the centile for the known gestational age e.g. AC 270.2mm 90th centile e. the z score e.g. AC 270.2mm z = 1.28 Additional response option f. Other (please specify)
b. A reference range eg 5th to 95th centile	3		
c. The centile for this gestational age	7	'sonographer worksheet' 'radiologist dependent'	
d. The number of standard deviations below or above the mean	0		
e. The z-score	0		
Equivalent weeks and days, reference range and centile	6		
Equivalent weeks and days and reference range	5		
Reference range and centile	1		
Blank	1		
Q6. My practice uses the following reference charts for fetal biometry measurements:			
Response option:	N	Written comments	Notes
a. ASUM charts (2000)	8		Responses indicate question requires rewording (especially the high number that selected both ASUM and Hadlock, & written comments 'Hadlock for EFW') May be possible to offer less response options e.g. a. ASUM (2000) b. Chitty (2002) c. Hadlock (1982) d. Jeanty (1984) e. Schulter (2004) f. IG21 (2014) Should add customised charts (e.g. GROW) as a response option, and an option for 'do not know'. Consider asking this question for each parameter separately in case charts by different authors are used for different parameters. Will use a dropdown menus for responses.
b. Chitty (2002)	0		
c. Hadlock (1982)	7		
d. Jeanty (1984)	0		
e. In-house reference range	0		
f. Schulter (2004)	0		
g. Snijders (1994)	0		
h. IG21 (2014)	0		
i. Other (please specify)	1	'unsure' (1)	
ASUM & Hadlock	1 2	'Hadlock for EFW' (5)	

Q7. All ultrasound machines in my practice have the same reference charts set as the default:			
Response option:	N	Written comments	Notes
a. No not know	7		Add question about whether report page generated by the ultrasound machine is used when reporting or whether a digital reporting tool is used (i.e. one that calculates centiles). Can use skip logic to include/exclude this question.
b. Yes	2 1		
c. No	0		
Q8. In my practice, the estimated fetal weight (EFW) is included in the report for third trimester growth scans			
Response option:	N	Written comments	Notes
a. Do not know	1		
b. Yes	2 2	'for sonographer, radiologist doesn't always report it' (2) 'dependent on radiologist doing final report' (2)	
c. No (go to question 11)	5		
Q9. In my practice, the estimated fetal weight (EFW) is calculated by:			
Response option:	N	Written comments	Notes
a. Do not know	4		Should have been 22 responses for this question – will use skip logic in electronic survey May be possible to offer less response options, e.g. a. Hadlock (BPD-HC-AC-FL) b. Hadlock (BPD-AC-FL) c. Hadlock (HC-AC-FL) d. Schild (sex specific BPD-AC-FL) e. Shepard (BPD-AC) f. IG21 (HC-AC) g. Combs (HC-AC-FL) Should add response options for 'do not know' and 'other'. Will use a dropdown menus for responses.
b. Hadlock (BPD-HC-AC-FL)	2 1		
c. Hadlock (BPD-AC-FL)			
d. Hadlock (BPD-HC-FL)			
e. Hadlock (AC-FL)			
f. Warsof (BPD-AC)			
g. Shepard (BPD-AC)			
h. Schild (Female BPD-AC-FL)			
i. Schild (Male BPD-AC-FL)			
j. Birnholtz (BPD-TAD)			
k. Birnholtz (BPD-OFD-TAD)			
l. Combs (HC-AC-FL)			
m. Other (please specify)			
Blank	2	'not sure which Hadlock formula'	
More than 1 selected	1		

10. In my practice, the EFW is usually reported alongside (tick all that apply):			
Response option:	N	Written comments	Notes
a. Do not know	2		Should have been 22 responses for this question – will use skip logic in electronic survey Respondents may be confused with options for reference range and centile - response option (c) may require rewording. For clarity, examples for each response option will be included: a. the centile or the known gestational age e.g. 1481 71st centile b. the percentage error of the estimation e.g. 1481g +/- 15% c. the error of the estimation in grams e.g. 1881 +/- 222g d. the z score e.g. 1418 z = 0.58 e. nothing – I just report the EFW in grams Additional response option f. Other (please specify)
b. An equivalent number of weeks and days	1	'in sonographers worksheet not all radiologists report this'	
c. A reference range eg 5th to 95th centile	4		
d. The centile for this gestational age	8	'dependant on radiologist some don't put EFW in report' 'not all radiologists report EFW'	
e. The number of standard deviations below or above the mean	0		
f. The z-score	0		
Equivalent weeks and days, reference range and centile	4		
Equivalent weeks and days and reference range	2		
Reference range and centile	3		
11. In my practice, the reference chart used for each fetal biometry measurement and/or EFW are cited in the report:			
Response option:	N	Written comments	Notes
a. Do not know	2	'visualised on machine generated report in PACS'	Reword question for clarity: The reference chart used for each measurement (BPD, HC, AC, FL) and EFW are cited in my reports. Can omit option (a) Add question : Reference charts used by this practice differ from those used by other practices I have worked at: a. yes b. no c. do not know d. not applicable
b. Yes	1 0		
c. No	1 5		
Blank	1		
12. In my practice, a fetus is reported as small for gestational age or growth restricted when:			
Response option:	N	Written comments	Notes
a. Do not know	7		Reword question to include 'threshold' or 'cut-off', e.g. I comment the fetus may be small for gestational age of growth restricted at the following cut-off Include additional response options: e. Both EFW and AC are below the 10th centile f. Both EFW and AC are below the 5th centile g. I don't comment on small for gestational age or growth restriction h. Other (please specify)
b. The EFW is below the 10th centile	5		
c. The EFW is below the 5th centile	5		
d. The AC is below the 10th centile	1		
e. The AC is below the 10th centile	3		
EFW <10th centile and AC <10th centile	7		
EFW <5th centile and AC <15thcentile	1		

13. In my practice, the Middle Cerebral Artery Doppler pulsatility index (PI) is included in a third trimester ultrasound assessment:			
Response option:	N	Written comments	Notes
a. As part of the standard ultrasound examination	16		Include specific questions on UA ultrasound – should not assume this is standard in third trimester protocols. Include specific questions on indices reported and charts used. Will employ skip logic and display logic to cover instances where Doppler is not performed, or only performed at specific gestational age in the third trimester. Need to research commonly used Doppler charts. Will use dropdown menus for responses to questions on charts.
b. When the EFW is below the 10th centile	0		
c. When the EFW is below the 5th centile	1		
d. When requested by the referring doctor	0		
e. When requested by the reporting doctor	1		
f. It is never a part of a third trimester ultrasound assessment	0		
Other (please specify)	3	'Yes on sonographers worksheet not all radiologists report this' (1) > 34 wks (2)	
Standard part of examination >34w & EFW <10th	1		
Standard part of examination >34w, EFW <10th & when requested	3		
Standard part of examination >34w, EFW <5th & when requested	1		
EFW <5th & other	1	Abnormal Doppler	
EFW <10th & other	1	> 30 weeks	
14. In my practice, Ductus Venosus Doppler is included in a third trimester ultrasound assessment:			
Response option:	N	Written comments	Notes
a. As part of the standard ultrasound examination	1		Include specific questions on indices reported and charts used. Will employ skip logic and display logic to cover instances where Doppler is not performed, or only performed at specific gestational age in the third trimester. Need to research commonly used Doppler charts. Will use dropdown menus for responses to questions on charts.
b. When the EFW is below the 10th centile	2		
c. When the EFW is below the 5th centile	1		
d. When requested by the referring doctor	4		
e. When requested by the reporting doctor	0		
f. It is never a part of a third trimester ultrasound assessment	6		
Other (please specify)	4	Abnormal UA & MCA (2) Abnormal MCA (1) Abnormal UA (1)	
EFW <10th centile & when requested by referrer	3		
When requested by referrer and other	4	Abnormal MCA and UA Doppler (3) FGR (1)	
EFW <5th centile & when requested by referrer	2		
When requested by either referrer/reporter	1		

14. In my practice, Uterine Artery Doppler is included in a third trimester ultrasound assessment:			
Response option:	N	Written comments	Notes
a. As part of the standard ultrasound examination	3		Include specific questions on indices reported and charts used. Will employ skip logic and display logic to cover instances where Doppler is not performed, or only performed at specific gestational age in the third trimester. Need to research commonly used Doppler charts. Will use dropdown menus for responses to questions on charts.
b. When the EFW is below the 10th centile	3		
c. When the EFW is below the 5th centile	0		
d. When requested by the referring doctor	8		
e. When requested by the reporting doctor	0		
f. It is never a part of a third trimester ultrasound assessment	5		
Other (please specify)	1	PHx PET	
EFW< 10th & when requested (2),	2		
When requested by referring & reporting doctor	4		
EFW <10th, EFW <5th & when requested	1		
EFW <10th, EFW<5th & other	1	Low PAPP-A, preeclampsia	

Table 3.2 *Summary of Pilot Study responses to questions on chart choice*

Q16. Recommendations and guidelines of professional bodies were an important consideration in the choice of reference chart used in my practice			
	N	Written comments	Notes
Strongly disagree	0	NA (2)	Blank responses may indicate respondent considers this question to be out of scope of practice Need to reword this section for e-survey to an overarching question applicable to each scenario e.g. To what extent do you agree that the following factors are important considerations in the choice of reference chart? Recommendation and guidelines of professional bodies Chart methodologies Referring practitioner preferences The software configuration of the ultrasound machine
Disagree	0	Don't know preset on machines	
Neutral	6		
Agree	11		
Strongly agree	8		
Blank	3		
Q17. Chart methodologies were an important consideration in the choice of reference chart used in my practice			
	No.	Written comments	Notes
Strongly disagree	0	NA (2)	Blank responses may indicate respondent considers this question to be out of scope of practice
Disagree	2		
Neutral	11		
Agree	6		
Strongly agree	5		
Blank	4		

Q18. Referring practitioner preferences were an important consideration in the choice of reference chart used in my practice			
	No.	Written comments	Notes
Strongly disagree	1	NA (2)	Blank responses may indicate respondent considers this question to be out of scope of practice
Disagree	10		
Neutral	11		
Agree	3		
Strongly agree	0		
Blank	3		
Q19. The software configuration of the ultrasound machine was an important consideration in the choice of reference chart used in my practice			
	No.	Written comments	Notes
Strongly disagree	1	NA (2)	Blank responses may indicate respondent considers this question to be out of scope of practice
Disagree	4		
Neutral	7		
Agree	10		
Strongly agree	4		
Blank	2		

Table 3.3 *Summary of Pilot Study invited comments*

Comments Site A (radiologist led medical imaging service in public hospital)	**Notes**
There is a lot of variation in final reports in our practice due to radiologists being rostered on a weekly basis and no continuity. Obstetricians do however have access to images and machine report pages	5/8 completed this question Themes: inconsistent reporting need for standardisation
Radiologist consistency is not always the norm but would be beneficial as would consistency across the state	
Clarification is needed in what report you are referring to in this study ie sonographers report or radiologists final report	
Inconsistency in how radiologists report scans, Obstetric scans should be standardised throughout the state.	
Inconsistency of reporting from varying radiologists. Would like more consistent guidelines. Clarification of charts display on various systems. ? centile v graph	

Comments site B (radiologist led private medical imaging practice)	Notes
Ductus venosus can be added for a standard 3rd trimester US	9/15 completed this question Themes: inconsistent reporting need for standardisation protocols for high risk pregnancies and low risk pregnancies differ
The report page we generate as part of the scan as all what I've said above however the radiologists reports vary and may not include all the data	
All serial scan data is not routinely graphed/entered	
There is some variability between the way radiologists report and which parameters they will report	
In my practice 3rd trimester us reporting needs to be updated to reflect current methodologies and local tertiary reporting methods/techniques	
N/A set up prior to my employment. Considerations into this are unknown.	
Have not been involved in decision making for above. Majority of 3rd tri scans are routine/low risk US. Rarely perform serial 3rd tri US for IUGR etc	
Referral to practice for 3rd trimester is mainly to assess placental localisation or fetal presentation, Hardly get any referrals for monitoring growth in IUGR cases.	
Yes should be standardised	

Table 3.4 *Summary of Pilot Study Sonologist interviews*

Q13. If ASUM recommended the adoption of a different chart, would your practice adopt the new chart?	
Site A	Notes
Personally, if ASUM made a recommendation then I would look at it very very carefully. It would be my default because I haven't had any issues with ASUM recommendations ant I refer to them as my go-to usually. So if they came up with a new thing I'd want a strong reason not to use it otherwise I would.	Recommendation of professional body important enough to change practice
Site B	Notes
Yes, I think so, yeah. Look, we haven't heard of them but if that comes from a reputable source like that, particularly if it's blessed by the referrers, particularly the specialist referrers, then I'd be very happy to do that. In the end what I'm trying to do is provide the service that they want.	Recommendation of professional body important enough to change practice however, opinions of referrers should also be considered
Site C	Notes
I guess I need… I'll need to see whether…how accurate…if ASUM recommended a chart…a growth scan, let's say for…. I guess if they are customised charts or not whether this will apply to…because everyone's background is different. Is it recommended for Chinese background or Caucasian background then yes I will use it, this country, you know. It depends on how good the data is. I think Chitty got…compare ASUM… if there's a huge amount of data then I'll use it.	Recommendation of professional body important enough to change practice provided enough evidence was provided
Site D	Notes
I honestly don't know. I'd need to look at the recommendation, look at the chart, and make a decision based on that. Um, as you know, one of my main areas of research interest now is stillbirth, and this whole question as how you actually manage third trimester pregnancies based on trying to reduce the risk of stillbirth. Um, I think there's a really big question as to what extent it's fetal biometry that guides you, or to what extent it's fetal Doppler, or to what extent it should be risk factors for stillbirth. Um, and there's probably an interaction between all three but I don't think it will ever be a single measure that is[sic] the determinant of clinical practice.	Would need to make informed decision to change measurement charts
Q14. Do you see any potential barriers in implementing new charts?	
Site A	Notes
The biggest barrier would be… for me would be if it's not easily integratable with the machines and with the read outs because personally I have a lot of difficulty… if the data's not on the scan…it's my practice to report what's on the image because then the mistake is mine if I make a mistake whereas once you take the data and then write your own chart and then report that, first of all there's a step there that hard for someone to go back and recheck. So anything needs to be integrated into the ultrasound machine. As long as it can be entered, and that's the default, then that's great. That would be the biggest barrier for me. Others barriers would be if the clinicians don't like it or this or that but that wouldn't be a barrier to me – I'd just quote it and explain why if I were questioned.	Software settings in ultrasound equipment

Site B	Notes
There are really 3 barriers: There's the barrier of the radiologists saying they don't want to do anything different to what they've done previously. The barrier of the sonographer saying essentially the same. And then there's the barrier probably of the receiver at the other end, which is the biggest barrier, saying 'What's this? this isn't what I'm used to'. Those are the three barriers.	Unwillingness of those requesting/reporting/performing ultrasound to change
Site C	**Notes**
It's the standardised issue. If we see an IUGR baby say with ASUM chart and I send it to my colleague who used a Chitty chart, you know then that hospital might have a different centile.	Standardisation
Site D	**Notes**
I don't think there'd be any barriers as far as the clinicians who refer to our unit and that I report to. I mean, if we just said we were going start reporting on new charts I suspect they wouldn't even notice. Because really what they do is read my report and read my recommendation.	Unlikely to be any barriers
Q15. Is there anything else you would like to add about how fetal growth is measured by ultrasound?	
Site A	**Notes**
Umm, I mean it would be really good if there was… I suppose this being in private we're a little bit left out of the current, you know…it would be great if there was clarity on what was wanted and uniformity on what was reported because that's in everyone's interest. So, umm, we don't do other than what's wanted deliberately it's probably because we're not up to date or whatever, umm, Sometimes the feedback contradicts what we've been told previously and that leaves you, you know…so it would be good if there was…and I guess that needs cooperation which is probably our fault if we're not involving ourselves in that process but.	Clear communication of current practice and engagement Uniform reporting
Site B	**Notes**
Um, there are a couple of things really. Firstly, at the top of the cheat sheet there will be age by LMP, when in fact it's not age by LMP but by first trimester US. And to me that's just a bit sloppy and makes it confusing from my perspective when I'm trying to dictate something. Secondly, what's the second thing I was thinking, we have a bit of disparity amongst sonographers in what is recorded. Some will record every detail, ah, detailing growth parameters and some will record only some details. Some don't bother recording centiles which is a nuisance for me because, um, either I have to chase them up physically if it's a XXX case or say additionally to the typist 'forget about centiles' and the typist has got to scrub them off the proforma chart I've got. So a little bit more, um, what's the word, uniformity of sonography I think would be helpful. That said, um, I think that probably the biggest challenge facing sonographers is these days particularly with obstetric ultrasound is that women are getting, pregnant women are getting fatter and fatter and the detail we're requiring is getting more and more and more. And how their shoulders and elbows and wrists stay stuck to the rest of their body at the end of a 40 min examination I do not know. Um, I have nothing but admiration for what they pull out.	Inconsistent communication between sonographer (via worksheet) and sonologist can impact report Number of technically challenging ultrasounds has increased due to increasing BMI

Site C	Notes
Other opinions on Fetal Growth charts...I think everyone measure slightly different. You know, sometimes sonographer measure and my measurement they could be a few centiles difference, or sometimes we could be 20 centile difference, so it's the consistency in training, you know, everyone measures so differently. I don't know how to improve that…unless we do more training. I guess the error would definitely decrease if we always use the same operator, it would be more accurate, you know. Because sometimes what I know that, you know, measure here the baby is about 50th centile, same chart, different operator, and the next one I measure again is about 15th centile. So, a lot of obstetricians look at it and look at 50th centile now and 2 weeks later it's 15th and next measurement about 2 weeks later is about 3rd centile, and I do it again and it's about 20th centile. So you've got 4 different operators and with it confusion. Better we just stick with one operator. I don't have the answer. Everyone measures so different. *Do you think that's just down to measurement or do you think that's also how the chart's constructed?* It could be. Operators are different in measurements, and the consistency and whether the fetal position could be part of it as well…	Need for image and measurement QC
Site D	**Notes**
Um, well! I guess I would make the comment that it's interesting we have this incredibly rigorous audit process around combined first trimester screening, whether it's the ultrasound measurement of the NT or the laboratory measurement of serum markers, and we really have no quality control around third trimester ultrasound when in relation to clinical practice and interventions there's probably a far greater impact. Um, my own unit spends a large amount of time doing giving sort of second opinion scans on, you know, scans that have been done either outside in the community or in the medical imaging department that have given funny reports about biometry and um, it's um, I think it's an area where there really does need to be some um, monitoring of quality of practice. I'm not quite sure how you'd do that but I think it's an area of significant risk, whether it's intervening inappropriately because of incorrect measurement or incorrect reporting, or whether it's the other way around where things are falsely reassured. So, I think it's an area that really needs some sort of ah, attention. The whole question about routine third trimester ultrasound in all pregnancies I think is a related comment, because you know there's ever going to be a recommendation about routine third trimester US, I mean, there's got to be some quality control of it. There's significant risk involved in introducing a new routine measurement. Again, I'm not quite sure how you would do that, but some thought need to be given as to how you actually do that. I'm not sure about the whole, the current audit process for NT, I mean it's relatively easy to provide images and say look this is how we do things routinely, these are fine; you could always do the same thing for your BPD, HC, AC measurements, it doesn't necessarily mean that's the way you practice every day. Um, if practices had to provide normal ranges for the data they're producing for, say if everybody had a routine 3rd trimester scan at 36 or 37 weeks, I guess you might get somewhere close to the truth if you found that one practice was an aberration in relation to whereabouts the, their median values were sitting for some of the fetal biometry. I think it's very hard to know quite how you manage to get much better quality control.	Need for image and measurement QC Should third trimester scans be routine practice?

3.4 Results

A low response rate was anticipated, however a disappointing total of 230 responses were received in response to the final survey of sonologists. The majority (204) were from RANZCOG members, with an estimated response rate of 15%, based on the number of clinicians fulfilling the pre-condition of performing/reporting ultrasound derived from the membership statistics reported in the 2018-2019 RANZCOG Annual Report. Thirteen responses were received from members of the RANZCR Obstetrics and Gynaecology Special Interest Group comprising 73 members (Fitzpatrick, personal communication) for an 18% response rate. Thirteen responses were received from ASUM members, however, it is difficult to estimate the response rate from those members involved with obstetric ultrasound. There are 650 medical members of ASUM but information on the specialty area(s) practiced is not routinely collected and furthermore, this membership cohort may also be RANZCOG or RANZCR members that have previously completed the survey.

Of the 230 returned surveys, 86 were excluded from analysis for the following reasons:

- consent not given (1)
- did not report ultrasound (13)
- too incomplete for analysis (72)

Of the remaining 144 responses, 125 were complete for both fetal biometry and fetal Doppler sections. Given the low number of responses, descriptive statistics were used to present data.

Most responses (80%) were from Australian sonologists inclusive of all states and territories. Most (70%) practiced in major cities as defined by the Australian Bureau of statistics Australian Statistical Geography Standard[177]. New Zealand respondents were from major urban centres as defined by Statistics New Zealand Urban Rural Indicator 2018 V1.0.0[178] and included seven of the twenty district health boards[179]. Respondent demographics are summarised in figures 3.2 – 3.4.

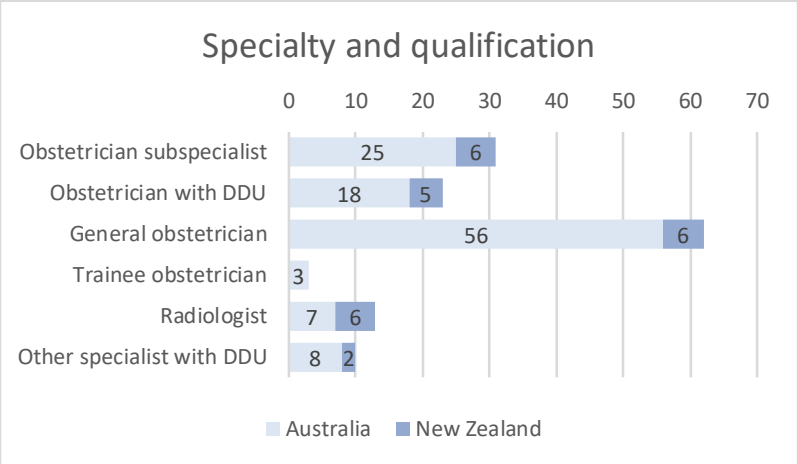

Figure 3.2 *Respondent specialty and practice. DDU is the Diploma of Diagnostic Ultrasound*

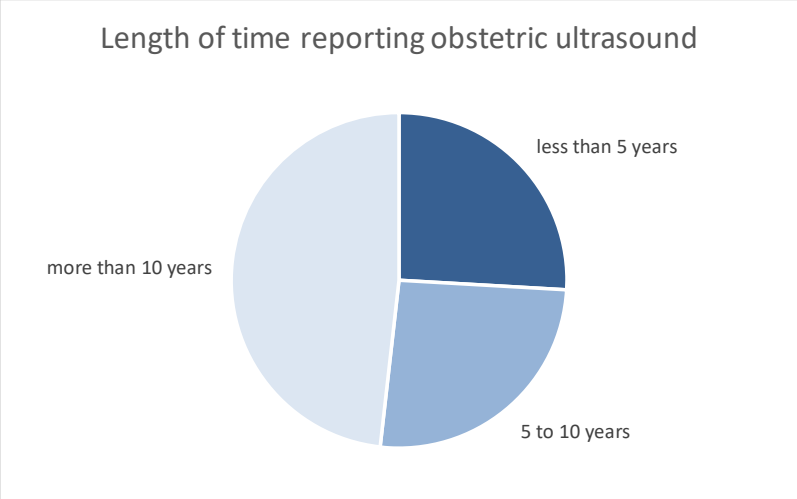

Figure 3.3 *Respondent experience*

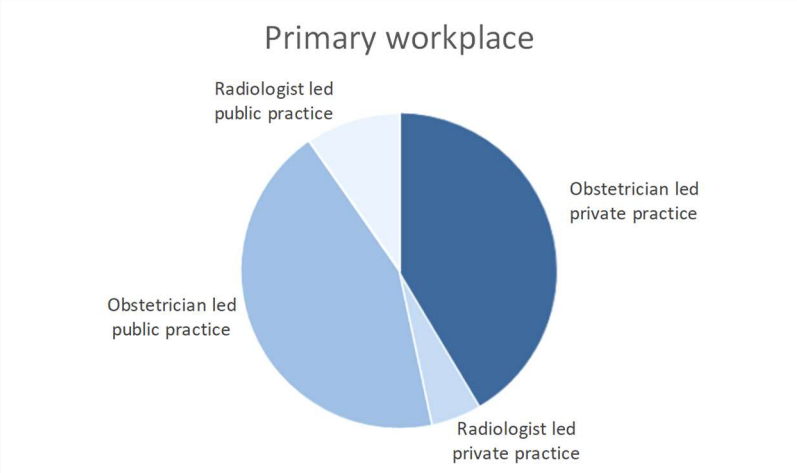

Figure 3.4 *Respondent primary place of practice*

3.4.1 Charts for fetal biometry and reporting fetal measurements

Charts currently used in Australia and New Zealand and how measurements are reported are listed in Table 3.5 (note two respondents did not provide geographic information). The most commonly used charts for fetal biometry were the Westerway[172] charts (also referred to as ASUM charts) and Hadlock[79, 180-182] charts, used by 35% and 26% of respondents respectively. Some respondents (10%) were unsure of which charts were used, and 11% indicated a combination of charts were used for standard fetal biometry measures of bi-parietal diameter (BPD), head circumference (HC), abdominal circumference (AC) and femur length (FL). In-house charts based on the Western Australian Raine Cohort (Newnham, personal communication) were used by 5%, but none outside of Western Australia.

A clear trend emerged in the way measurements were reported with a majority (78%) reporting the centile for known gestational age (GA) alongside measurements. Some respondents (13%) co-reported centiles with equivalent weeks and days, with 11% only reporting equivalent weeks and days for each parameter. Most (63%) did not cite the reference chart in the report. Most respondents (83%) had previous employment experience at other practices, with 39% indicating charts at those practices were different to those used at the current practice, 30% indicating the same charts were used, and 31% were unsure.

Ultrasound machines produce a report page summarising measurements made during the examination, the average equivalent weeks and days for each measurement, and the centile for each measurement, based on the charts configured within the machines software. This was typically used by clinicians reporting fetal measurements (74%). Most (75%) indicated all machines in their department were configured with the same fetal measurement charts, however, 21% were unsure, and 4% indicated machines in their department were not configured with the same fetal measurement charts.

Table 3.5 *Reporting practices for fetal biometry*

	Obstetric Practice AU† *N*	Obstetric Practice NZ‡ *N*	Radiology Practice AU *N*	Radiology Practice NZ *N*	TOTAL *N (%)*
Chart used 142/142					
ASUM[172](BPD,HC,AC,FL)	28	11	6	7	50 (35)
Chitty[99, 183, 184](BPD,HC,AC,FL)	16	0	0	0	16 (11)
Hadlock[79, 180-182] (BPD,HC,AC,FL)	30	6	1	0	37 (26)
GROW[185] (BPD,HC,AC,FL)	1	2	0	0	3 (2)
Unsure (BPD,HC,AC,FL)	13	0	1	0	14 (10)
Raine *unpublished data* (BPD,HC,AC,FL)	6	0	1	0	7 (5)
Combination of charts	13	0	2	0	15 (11)
Reported alongside 142/142					
Centile for known GA§	69	12	4	7	92 (65)
Equivalent weeks and days	13	1	1	0	15 (11)
Reference range	1	1	0	0	2 (1)
Equivalent weeks and days & centile	13	0	3	0	16 (11)
Plotted on chart	4	2	1	0	7 (5)
Nothing	3	1	0	0	4 (3)
Other	3	2	0	1	6 (4)

ł Australia
‡ New Zealand
§ Gestational age

External digital reporting packages are linked to ultrasound equipment and incorporate ultrasound measurements into the body of the report. The software can be configured for particular charts and to present data in a variety of ways, including centiles for gestational age, Z-scores, or graphically. These systems were used by 16% of respondents.

3.4.2 Estimated Fetal Weight

Table 3.6 lists reporting practices for estimated fetal weight (note 2/144 respondents did not provide geographic information). Hadlock[85, 102] (BPD, HC, AC, FL) was the most commonly used algorithm for calculating estimated fetal weight (69% of respondents), typically reported alongside the centile for the known gestational age according to fetal weight charts[104], rather than birthweight charts[186-188]. A minority (6%) used in-house birthweight charts[189], and 14% used customised estimated fetal weight charts[185, 190].

Table 3.6 *Reporting practices for estimate fetal weight*

	Obstetric Practice AU[ł] *N*	Obstetric Practice NZ[‡] *N*	Radiology Practice AU *N*	Radiology Practice NZ *N*	TOTAL *N (%)*
EFW[§] algorithm 142/142					
Hadlock[35, 36] (BPD-HC-AC-FL)	69	16	7	7	99 (70)
Hadlock[35, 36](HC-AC-FL)	18	1	1	0	20 (14)
Hadlock[35, 36](BPD-AC-FL)	7	0	0	0	7 (5)
Unsure	13	1	1	0	15 (11)
Other	0	1	0	0	1 (1)
Reported alongside 141/142					
Centile for known GA[¶]	74	10	4	1	89 (63)
Error as %	9	1	0	1	11 (8)
Error in grams	6	1	1	0	8 (6)
Nothing	6	2	1	0	9 (6)
Centile & error (%)	3	0	1	4	8 (6)
Centile & error (g)	5	0	2	0	7 (5)
Plotted onto customised chart	0	3	0	0	3 (2)
Other	3	2	0	1	6 (4)
Chart used 139/142					
Roberts[38] *(birthweight)*	5	0	0	0	5 (4)
Hadlock[37] *(fetal weight)*	55	3	7	4	69 (50)
WHO [39]*(fetal weight)*	2	0	0	0	2 (1)
Dobbins [40]*(birthweight)*	6	0	0	0	6 (4)
NZ customised [34]*(GROW, fetal weight)*	0	13	0	3	16 (12)
NZ WHO [42] *(birthweight)*	0	1	0	0	1 (1)
Unsure	23	2	2	1	28 (20)
GROW [34](Australian, fetal weight)	2	0	0	0	2 (2)
Mercy [41](in-house, population customised)	6	0	0	0	6 (4)
Raine (unpublished,in-house)	2	0	0	0	2 (2)
Other	2	0	0	0	2 (2)

ł Australia
‡ New Zealand
§ Estimated fetal weight
¶ Gestational age

3.4.3 Reporting small for gestational age and/or fetal growth restriction

Thresholds for reporting small for gestational age (SGA) and/or fetal growth restriction (FGR) were variable. The majority of respondents (63%) used a cut-off of estimated fetal weight below the 10th centile for gestational age, however most also considered the abdominal circumference centile with 36% indicating a threshold of below the 10th centile, and 11% using below the 5th centile. Other factors such as

interval growth and asymmetric growth were considerations by 12% of respondents when reporting SGA or FGR. A minority (3%) indicated they did not comment on SGA or FGR in their reports.

3.4.4 Third trimester Doppler

Tables 3.7 and 3.8 summarise third trimester umbilical artery and middle cerebral artery Doppler practices from the 125 respondents that completed the entire survey. Umbilical artery Doppler was performed in all third trimester ultrasound examinations by 61% of respondents and at estimated fetal weights less than the 5th or 10th centile by 31%. Most (75%) reported the pulsatility index either as the only index (59%) or alongside other indices (16%).

Middle cerebral artery Doppler was performed for indications including estimated fetal weight below the 10th centile, abnormal umbilical artery Doppler, and suspected fetal anaemia, however, 24% performed middle cerebral artery Doppler in all third trimester ultrasound examination. Most (52%) reported the pulsatility index with 36% indicating the peak systolic velocity was also reported. When middle cerebral artery Doppler was performed, the ratio of the middle cerebral artery pulsatility index and the umbilical artery pulsatility index, known as the cerebroplacental ratio, was always reported in 55% of cases. Most respondents (80%) used a threshold of below the 5th centile for gestational age to define an abnormal cerebroplacental ratio.

Third trimester ductus venosus Doppler practices varied. Although performed by 75% of respondents, indications for doing so differed in terms of gestational age cut-off, estimated fetal weight thresholds, umbilical artery and middle cerebral artery Doppler parameters, and combinations of these factors. The pulsatility index was the most commonly reported index (27%), followed by the pulsatility index for veins (20%). Positivity or negativity of the A-wave was reported by 21%. Half of the respondents did not perform uterine artery Doppler in the third trimester and for those that did, indications included estimated fetal weight below the 5th or 10th centile (15% of responses) and a history of fetal growth restriction (8% of

responses). Most (65%) reported the pulsatility index. Details for ductus venosus and uterine artery Doppler reporting practices are provided in table 3.9.

The majority of respondents were not sure of which Doppler charts were used in their practice and when charts were selected from the response options, it was evident a wide variety of charts were used. Umbilical artery charts could be named by 42% of respondents, and while charts by Acharya[191] and Ebbing[192] were most popular, this only accounted for 12% and 13% of responses respectively. A similar pattern was observed for middle cerebral artery, ductus venosus, and uterine artery Doppler measurements.

Table 3.7 *Reporting practices for umbilical artery Doppler*

	Obstetric Practice AU† *N*	Obstetric Practice NZ‡ *N*	Radiology Practice AU *N*	Radiology Practice NZ *N*	TOTAL N (%)
UA§ Doppler performed: 123/123					
In all third trimester scans	65	3	7	0	75 (61)
At specific GA¶	2	0	0	0	2 (2)
Never performed	4	0	1	0	5 (4)
When EFW‡‡<10th centile	12	13	0	7	32 (26)
When EFW<5th centile	3	1	0	0	4 (3)
Other	5	0	0	0	5 (4)
Doppler index/indices reported: 118/118 (5 never performed UA Doppler)					
SD‡‡	18	1	1	0	20 (17)
PI§§	45	15	2	7	69 (58)
SD&PI	8	1	3	0	12 (10)
SD,PI & RI¶¶	8	0	0	0	8 (7)
PI & RI	3	0	0	0	3 (3)
RI	2	0	0	0	2 (2)
SD & RI	3	0	1	0	4 (3)
UA Doppler chart used: 118/118					
Unsure	54	9	4	2	69 (58)
Acharya[191]	12	2	2	0	14 (12)
Ebbing[192]	5	5	0	5	15 (13)
Trudinger[121, 193]	5	0	0	0	5 (4)
Baschat[194]	3	1	0	0	4 (3)
Schaffer (unpublished)	3	0	0	0	3 (3)
Medina Castro[195]	1	0	0	0	1 (1)
Parra Cordero[196]	1	0	0	0	1 (1)
Arduini[197]	1	0	1	0	2 (2)
Other	2	0	0	0	2 (2)

† Australia
‡ New Zealand
§ umbilical artery
¶ gestational age
‡‡ estimated fetal weight
‡‡ systolic diastolic ratio
§§ pulsatility index
¶¶ resistive index

Table 3.8 *Reporting practices for middle cerebral artery Doppler*

	Obstetric Practice AU† *N*	Obstetric Practice NZ‡ *N*	Radiology Practice AU *N*	Radiology Practice NZ *N*	TOTAL N (%)
MCA§ Doppler performed: 123/123					
In all third trimester scans	28	0	1	0	29 (24)
All scans above 34w GA¶	1	0	0	0	1 (1)
All scans above 28w GA	1	0	0	0	1 (1)
Never performed	15	0	2	0	17 (14)
When EFW ǂ <10th centile	8	4	0	2	14 (11)
When UA‡‡ Doppler abnormal	11	2	1	2	16 (13)
Both EFW<10th centile & abnormal UA Doppler	14	8	1	2	25 (20)
Suspected fetal anaemia	9	2	3	1	15 (12)
Other	2	0	0	0	2 (2)
Doppler index/indices reported: 106/106 (17 never performed MCA Doppler)					
SD§§	3	0	0	0	3 (3)
PI ¶¶	37	10	0	5	52 (49)
RI ǂǂ	3	0	0	0	3 (3)
PSV‡‡‡	2	1	0	0	3 (3)
PI&PSV	23	6	5	2	36 (34)
Other co-reporting combinations	8	0	1	0	9 (8)
MCA Doppler chart used: 105/106					
Unsure	47	9	3	2	61 (58)
Ebbing[192]	13	6	3	5	27 (25)
Schaffer (unpublished)	5	1	0	0	6 (6)
Baschat[194]	7	1	0	0	8 (8)
Medina Castro[195]	1	0	0	0	1 (1)
Ayoola[198]	1	0	0	0	1 (1)
Arduini[197]	1	0	0	0	1 (1)
CPR§§§reported: 106/106					
Always when MCA performed	34	16	1	7	58 (55)
Never reported	42	1	5	0	48 (45)
Cut-off used for abnormal CPR: 58/58 (42 never reported CPR)					
<10th centile for GA	1	0	0	0	1
<5th centile for GA	23	15	1	7	46
Ratio < 1	6	0	0	0	6
Other	4	1	0	0	5
CPR chart used: 58/58					
Unsure	8	8	1	2	19 (33)
Ebbing[192]	12	7	0	5	24 (41)
Baschat [194]	4	1	0	0	5 (9)
No chart (ratio)	6	0	0	0	5 (9)
Morales Rosello[199]	3	0	0	0	3 (5)
Fetal Medicine Foundation online calculator[200]	1	0	0	0	1 (1)

† Australia
‡ New Zealand
§ middle cerebral artery
¶ gestational age
ǂ estimated fetal weight
‡‡ umbilical artery
§§ systolic diastolic ratio
¶¶ pulsatility index
ǂǂ resistive index
‡‡‡ peak systolic velocity
§§§ cerebroplacental ratio

Table 3.9 *Reporting practices for ductus venosus and uterine artery Doppler*

	Obstetric Practice AU† *N*	Obstetric Practice NZ‡ *N*	Radiology Practice AU *N*	Radiology Practice NZ *N*	TOTAL N (%)
DV§ Doppler performed: 123/123					
In all third trimester US	3	0	6	0	9 (7)
All third trimester US <32w	1	0	0	0	1 (1)
All third trimester US <34w	5	0	0	0	5 (4)
Never performed	26	3	2	0	31 (25)
When EFW¶ <5th centile	3	0	0	0	3 (2)
When EFW<10th centile	5	2	0	0	5 (4)
When UA‡‡ Doppler abnormal	5	3	0	1	8 (7)
When MCA‡‡ Doppler abnormal	4	2	0	4	10 (8)
When UA & MCA Doppler abnormal	9	3	0	2	14 (11)
EFW<10th centile & abnormal UA Doppler, MCA Doppler, or both	14	1	0	0	15 (12)
EFW<5th centile & abnormal UA & MCA Doppler	11	2	0	0	13 (11)
For other conditions	8	1	0	0	9 (7)
Doppler index/indices reported: 92/93 (31 never performed DV Doppler)					
SD§§	5	0	0	0	5 (5)
PI¶¶	10	10	1	4	25 (27)
RI ‡‡	2	0	0	0	2 (2)
PVIV‡‡‡	18	1	0	1	20 (22)
PI & A-wave	4	1	0	1	6 (7)
PVIV & A-wave	5	0	0	0	5 (5)
A-wave	16	1	2	0	19 (21)
Other	6	1	3	1	10 (11)
DV Doppler chart: 93/93					
Unsure	34	11	4	2	51 (55)
Kessler[201]	7	2	0	5	14 (15)
Hecher[146]	6	1	0	0	7 (8)
Turan[202]	2	0	0	0	2 (2)
Baschat[203]	1	0	0	0	1 (1)
No chart – A-wave only	14	2	2	0	18 (19)
UtA§§§Doppler performed: 122/123					
In all third trimester scans	4	0	0	0	4 (3)
Never performed in third trimester	51	7	6	3	67 (55)
When EFW<5th centile	4	1	0	0	5 (4)
When EFW<10th centile	9	4	1	1	14 (11)
Risk of FGR¶¶¶	8	2	1	0	11 (9)
Other	14	3	0	3	20 (16)
Doppler index/indices reported: 60/63 (60 never performed UtA Doppler)					
PI	24	9	1	5	39 (65)
RI	4	0	0	0	4 (7)
SD	4	0	0	0	4 (7)
Presence of diastolic notch	3	0	0	0	3 (5)
Co-reporting of indices	5	1	1	2	10 (17)
UtA Doppler chart: 61/63					
Unsure	25	4	0	2	31 (51)
Gomez[204]	7	5	2	5	18 (30)
Achayra[191]	6	1	0	0	7 (11)
Geipel[205]	1	0	0	0	1 (1)
Kaminopetros[206]	1	0	0	0	1 (1)
Merz[207]	1	0	0	0	1 (1)
Schaffer (unpublished)	1	0	0	0	1 (1)

ǂ Australia
‡ New Zealand
§ ductus venosus
¶ estimated fetal weight
ǂǂ umbilical artery
‡‡ middle cerebral artery
§§ systolic diastolic ratio
¶¶ pulsatility index
ǂǂǂ resistive index
‡‡‡ pulsatility index for veins
§§§ uterine artery
¶¶¶ fetal growth restriction

3.4.5 Choice of reference chart

Responses (125/125) to questions on the choice of reference chart are illustrated in figure 3.5. Recommendations and guidelines of professional bodies and chart methodologies were the most important considerations in the choice of reference chart.

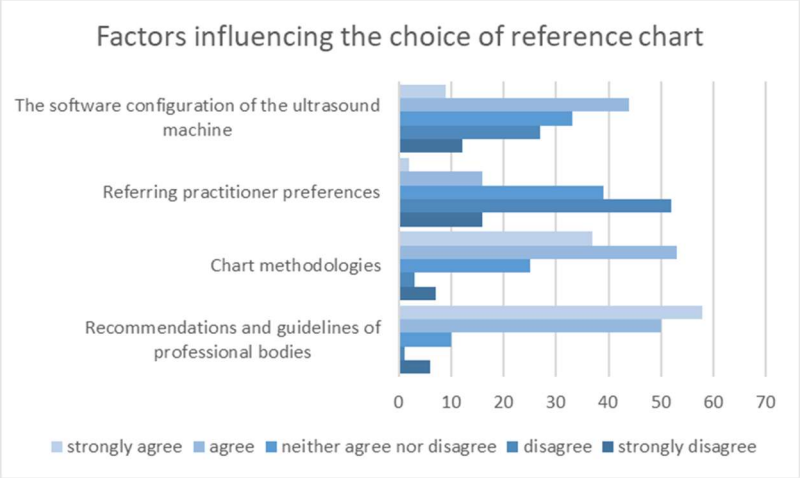

Figure 3.5 *Factors influencing chart choice*

The open ended question '*Is there anything you would like to add about how third trimester growth is performed and reported?*' elicited 32 comments. A consistent theme emerged stressing the need for national standardisation of reference charts used in third trimester ultrasound and for standardised reporting (34%). Other aspects of third trimester ultrasound commented on were poor performance of ASUM femur length centiles (9%), the need for standardisation when reporting interval growth (13%), standardisation in reporting the amniotic fluid index (9%), and that adopting new reference charts would present difficulties (6%).

3.5 Discussion

This survey revealed inconsistent reporting practices still continue for third trimester ultrasound. There are four population-based charts for fetal biometry in current use: ASUM[172], Hadlock[79, 180-182], Chitty[99, 183, 184], and Raine (Newnham, personal communication). These findings are comparable to an Italian survey conducted in 2020 reporting wide variation in the choice of fetal biometry chart[208]. An interesting finding was that the author of the most commonly used charts in Italy for bi-parietal diameter, head circumference and abdominal circumference did not provide reference charts for femur length or estimated fetal weight, suggesting the need to use different charts for these measures.

Selective use of charts derived from different populations for different biometry measures was also demonstrated by this study. Although numbers were small (n=10), Chitty[184] charts were used by some respondents for femur length who used ASUM[172]or Hadlock[79, 180-182] charts for other measures. Older charts typically overestimate the femur length; as ultrasound technology has improved over the past two decades, narrower beamwidth and higher scan-line density has improved lateral resolution such that a femur measured with new equipment at mid trimester is shorter by 1mm on average than one measured with pre 1998 equipment[209]. At the same time this survey was conducted, an audit by the NSW Government Clinical Excellence Commission was underway to establish which charts performed best for the NSW population[210]. Ultrasound measurements from a cohort of 3745 low risk third trimester pregnancies between 34 and 42 weeks' gestation were evaluated to determine which charts provided the best fit for measurement data[210]. This led to the recommendation for ASUM[172] charts to be used for head circumference and abdominal circumference, and Chitty[184] charts for femur length[210]. The apparent over-representation of femur lengths in the lower centiles may have influenced these sonologists to proactively adopt Chitty[184] charts for femur length, or perhaps some were aware of preliminary findings of the NSW Government Clinical Excellence Commission audit (seven of the ten respondents were from NSW). Given

this recommendation, it appears prudent that further research into development of new charts of fetal measurements is undertaken.

When compared to an Australian and New Zealand survey in 2013[34] this study has shown improved consistency in biometry charts used in current practice and a greater awareness of which chart is used. How measurements are reported appears to be unchanged with most respondents using the centile for known gestational age, and none using the Z-score.

The survey revealed the extent to which customised charts for EFW have been adopted (14% of all respondents). A majority of respondents from New Zealand (73%) either report estimated fetal weight centiles using customised charts, or include advice to plot measurements on a GROW[185] chart in the ultrasound report. This consistency from New Zealand respondents indicates awareness of and adherence to local guidelines[211, 212]. As described in chapter two, customisation takes into account maternal and fetal characteristics which may impact growth, namely maternal height and weight, parity, ethnic origin, and fetal sex. GROW[185] software calculates an adjusted optimal fetal weight at 40 weeks' gestational age and generates a proportionality curve based on the Hadlock[104] model. In addition to this individualised approach, population customised estimated curves may be produced[33], and formed the basis for charts used by a further 4% of respondents. An additional 2% of respondents reported using estimated fetal weight charts derived from the Raine Cohort (Newnham, personal communication), but did not specify if these were population customised[213].

Most respondents (72%) indicated using a fetal weight chart to derive estimated fetal weight centiles rather than a birthweight chart. This differs from the 2011 study by Gibbons and colleagues[214], although these researchers acknowledged a degree of confusion exists amongst practitioners as to differences between population-based birthweight charts, customised birthweight charts, and fetal weight charts.

In the 2013 survey[34], McCarthy and colleagues speculated that chart choice may in part be due to a sense of 'ownership'. Indeed, findings of this study could be interpreted similarly with the use of Raine (Newnham, personal communication) in-house charts in Western Australia and the Mercy[189] population-customised estimated fetal weight charts in Victoria.

There is diversity in Doppler practices, including when Doppler is performed, how it is reported, and the choice of reference charts. The thresholds for the use of fetal and maternal Doppler in third trimester ultrasound varied in terms of the gestational age and estimated fetal weight cut-off. How measures were reported also varied, with some respondents indicating particular Doppler measures were performed in all third trimester ultrasounds, no respondents performed umbilical artery, middle cerebral artery, ductus venosus and uterine artery Doppler in every examination. Of the 22% of respondents reporting multiple indices for umbilical artery Doppler, the majority (70%) did not use a digital reporting package, suggesting deliberate co-reporting of indices. Awareness of which umbilical artery Doppler chart is used remains unchanged from the 2013 survey[170] with 58% of respondents indicating they were unsure of which chart was used. There was however, a change in reporting practice for umbilical artery Doppler evidenced by the decline in the use of the SD ratio favour of the PI. Responses from New Zealand sonologists demonstrated more consistent practice, again suggesting adherence to local guidelines[168, 211, 212].

Comments made by respondents raised concerns regarding the lack of standardisation in how third trimester ultrasound is performed and the potential for diagnostic error:

> *'Non uniformity makes ultrasound a potentially dangerous tool in my public hospital clinic. Standard reporting and reference ranges would be enormously useful.'*

Some of these concerns may have since been addressed by the NSW consensus statement: Choice of Fetal Biometry Charts[210] in March 2021 and the reporting template for third trimester fetal growth scans endorsed by ASUM, RANZCOG and RANZCR[215] in March 2019. Of note, the ASUM Normal Ultrasonic Fetal

Measurements Standard[166] (updated in 2018) recommended the Hadlock (HC-AC-FL)[85, 102] algorithm for EFW, yet 70% of respondents reported using the Hadlock (BPD-HC-AC-FL)[85, 102] algorithm. As stated by Fischer and colleagues[216], the publication and dissemination of guidelines does not, on its own, automatically result in their use.

A weakness of this survey is the lower than expected response rate, even when the general decline in response rates in health research and the low reported response rates typical of medical specialists[175] is considered. The impact of this on interpretation of these findings is unclear as it has been shown response rate is not always predictive of nonresponse bias when the target population is relatively homogenous, as is the case with clinicans[217]. Mode of administration may have also contributed to the low response rate. It has been recently reported that the mode of survey administration does not affect the response rate from clinicians, however, emails inviting survey participation may be easily overlooked when the volume of emails is high[218]. Participant interest in the survey topic is another important factor influencing survey response rates[175] and perhaps this topic of research only appealed to a small cohort. It was disappointing general radiologists were not part of this survey. Most radiologists in Australia and New Zealand are generalists, 92% are involved in reporting ultrasound[219] and most obstetric ultrasounds are performed at general radiology practices[37].

This study revealed inconsistent reporting practices persist for third trimester ultrasound, but this did not come as a surprise to some survey participants who expressed concern regarding the lack of standardisation and the potential for diagnostic error. Areas for future research include the development of new fetal measurement charts using methodologies accepted by the wider obstetric imaging community, as this may help with widespread adoption. Research in how to best disseminate information regarding the standardisation of third trimester ultrasound would be beneficial in the acceptance of new guidelines and adoption into clinical practice. Engagement with all obstetric ultrasound providers is an

important element of guideline acceptance, and input from general radiologists was sought via semi-structured interviews.

3.6 Semi-structured interviews with general radiologists

To gain input from the general radiology cohort, semi-structured interview was developed from the question guide employed in the pilot study. The variation to the study protocol was approved by the Australian National University human research ethics committee (ANU HREC 2017/418). Questions were adapted from those used in the pilot study to be in an open ended format. The interview script is included in Appendix A. Emails were sent to the practice managers of four large medical imaging practices (each with multiple sites) inviting general radiologists to participate in an interview. Invitations to participate were also disseminated via the Australian Radiopaedia Facebook group. Four radiologists responded to the invitation and interviews were conducted via Zoom or by phone between 31 March 2021 and 2 September 2021. Interview transcripts are included in Appendix A.

3.6.1 Interview results

Three interviewees were from metropolitan practices with one was from an inner regional practice. All worked in private medical imaging practices with one interviewee also working in a medical imaging department within a public hospital, although obstetric ultrasound was not performed in this department. Three had more than ten years' experience reporting obstetric ultrasound and one had less than five years' experience. A summary of interview findings is presented in table 3.10. This small cohort of general radiologists were aware of charts used for standard fetal biometry at their practices and named charts by Westerway (commonly referred to as ASUM charts), Hadlock, Chitty and Raine (Newnham, personal communication). This finding is comparable to that of the on-line survey where Westerway and Hadlock charts were most popular, and Raine (Newnham, personal communication) charts used in Western Australia. Most reported measurements alongside centiles, with one radiologist co-reporting equivalent

weeks and days, and one plotting measurements on a chart. Charts were typically not cited in ultrasound reports. All were unsure of the chart used to generate centiles for estimated fetal weight.

"I think it's Hadlock, but I don't know the formula." *Radiologist 4*

All defined SGA as EFW below the 10th centile for gestational age with two radiologists also considering a drop in growth rate as diagnostic of SGA.

All indicated umbilical artery Doppler was performed in all third trimester examinations and the pulsatility index was reported, however, one radiologist indicated this was only reported when specifically requested. Middle cerebral artery Doppler practices, including calculation and reporting of the cerebroplacental ratio varied, ranging from always performed and reported, conditionally performed and reported, and always performed but not necessarily reported.

"…and then if they're abnormal [umbilical artery] you do the middle cerebral artery, and if that's abnormal then you calculate a CPR ratio." *Radiologist 4*

In this small group, none performed uterine artery Doppler in the third trimester, and Doppler charts could be named by one radiologist.

All indicated professional body or college recommendation would encourage the adoption of new charts, and despite the expressed desire for consistency, barriers such as reconfiguring ultrasound equipment, changing reporting templates, educating staff and referrers, and conforming to preferences of tertiary centres were identified.

"I presume it depends on the vendors, 'cause I can tell you from the radiologists reporting perspective whatever's there on the machine is what we report." *Radiologist 4*

"…no point in using what we've got if everyone else is changing to some more national [chart], or whatever." *Radiologist 1*

Table 3.10 *Summary of general radiologist reporting practices*

	Radiologist 1 (NSW inner regional practice)	**Radiologist 2** (ACT metropolitan practice)	**Radiologist 3** (WA metropolitan practice)	**Radiologist 4** (ACT metropolitan practice)
Experience	20+ years	3 years	10 years	22 years
Case mix third trimester ultrasound	5-10% in total 30% of obstetric ultrasound	2%	1%	30% of obstetric ultrasound
Indications for third trimester ultrasound	Previous obstetric history Reassurance of normal fetal size and wellbeing	Fetal size/growth Placenta location	Fetal growth/wellbeing Placenta location	Growth and Doppler Previous obstetric history (SGA[ł]) Reassurance of normal fetal size and wellbeing
Charts used	ASUM Unsure for EFW[‡]	Hadlock for all	Raine for biometry Hadlock for EFW[‡], however US equipment and digital reporting software within practice configured with different charts	ASUM, Hadlock and Chitty – probably others Hadlock for EFW[‡]
Centiles reported	yes	yes	No – plotted onto a chart	Weeks & days and centile
Charts cited	EFW algorithm	no	no	no
Reporting SGA [ł]	Not always If a there is a specific question on request then <10th for EFW[‡]	<10th centile	Not always commented on, occasionally when <10th centile or drop in growth rate (as determined visually)	<10th centile Drop in AC[§]
UA[¶] Doppler	Always performed PI [ǂ] reported, not centile	Always performed PI [ǂ] reported	Always performed, not reported unless requested	Always performed PI [ǂ] reported
MCA[‡‡] Doppler	Conditional PI [ǂ] reported, not centile	Always performed CPR[§§] reported	Always performed, not reported unless requested	Conditional May calculate CPR[§§]
UtA[¶¶] Doppler	Not performed	Not performed	Not performed	Not performed
Doppler charts used	Ebbing	Not known	Not known	Not known
Barriers to adopting new charts	Change needs to be justified with evidence	Changing equipment settings & reporting templates Educating staff Educating referrers	Referrers resistant to change Radiologist dismay/annoyance at change Tertiary hospital and referrer preference	Vendors configuring ultrasound equipment
Drivers to adopting new charts	Desire for consistent practice Conform with tertiary hospital Professional body recommendation	College recommendation	Desire for consistent practice Recommended charts	Professional body recommendation

ł small for gestational age
‡ estimated fetal weight
§ abdominal circumference
¶ umbilical artery
ǂ pulsatility index
‡‡ middle cerebral artery
§§ cerebroplacental ratio
¶¶ uterine artery

3.6.2 Discussion

There were clear similarities in reporting practices and knowledge of measurement charts used by the interview participants and survey respondents. All were aware of which fetal measurement charts were used in their practice, but this did not extend to Doppler charts which were largely unknown.

Consistency in chart use within the practice was a challenge for this practitioner, who stated charts configured on ultrasound equipment were different to those in the electronic reporting system. Both were different from the hard copy charts on which measurements were plotted. Inconsistencies between reported centiles and those plotted on charts appeared to be accepted as the norm.

"Everyone seems to be quite comfortable with that, like what is plotted is not the same centile as what we're saying is the centile, unless no-one's noticed." *Radiologist 3*

When asked what led to this practice, the response was that it was referrer preference.

"It's because that's what they're used to seeing and change is difficult…" *Radiologist 3*

Inconsistencies between imaging guidelines and referrer preferences created a potential source of conflict in the standard of ultrasound report.

"…we do take measurements on everyone in case someone says 'what was it?' but it's only reported if it's part of that algorithm." *Radiologist 3*

Poor communication between professional bodies providing dissemination of guidelines was identified by one interviewee.

"…they don't send out a newsletter. So therefore, we don't know the guidelines have been updated."

Radiologist 4

This group saw themselves essentially as service providers, adopting practices to conform to that of the local tertiary centre or preferences of referring clinicians. Questions regarding choice of fetal

measurement chart did not cause as much concern as it does for those in specialist obstetric ultrasound fields.

"… I mean, I do a lot of different specialties like I do breast, I do obstetrics, there's reference charts and things for everything and things are forever changing. So it would be like oh, God, something else has changed" *Radiologist 3*

The rationale for conducting interviews with general radiologists was that the opportunity to discuss issues regarding third trimester ultrasound and contribute to the debate would be welcomed. Questions regarding choice of fetal measurement chart, third trimester ultrasound imaging and reporting guidelines were regarded as issues for others to address. Perhaps this sentiment helps explain the difficulty experienced in recruiting interview participants.

3.7 Chapter Summary

This survey revealed inconsistent reporting practices persist for third trimester ultrasound. There are four population-based charts for fetal biometry in current use: ASUM[172], Hadlock[79, 180-182], Chitty[99, 183, 184], and Raine (Newnham, personal communication). Some respondents indicated they used charts selectively, using charts derived from different populations for different measurement parameters.

When compared to Australian and New Zealand survey in 2013[34] this study has shown improved consistency in biometry charts used in current practice and a greater awareness of which chart is used. Most respondents reported measurements with the centile for known gestational age, and most calculated EFW centile from a fetal weight chart. Customised charts for EFW have been adopted by 14% of all respondents. A majority of respondents from New Zealand (73%) either report estimated fetal weight centiles using customised charts, or include advice to plot measurements on a GROW[185] chart in the ultrasound report. This consistency from New Zealand respondents indicates awareness of and

adherence to local guidelines[211, 212]. There is diversity in Doppler practices, including when Doppler is performed, how it is reported, and the choice of reference charts. Knowledge of which Doppler charts were used was poor.

Comments made by respondents raised concerns regarding the lack of standardisation in how third trimester ultrasound is performed and the potential for diagnostic error. Responses from interview participants echoed that of survey respondents. Questions regarding choice of fetal measurement chart, third trimester ultrasound imaging and reporting guidelines appeared to be regarded as concerns for others to address.

The potential for false positive and false negative diagnosis of FGR exists, and it remains possible for a fetus to have conflicting diagnoses based on the providers' choice of reference chart. This situation will not change until there is consensus on which reference charts should be used. This could be achieved by an Australian and New Zealand collaboration to establish new charts constructed using best research practice.

The response rate for both survey and interview were disappointingly low and while low response rates are typical of medical specialists, participant interest in the survey topic also influences survey response rates[175]. In recent years there has been an exponential increase in literature exploring this topic and perhaps this saturation has dampened enthusiasm from the obstetric ultrasound community.

Nonetheless, this study revealed inconsistent reporting practices persist for third trimester ultrasound, but this did not come as a surprise to some survey participants who expressed concern regarding the lack of standardisation and the potential for diagnostic error. Areas for future research include ways to best disseminate information regarding the standardisation of third trimester ultrasound to help improve adoption of guidelines into clinical practice. Another area is the development of new fetal measurement charts for the Australian population, using methodologies accepted by the wider obstetric imaging

community, which may assist with widespread chart adoption across Australia. This is no minor undertaking, noting continued resistance to adoption of the ASUM recommended Westerway charts[172], with at least three other charts in current use. Another area of research is validation of the recently published Intergrowth-21st (IG21) charts[38]. These charts are longitudinal, prescriptive, international standards based on the premise that all fetuses, regardless of ethnicity or country of birth, have the potential to grow at the same rate throughout gestation. The longitudinal design makes these charts appropriate for fetal growth evaluation and they may be well suited for use in Australia's multi-ethnic population. A study to validate the IG21 charts for the Australian population was undertaken and is discussed in the next chapter.

Chapter Four

Validation of IG21 charts for the Australian population

4.1 Introduction

With widespread adoption of ultrasound into obstetric practice, the questions of how to discriminate between normal and pathological growth, which charts to reference the ultrasound measurements to, and when to perform the measurements remain a contentious issue. Variations in chart methodologies have contributed to substantial differences in median values and centile curves with a study reporting up to a six-fold increase in measurements classified as below the 5th centile when comparing three reference charts[29]. Opinions differ on whether to use a descriptive chart derived from an unselected population or a prescriptive chart (standard) based on a low risk or ideal population, and whether charts should be based on cross-sectional or longitudinal data, noting that cross-sectional charts are not considered ideal for evaluating growth[149]. Similarly, the suitability of a reference chart derived from one population for use on a different population is an unresolved issue and problematic in multiethnic populations.

Which fetal measurement reference chart to use for the Australian population has been a contentious issue in Australian ultrasound practices for the past two decades. In 2001 the Australasian Society of Ultrasound in Medicine (ASUM) recommended the use of the Westerway charts for fetal biometry which were formulated from an Australian population[172]. Despite this, there at currently at least four fetal growth charts in clinical use in Australia as discussed in the previous chapter. The potential for misdiagnosis of fetal growth restriction leading to additional interventions and patient anxiety cannot be underestimated. Similarly, the opportunity for timely interventions may be missed by underdiagnoses of fetal growth restriction. For example, it is possible for a fetus to be diagnosed as small for gestational age (SGA) by one practitioner, and later that day found to be normally grown by a practitioner using a different

reference chart. Differences in median values and centile curves of published fetal measurement reference charts can be attributed to racial and biological characteristics of the study population, differences in study design, and methods of data analysis[154].

In 2014 the Intergrowth 21st (IG21) charts were published[38]. IG21 are international standards, or prescriptive charts, formulated from data collected from over 4,300 low risk pregnant women and are based on the premise that all fetuses, regardless of ethnicity or country of birth, have the potential to grow at the same rate throughout gestation. The charts were developed from multiethnic populations from diverse geographical regions including Brazil, China, India, Italy, Kenya, Oman, United Kingdom and United States. Extensive exclusion criteria relating to obstetric history, sociodemographic and clinical factors were applied to ensure measurement data were sourced from a low-risk or 'ideal' population[153]. The longitudinal design makes these charts appropriate for fetal growth evaluation and they may be well suited for use in Australia's multi-ethnic population. However it is necessary to determine whether these charts are a good 'fit' for the Australian population before they are implemented in clinical practice.

4.2 Study design

The full study protocol is provided in Appendix B and was approved by ACT Health Human Research Ethics Committee 2018.ETH.00222/ETH02432, ANU Human Research Ethics Committee 2019/497, Western NSW Local Health District Human Research Ethics Committee 2020-074, Sydney Local Health District Human Research Ethics Committee 2020/PID02715, and Western Health Office for Research 67092. This research aimed to provide evidence to allow adoption of a consistent way to measure and report fetal growth and, in particular, to help reach a consensus about implementation of IG21 charts in Australian practices.

In summary, an observational, prospective, cross-sectional multicentre study was conducted to assess fetal biometry in pregnant women in the second and third trimester and aimed to recruit 2000 participants (500 from each site).

Published studies that have compared local populations to the IG21 charts have used retrospective data collection[220, 221] and prospective data collection[222]. Collecting data prospectively has the advantage of allowing processes to be implemented to reduce measurement error and bias. Measurements can be made in triplicate to reduce random error[223], sonographers can be blinded to the measurements to reduce operator bias[224], and participate in standardization exercises that have been shown to further improve quality and consistency of ultrasound measurements[225]. Additionally, data on maternal characteristics and risk factors for abnormal fetal growth[226-228] can be collected at the time of the ultrasound examination, instead of relying on retrospective assessment of patient files.

Cross-sectional data, that is, the measurements from one ultrasound examination performed during the pregnancy were collected for the purposes of this study and sourced from clinically indicated ultrasounds. In Australia, routine ultrasound examinations are performed at 11 to 14 weeks for first trimester screening, and at 18 to 22 weeks for fetal morphology assessment. Ultrasound after 22 weeks is performed for clinical indications, and an audit of current practice in an Australian hospital reported over 50% of singleton pregnancies have at least one ultrasound in the third trimester[37]. While inclusion of data from clinically indicated ultrasounds has the potential to be a source of bias, the aim of this research was not to create new charts of fetal size, but to assess the performance of the IG21 charts in the Australian clinical setting.

There are both statistical and practical considerations in determining an appropriate sample size. If the sample size for this study is too small, results will not be generalizable, and an overly large sample size will unnecessarily extend the time for data collection.

In general, fetal measurements approximate a normal distribution[155, 229] and the sample size for this study can be determined by calculations for demonstrating equivalence [230]. The 3rd centile is generally considered to be clinically significant, and abdominal circumference (AC) measurements less than the 3rd centile form part of the criteria to diagnose fetal growth restriction (FGR) [231] and increase clinical surveillance or intervention. When considering standard error in the estimation of the 3rd centile, if a 50% error was acceptable, then 4.5% of the population would be misclassified as representing the lower 3% of the population. If the null hypothesis is that the Australian population is the same as the IG21 population, 1-sample equivalence testing with power is 0.9 and type 1 error, α is 0.025 (half of that required in a 2 sided test for equivalence), a sample size of 510 is required per site. A further consideration is data that may be excluded during the study, lost to follow up, or withdrawn following participant's request. It is estimated that this may be as high as 6% [38].

Taking these factors into consideration, this study aims for at least 2000 observations in total with a minimum of 500 observations from each participating site.

As discussed in the previous chapter, Australian charts of fetal biometry are based on a local or state populations and this study aimed to collect data from a truly representative sample of Australian pregnant women by inviting institutions across Australia to participate.

4.2.1 Data collection

Several sites across Australia were approached from 2019 to 2022 to participate in this prospective cross-sectional study with the final cohort comprising data compiled from three sites. Site 1, Canberra Health Services, contributed 514 datasets, and included data from the Fetal Medicine Unit, Canberra Hospital and Medical Imaging, North Canberra Hospital. Site 2, the Obstetric Ultrasound Department, Royal Prince Alfred Hospital contributed 672 datasets, and Site 3, Medical Imaging, Orange Base Hospital, contributed 533 datasets. Western Health were unable to continue meaningful recruitment due to ongoing staff

shortages and withdrew from the study in 2024 after recruiting 42 participants with completed outcome data for 20 participants.

The timing of this study unfortunately coincided with the Covid-19 pandemic which contributed to the lower than anticipated recruitment of participating sites and therefore study participants. This was due to a combination of health workforce shortages and reassignment of staff to critical health areas, and modified imaging protocols aimed at reducing face-to-face time between sonographers and patients. Data collection was also suspended at different periods during the COVID-19 pandemic. Instead of an Australia-wide study, participating sites came from metropolitan and regional New South Wales (NSW) including the Australian Capital Territory (ACT).

Each participating site used modern, well maintained ultrasound equipment in accordance with Australian Diagnostic Imaging Accreditation guidelines[232] and all ultrasound examinations were performed by qualified and accredited sonographers[233] with more than five years' experience.

4.2.2 Measurements

Ultrasound measurements were performed in accordance with the Australasian Society of Ultrasound in Medicine (ASUM) guidelines[166] and according to the methodology published with the reference charts[38, 172, 184].

Cranial biometry (BPD and HC) was measured on an axial plane through the fetal head that was well magnified, the head was horizontal across the screen, intracranial anatomy was symmetric with the interhemispheric fissure (falx cerebri) central and broken in the anterior third by the cavum septum pellucidum. The BPD was measured with the callipers placed outer to inner and the HC was measured using the ellipse tool with callipers placed on the outer perimeter of the bony skull. An additional BPD measurement was performed with callipers placed at the outer edges of the parietal bones as described in IG21 chart methodology (figure 4.1).

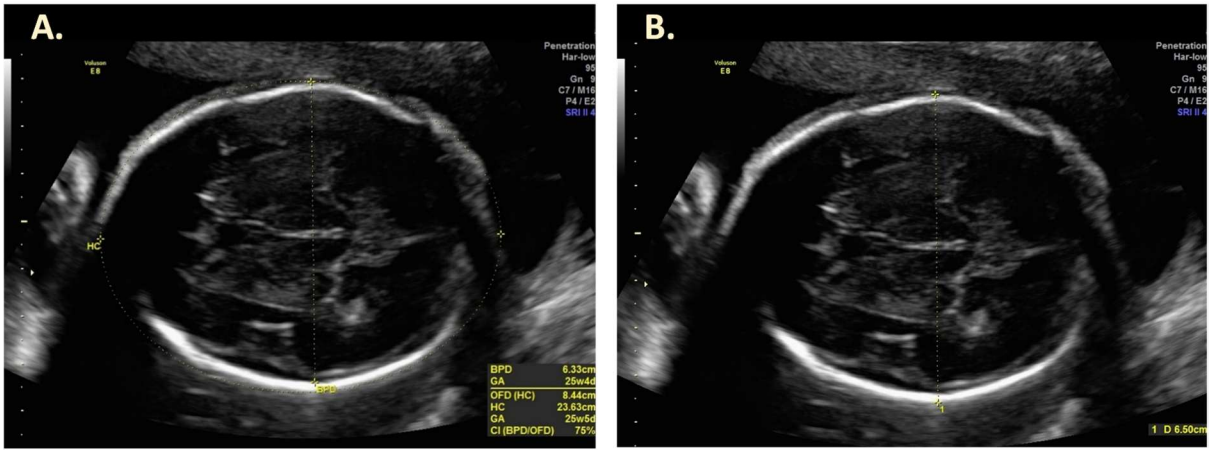

Figure 4.1 *Imaging plane for cranial biometry* ***A****. BPD measured with callipers placed on the outer edge of the parietal bone to the inner edge and HC measured on the same image with the ellipse on the outer perimeter of the bony skull.* ***B****. BPD measured according to IG21 methodology with the callipers placed on the outer edges of the parietal bones*

The abdominal circumference was measured on a well magnified axial plane of the fetal abdomen providing a circular section with the spine lateral (3 o'clock or 9 o'clock), with stomach and a short segment of umbilical vein at the level of the portal sinus visible. Measurement was made with the ellipse tool placed as close as possible to the skin and including the fat layer (figure 4.2).

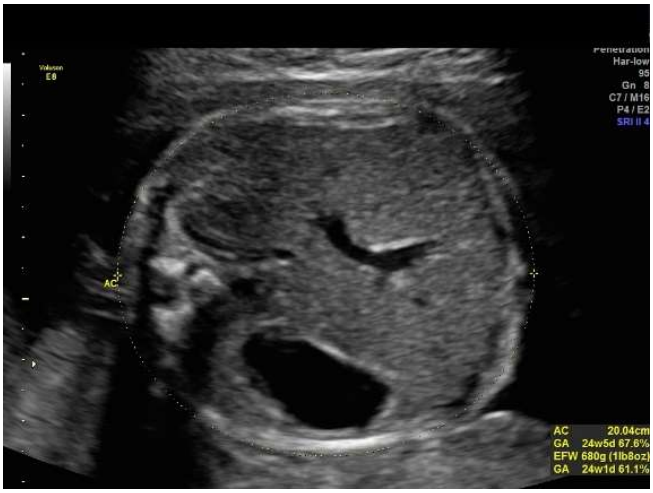

Figure 4.2 *Imaging plane for abdominal circumference with ellipse placed on the outer margin of the skin*

The femur length was measured on a well magnified image demonstrating the entire femoral diaphysis as close to horizontal as possible across the screen with callipers placed on the outer edges of the diaphysis at the junction of bone and cartilage (figure 4.3).

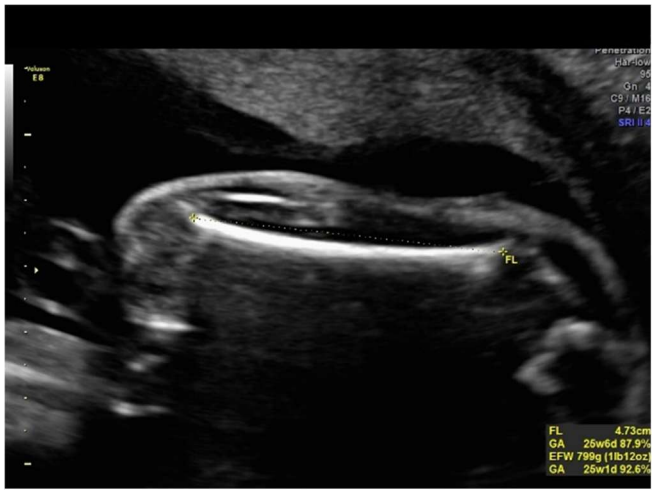

Figure 4.3 *Imaging plane for femur length demonstrating calliper placement at the junction of bone and cartilage*

4.2.3 Quality assurance

Prior to study commencement, all participating sonographers attended a tutorial by the principal investigator discussing optimal planes for fetal measurement and calliper placement. A hard copy of the measurement protocol was made available as reference material to ensure standardised measurements were obtained. Each measure was performed in triplicate so that there were three measurements for each parameter from three separate images. Additionally, operators were blind to the equivalent gestational age in weeks and days for each measurement during the examination. This was achieved by covering the bottom corner of the ultrasound monitor where this information is displayed (often referred to as the measurement box) as shown in figure 4.4. The potential impact of expected-value bias was reported by an eye tracking study in 2019[234]. In this study researchers evaluated how frequently operators looked at measurement box and how calliper placement was affected. The study reported operators

tended to correct calliper placement toward the expected measurement for gestational age after looking at the measurement box, introducing expected-value bias.

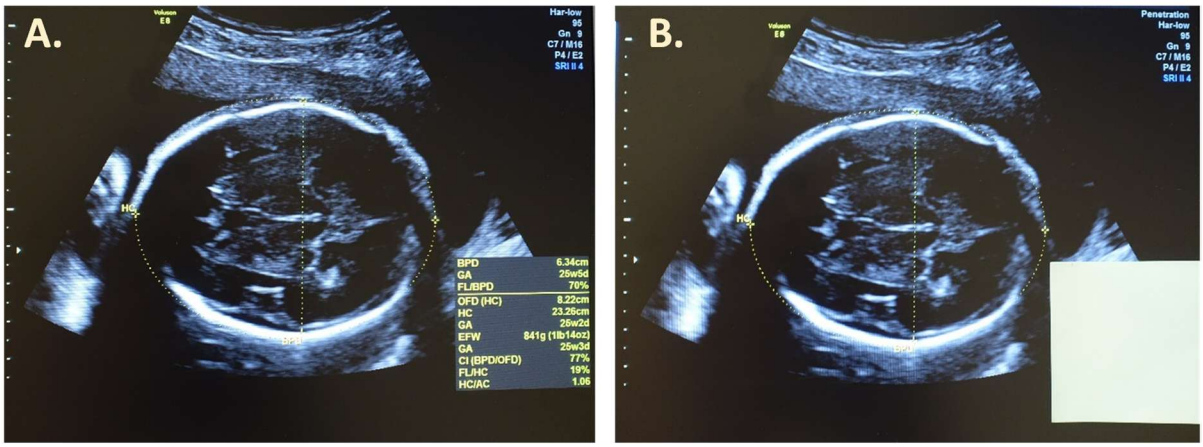

Figure 4.4 A. *Image of ultrasound monitor demonstrating biometric data displayed in the lower right corner and* ***B.*** *covered by self adhesive note paper*

4.2.4 Participant recruitment

Written information explaining the aim of the study and nature of data requested was provided to prospective study participants upon arrival to the ultrasound department or by the sonographer prior to commencing the ultrasound examination and provided signed consent. For inclusion in this study the following criteria applied:

- Singleton viable pregnancies with an estimated date of birth (EDB) as confirmed by ultrasound at 8 – 14 weeks of pregnancy or by transfer date and embryo age for assisted conceptions
- Ultrasound examination performed in the second or third trimester of pregnancy

The following exclusion criteria applied:

- Pregnancies with a known fetal abnormality
- Pregnancies with significant maternal disease such as cancer or renal disease
- Multiple pregnancy
- Gestational age not confirmed by ultrasound at 8 – 14 weeks of pregnancy

No participants withdrew from the study. Participation was voluntary and participants were aware they could withdraw from the study up until data de-identification.

4.2.5 Collection of participant data

Participants were asked to complete a brief questionnaire to record possible maternal risk factors for abnormal fetal growth and maternal characteristics that may also influence fetal growth. A hard copy questionnaire was used by Sites 1 and 3, while Site 2 used a digital questionnaire.

These included:

- Pre-existing diabetes or diabetes in pregnancy
- Hypertension
- Smoking
- History of pre-eclampsia
- Height
- Weight
- Ethnicity
- Previous pregnancy history
- Other medical conditions
- Family history of disease

The sonographer performing the ultrasound examination recorded a patient identifier to allow birth outcome data to be collected at a later date, the estimated due date (EDD), the gestational age (GA) at the time of the ultrasound, and first trimester biomarkers pregnancy associated plasma protein A (PAPP-A) and placental growth factor (PlGF).

Data were collated by the nominated site lead in an Excel spreadsheet (Microsoft® Excel®2016).

4.2.6 Collection of birth outcome data

Birth outcome data were collected from the birth outcome summary by the nominated site lead from each participating centre and included:

- Gestational age at birth
- Birthweight
- Method of delivery
- Apgar scores (routine measures at 1minute and 5 minutes after birth, of baby's colour, heart rate, reflexes, tone, & respiratory effort)
- Cord gases (arterial cord blood pH) if performed
- Days of admission to the neonatal intensive care unit or special care nursery

Following this step, a new unique identifier was assigned to the complete dataset and the patient identifier deleted.

4.3 Results

Spreadsheets containing de-identified data were uploaded via a secure link to the Australian National University OneDrive account of the principal investigator. Data were formatted so that each column was correctly aligned and datasets were scanned for obvious exclusions such as missing data. Measurements were graphed in scatter plots to evaluate erroneous outliers potentially due to typographical errors and original datasheets were inspected to make corrections where appropriate. Overall, 75 datasets were excluded as described in table 4.1 with most exclusions due to missing outcome data. Analysis was performed on 1642 datasets with Site 1 contributing 481 datasets, Site 2 635, and Site 3 526.

Table 4.1 *Exclusions*

Exclusion criteria	*n*
Gestational age not confirmed by first trimester ultrasound or known IVF details	9
Significant fetal anomaly	5
Multiple pregnancy	2
Consent form not signed	1
Missing data (outcome)	42
Missing data (collection)	13
Data contributed from previous ultrasound	1
Erroneous data	1
Significant maternal disease	1
Total	**75**

4.3.1 Maternal characteristics

Participant characteristics are summarised in table 4.2. Small differences in population demographics were observed and may be attributed to the case-mix of each site. Site 1 (metropolitan, major city[177]) being a high risk pregnancy unit generally did not perform routine ultrasound examinations. The wide referral base for tertiary review included regional New South Wales, which meant many patients presenting for an ultrasound examination did not birth at this centre. Site 2 (metropolitan, major city[177]) performed routine ultrasound examinations from a local referral base where the majority of patients birthed at the centre. Site 3 (regional city, inner regional Australia[177]) performed routine ultrasound examinations for a wide referral base where the majority of patients also birthed at the centre.

Maternal age

According to the Australian Institute of Health and Welfare (AIHW) Australia's mothers and babies report[235], in 2022 the average maternal age for nulliparous women was 29.8 years, for multiparous women 32.3 years, and the highest proportion of women who gave birth were aged between 30 and 34 years. In the time period applicable to this study (2020 – 2022) the proportion of women aged 30 – 34 who gave birth was 36.7% in 2020, 37.5% in 2021 and 37% in 2022. The average age of mothers in the

study cohort was also in the age range 30 – 34 years: 31 years at Site 1, 34 years at Site 2 and 31 years at Site 3.

Body Mass Index

The body mass index (BMI) is considered a useful method to identify overweight or obesity in populations and is a ratio of an individual's height and weight given by the equation:

$$BMI = \frac{weigh\ \ (kg)}{heigh\ \ (m)^2} \qquad 4.1$$

The AIHW define a healthy range of BMI as 18.5 – 24.9 kg/m^2, with 25 – 29.9 kg/m^2 considered overweight, greater than 30 kg/m^2 considered obese, and less than 18.5 underweight[235].

The average BMI for participants from Site 1 and 3 was in the overweight range and in the healthy weight range for Site 2. Compared to national data from the AIHW[235], 47% of women who gave birth in 2020 were in the healthy weight range, 26.3% were overweight, and 21.2% were obese. In 2021 45.3 % were in the healthy weight range, 26.9% were overweight, and 22.1% obese. In 2022 44.1% of women were in the healthy weight range, 27.1% were overweight and 23.1% obese.

Parity

Most participants from Site 1 (60%) and Site 3 (59%) were parous (i.e. had given birth previously) with participants from Site 2 evenly split between parous and nulliparous.

Maternal medical conditions

Overall, 15.6% of participants reported having pre-existing diabetes or gestational diabetes requiring medication, and 4.3% of participants were gestational diabetics with diet and exercise management. National AIHW data indicates 1.1% of women who gave birth in 2020 reported pre-existing diabetes, in 2021 this was 1.0%, and 1.1% in 2022. Gestational diabetes was reported in 14.3% of women who gave

birth in 2020, 15.2% in 2021, and 16.5% in 2022. Site 2 reported the highest proportion of diabetics and site 3 the lowest. The higher average maternal age at Site 2 may be a contributing factor, as women aged over 40 years have the highest proportions of gestational diabetes[235]. Similarly, maternal age may also account for the higher rate of maternal hypertension at this site, although rates of pre-existing hypertension in the study cohort were higher than the reported national average of 0.9% in 2020, 2021 and 2022 [235].

Maternal smoking

Smokers accounted for 3% of the total cohort with 5.6% from Site 1 and 3.8% from Site 3 - less than 8.3% reported in the 2022 national data for smoking status in pregnancy[235]. A history of pre-eclampsia was reported in 4% of participants. Site 2 did not report any; this may be attributed in part to the slightly higher number of nulliparous participants in this cohort.

First trimester biomarkers

PAPP-A is a placental biomarker measured in the first trimester as part of the combined first trimester risk assessment for common fetal aneuploidies. It is typically expressed as multiples of the median (MoM) for the known gestational age and values less than 0.4 MoM are associated with pre-eclampsia and fetal growth restriction[236]. Data were provided for 42.9% of participants which is relatively low given the uptake of the 11 – 13 week ultrasound element of combined first trimester screening[237]. It is possible PAPP-A could not be recorded at the time of the participant's ultrasound as the data was not readily available (e.g. first trimester biochemistry was not included with the imaging request), or because serum testing was not performed. With regard to the latter, the increasing uptake of non-invasive prenatal testing (NIPT) is also a consideration. NIPT is a maternal blood test where cell-free fetal DNA can be screened for common fetal aneuploidies as early as 10 weeks gestational age for a detection rate of 99.2% and false positive rate of 0.09% for trisomy 21[238]. Currently a self-funded test, the uptake of NIPT in Australia is

difficult to determine in the absence of Medicare Benefits Schedule (MBS) data but may be as high as 25% in New South Wales and 50% in the Australian Capital Territory[239].

Table 4.2 *Maternal characteristics of the study cohort*

Maternal characteristics	Total n=1642		Site 1 n=481		Site 2 n=635		Site 3 n=526	
Average age (years)	32		31		34		31	
Median age (years)	33		32		34		31	
Range (years)	17 – 47		19 – 43		20 – 47		17 – 45	
Average BMI (kg/m^2)	27.42		28.71		24.79		29.41	
Median BMI (kg/m^2)	25.98		26.90		23.67		28.72	
Range (kg/m^2)	*16.53 – 65.47*		*16.73 – 65.47*		*16.53 – 55.03*		*16.61 – 54.08*	
Average height (cm)	164.77		164.52		163.50		166.56	
Median height (cm)	165.00		165.00		163.00		167.00	
Range (cm)	*145 – 188*		*147 – 185*		*145 – 188*		*147 – 187*	
Maternal conditions not excluded	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***
Pre-existing diabetes and insulin requiring gestational diabetes	257	*(15.6)*	56	*(11.6)*	130	*(20.5)*	23	*(4.4)*
Gestational diabetes (diet and exercise controlled)	71	*(4.3)*	38	*(7.9)*	11	*(17.2)*	22	*(4.2)*
Pre-existing hypertension	89	*(5.4)*	20	*(4.2)*	45	*(7.1)*	24	*(4.6)*
Smoker	49	*(3.0)*	27	*(5.6)*	2	*(0.3)*	20	*(3.8)*
History of pre-eclampsia	66	*(4.0)*	27	*(5.6)*	0	-	39	*(7.4)*
Low PAPP-A (<0.4 MoM)	65	*(9.2)*	33	*(11.7)*	-	-	32	*(6.5)*
number performed/recorded	*705/1642*		*281/481*		*0/635*		*492/526*	
Parity	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***
Nulliparous	673	*(41.0)*	188	*(39)*	317	*(50.0)*	168	*(31.9)*
para 1	657	*(40.0)*	192	*(40)*	248	*(39.2)*	107	*(20.0)*
para 2	228	*(13.8)*	67	*(13.9)*	54	*(8.5)*	167	*(31.7)*
para 3	63	*(3.8)*	23	*(4.8)*	11	*(1.7)*	29	*(5.5)*
para 4	15	*(9.1)*	7	*(1.2)*	3	*(0.5)*	5	*(1.0)*
para 5	4	*(0.2)*	3	*(0.6)*	1	*(0.2)*	0	-
para 6	1	*(0.1)*	1	*(0.2)*	0	-	0	-
para 7	1	*(0.1)*	0	-	1	*(0.2)*	0	-

It has also been reported that up to 75% of patients in private obstetric care choose NIPT for first trimester screening compared to less than 25% of public patients[239]. The steady increase in NIPT uptake over the past decade has also been linked to a reduction (up to 40%) in patients undertaking first trimester biochemistry[237].

Self-reported ethnicity

Participant ethnicities are summarized in tables 4.3 and 4.4. Most participants described themselves as Australian or Caucasian. Overall, 89 different ethnicities were reported by 1601 participants (40 elected not to provide a response and in one case the response was inadequately described as 'mixed').

Responses were coded according to the Australian Standard Classification of Cultural and Ethnic Groups (ASCCEG) 2019[240]. As defined by the ASCCEG,

"…'ethnicity' refers to the shared identity or similarity of a group of people on the basis of one or more distinguishing characteristics.

These characteristics include:

- *A long shared history, the memory of which is kept alive.*
- *A cultural tradition, including family and social customs, sometimes religiously based.*
- *A common geographic origin.*
- *A common language (but not necessarily limited to that group).*
- *A common literature (written or oral).*
- *A common religion.*
- *Being a minority (often with a sense of being oppressed).*
- *Being racially conspicuous."*

The comprehensive ASCCEG coding index provides codes for broad, narrow, or cultural and ethnic groups, and includes codes for responses that are not specific, for example, 'Caucasian', 'Asian', and 'African'. Where multiple responses were provided, coding was allocated according to the narrow or broad group

appropriate for the response. For example, a response of 'Yugoslav/Czech' was coded as 'Eastern European 3300'.

The way participants interpreted the term 'ethnicity' was variable, which was unsurprising given there is no standard definition of the term and identity is self-perceived. Country of birth is often used as a surrogate for ethnicity[241], and this may have been the case for many study participants. Many participants provided non-specific ethic groups for their responses such as 'Caucasian', 'Asian', and 'African' while others were much more specific, for example. 'Sikh'.

Table 4.3 *The ten most commonly reported ethnicities by the study cohort*

Ethnicity	TOTAL *n=1642*		Site 1 *n=481*		Site 2 *n=635*		Site 3 *n=526*	
	n	***(%)***	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***
Australian	844	*(51.4)*	71	*(14.8)*	333	*(52.4)*	440	*(83.7)*
Caucasian	173	*(10.5)*	173	*(36.0)*	0	-	0	-
Indian	64	*(3.9)*	33	*(6.9)*	27	*(4.3)*	4	*(0.8)*
Aboriginal	47	*(2.9)*	15	*(3.1)*	0	-	32	*(6)*
Nepalese	35	*(2.1)*	13	*(2.7)*	18	*(2.8)*	4	*(0.8)*
Filipino	33	*(2.0)*	10	*(2.1)*	20	*(3.1)*	3	*(0.6)*
Chinese	27	*(1.6)*	6	*(1.2)*	21	*(3.3)*	0	-
English	27	*(1.6)*	3	*(0.6)*	20	*(3.1)*	4	*(0.8)*
Vietnamese	25	*(1.5)*	11	*(2.3)*	13	*(2.1)*	1	*(0.2)*
European	24	*(1.5)*	22	*(4.6)*	0	-	2	*(0.4)*

Table 4.4 *All ethnicities reported by the study cohort*

Ethnicity	TOTAL *n*	Site 1 *n*	Site 2 *n*	Site 3 *n*	Ethnicity	TOTAL *n*	Site 1 *n*	Site 2 *n*	Site 3 *n*
Australian	844	71	333	440	Sikh	2	2	0	0
Caucasian	173	173	0	0	Channel Islander	2	0	2	0
Indian	64	33	27	4	Maltese	2	1	0	1
Aboriginal	47	15	0	32	South East Asian	2	2	0	0
Not stated	40	40	0	0	Ukrainian	2	0	2	0
Nepalese	35	13	18	4	Hispanic	2	2	0	0

Filipino	33	10	20	3	Portuguese	2	1	0	1
Chinese	27	6	21	0	Zimbabwean	2	0	0	2
English	27	3	20	4	Nigerian	2	1	0	1
Vietnamese	25	11	13	1	South Sudanese	2	2	0	0
European	24	22	0	2	Eastern European	2	2	0	0
Italian	16	5	6	5	Bosnian	2	0	2	0
British	15	3	9	3	Hungarian	2	1	1	0
Korean	15	3	11	1	Burmese	2	1	1	0
Irish	15	3	12	0	Jordanian	2	0	2	0
Bangladeshi	14	7	7	0	Bengali	2	1	1	0
Indonesian	12	1	9	2	Papua New Guinean	1	0	1	0
Pakistani	10	7	1	2	Solomon Islander	1	0	1	0
New Zealander	9	1	5	3	Spanish	1	1	0	0
Lebanese	9	0	8	1	Latvian	1	0	1	0
South African	9	2	5	2	Belarusian	1	0	1	0
American	8	0	8	0	Greek	1	0	1	0
Malay	8	1	7	0	Croatian	1	1	0	0
Sri Lankan	7	3	4	0	Czech	1	0	1	0
German	7	0	4	3	Emirati	1	0	1	0
Chinese Asian	7	0	7	0	Iranian	1	0	1	0
Mongolian	6	0	6	0	Turkish	1	0	1	0
Scottish	6	0	4	2	Chilean	1	0	1	0
French	6	0	6	0	Jamaican	1	0	1	0
Canadian	6	0	5	1	Somali	1	1	0	0
Brazilian	6	1	5	0	Bulgarian	1	0	1	0
Asian	4	4	0	0	Fijian	1	1	0	0
Tongan	4	3	0	1	Syrian	1	0	1	0
Japanese	4	0	4	0	Jewish	1	0	1	0
Singaporean	4	0	4	0	Mexican	1	0	1	0
Russian	4	1	3	0	Uruguayan	1	0	1	0
Thai	4	0	4	0	Venezuelan	1	0	1	0
African	3	3	0	0	Taiwanese	1	0	1	0
Samoan	3	3	0	0	Khmer	1	0	0	1
Saudi Arabian	3	0	2	1	Sierra Leonean	1	0	1	0
Mauritian	3	3	0	0	Norwegian	1	0	1	0
Colombian	3	1	2	0	Dutch	1	0	1	0
Macedonian	3	3	0	0	Southern Asian	1	1	0	0
Polish	3	0	0	3	Central and West African	1	0	1	0
Iraqi	3	1	2	0	Other North African and Middle Eastern	1	1	0	0
Maori	2	2	0	0	Not adequately stated	1	1	0	0

4.3.2 Indications for ultrasound examination

The indication for each ultrasound examination was recorded as data were collected from clinically indicated studies. In Australia, routine ultrasound examinations are performed at 12 – 14 weeks GA for first trimester screening and again at 18 – 20 weeks GA for fetal anatomy assessment. Routine third trimester ultrasound is not generally performed, however, there are numerous indications for performing ultrasound in the third trimester. Additionally, serial growth scans and dedicated cardiac assessment are recommended by many obstetric management guidelines[36], and these indications were categorised as routine. At the time of this study, Site 2 had adopted the policy of routine third trimester ultrasound examinations around 36 weeks GA for women birthing at that centre and recorded the indication as 'unspecified'. Clinical indications were grouped as fetal indications (e.g. known or suspected fetal anomaly, clinical suspicion of abnormal fetal growth), maternal indications (e.g. maternal diabetes, hypertension), and pregnancy indications (e.g. clinical suspicion of placental or umbilical cord abnormalities, antepartum haemorrhage). Indications for ultrasound are summarized in figures 4.5 – 4.8. The majority of ultrasound examinations in this cohort were performed for inadequately specified indications (15.7%). Routine fetal anomaly scans accounted for 14.5% (including those performed as repeat examinations following suboptimal assessments) and 11.8% were indicated by maternal diabetes (including gestational diabetes). The most common fetal indications were suspected or known growth restriction (5.8%) and follow up for minor fetal anomaly, for example mild pyelectasis, (3.7%). Suspected placental abnormalities (most commonly low lying placenta at mid trimester) comprised 4.9% of indications for ultrasound.

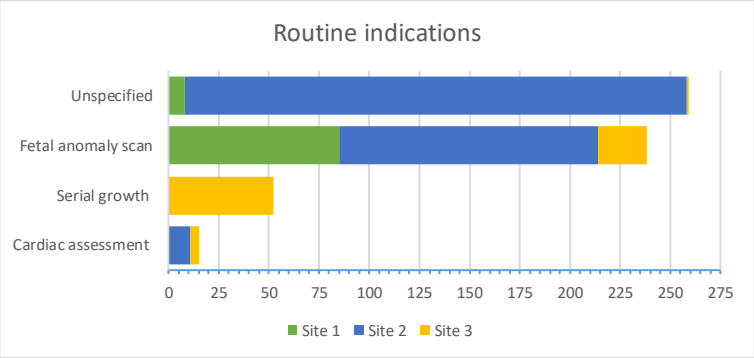

Figure 4.5 *Routine indications for fetal ultrasound*

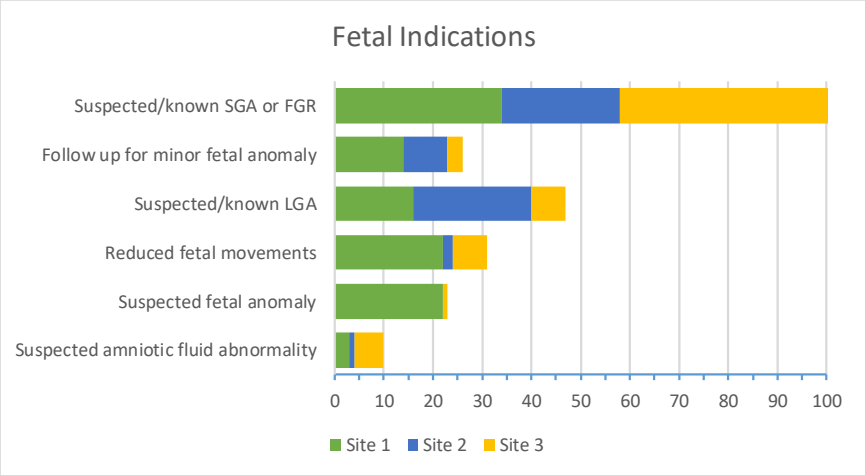

Figure 4.6 *Fetal indications for fetal ultrasound. SGA: small for gestational age, FGR: fetal growth restriction, LGA: large for gestational age*

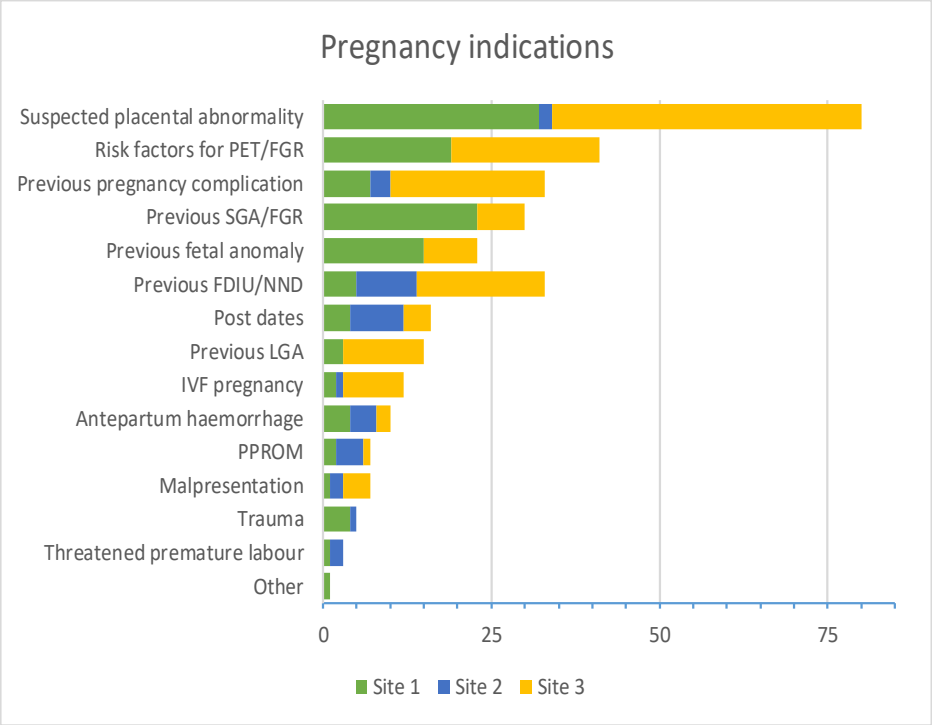

Figure 4.7 *Pregnancy indications for ultrasound. PET: pre-eclampsia, FGR: fetal growth restriction, SGA: small for gestational age, FGR: fetal growth restriction, FDIU: fetal death in utero, NND: neonatal death, LGA: large for gestational age, IVF: in-vitro fertilisation, PPROM: preterm premature rupture of membranes*

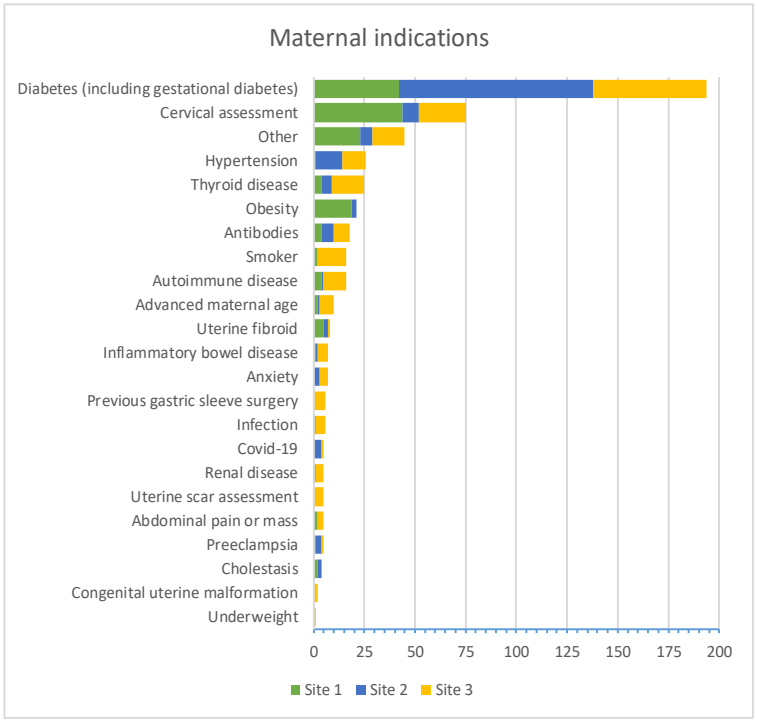

Figure 4.8 *Maternal indications for fetal ultrasound*

4.3.3 Birth Outcome Data

Birth outcome data were collected from the birth outcome summary by the nominated site lead from each participating centre. Outcome data are summarised in tables 4.5 – 4.8. There were 1640 live births and 2 stillbirths and the majority (92.8%) of births occurred at term (37 - 42 weeks). Moderate pre-term births (32 – 37 weeks) accounted for 6.2% of the cohort, and the proportions of very pre-term (28 – 32 weeks), extremely pre-term (less than 28 weeks), and post-dates (after 42 weeks) were below 1%. Non-instrumental vaginal births accounted for 48.7% of births in this cohort (when including induction of labour figures recorded by Sites 1 and 3), instrumental vaginal births were 11.3% (including vacuum extraction and forceps), and Caesarean section births were 40.2% (including elective and emergency procedures). When compared to national data from the AIHW[235], rates of non-instrumental vaginal births in the cohort were lower: 50% of women who gave birth in Australia in 2020 had a non-instrumental vaginal birth, 49.7% in 2021 and 50.6% in 2022. Caesarean section rates in the cohort were higher: in 2020 37.3% of women who gave birth in Australia had a Caesarean section birth, 38.2% in 2021 and 39.2% in 2022.

When comparing method of birth recorded at each site to relevant AIHW state and territory data, Caesarean section rates from the Site 1 cohort were lower at 31.9% compared to ACT rates: 38.6% in 2020, 42.1% in 2021 and 42.2% in 2022. For Site 2 and Site 3 the Caesarean section rates were 42.4% and 45.1% respectively and higher than NSW rates: 36.7% in 2020, 37.6% in 2021 and 38.4% in 2022. It should be noted that the study cohort comprised of singleton pregnancies and national, state and territory data includes multiple pregnancies. As reported in 2022 AIHW data, the rate of Caesarean section birth in multiple pregnancies is 75%, but as these comprise just 1.4% of pregnancies,[235] there is little effect on the overall rate of Caesarean section births[242]. Nonetheless, according to the National Core Maternity Indicators 2022 report[243] the proportion of women giving birth by Caesarean section rates have increased

over the last 20 years. Rates are higher in private hospitals than in public hospitals and slightly higher for women living in areas of least disadvantage.

Table 4.5 *Birth outcome data of total cohort*

All Sites	Term >37w		Post dates >42w		Moderate preterm 32w - 37w		Very preterm 28w - 32w		Extremely preterm <28w		Total	
Birth Outcome	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***
Live birth	1523	*(92.8)*	2	*(0.1)*	101	*(6.2)*	10	*(0.7)*	4	*(0.2)*	1640	*(99.9)*
Stillbirth	1	*(0.1)*	0	-	0	-	0	-	1	*(0.1)*	2	*(0.1)*
Male	746	*(49.0)*	2	*(0.1)*	59	*(58.4)*	5	*(50)*	3	*(75.0)*	815	*(49.6)*
Female	778	*(51.0)*	0	-	42	*(41.6)*	5	*(50)*	2	*(25.0)*	827	*(50.4)*
Birth weight		***g***		***g***		***g***		***g***		***g***		***g***
Average		3371		4360		2765		1926		740		3320
Median		3370		-		2760		1732		670		3340
Range	1840 – 5224		4250g– 4470		1370 – 5145		857 – 3780		582 – 1000		582 – 5224	
Birth method	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***
Spontaneous vaginal birth	645	*(42.3)*	0	-	39	*(38.6)*	3	*(30.0)*	2	*(40.0)*	691	*(42.1)*
Induction of labour	105	*(6.9)*	0	-	3	*(3.0)*	1	*(10.0)*	0	-	109	*(6.6)*
Assisted vaginal birth	180	*(11.8)*	1	*(50.0)*	4	*(4.0)*	0	-	0	-	185	*(11.3)*
Elective CS	369	*(24.2)*	0	-	31	*(30.7)*	1	*(10.0)*	0	-	402	*(24.5)*
Emergency CS	225	*(14.8)*	1	*(50.0)*	24	*(23.8)*	5	*(50.0)*	3	*(60.0)*	258	*(15.7)*
Outcome measures	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***
5min Apgar <7	22	*(1.4)*	0	-	3	*(3.0)*	0	-	2	*(50.0)*	27	*(1.6)*
Arterial cord blood * pH <7	8	*(0.5)*	0	-	0	-	0	-	0	-	8	*(0.5)*
NNICU/SCN admission	160	*(10.5)*	0	-	62	*(61.4)*	7	*(70.0)*	4	(*100)*	233	*(14.4)*
Combined outcome measures	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***
NNICU/SCN admission, Apgar<7, Arterial cord blood pH<7	0	-	0	-	0	-	0	-	0	-	0	-
NNICU/SCN admission, Apgar<7	9	*(0.6)*	0	-	1	*(1.0)*	0	-	1	*(25.0)*	11	*(0.7)*
NNICU/SCN admission, Arterial cord blood pH<7	0	-	0	-	0	-	0	-	0	-	0	-

* Arterial cord blood collected in 550/1646,
CS: Caesarean section, NNICU: neonatal intensive care unit, SCN: special care nursery

Table 4. 6 *Birth outcome data Site 1*

Site 1	Term >37w		Post dates >42w		Moderate preterm 32w - 37w		Very preterm 28w - 32w		Extremely preterm <28w		Total	
Birth Outcome	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***
Live birth	440	*(91.7)*	1	*(0.2)*	30	*(6.2)*	6	*(1.2)*	3	*(0.6)*	480	*(99.8)*
Stillbirth	1	*(0.2)*	0	-	0	-	0	-	0	-	1	*(0.2)*
Male	217	*(49.1)*	1	*(100.0)*	17	*(56.7)*	3	*(50.0)*	2	*(66.7)*	240	*(49.9)*
Female	224	*(50.7)*	0	-	13	*(43.3)*	3	*(50.0)*	1	*(33.3)*	241	*(50.1)*
Birth weight		***g***		***g***		***g***		***g***		***g***		***g***
Average		3364		4470		2608		2028		823		3286
Median		3362		-		2550		2033		800		3320
Range		1840 – 4845		-		1370 – 5145		1160 – 2760		670 – 1000		670 – 5145
Birth method	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***
Spontaneous vaginal birth	170	*(38.5)*	0	-	14	*(47.7)*	3	*(50.0)*	1	(33.3)	188	*(39.1)*
Induction of labour	89	*(20.1)*	0	-	2	*(6.7)*	1	*(16.7)*	0	-	92	*(19.1)*
Assisted vaginal birth	47	*(10.6)*	0	-	0	-	0	-	0	-	47	*(9.8)*
Elective CS	61	*(13.8)*	0	-	6	*(20.0)*	1	*(16.7)*	0	-	67	*(13.9)*
Emergency CS	74	*(16.7)*	1	*(100.0)*	8	*(26.7)*	2	*(33.3)*	2	(66.7)	87	*(18.0)*
Outcome measures	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***
5min Apgar <7	6	*(1.4)*	0	-	0	-	0	-	1	*(33.3)*	7	*(1.5)*
Arterial cord blood* pH <7	2	*(0.5)*	0	-	0	-	0	-	0	-	2	*(0.4)*
NNICU/SCN admission	38	*(8.6)*	0	-	22	*(73.3)*	4	*(66.7)*	3	*(100.0)*	67	*(13.9)*
Combined outcome measures	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***
NNICU/SCN admission, Apgar<7, Arterial cord blood pH<7	0	-	0	-	0	-	0	-	0	-	0	-
NNICU/SCN admission, Apgar<7	1	*(0.2)*	0	-	0	-	0	-	1	*(33.3)*	2	*(0.4)*
NNICU/SCN admission, Arterial cord blood pH<7	0	-	0	-	0	-	0	-	0	-	0	-

* Arterial cord blood collected in 228/481

CS: Caesarean section, NNICU: neonatal intensive care unit, SCN: special care nursery

Table 4.7 *Birth outcome data Site 2*

Site 2	Term >37w		Post dates >42w		Moderate preterm 32w - 37w		Very preterm 28w - 32w		Extremely preterm <28w		Total	
Birth Outcome	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***
Live birth	589	*(92.7)*	1	*(0.2)*	40	*(6.3)*	3	*(0.5)*	1	*(0.2)*	634	*(99.8)*
Stillbirth	0	-	0	-	0	-	0	-	1	*(0.2)*	1	*(0.2)*
Male	297	*(50.4)*	1	*(100.0)*	23	*(57.5)*	1	*(33.3)*	1	*(50.0)*	323	*(50.9)*
Female	292	*(49.6)*	0	-	17	*(42.5)*	2	*(66.7)*	1	*(50.0)*	312	*(49.1)*
Birth weight		***g***		***g***		***g***		***g***		***g***		***g***
Average		3382		4360		2798		1084		617		3330
Median		3376		-		2776		1100		-		3350
Range		1870 – 5224		-		1100 – 3910		857 – 1295		582 – 651		582 – 5224
Birth method	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***
Spontaneous vaginal birth	252	*(42.8)*	0	-	12	*(30.0)*	0	-	1	*(50.0)*	263	*(41.4)*
Induction of labour*		-		-		-		-		-		-
Assisted vaginal birth	99	*(16.9)*	1	*(100.0)*	3	*(7.5)*	0	-	0	-	103	*(16.2)*
Elective CS	116	*(19.7)*	0	-	13	*(32.5)*	0	-	0	-	130	*(20.5)*
Emergency CS	123	*(20.9)*	0	-	12	*(30.0)*	3	(100.0)	1	*(50.0)*	139	*(21.9)*
Outcome measures	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***
5min Apgar <7	12	*(2.0)*	0	-	2	*(5.0)*	0	-	1	*(100.0)*	15	*(2.4)*
Arterial cord blood** pH <7	6	*(1.0)*	0	-	0	-	0	-	0	-	6	*(0.9)*
NNICU/SCN admission	52	*(8.8)*	0	-	20	*(50.0)*	3	*(100.0)*	1	*(100.0)*	76	*(12.0)*
Combined outcome measures	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***
NNICU/SCN admission, Apgar<7, Arterial cord blood pH<7	0	-	0	-	0	-	0	-	0	-	0	-
NNICU/SCN admission, Apgar<7	6	*(1.0)*	0	-	0	-	0	-	0	-	6	*(0.9)*
NNICU/SCN admission, Arterial cord blood pH<7	0	-	0	-	0	-	0	-	0	-	0	-

* Induction of labour not recorded ** Arterial cord blood collected in 322/637

CS: Caesarean section, NNICU: neonatal intensive care unit, SCN: special care nursery

Table 4.8 *Birth outcome data Site 3*

Site 3	Term >37w		Post dates >42w		Moderate preterm 32w - 37w		Very preterm 28w - 32w		Extremely preterm <28w		Total	
Birth Outcome	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***	***n***	***(%)***
Live birth	494	*(93.9)*	0	-	31	*(5.9)*	1	*(0.2)*	0	-	526	*(100.0)*
Stillbirth	0	-	0	-	0	-	0	-	0	-	0	-
Male	232	*(47.0)*	0	-	19	*(61.3)*	1	*(100.0)*	0	-	252	*(47.9)*
Female	262	*(53.0)*	0	-	12	*(38.7)*	0	-	0	-	274	*(52.1)*
Birth weight	***g***		***g***		***g***		***g***		***g***		***g***	
Average	3369		-		2825		3780		-		3338	
Median	3370		-		2850		-		-		3340	
Range	2101 – 4680		-		1620 – 4380		-		-		1620 – 4680	
Birth method	***n***	***(%)***	***n***		***n***	***(%)***	***n***	***(%)***	***n***		***n***	***(%)***
Spontaneous vaginal birth	224	*(45.3)*	-		13	*(41.9)*	0	-	-		237	*(45.1)*
Induction of labour	16	*(3.2)*	-		1	*(3.2)*	0	-	-		17	*(3.2)*
Assisted vaginal birth	34	*(6.9)*	-		1	*(3.2)*	0	-	-		35	*(6.6)*
Elective CS	192	*(38.9)*	-		12	*(38.7)*	1	(100.0)	-		205	*(39.0)*
Emergency CS	28	*(5.7)*	-		4	*(12.9)*	0	-	-		32	*(6.1)*
Outcome measures	***n***	***(%)***	***n***		***n***	***(%)***	***n***	***(%)***	***n***		***n***	
5min Apgar <7	4	*(0.8)*	-		1	*(3.2)*	0	-	-		5	*(1.0)*
Arterial cord blood* pH <7	-		-		-		-		-		-	
NNICU/SCN admission	70	(14.2)	-		20	*(64.5)*	0	-	-		90	*(17.1)*
Combined outcome measures	***n***	***(%)***	***n***		***n***	***(%)***	***n***	***(%)***	***n***		***n***	***(%)***
NNICU/SCN admission, Apgar<7, Arterial cord blood pH<7	-	-	-		-	-	-	-	-		-	-
NNICU/SCN admission, Apgar<7	2	*(0.4)*	-		1	*(3.2)*	0	-	-		3	*(0.6)*
NNICU/SCN admission, Arterial cord blood pH<7	-	-	-		-	-	-	-	-		-	-

* Arterial cord blood not recorded

CS: Caesarean section, NNICU: neonatal intensive care unit, SCN: special care nursery

A study comparing Caesarean section rates in western Sydney before and during the Covid-19 pandemic reported a 4.1% increase in Caesarean section rates[244] which may account for the higher rates reported in the study cohort.

The average and median birthweights are summarized in figure 4.9. Of note, average and median birthweights for babies born at term (37 weeks – 42 week GA) were comparable between sites.

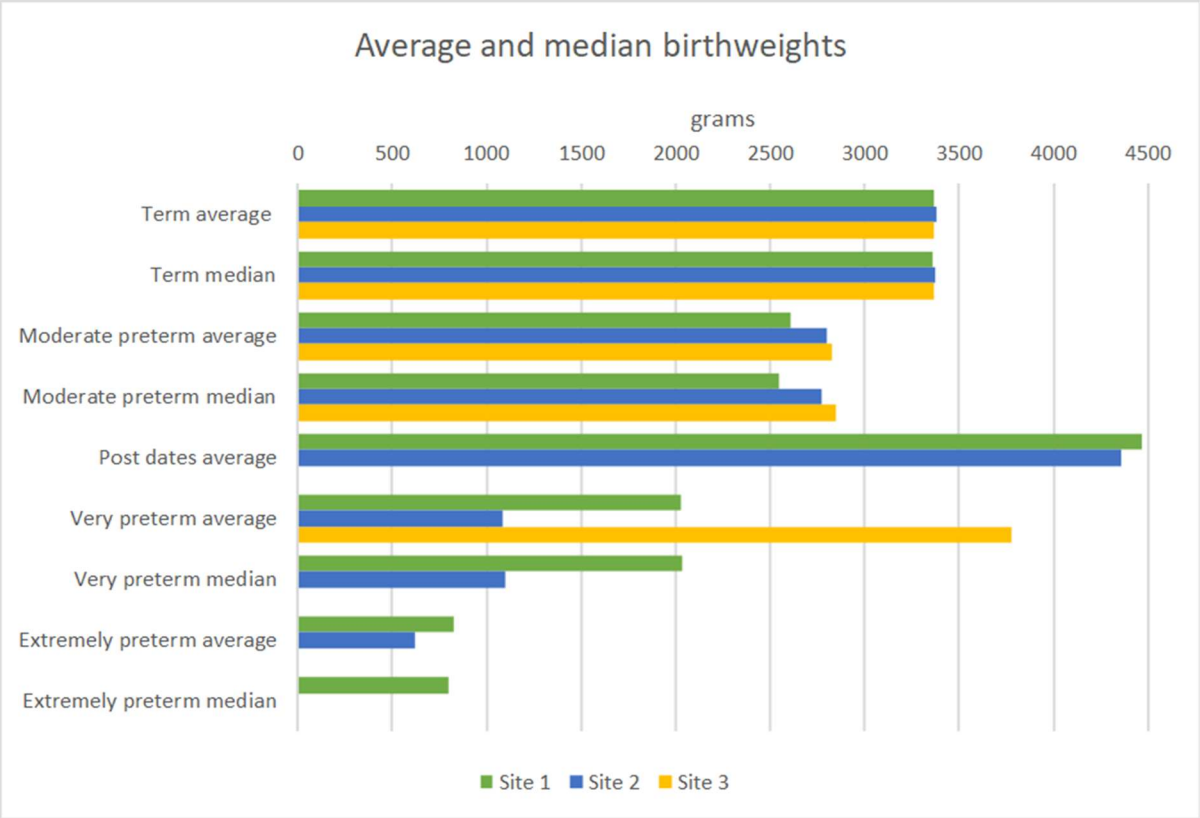

Figure 4.9 *Average and median birthweights for babies born at different gestational ages. Term: 37 weeks – 42 weeks, moderate preterm: 32 weeks – 37 weeks, Post dates: greater than 42 weeks, Very preterm: 28 weeks – 32 weeks, Extremely preterm: less than 28 weeks*

4.3.4 Ultrasound measurements

The distribution of observations is summarised in table 4.9. Observations were recorded between 14 and 41 weeks with the peak number of observations occurring at time points in the third trimester when ultrasound is commonly performed (28, 32, 34 and 36 weeks).

The average measurements for each observation were plotted with reference to gestational age (figures 4.10 – 4.14).

Table 4.9 *Distribution of ultrasound observations*

GA *completed weeks*	Observations *n*				**GA *completed weeks***	Observations *n*			
	Total	Site 1	Site 2	Site 3		Total	Site 1	Site 2	Site 3
14	7	5	2	0	**28**	215	50	75	91
15	29	22	7	0	**29**	63	9	23	31
16	42	22	19	1	**30**	43	7	10	26
17	13	3	10	0	**31**	52	8	16	28
18	21	17	4	0	**32**	102	27	25	50
19	35	31	2	2	**33**	55	19	10	26
20	39	25	13	1	**34**	108	27	3	78
21	87	7	79	1	**35**	64	22	16	26
22	46	12	31	3	**36**	198	28	127	43
23	30	11	11	8	**37**	66	17	23	25
24	58	26	18	14	**38**	65	26	25	15
25	44	15	18	11	**39**	20	7	10	3
26	41	11	21	9	**40**	11	5	4	2
27	78	20	28	30	**41**	10	2	6	2

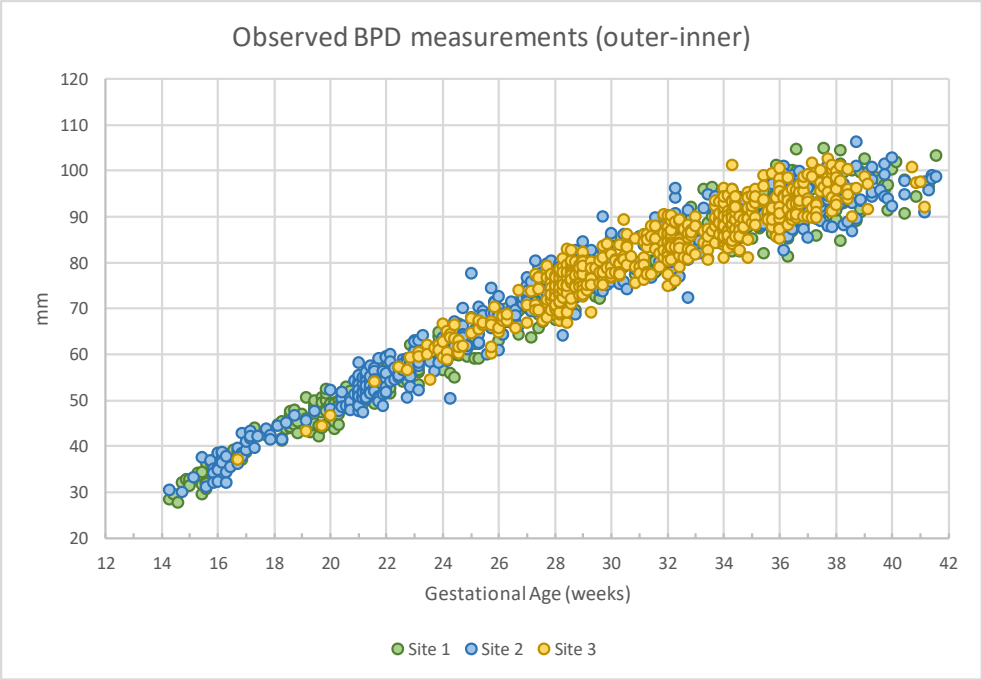

Figure 4.10 *Distribution of BPD observations (measured outer to inner)*

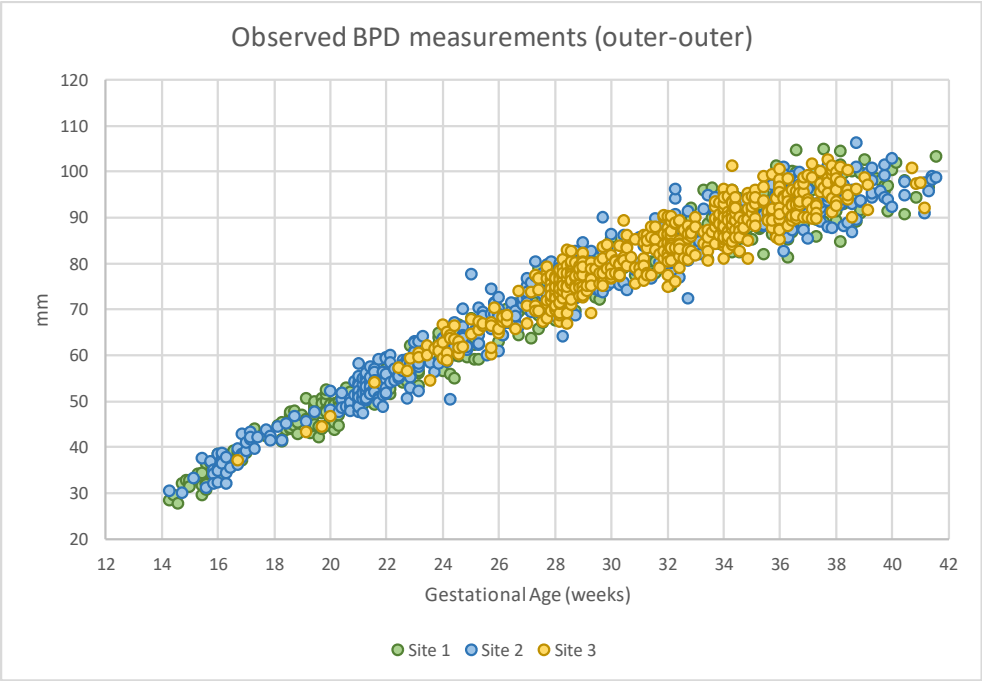

Figure 4.11 *Distribution of BPD measurements (measured outer to outer)*

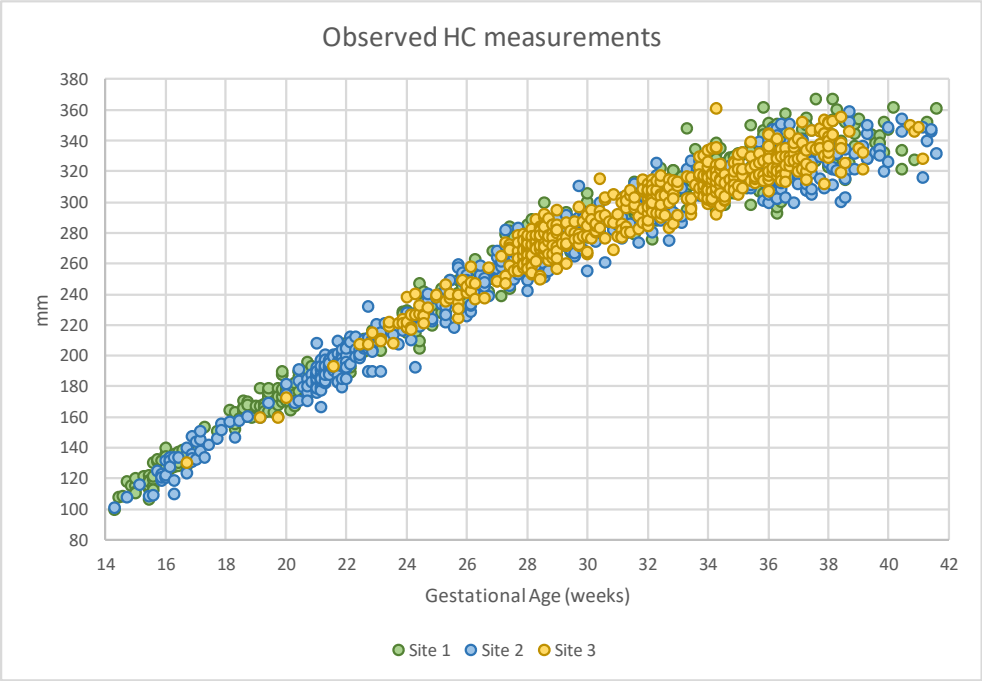

Figure 4.12 *Distribution of HC measurements*

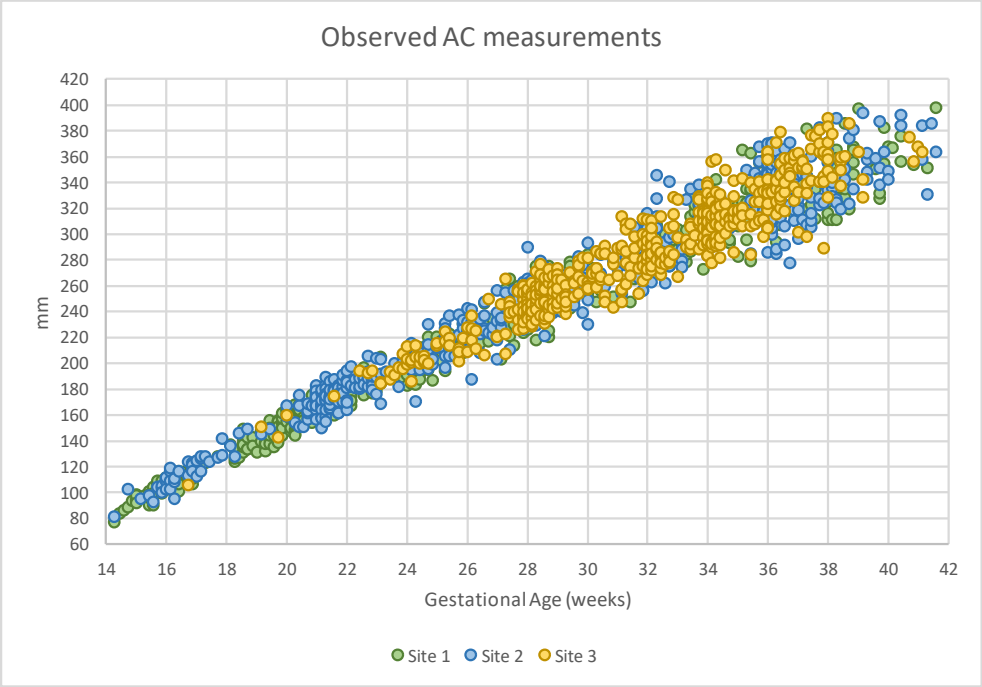

Figure 4.13 *Distribution of AC measurements*

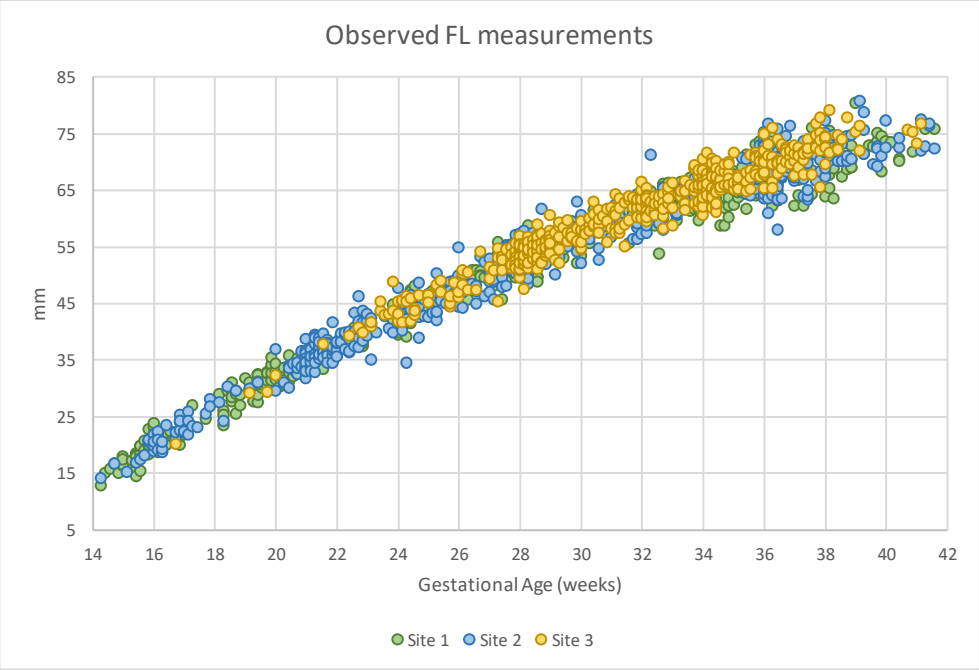

Figure 4.14 *Distribution of FL measurements*

4.3.5 Measurement reliability

Intra-observer agreement was assessed by comparing the first and last measurement of the three measurements made for each observation. Bland-Altman analysis was performed using IBM SPSS (IBM SPSS Statistics for Windows, Version 30; IBM Corp., Armonk, NY, USA). The mean difference or bias measures the tendency for an operator to over or under measure relative to the first measurement, with values close to zero indicating less bias. The limits of agreement refer to the range where 95% of measurement differences will fall and can be interpreted as a measure of expected random error between the two measurements. A narrow range implies there is greater agreement between observers[245]. Bland-Altman graphs are presented in figures 4.15 – 4.19. Differences are expressed in distance (mm) for straight

line measurements (BPD and FL), and as percentage differences for circumference measurements (HC and AC). The graphs illustrate low bias and a narrow range for random error.

Five sonographer participants took part in an inter-rater reliability exercise to assess calliper placement. Ten cases were randomly selected at different gestational ages, each with three images recorded for each measurement plane (30 images in total). Each case was reloaded to the ultrasound machine and previous measurement data was deleted before each participant was invited to measure the BPD (outer to inner), BPD (outer to outer), HC, AC and FL. Participants were blinded to the gestational age and centile for each measurement using methods previously described.

The intraclass correlation coefficient (ICC) was calculated using IBM SPSS (IBM SPSS Statistics for Windows, Version 30; IBM Corp., Armonk, NY, USA). For all measures, the correlation coefficients were greater than 0.95, which is considered acceptable[245].

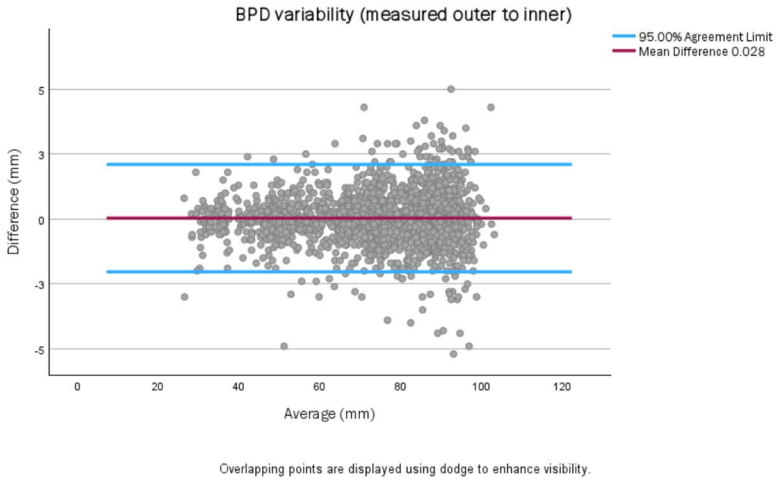

Figure 4.15 *Intra-rater variability for BPD (measured outer to inner)*

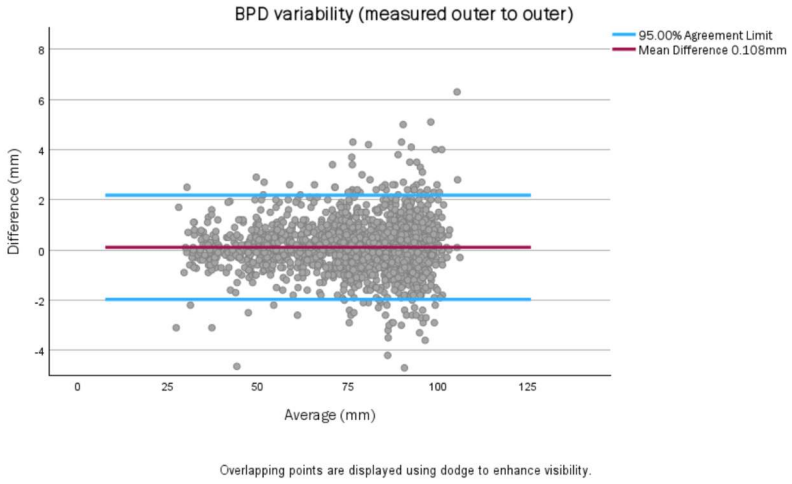

Figure 4.16 *Intra-rater BPD variability (measured outer to outer)*

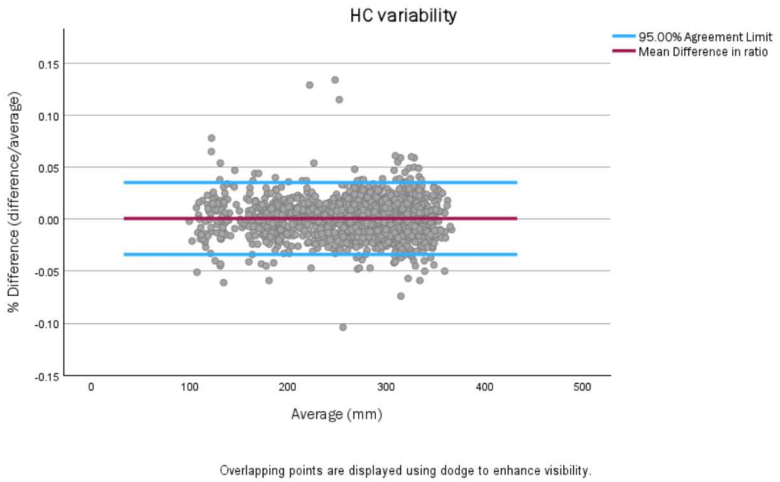

Figure 4.17 *Intra-rater HC variability*

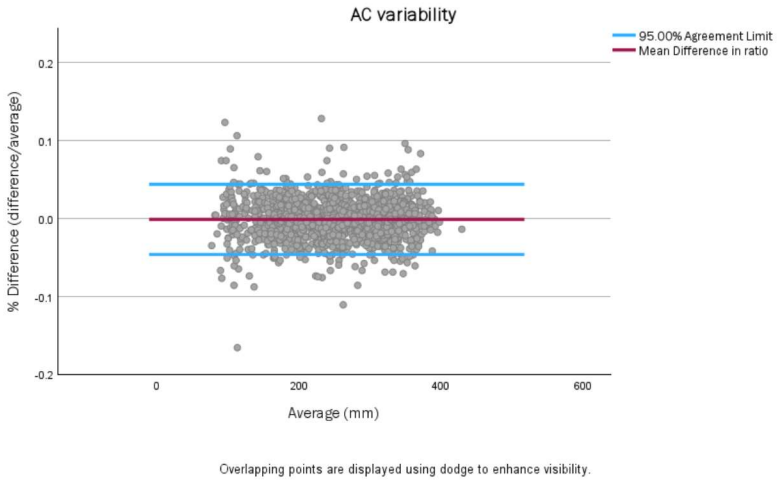

Figure 4.18 *Intra-rater AC variability*

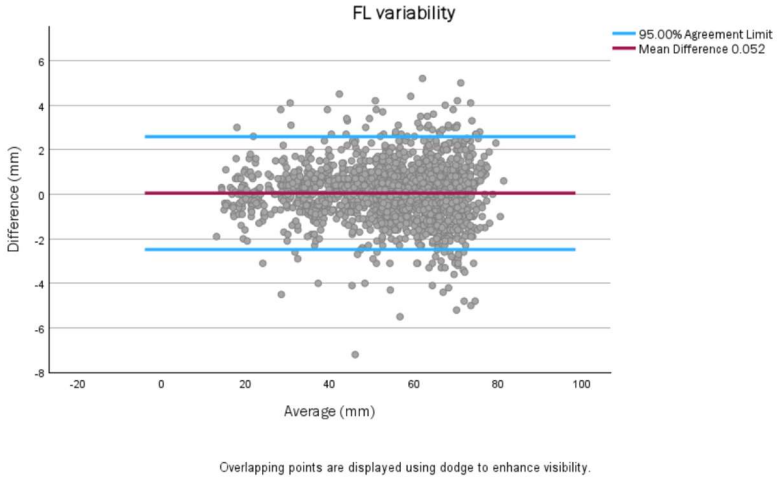

Figure 4.19 *Intra-rater FL variability*

4.3.6 Data Pooling

There is no consensus on how to determine if data from each site are similar enough to pool, however, methods have been described by the World Health Organisation (WHO) Multicentre growth reference study (MGRS)[246] and the Intergrowth-21st consortium[247]. The rationale for pooling data for the IG21 charts was based on differences in head circumference measures. A standard deviation (SD) difference less than 50% between values for each site and SD of combined averages was considered sufficiently similar. It was noted that a stricter criteria (less than 32% difference) may be preferable when assessing the tails of the distribution[247].

Pooled average measurements were grouped according to completed gestational age (i.e. 20 weeks 5 days was equivalent to 20 weeks) and the pooled means were calculated. The means and standard deviations for each site were calculated and compared to the pooled means and standard deviations. These data were plotted with respect to gestational age to enable visual assessment of significant differences between sites (figures 4.20 - 4.24)

Figure 4.20 *Biparietal diameter (BPD) means for each completed week (measured outer to inner). Standard deviations indicated by error bars.*

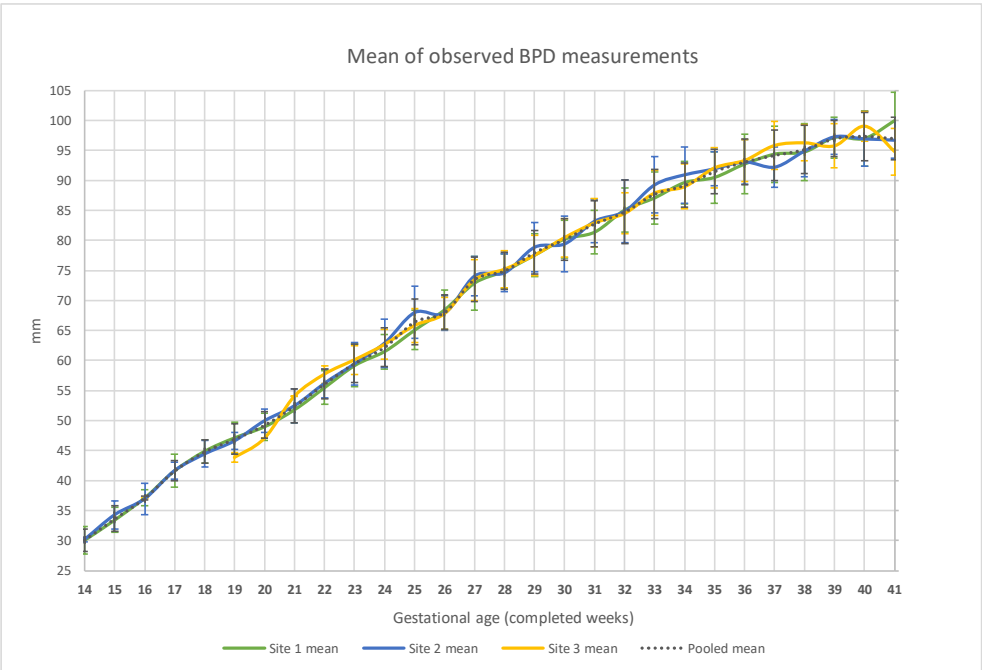

Figure 4.21 *Biparietal diameter (BPD) means for each completed week (measured outer to outer). Standard deviations indicated by error bars.*

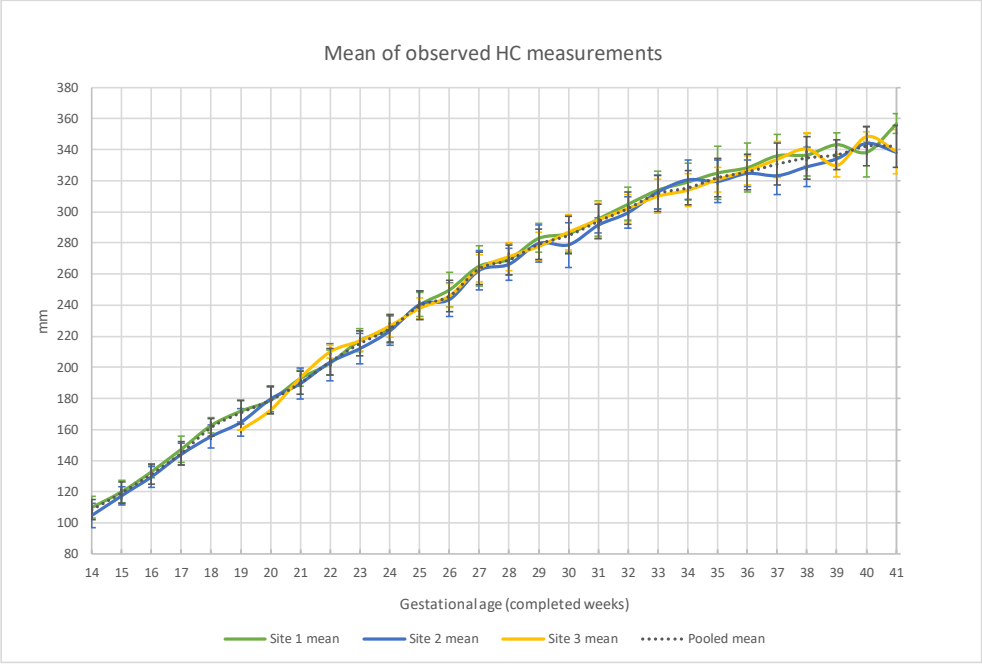

Figure 4.22 *Head circumference (HC) means for each completed week. Standard deviations indicated by error bars.*

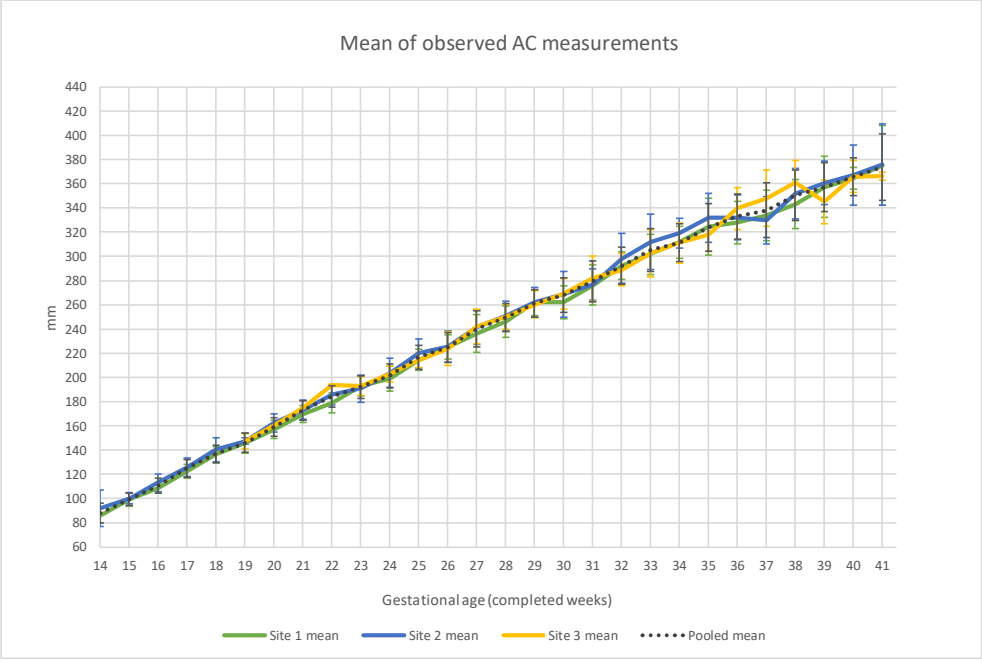

Figure 4.23 *Abdominal circumference (AC) means for each completed week. Standard deviations indicated by error bars.*

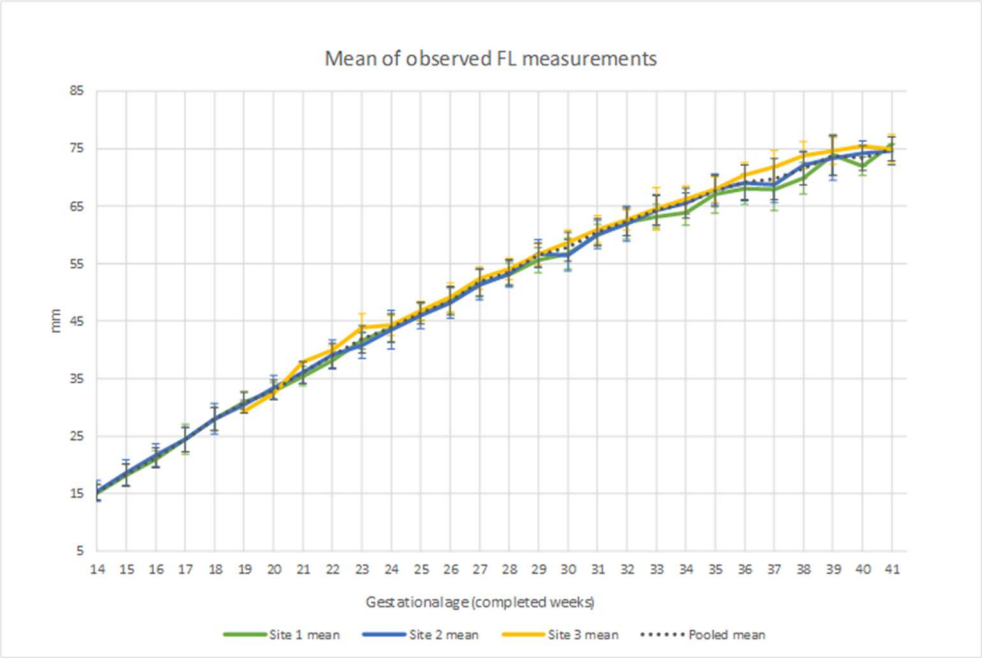

Figure 4.24 *Femur length (FL) means for each completed week. Standard deviations indicated by error bars.*

Observations in 28th week (215 observations) and 36th week (198 observations) were assessed for differences that may be evident at later gestations. Standard deviations for each measure were compared to the pooled standard deviations by calculating the percentage difference (tables 4.10 and 4.11). For all measurement parameters, the percentage difference in standard deviation did not exceed the recommended 32%, indicating data from each site was similar enough to allow pooling.

Table 4.10 *Differences in standard deviations for each site for observations at 28 completed weeks*

Parameter	Total mean mm	*n=215* SD mm	**Site 1** mean mm	*n=50* SD mm	Δ SD (%)	**Site 2** mean mm	*n=75* SD mm	Δ SD (%)	**Site 3** mean mm	*n=91* SD mm	Δ SD (%)
BPD	75.0	3.1	74.9	2.9	6.4	74.6	3.1	0.0	75.2	3.1	0.0
HC	269.1	9.4	269.7	9.9	5.3	266.3	9.0	0.0	271.2	8.9	5.8
AC	249.4	11.7	246.4	12.9	9.3	250.6	12.4	19.8	250.1	10.3	12.0
FL	53.5	2.1	53.1	2.1	0.0	53.2	2.3	9.3	54.0	1.9	11.4

BPD: biparietal diameter, HC: head circumference, AC: abdominal circumference, FL: femur length
SD: standard deviation, Δ SD: difference in standard deviation

Table 4.11 *Differences in standard deviations for each site for observations at 36 completed weeks*

Parameter	Total mean mm	*n=198* SD mm	**Site 1** mean mm	*n=28* SD mm	Δ SD %	**Site 2** mean mm	*n=127* SD mm	Δ SD %	**Site 3** mean mm	*n=43* SD mm	Δ SD %
BPD	93.1	3.8	92.7	5.0	23.3	93.1	3.7	3.58	93.4	3.5	8.3
HC	325.7	11.5	328.5	15.8	27.3	324.7	11.1	4.04	326.5	9.3	19.6
AC	333.0	18.7	327.9	17.7	5.0	332.1	18.9	1.05	339.8	17.3	7.5
FL	69.1	3.0	68.0	2.6	11.3	69.0	3.1	5.21	70.4	2.2	25.0

BPD: biparietal diameter, HC: head circumference, AC: abdominal circumference, FL: femur length
SD: standard deviation, Δ SD: difference in standard deviation

4.4 Analysis

Fetal biometry charts recommended for use across NSW and the ACT are ASUM charts for head circumference and abdominal circumference, and Chitty for femur length[210]. The charts endorsed by the Australasian Society for Ultrasound in Medicine (ASUM) were published in 2000 by Westerway et al, and are commonly referred to as the ASUM charts[172].

In 2014 the Intergrowth 21st (IG21) charts were published as international standards for fetal size[38]. The longitudinal design makes these charts appropriate for fetal growth evaluation and they may be well suited for use in Australia's multi-ethnic population.

The distribution of observations from this study were compared to current charts and IG21 charts to determine which reference best suited the study population by:

- Visual comparison
- Comparison of Z-score distribution
- Assessment of proportion of observations falling above or below fixed centiles

Visual comparison

The average measurement for each parameter was plotted with respect to gestational age in exact weeks. Centile curves from the respective charts were calculated using reported formulae as shown in table 4.12 and centile curves were generated from $mean \pm Z\ SD$ where Z = -1.881, -1.282, 1.282 and 1.881 for the 3rd, 10th, 90th and 97th centiles respectively. These were overlayed on the scatter plots (figures 4.25 – 4.29).

The distribution of observed BPD measurements (measured from the outer edge of the proximal parietal bone to the inner edge of the distal) were largely within the 3rd and 97th centiles of the ASUM chart, however, more observations than expected fell outside the extreme centiles. The plots of HC measurements and AC measurements demonstrate more observations than expected above the 97th centile curve. Plots of FL observations were overlayed with ASUM centiles and Chitty centiles, with distribution fitting the Chitty curves well.

The distribution of observed BPD measurements (measured from the outer edge of the proximal parietal bone to the outer edge of the distal) were largely within the 3rd and 97th centiles of the IG21 chart. The

plots of observed HC measurements, AC measurements and FL measurements demonstrate more observations than expected above the 97th centile curve.

Table 4.12 *Formulae used to calculate centiles and Z-scores*

Chart		Formula
BPD (ASUM)[172]	*mean*	$-0.0371(GA)^2 + 4.69\ (GA) - 31.546$
	SD	2mm GA<15w, 2.25mm GA< 22w, 2.5mm GA<20w, 2.75mm GA<31w, 3mm GA<35w, 3.25mm GA<39w, 3.5mm GA<41w, 3.75mm 41w
HC (ASUM)[172]	*mean*	$-0.1699(GA)^2\ + 18.494\ (GA) - 127.91$
	SD	7mm GA<18w, 10mm GA<29w, 12.25mm GA≤41w
AC (ASUM)[172]	*mean*	$-0.0469 \times GA^2 + 13.204\ \times GA - 90.946$
	SD	5mm GA<17w, 7.5mm GA<21w, 10mm GA<26w, 12.5mm GA<31w, 15mm GA<36w, 17.5mm GA≤41w
FL (ASUM)[172]	*mean*	$-0.0004(GA)^3 + 0.0032(GA)^2 + 3.1263\ (GA) - 28.489$
	SD	1.5mm at GA 14w, 1.75mm at GA 15w, 2mm GA<18w, 2.25mm GA<25w, 2.5mm GA<35w, 2.75mm GA<39w, 3mm GA≤41w
FL (Chitty)[184]	*mean*	$-32.43 + 3.416\ \times GA - 0.0004791 \times GA^3$
	SD	$1.060 + 0.05833 \times GA$
BPD (IG21)[38]	*mean*	$5.60978 + 0.158369 \times (GA)^2 - 0.00256379\ \times (GA)^3$
	SD	$\exp(0.101242 + 0.00150557\ \times (GA)^3\ - 0.000771535\ \times (GA)^3\ + \log(GA) + 0.0000999638\ \times GA^3\ \times log(GA)^2)$
HC (IG21)[38]	*mean*	$-28.2849 + 1.69267 \times GA^2 - 0.397485 \times GA^2 \times \ln GA$
	SD	$1.98735 + 1.0136772 \times GA^3 - 0.00726264 \times GA^3 \times \ln(GA) + 0.00976253 \times (GA)^3 \times \ln(GA)^2$
AC (IG21)[38]	*mean*	$-81.3243 + 11.6772 \times GA - 0.000561865 \times (GA)^3$
	SD	$-4.36302 + 0.121445 \times (GA)^2 - 0.0130256 \times (GA)^3 + 0.00282143 \times (GA)^3 \times \ln GA$
FL (IG21)[38]	*mean*	$-39.9616 + 4.32298 \times GA - 0.0380156 \times (GA)^2$
	SD	$\exp(0.605843 - 42.0014 \times (GA)^{-2} + 0.00000917972 \times GA^3)$

BPD: biparietal diameter, HC: head circumference, AC: abdominal circumference, FL: femur length
SD: standard deviation

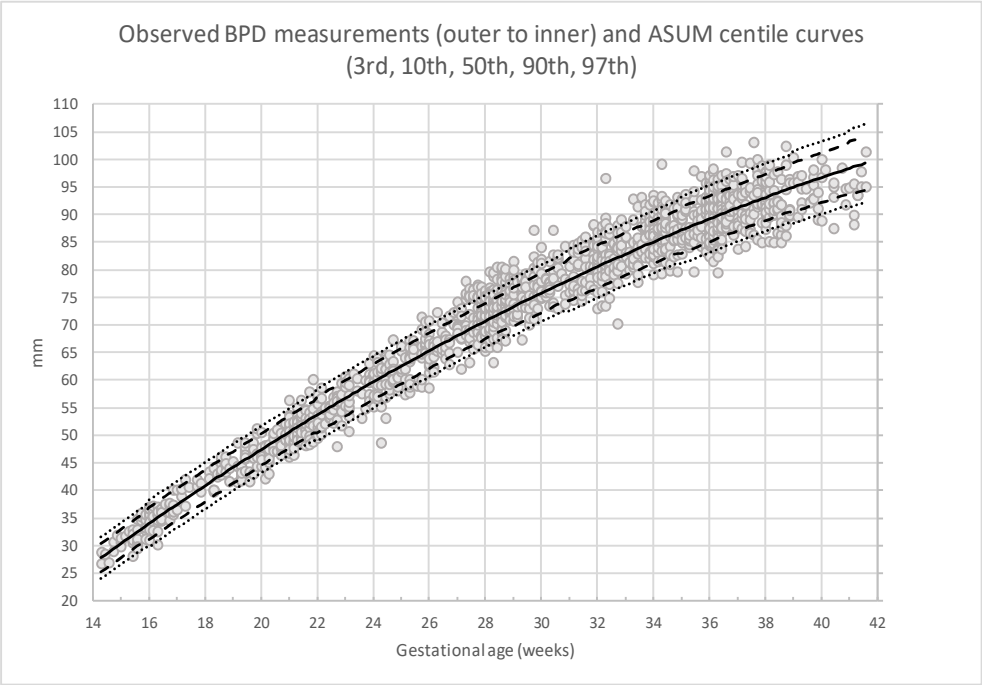

Figure 4.25 *Observed biparietal diameter measures and ASUM centile curves*

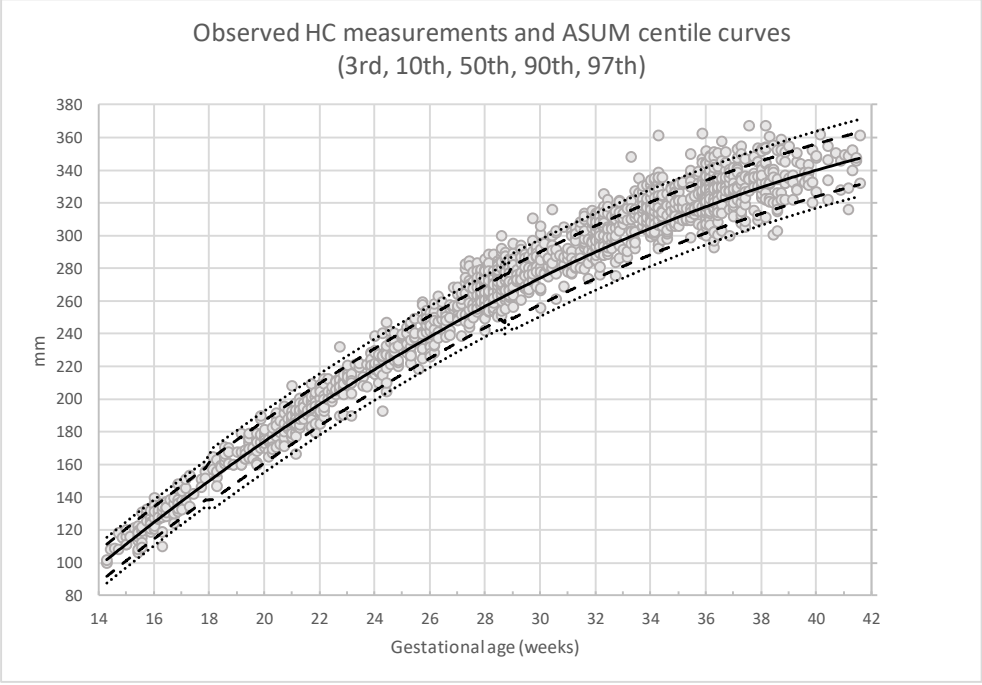

Figure 4.26 *Observed head circumference measures and ASUM centile curves*

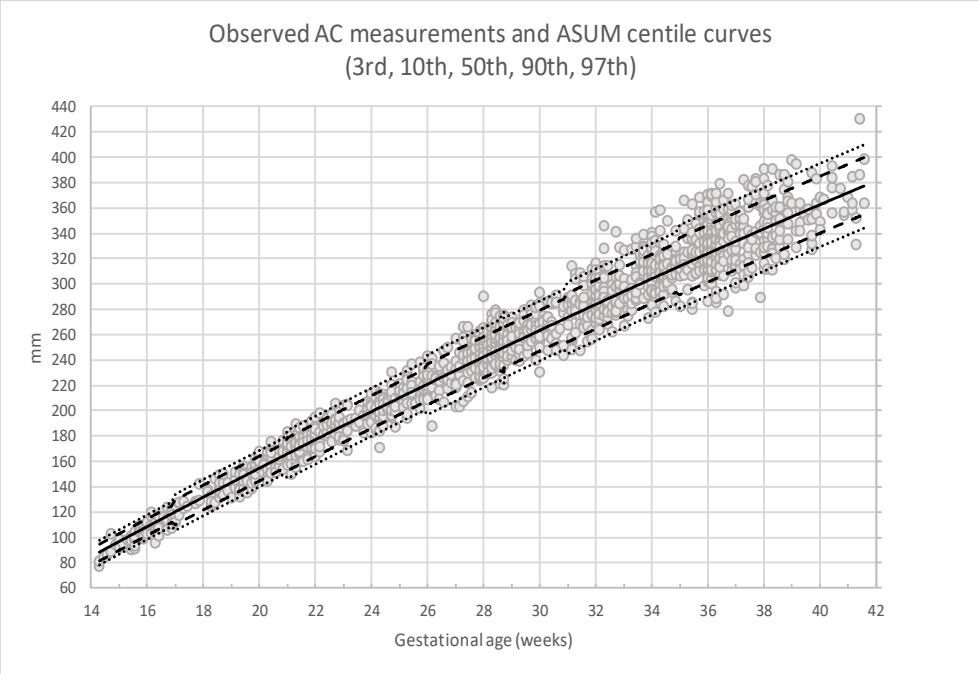

Figure 4.27 *Observed abdominal circumference measures and ASUM centile curves*

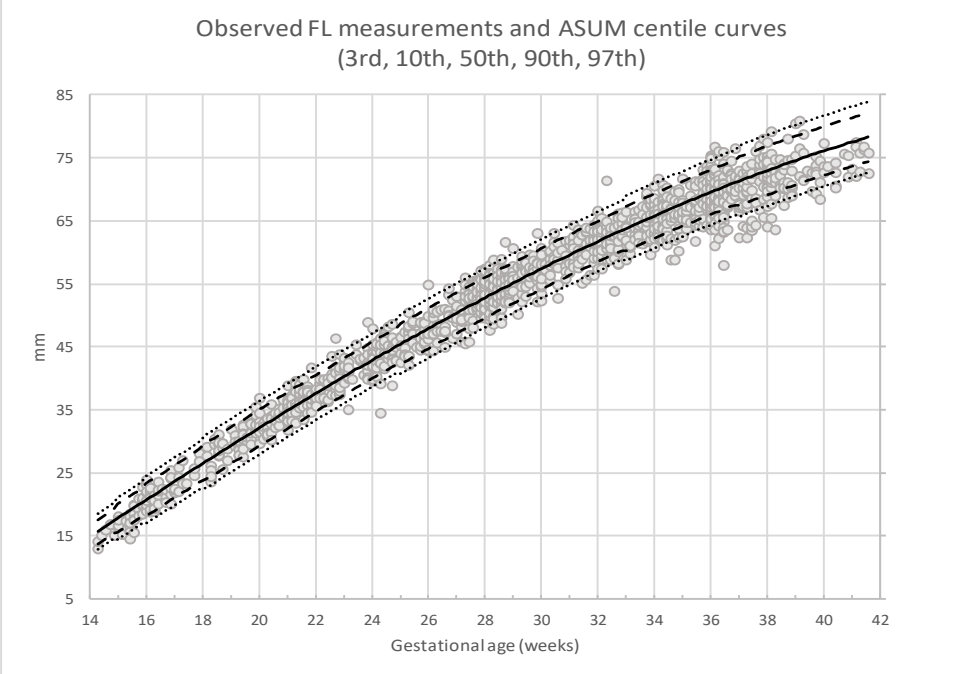

Figure 4.28 *Observed femur length measures and ASUM centile curves*

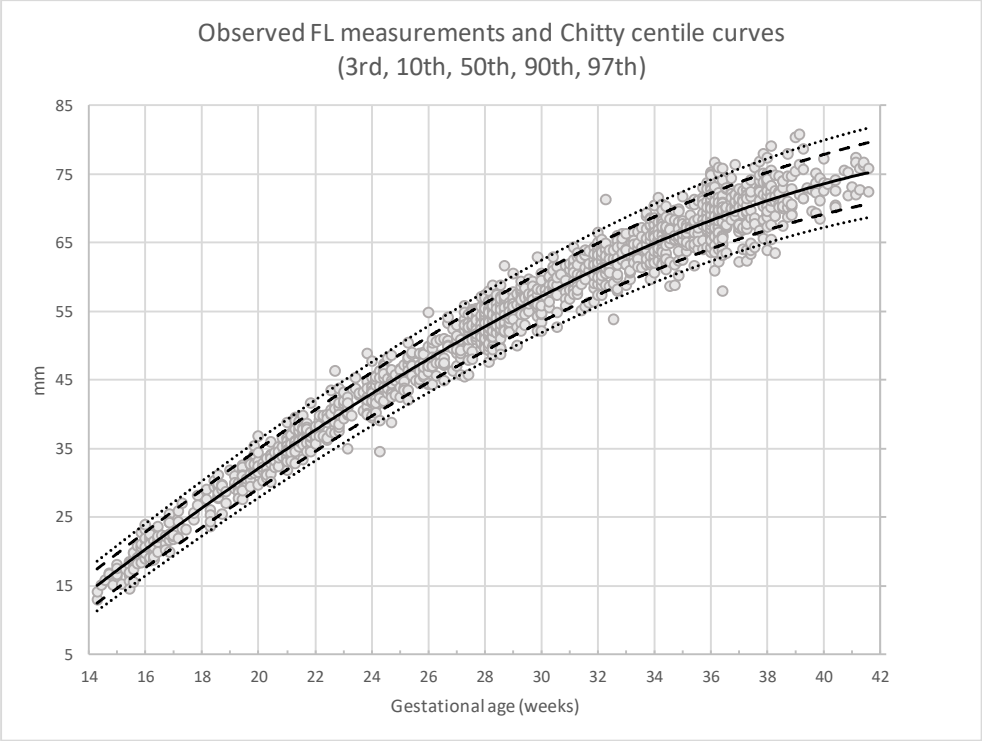

Figure 4.29 *Observed femur length measures and Chitty centile curves*

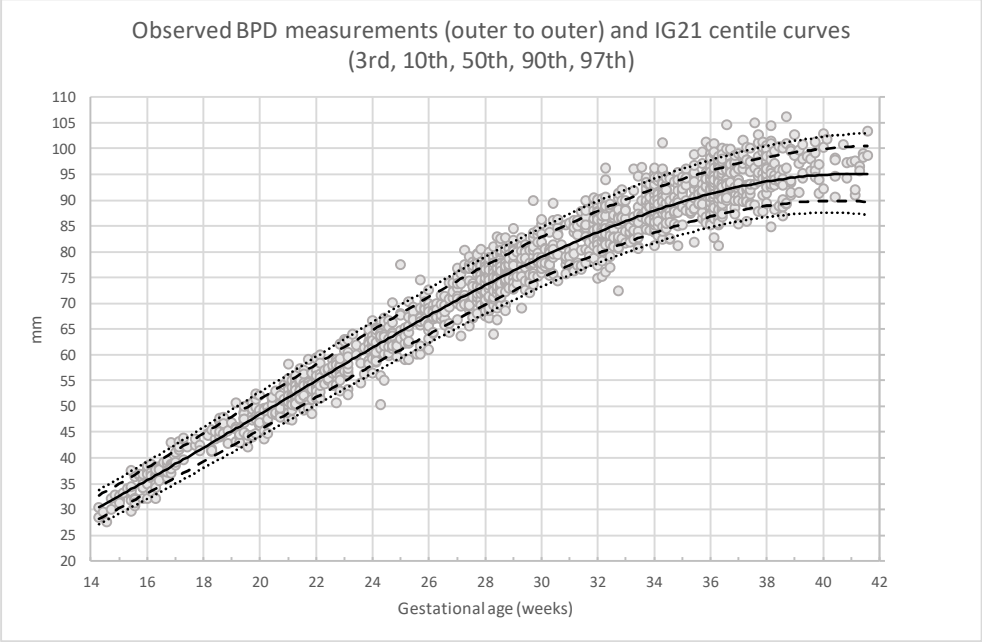

Figure 4.30 *Observed biparietal diameter measures and IG21 centile curves*

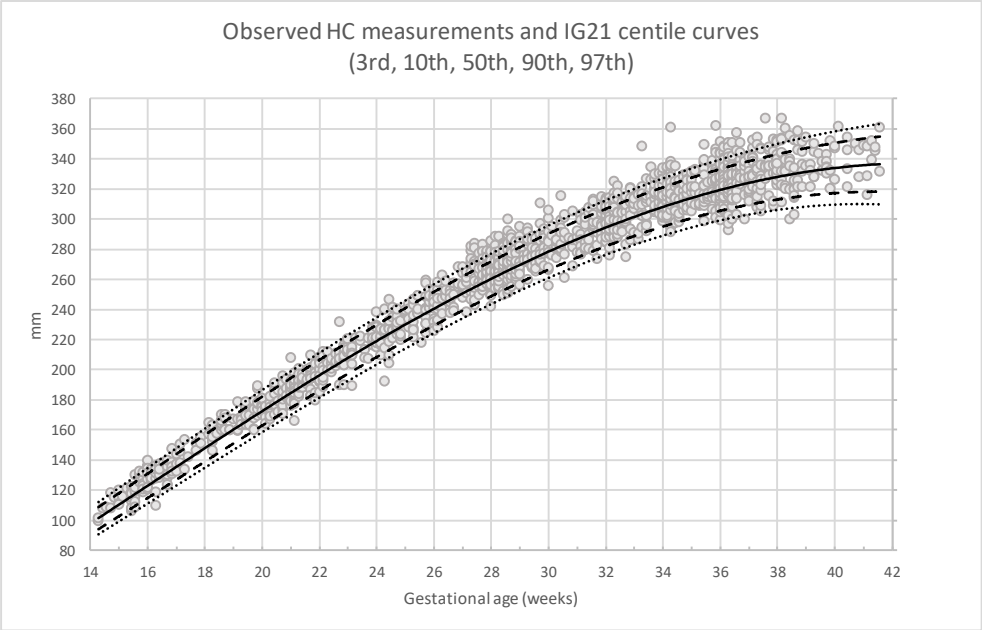

Figure 4.31 *Observed head circumference measures and IG21 centile curves*

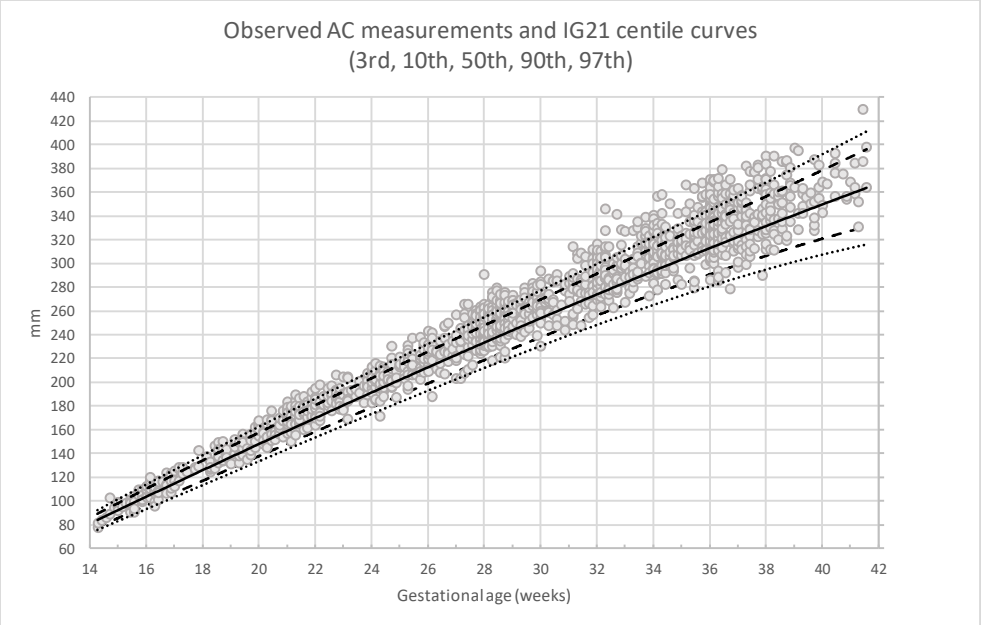

Figure 4.32 *Observed abdominal circumference measures and IG21 centile curves*

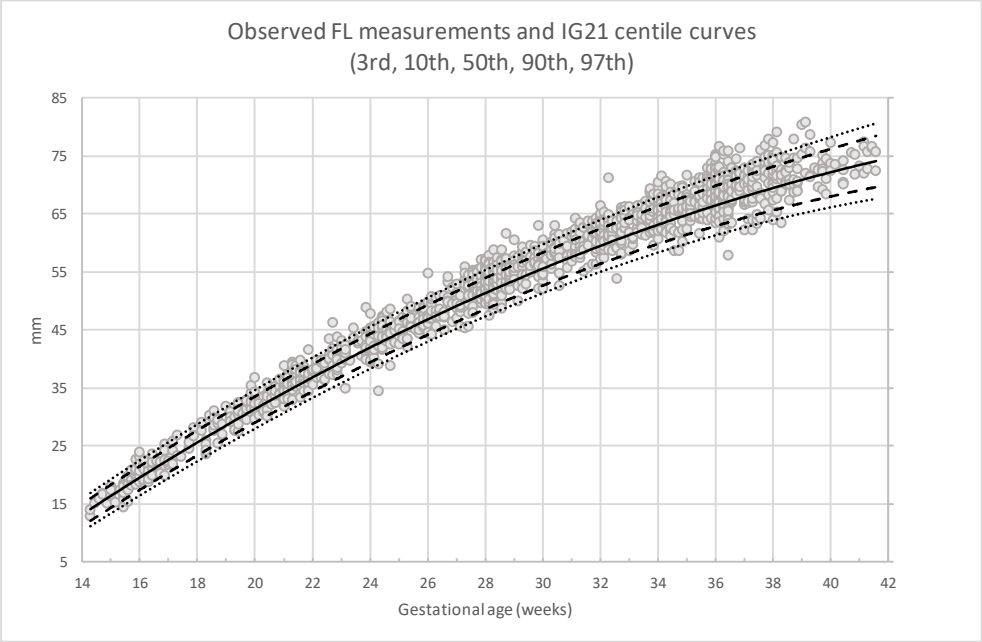

Figure 4.33 *Observed femur length measures and IG21 centile curves*

Comparison of Z score distributions

The Z-score or standard score is the number of standard deviations the raw or observed measurement is away from the mean. Z-scores should follow a non-skewed normal distribution with a mean of 0 and standard deviation 1 when observed measurements are consistent with the reference population used to construct the biometry chart. Z-scores may be used to assess the suitability of a reference chart, and using methods described in 2005 by Salomon et al[29] the average measurement for each observation was transformed into Z-scores calculated by:

$$Z = \frac{observed\ measurement - mean\ measurement\ for\ gestational\ age}{SD} \qquad 4.2$$

where Z = standard score, SD = standard deviation

Means and standard deviations according to current charts were calculated from published equations. Data were analysed using IBM SPSS (IBM SPSS Statistics for Windows, Version 30; IBM Corp., Armonk, NY, USA). Histograms were produced as a visual representation of the Z-score distribution. Means and standard deviations of the Z-scores were calculated and the distribution of Z-scores was assessed for skewness, kurtosis, and normality. Z-score means close to 0 and SD close to 1 indicate the chart is a good fit for the observed data. Normality was tested using a continuous Kolmogorov-Smirnov one sample test. Non-normality is indicated by a p value < 0.05. The D statistic describes the magnitude of difference between distributions and ideally should be small. Skewness measures the symmetry of the distribution and for normally distributed data this value is close to zero. Positive values indicate more values lie to the left of the mean and negative values indicate more values lie to the right of the mean. Kurtosis is a measure of the peakedness of the distribution curve. When calculated in SPSS (IBM SPSS Statistics for Windows, Version 30; IBM Corp., Armonk, NY, USA) the value represents the excess kurtosis and should ideally be zero for a normal distribution. A positive kurtosis indicates a distribution curve with a high peak, or leptokurtic, and a negative kurtosis indicates a flattened peak, or platykurtic.

Biparietal diameter

Statistics are summarised in tables 4.13 and 4.14 and histograms of the BPD Z-scores are shown in figure 4.34. BPD measurements were performed according to the methodology published with the reference chart, namely, from the outer edge of the nearest parietal bone to the inner edge of the farthest for comparison to ASUM charts and outer edges of the parietal bones for comparison to IG21 charts. Z-scores were considered normally distributed as assessed by normality tests and/or a normal histogram. Distributions at specific gestations (20 – 22 weeks, 27 – 29 weeks, and 35 – 37 weeks) were evaluated for gestation dependent variability. The IG21 Z-scores at 20 – 22 weeks high kurtosis indicated a leptokurtic curve. Means of Z-score values were statistically different from 0 as assessed by Student's t-test ($p < 0.05$).

Histograms are presented with the expected normal distribution curve (centred on zero) to assist visual interpretation of goodness of fit. Negative skewness is demonstrated for IG21 Z-scores in all instances and ASUM Z-scores for 27 – 29 weeks and 35 – 37 weeks.

Table 4.13 *Biparietal diameter Z-score normality statistics*

	Mean	SD	Skewness	Kurtosis	K-S D	K-S p
ASUM BPD chart (n)						
14 – 41 completed weeks *(1642)*	0.197	1.188	0.033	0.313	0.017	0.200
20 – 22 completed weeks *(170)*	-0.298	0.966	0.295	0.846	0.044	0.200
27 – 29 completed weeks *(279)*	0.540	1.175	-0.054	0.439	0.033	0.200
35 – 37 completed weeks *(328)*	0.200	1.141	-0.061	-0.175	0.027	0.200
IG21 BPD chart						
14 – 41 completed weeks *(1642)*	0.179	1.110	-0.098	0.013	0.613	0.200
20 – 22 completed weeks *(170)*	-0.151	0.998	-0.761	4.183	0.065	0.075
27 – 29 completed weeks *(279)*	0.181	1.042	-0.158	0.631	0.031	0.200
35 – 37 completed weeks *(328)*	0.383	1.096	-0.047	-0.155	0.043	0.200

SD: standard deviation, K-S: Kolmogorov-Smirnov, d: Kolmogorov-Smirnov statistic or D value, p: significance value

Table 4.14 *Biparietal diameter Z-score Student's one sample t-test statistics*

				95% Confidence interval	
	t	p	mean	lower	upper
ASUM BPD chart (n)					
14 – 41 completed weeks *(1642)*	6.711	<0.001	0.197	0.139	0.254
20 – 22 completed weeks *(170)*	-4.03	<0.001	-0.298	-0.445	-0.152
27 – 29 completed weeks *(279)*	7.680	<0.001	0.540	0.402	0.679
35 – 37 completed weeks *(328)*	3.179	<0.001	0.200	0.076	0.324
IG21 BPD chart (n)					
14 – 41 completed weeks *(1642)*	6.537	<0.001	0.179	0.125	0.233
20 – 22 completed weeks *(170)*	-1.974	0.025	-0.151	-0.302	0.000
27 – 29 completed weeks *(279)*	2.901	0.002	0.181	0.582	0.304
35 – 37 completed weeks *(328)*	6.338	<0.001	0.383	0.264	0.503

t: t-statistic, p: significance value

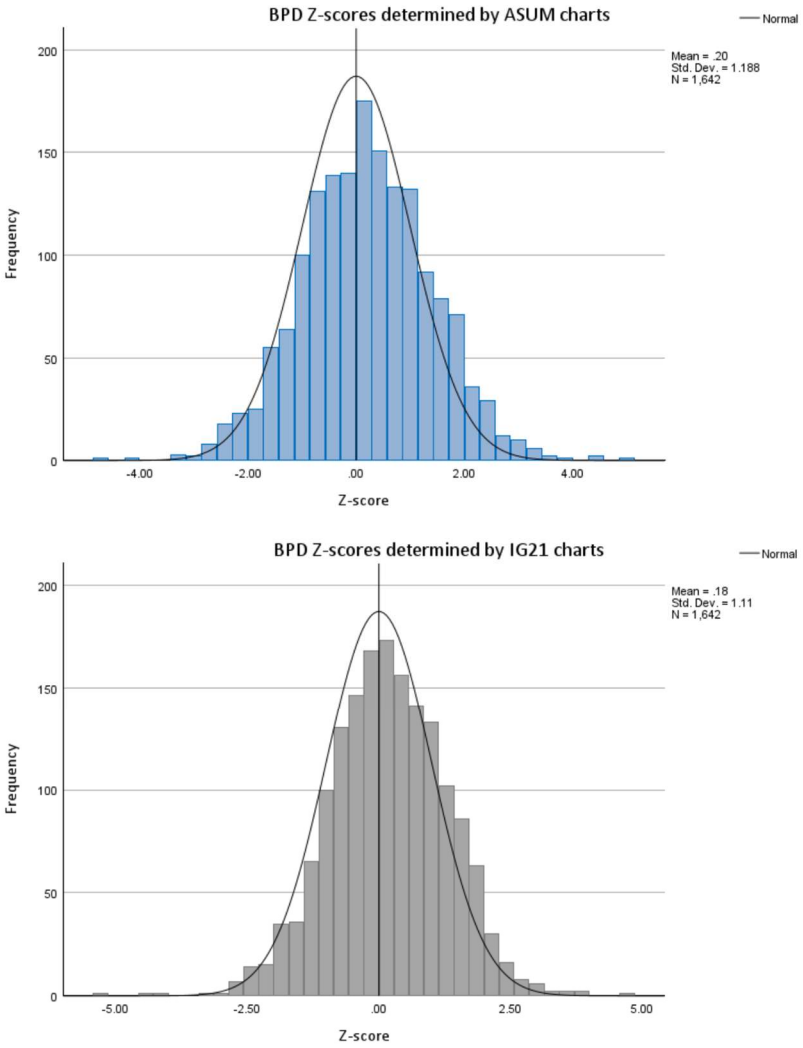

Figure 4.34 *Z-score distributions for ASUM chart (blue) and IG21 chart (grey)*

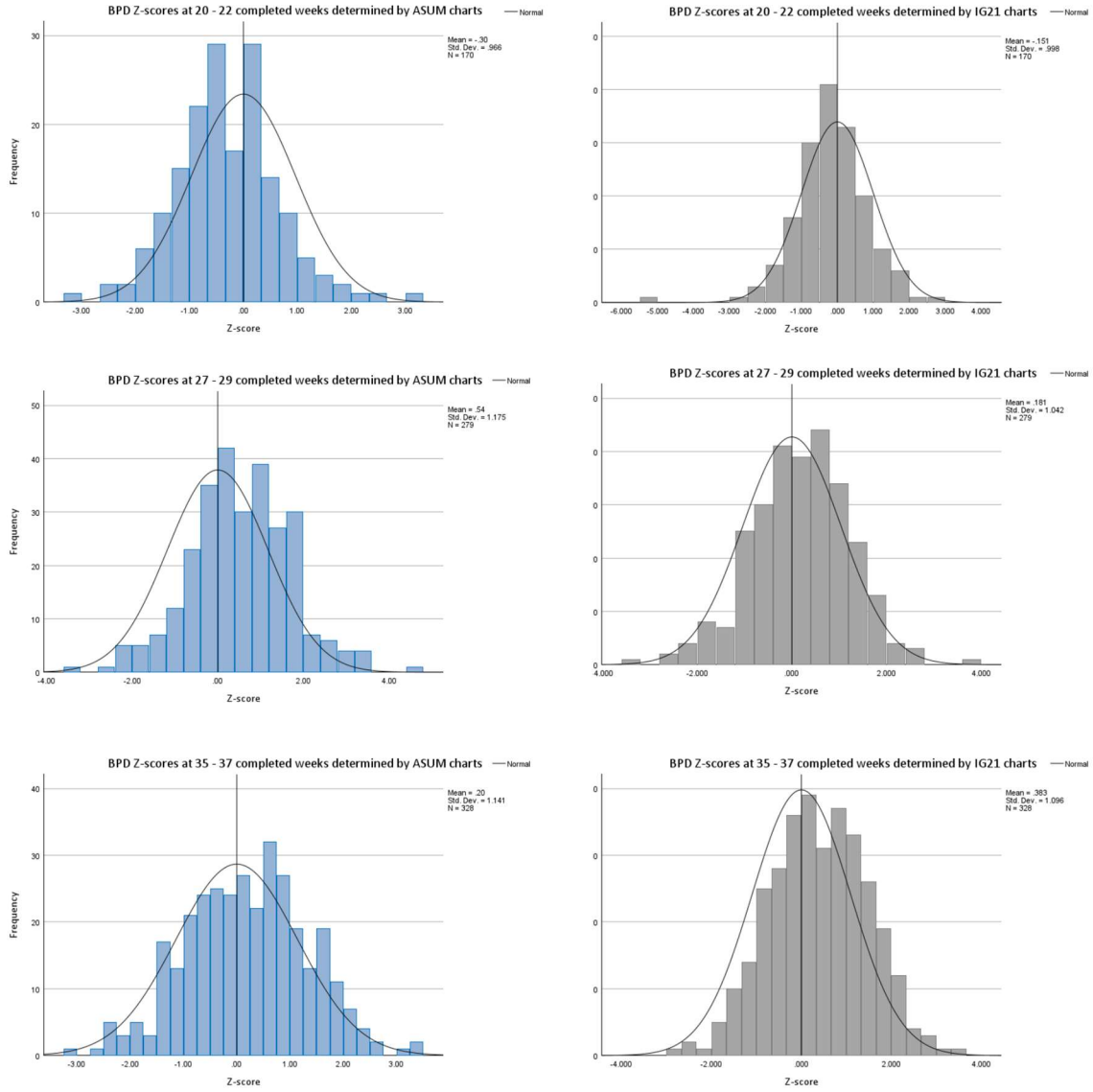

Figure 4.35 *Z-score distributions at 20 – 22 weeks, 27 – 29 weeks and 35 – 37 weeks for ASUM chart (blue) and IG21 chart (grey)*

Head circumference

Statistics are summarised in tables 4.15 and 4.16 and histograms of the HC Z-scores are shown in figures 4.36 and 4.37. Z-score distributions were assessed by normality tests and histograms, with distributions at specific gestations (20 – 22 weeks, 27 – 29 weeks, and 35 – 37 weeks) evaluated for gestation dependent variability. Normality tests indicated non-normal distribution for ASUM Z-scores (p value 0.002), ASUM Z-scores at 20 – 22 weeks (p value 0.038, and IG21 Z-scores at 20 – 22 weeks (p value 0.035). Means of Z-score values were statistically different from 0 as assessed by Student's t-test ($p < 0.05$).

Table 4.15 *Head circumference Z-score normality statistics*

	Mean	SD	Skewness	Kurtosis	K-S D	K-S p
ASUM HC chart (n)						
14 – 41 completed weeks *(1642)*	0.566	0.982	0.094	0.504	0.029	0.002
20 – 22 completed weeks *(170)*	0.107	0.690	0.084	1.461	0.071	0.038
27 – 29 completed weeks *(279)*	0.918	0.878	0.147	-0.033	0.040	0.200
35 – 37 completed weeks *(328)*	0.501	0.955	0.076	0.231	0.045	0.200
IG21 HC chart						
14 – 41 completed weeks *(1642)*	0.506	1.040	0.076	0.464	0.018	0.200
20 – 22 completed weeks *(170)*	0.233	0.880	0.047	1.355	0.071	0.035
27 – 29 completed weeks *(279)*	0.637	1.016	0.137	-0.051	0.038	0.200
35 – 37 completed weeks *(328)*	0.464	1.089	0.114	0.175	0.043	0.200

SD: standard deviation, K-S: Kolmogorov-Smirnov, d: Kolmogorov-Smirnov statistic or D value, p: significance value

Table 4.16 *Head circumference Z-score Student's one sample t-test statistics*

				95% Confidence interval	
	t	p	mean	lower	upper
ASUM HC chart (n)					
14 – 41 completed weeks *(1642)*	24.990	<0.001	0.566	0.522	0.611
20 – 22 completed weeks *(170)*	2.021	0.022	0.107	0.002	0.211
27 – 29 completed weeks *(279)*	17.463	<0.001	0.918	0.814	1.021
35 – 37 completed weeks (328)	9.514	<0.001	0.501	0.398	0.605
IG21 HC chart					
14 – 41 completed weeks *(1642)*	19.702	<0.001	0.506	0.455	0.556
20 – 22 completed weeks *(170)*	3.461	<0.001	0.233	0.100	0.367
27 – 29 completed weeks *(279)*	10.467	<0.001	0.637	0.517	0.757
35 – 37 completed weeks *(328)*	7.715	<0.001	0.464	0.346	0.582

t: t-statistic, p: significance value

Histograms are presented with the expected normal distribution curve (centred on zero) to assist visual interpretation of goodness of fit. Histograms demonstrated a normal distribution but means were not at zero (i.e. distribution shifted to the right).

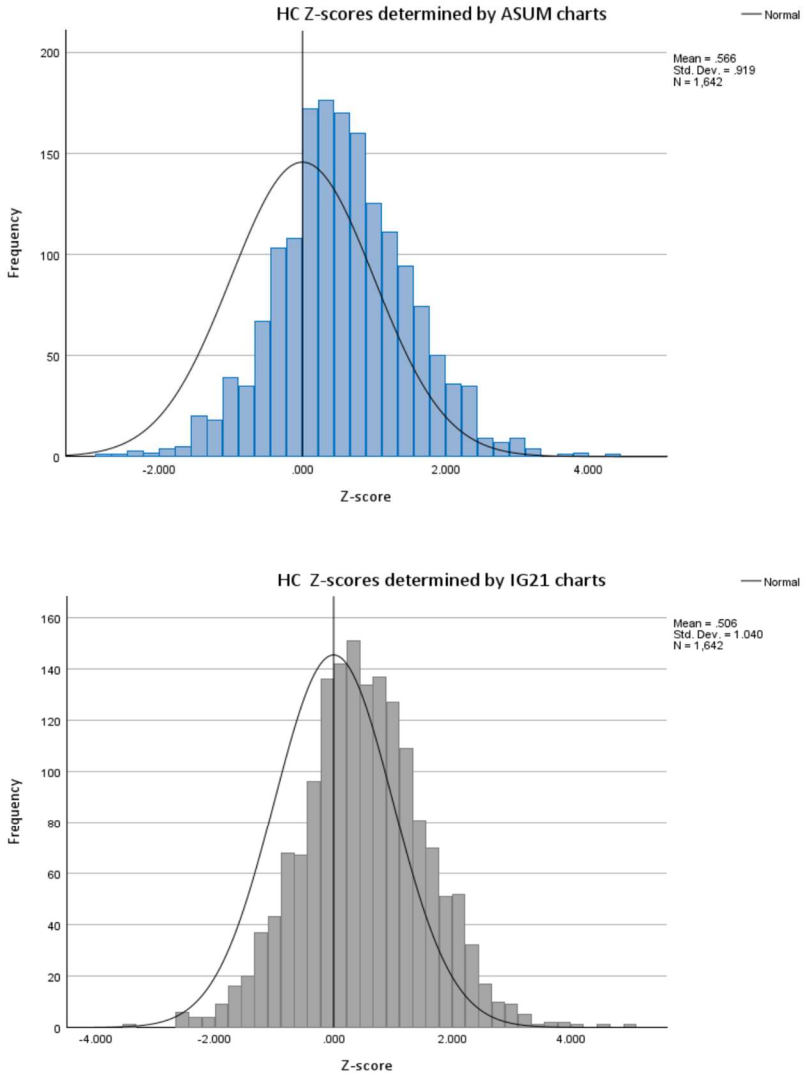

Figure 4.36 *Z-score distributions for ASUM chart (blue) and IG21 chart (grey)*

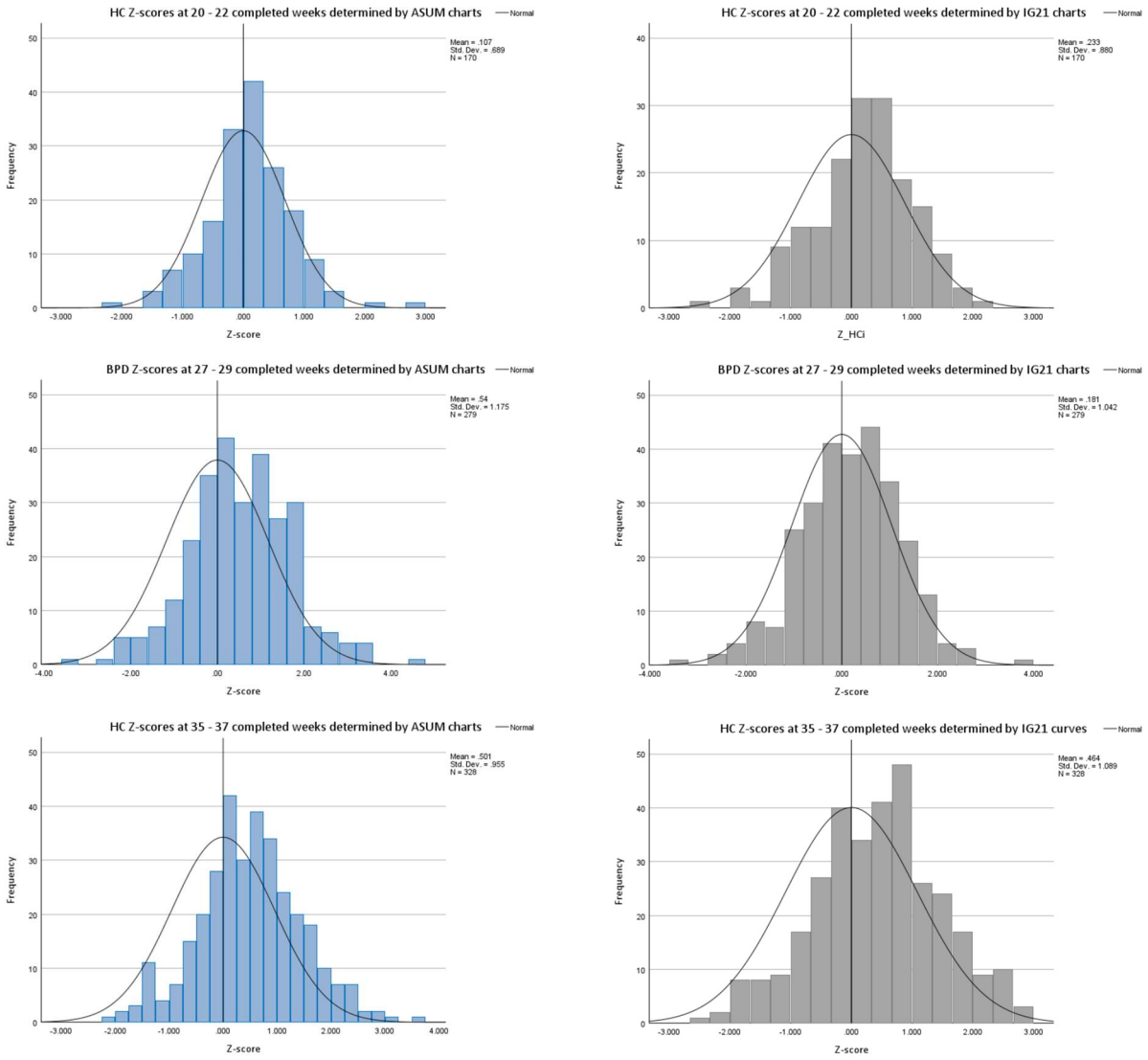

Figure 4.37 *Z-score distributions at 20 – 22 weeks, 27 – 29 weeks and 35 – 37 weeks for ASUM chart (blue) and IG21 chart (grey)*

Abdominal circumference

Statistics are summarised in tables 4.17 and 4.18 and histograms of the AC Z-scores are shown in figures 4.38 and 4.39. Z-score distributions were assessed by normality tests and histograms, with distributions at specific gestations (20 – 22 weeks, 27 – 29 weeks, and 35 – 37 weeks) evaluated for gestation dependent variability.

Normality tests indicated non-normal distribution for ASUM Z-scores at 20 – 22 weeks (p value 0.045). However, all histograms demonstrated a normal distribution but means were not at zero (i.e. distribution shifted to the right). Means of Z-score values were statistically different from 0 as assessed by Student's t-test ($p < 0.05$).

Table 4.17*Abdominal circumference Z-score normality statistics*

	Mean	SD	Skewness	Kurtosis	K-S D	K-S p
ASUM AC chart						
14 – 41 completed weeks *(1642)*	0.194	1.052	0.026	0.246	0.18	0.200
20 – 22 completed weeks *(170)*	0.256	0.839	-0.161	-0.369	0.069	0.045
27 – 29 completed weeks *(279)*	0.313	0.949	-0.180	1.384	0.044	0.200
35 – 37 completed weeks *(328)*	0.320	1.147	-0.046	0.069	0.040	0.200
IG21 AC chart						
14 – 41 completed weeks *(1642)*	0.943	1.070	0.028	0.182	0.017	0.200
20 – 22 completed weeks *(170)*	1.159	0.940	-0.128	-0.402	0.065	0.098
27 – 29 completed weeks *(279)*	1.101	1.022	-0.118	1.275	0.046	0.200
35 – 37 completed weeks *(328)*	0.941	1.114	-0.039	0.016	0.041	0.200

SD: standard deviation, K-S: Kolmogorov-Smirnov, d: Kolmogorov-Smirnov statistic or D value, p: significance value

Table 4.18 *Abdominal circumference Z-score Student's one sample t-test statistics*

				95% Confidence interval	
	t	p	mean	lower	upper
ASUM chart *(n)*					
14 – 41 completed weeks *(1642)*	7.487	<0.001	0.194	0.144	0.245
20 – 22 completed weeks *(170)*	3.985	<0.001	0.256	0.129	0.384
27 – 29 completed weeks *(279)*	5.515	<0.001	0.313	0.202	0.425
35 – 37 completed weeks *(328)*	5.056	<0.001	0.320	0.195	0.445
IG21 AC chart					
14 – 41 completed weeks *(1642)*	19.702	<0.001	0.943	0.892	0.995
20 – 22 completed weeks *(170)*	16.007	<0.001	1.158	1.016	1.300
27 – 29 completed weeks *(279)*	17.996	<0.001	1.101	0.981	1.221
35 – 37 completed weeks *(328)*	15.296	<0.001	0.941	0.820	1.061

t: t-statistic, p: significance value, CI: confidence interval

Histograms are presented with the expected normal distribution curve (centred on zero) to assist visual interpretation of goodness of fit.

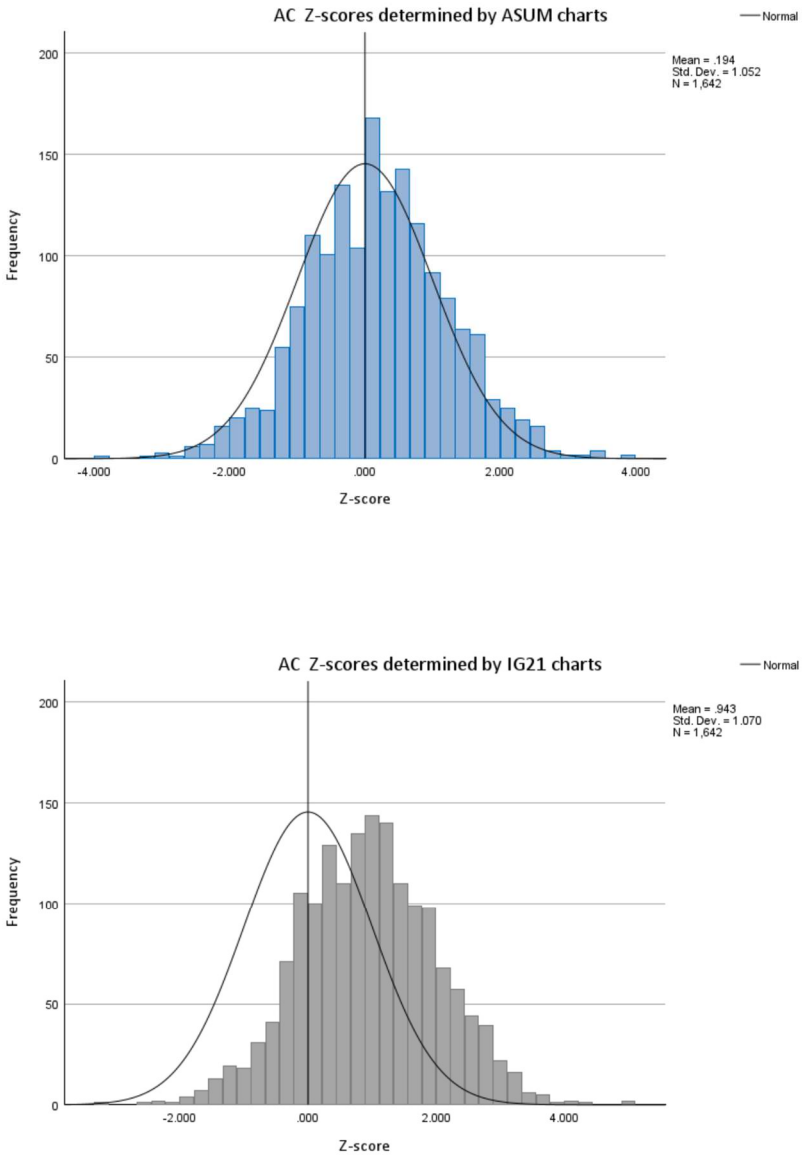

Figure 4.38 *Z-score distributions for ASUM chart (blue) and IG21 chart (grey)*

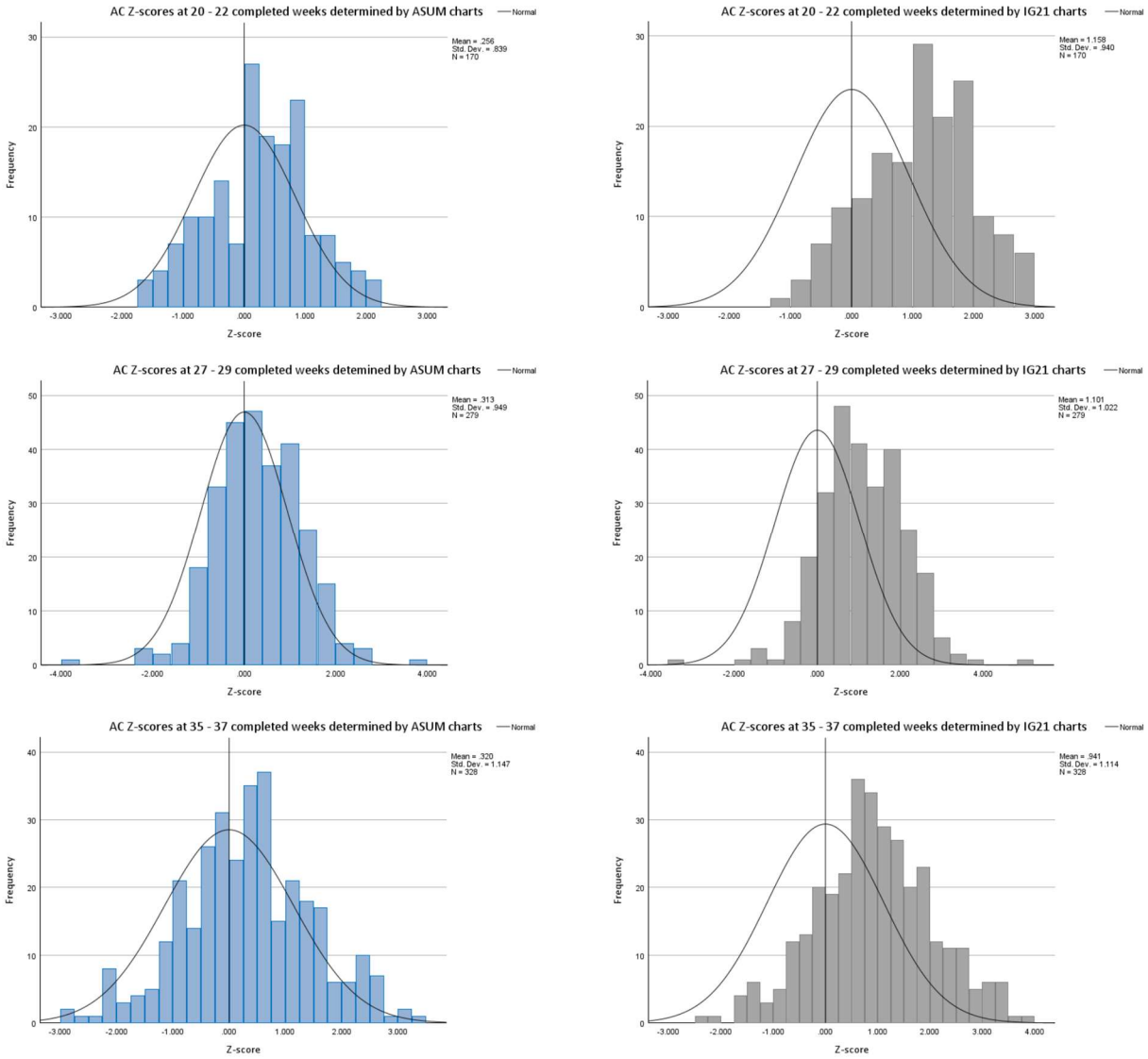

Figure 4.39 *Z-score distributions at 20 – 22 weeks, 27 – 29 weeks and 35 – 37 weeks for ASUM chart (blue) and IG21 chart (grey)*

Femur Length

Statistics are summarised in tables 4.19 and 4.20 and histograms of the FL Z-scores are shown in figures 4.40 and 4.41. Z-score distributions were assessed by normality tests and histograms, with distributions at specific gestations (20 – 22 weeks, 27 – 29 weeks, and 35 – 37 weeks) evaluated for gestation dependent variability. Normality tests indicated non-normal distribution for ASUM Z-scores (p value 0.005), however, the histogram demonstrated a normal distribution. Normality tests indicated normal distribution for all other Z-scores. For ASUM Z-scores at 27 – 29 weeks, high kurtosis indicated a leptokurtic curve. Means of Z-score values were not statistically different from 0 as assessed by Student's t-test ($p > 0.05$) for ASUM Z-scores at 20 – 22 weeks and 27 – 29 weeks and Chitty Z-scores. Means of Z-score values were statistically different from 0 as assessed by Student's t-test ($p < 0.05$) for IG21 Z-scores.

Table 4.19*Femur length Z-score normality statistics*

		mean	SD	Skewness	Kurtosis	K-S D	K-S p
ASUM FL chart	*(n)*						
14 – 41 completed weeks	*(1642)*	-0.173	0.957	-0.273	1.090	0.028	0.005
20 – 22 completed weeks	*(170)*	0.063	0.751	0.686	1.074	0.052	0.200
27 – 29 completed weeks	*(279)*	0.012	0.884	-0.607	4.170	0.043	0.200
35 – 37 completed weeks	*(328)*	-0.409	1.073	-0.192	0.417	0.034	0.200
Chitty FL chart							
14 – 41 completed weeks	*(1642)*	0.049	0.842	-0.124	0.883	0.018	0.200
20 – 22 completed weeks	*(170)*	0.053	0.728	0.660	0.953	0.049	0.200
27 – 29 completed weeks	*(279)*	0.058	0.797	-0.346	2.371	0.037	0.200
35 – 37 completed weeks	*(328)*	0.088	0.946	-0.202	0.307	0.031	0.200
IG21 FL chart							
14 – 41 completed weeks	*(1642)*	0.674	1.030	-0.106	0.761	0.016	0.200
20 – 22 completed weeks	*(170)*	0.527	0.921	0.668	0.990	0.51	0.200
27 – 29 completed weeks	*(279)*	0.758	1.003	-0.279	1.957	0.035	0.200
35 – 37 completed weeks	(328)	0.746	1.089	-0.200	0.361	0.031	0.200

SD: standard deviation, K-S: Kolmogorov-Smirnov, d: Kolmogorov-Smirnov statistic or D value, p: significance value

Table 4.20 *Femur length Z-score Student's one sample t-test statistics*

					95% Confidence interval	
		t	p	mean	lower	upper
ASUM FL chart	*(n)*					
14 – 41 completed weeks	*(1642)*	-7.323	<0.001	-0.173	-0.219	-0.127
20 – 22 completed weeks	*(170)*	1.085	0.140	0.063	-0.051	0.176
27 – 29 completed weeks	*(279)*	0.226	0.411	0.012	-0.092	0.116
35 – 37 completed weeks	*(328)*	-6.905	<0.001	-0.409	-0.526	-0.293
Chitty FL chart						
14 – 41 completed weeks	*(1642)*	2.349	0.019	0.488	0.008	0.090
20 – 22 completed weeks	*(170)*	0.953	0.171	0.053	-0.057	0.164
27 – 29 completed weeks	*(279)*	1.221	0.112	0.058	-0.036	0.152
35 – 37 completed weeks	*(328)*	1.682	0.047	0.088	-0.015	0.191
IG21 FL chart						
14 – 41 completed weeks	*(1642)*	26.526	<0.001	0.674	0.625	0.724
20 – 22 completed weeks	*(170)*	7.466	<0.001	0.527	0.388	0.667
27 – 29 completed weeks	*(279)*	12.625	<0.001	0.758	0.640	0.877
35 – 37 completed weeks	*(328)*	12.412	<0.001	0.746	0.628	0.865

t: t-statistic, p: significance value

Histograms are presented with the expected normal distribution curve (centred on zero).

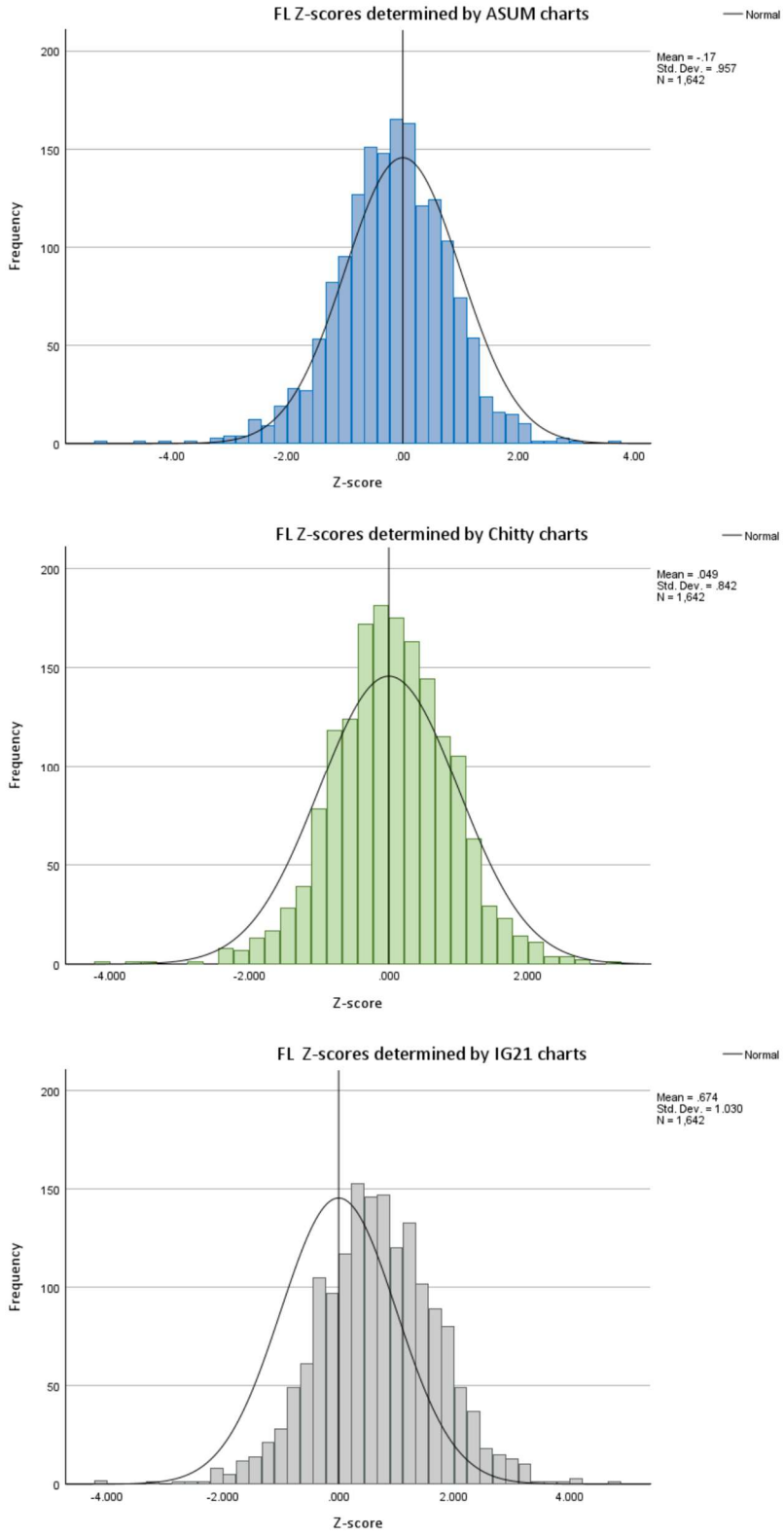

Figure 4.40 *Z-score distributions for ASUM chart (blue), Chitty chart (green) and IG21 chart (grey)*

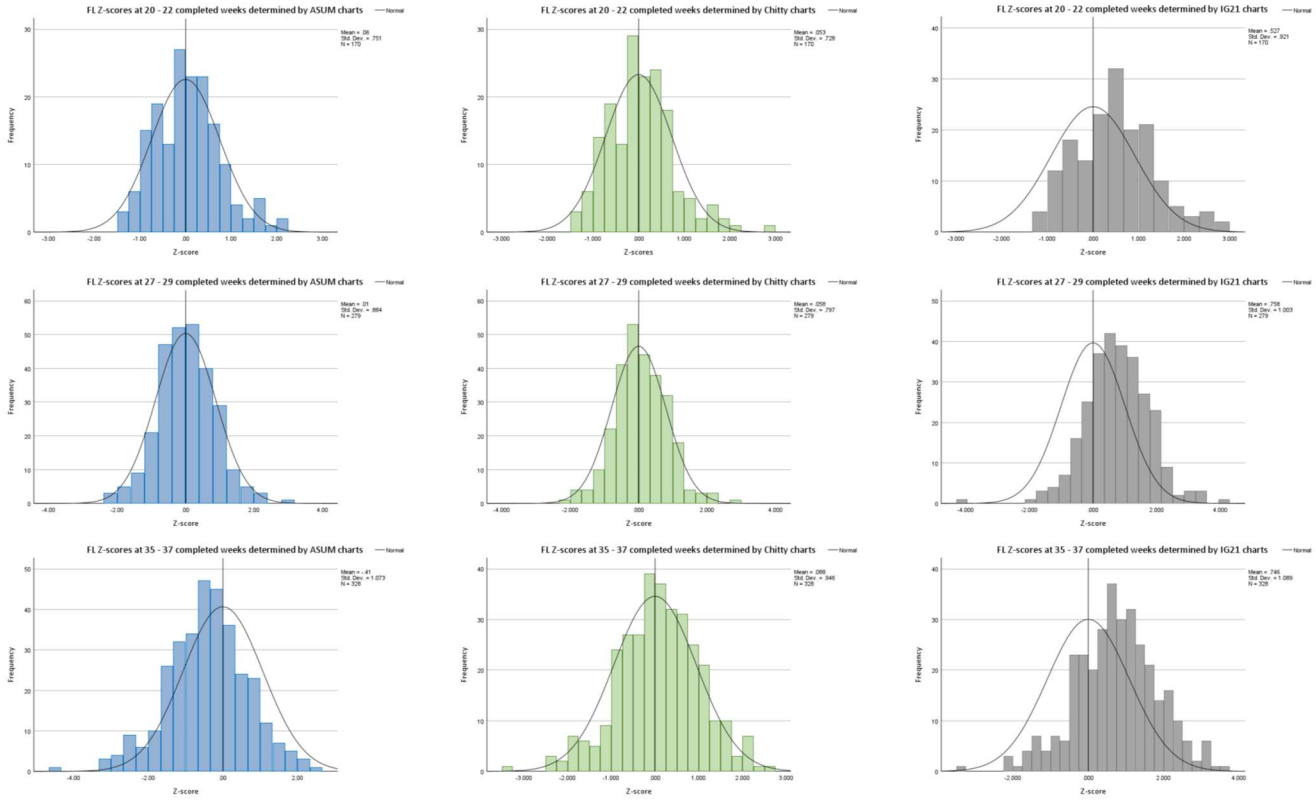

Figure 4.41 *Z-score distributions at 20 – 22 weeks, 27 – 29 weeks and 35 – 37 weeks for ASUM chart (blue), Chitty chart (green) and IG21 chart (grey)*

Assessment of proportion of observations falling above or below fixed centiles

Observed measurement data was assessed to determine the proportion of measurements for each parameter that were below the 3rd and 10th centile and above the 90th and 97th centile as determined by ASUM charts, Chitty FL chart and IG21 charts. Means and standard deviations according to current charts were calculated from published equations. Data were analysed using IBM SPSS (IBM SPSS Statistics for Windows, Version 30; IBM Corp., Armonk, NY, USA) and Excel (Microsoft Corporation, Microsoft Excel 2016). The 3rd centile was defined as a Z-score of -1.88, the 10th centile was defined as a Z-score of -1.29, the 90th centile was defined as a Z-score of 1.29 and the 97th centile was defined as a Z-score of 1.881. The proportion of observations falling below and above these thresholds are presented in table 4.22 – 4.26 for all observations and at 20 – 22 weeks gestation, 27 – 20 weeks gestation, and 35 – 37 weeks gestation, to assess the possible impact of gestation on the distributions.

All measurements were performed according to the methodology published with the reference chart. BPD measurements were performed from the outer edge of the nearest parietal bone to the inner edge of the farthest for comparison to ASUM charts[172] and outer edges of the parietal bones for comparison to IG21 charts[38].

Presenting data in this format allows comparison of the number of observations below or above given centile thresholds and the expected proportions, i.e. 3% of the measurements in the study population would be expected to be below the 3rd centile and above the 97th centile, and 10% would be expected to be below the 10th centile and above the 90th.

Biparietal diameter

As demonstrated in table 4.21, the proportion of all observations below the 3rd centile according to ASUM and IG21 charts is similar, and close to the expected 3%. Observations at 35 – 37 weeks show minor deviation for IG21 centiles with 1.5% below the 3rd centile. Higher proportions for all observations were

shown above the 90th and 97th centile for both charts. This was also apparent for observations between 27 – 29 weeks and 35 – 37 weeks, however, this trend was not observed at 20 – 22 weeks.

Table 4.21 *Proportion (%) of BPD observations falling above or below fixed centiles*

Reference centile	14 – 42w (n=1642)		20 - 22w (n=170)		27 - 29w (n=279)		35 - 37w (n=328)	
	Chart		Chart		Chart		Chart	
	ASUM	IG21	ASUM	IG21	ASUM	IG21	ASUM	IG21
Proportion < 3rd	4.08	3.05	4.71	3.53	3.94	4.30	3.66	1.52
Proportion < 10th	10.05	7.98	14.12	8.24	7.89	8.96	10.06	6.10
Proportion > 90th	17.78	16.20	5.29	6.47	34.41	22.22	17.38	1.52
Proportion > 97th	7.31	5.79	2.35	1.18	17.92	7.53	5.79	7.93

Head circumference

The proportion of observations below and above given centile thresholds (table 4.22) reflect the right shift demonstrated in the z-score histograms. In general, higher proportions than expected fell above the 90th and 97th centile, however, this trend was not observed at 20 – 22 weeks. At this gestational age range, the IG21 charts demonstrated 8.8% above the 90th centile and 2.4% above the 97th and ASUM charts 2.9% above the 90th centile and 1.2% above the 97th centile.

Table 4.22 *Proportion (%) of HC observations falling above or below fixed centiles*

Reference centile	14 – 42w (n=1642)		20 - 22w (n=170)		27 - 29w (n=279)		35 - 37w (n=328)	
	Chart		Chart		Chart		Chart	
	ASUM	IG21	ASUM	IG21	ASUM	IG21	ASUM	IG21
Proportion < 3rd	0.49	1.22	0.59	1.76	0.00	0.36	0.30	1.22
Proportion < 10th	2.44	4.14	2.35	4.12	0.36	3.58	4.57	6.10
Proportion > 90th	21.19	21.56	2.94	8.82	46.24	36.56	19.82	21.04
Proportion > 97th	7.73	9.26	1.18	2.35	19.35	16.49	7.62	9.45

Abdominal circumference

The proportion of observations below and above given centile thresholds (table 4.23) for IG21 charts reflect the right shift demonstrated in the z-score histograms. Proportions for ASUM charts are close to expected overall, with increasing proportions above the 90th centile observed at 27 – 29 weeks and 35 – 17 weeks, and 97th centile at 35 – 37 weeks.

Table 4.23 *Proportion (%) of AC observations falling above or below fixed centiles*

Reference centile	14 – 42w (n=1642)		20 - 22w (n=170)		27 - 29w (n=279)		35 - 37w (n=328)	
	Chart		Chart		Chart		Chart	
	ASUM	IG21	ASUM	IG21	ASUM	IG21	ASUM	IG21
Proportion < 3rd	2.56	0.49	0.00	0.00	3.23	0.72	3.66	0.61
Proportion < 10th	6.76	2.07	3.53	0.00	5.02	3.58	7.01	3.35
Proportion > 90th	15.04	36.24	10.00	46.47	19.71	55.91	19.82	34.76
Proportion > 97th	5.24	19.00	2.35	21.18	3.94	31.90	9.45	18.90

Femur length

The proportion of observations below and above given centile thresholds (table 4.24) for IG21 charts reflect the right shift demonstrated in the z-score histograms. Proportions for ASUM charts are close to expected overall, but demonstrate higher proportions below the 3rd centile and 10th centile at 35 – 37 weeks. Proportions for Chitty charts overall are less than expected for observations below the 3rd and 10th centile thresholds, and less than expected above the 90th and 97th centile.

Table 4.24 *Proportion (%) of FL observations falling above or below fixed centiles*

Reference centile	14 – 42w (n=1642)			20 - 22w (n=170)			27 - 29w (n=279)			35 - 37w (n=328)		
	Chart			Chart			Chart			Chart		
	ASUM	Chitty	IG21	ASUM	Chitty	IG21	ASUM	Chitty	IG21	ASUM	Chitty	IG21
Proportion < 3rd	4.32	1.64	0.91	0.00	0.00	0.00	3.23	2.51	1.08	8.54	2.74	1.22
Proportion < 10th	10.90	5.24	2.92	1.76	1.18	0.59	7.17	5.73	3.94	19.21	7.01	4.57
Proportion > 90th	4.87	5.79	26.67	5.88	5.88	17.06	6.81	6.09	36.56	5.49	8.54	29.57
Proportion > 97th	1.71	1.52	11.75	2.35	1.76	7.65	2.51	1.43	16.49	2.44	2.74	15.24

4.5 Discussion

The aim of this research was to assess whether the IG21 growth standards were suitable to assess fetal biometry in Australian clinical practice. The distribution of observations from this study were compared to the currently recommended population charts and the IG21 charts to determine which reference best suited the study population. The findings indicate that adoption of the IG21 charts would result in over-diagnosis of LGA, and that cases of growth restriction may go unrecognised.

Data distribution was similar for IG21 and ASUM BPD charts, however, IG21 did not demonstrate a substantial improvement over ASUM to warrant changing measurement technique and adopting the IG21 chart. Furthermore, in clinical practice, outlying BPD measurements often reflect variation in head shape, and in most cases the HC measurement will be in an acceptable range. Similarly, the IG21 HC chart did not demonstrate improvement over the ASUM chart as distributions for both charts were similar (both with right shifted distributions).

The IG21 AC chart demonstrated substantial right shifted distributions as evidenced by high proportions of AC measurements that fell above the 90th centile. Overall (i.e. 14 – 42 weeks) this was 36%, but was almost 56% for measurements collected at 27 – 29 weeks. At the other end of the scale, the proportion of measurements that fell below the 10th centile was 2% overall, and ranged from 0 at 20 – 22 weeks to 3.6% at 27 – 29%. The proportion of measurements that fell below the 3rd centile was just 0.5% overall. In terms of assessing fetal growth, the AC has more clinical impact than other parameters, as measurements at thresholds below the 3rd centile are used to define fetal growth restriction and measurements below the 10th centile are used to define small for gestational age. Measurements above the 90th and 97th centiles are used to define large for gestational age and macrosomia. The distribution according to the IG21 chart would result in a higher proportion of fetuses being classified as large for gestational age or macrosomic, with the clinical consequence of affecting timing and method of birth. Lower proportions below the 3rd and 10th centile have the potential to underdiagnose fetal growth

restriction and small for gestational age. It has been suggested that the 3rd, 10th, 90th and 97th thresholds determined by measurement standards, may not necessarily confer the same interpretation as when these thresholds are applied to population charts[110].

The IG21 FL chart also demonstrated substantial right shifted distributions. While shorter FL measurements are observed in fetuses with suboptimal growth, fetal anomalies such as skeletal dysplasia may also be responsible[34]. Using IG21 FL charts may result in under-diagnosis of skeletal dysplasia in the Australian population. Data distribution for ASUM and Chitty FL charts was similar, although higher proportions were observed below the 3rd centile and 10th centile for ASUM charts at 35 – 37 weeks. This has the potential to over-call the suspected diagnosis of skeletal dysplasia and result in unnecessary additional testing.

Fetal FL is measured across the ultrasound beam, with lateral resolution being influenced by beam width. Modern ultrasound equipment has improved image quality due to narrow beam widths, and this has been shown to reduce FL measurements by approximately 1mm when compared to older ultrasound equipment. The implication is that charts created with older equipment (between 1987 and 1992) will result in left shifted distributions when applied to measurements collected with modern equipment[209, 248].

The right shift in Z-score distributions for the AC and FL suggests the possibility that the cohort of fetuses measured in this research are larger than those in the IG21 cohort. A recent systematic review reported term birthweights have increased globally since 1950[249]. In an analysis of birthweights in NSW 1990 – 2005, an increasing trend in the proportion of LGA birthweights was reported[250]. Authors attributed this in part to increasing rates of gestational diabetes, and other studies have reported an association with maternal obesity and high birthweights[251, 252]. The average term birthweight recorded in this research was 3371g, 2.3% heavier than the term birthweight 3300g reported for the IG21 cohort[38]. Future research

examining the relationship between the trend in increasing birthweight and fetal measurements may prove insightful.

Methods for pregnancy dating are also a consideration when comparing observed measurements to different charts. There is the potential for gestational age to be overestimated when pregnancies are dated from the last menstrual period (LMP) due to inconsistencies in cycle length and poor recall of LMP dates[91, 92]. Charts dating pregnancies from LMP could therefore result in smaller than expected measurements for a given gestation[253]. For the IG21 charts, pregnancies were dated by LMP confirmed by ultrasound measurement of crown rump length (CRL) between 9 and 14 weeks. If the gestational age estimated by CRL had a discrepancy greater than 7 days from the dates based on LMP, the participant was excluded from the study[153]. For ASUM[172] and Chitty[152] charts, gestational age was determined by known LMP dates. In this research, gestational age was determined by ultrasound performed between 8 – 14 weeks or by embryo transfer dates for assisted conceptions. This raises the possibility that the dating methods used in this research, namely, ultrasound measurement of crown-rump-length between 8 and 14 weeks or embryo transfer date and embryo age for assisted conceptions, may have contributed to the right shift in distributions.

Several maternal characteristics have been associated with altered fetal growth, including smoking and hypertension with small for gestational age fetuses[13], and maternal diabetes and obesity with large for gestational age fetuses[7, 8]. The Intergrowth project aimed to select a very healthy study population and strict inclusion criteria were employed at enrolment. Maternal characteristics included age between 18 and 35 years, BMI between 18.5 and 30 kg/m2, height above 153 cm, natural conception, known LMP confirmed by early ultrasound, no pre-existing medical conditions requiring long-term medication, and normal blood pressure. Participants were excluded if obstetric history included more than one miscarriage in the two previous consecutive pregnancies, previous pre-term birth, growth restriction or macrosomia, fetal or neonatal death, congenital malformation, and maternal pre-eclampsia. Other exclusion criteria

included exposures such as tobacco, recreational drugs, more than 5 units of alcohol per week, occupational chemicals or toxic substances, and physically demanding activities. Additionally, participants were screened for socio-economic restraint that may impede fetal growth. Environmental factors were also considered in the selection of participating sites with an altitude <1600m and absence of known contaminants[153]. This strict exclusion criteria was not applied to this research making the potential impacts of these exposures in the study population difficult to assess.

Differences between maternal characteristics of the study cohort and the IG21 cohort are summarised in table 4.25. In this research, on average, participants were older, taller, and heavier, and therefore reflective of a typical clinical population (not an 'ideal' population as in the IG21 cohort). Nonetheless, these maternal characteristics may have contributed in part to the larger AC measurements observed in the study cohort. Sub-analysis of data from research participants meeting the IG21 inclusion criteria could potentially demonstrate measurement distributions in keeping with those of the IG21 charts, and may be an area of future research.

Table 4.25 *Comparison of reported maternal characteristics*

Maternal characteristics	IG21 cohort[38]	This study
Age	28.4	32
Height	162.2	164.8
BMI	23.3	27.4
Underweight (BMI<18.5)	0	2.1%
Overweight (BMI 25 – 29.9)	-	28.3%
Obese (BMI > 30)	0	29.2%
Pre-existing diabetes and insulin requiring gestational diabetes	0	15.6%
Gestational diabetes (diet and exercise control)	0	4.3%
Smoker	0	3%
Previous pre-eclampsia	0	4%
Pre-existing hypertension	0	5.4%
IVF conception	0	2.7%

BMI: body mass index, IVF: in-vitro fertilisation

The right shift in Z score distributions observed for ASUM AC charts at 27 – 29 weeks and 35 – 37 weeks is an interesting observation. Data were collected for these charts are now more than 25 years ago, indicating improved ultrasound equipment, changing maternal demographics, increasing birthweights, and accurate pregnancy dating method may each have a contributory role.

Comparison to other studies

A cross-sectional prospective study conducted in France concluded fetal size in France was similar to that of the population used to construct the IG21 charts[222]. Data were sourced from examinations with routine indications, which in France is as 11-14 weeks, 21-24 weeks and 30 – 34 weeks, and final analysis was performed on pregnancies that met the same inclusion criteria as IG21. Authors reported the largest discrepancy was found for FL measurements and attributed this to improved lateral resolution of modern ultrasound equipment.

In a cross-sectional prospective study of pregnancies between 18 and 23 weeks in the Netherlands[253], IG21 charts were found to perform well for BPD and HC, but not for AC and FL. Authors speculated this may be because the population of Dutch fetuses is larger than those from the Intergrowth study, or due to a low population incidence of growth restriction (meaning fewer observations at low centiles is acceptable), or due to maternal characteristics such as greater average height influencing fetal size.

A retrospective study of pregnancies between 14 and 42 weeks conducted in Perth, Western Australia, evaluated the applicability of different charts to AC measurements[254]. This study also reported the IG21 chart did not perform well for AC with high proportions of AC measurements above the 90th and 97th centiles, and fewer below the 10th and 3rd centiles. Authors suggested this may be due to a relatively high proportion of mothers with diabetes and obesity in their cohort. Similar findings were reported in an American study[255].

An Italian study investigated the performance of IG21 AC charts in a cohort of pregnancies with an increased risk of placental insufficiency[220]. Key findings were that the IG21 and local charts demonstrated similar performance for identifying SGA fetuses, but accuracy in predicting birthweight below the 10th centile was limited.

The New South Wales Clinical Excellence Commission working group evaluated the performance of IG21, ASUM, Hadlock and Chitty charts in an audit of ultrasound data collected from routine examinations performed between 34 and 42 weeks[210]. The audit found IG21 charts did not perform well for HC, AC and FL measurements, with high proportions of measurements falling above the 90th and 97th centiles.

4.6 Conclusion

The findings of this study do not support adoption of the IG21 charts in clinical practice. The right – shift in distributions for the AC in particular, has the potential to influence timing of birth and may confer neonatal morbidity associated with late gestation prematurity. The Royal Australasian College of Obstetricians and Gynaecologists guideline for the diagnosis and management of suspected fetal macrosomia recommend induction of labour before 39 weeks of gestation, primarily to reduce the risk for shoulder dystocia, brachial plexus injury and fractures[7].

Neonatal complications for late preterm birth (between 34 and 37 weeks) include respiratory distress, hypoglycaemia, poor temperature control, and admission to a neonatal intensive special care unit. Long term complications include an increased risk of childhood death, re-admission to hospital, cerebral palsy, and developmental delay. More recently, these complications have also been identified in neonates born up to 38 weeks and 6 days[256].

Additionally, an there is an increased risk of Caesarean section due to prolonged labour, particularly for birthweights more than 4500g. Other maternal complications include postpartum haemorrhage and birth trauma[7].

The right – shift in distributions for the AC would result in under-recognition of SGA and FGR, a potentially significant consequence as undiagnosed FGR is the strongest risk factor for stillbirth[3].

4.7 Chapter Summary

An observational, prospective, cross-sectional multicentre study was undertaken to assess whether the IG21 charts were suitably robust to be adopted into Australian clinical practice. A prospective design was selected so that processes to reduce measurement error and bias could be implemented. This included:

- Blinded measurements (sonographers were blinded to the corresponding gestational age and centiles during the ultrasound examination)
- Measurements performed in triplicate to assess intra-rater reliability

After exclusions, analysis was performed on 1642 datasets, with each dataset including the indication for the ultrasound examination, maternal characteristics collected at time of recruitment and birth outcome data collected by the principal investigator at each site.

The distribution of observations from this study were compared to the current charts and IG21 charts to determine which reference best suited the study population by:

- Visual comparison
- Comparison of Z-score distribution
- Assessment of proportion of observations falling above or below fixed centiles

ASUM charts for BPD measurements (measured from the outer edge of the proximal parietal bone to the inner edge of the distal) proved suitable for the study population. The IG21 BPD charts were also suitable, but it should be noted the IG21 BPD measurement technique is from the outer edge of the proximal parietal bone to the outer edge of the distal bone. Both ASUM and IG21 charts for HC measurements

demonstrated more observations above the 90th and 97th centile. This was most pronounced at 27 – 29 weeks gestation and 35 – 37 weeks gestation.

Overall, ASUM charts for AC measurements proved suitable for the study population, albeit with a right shifted distribution at 27 – 29 weeks and 35 – 37 weeks. The IG21 charts proved unsuitable for AC measurement with substantial right shifted distributions across all gestational ages. Both ASUM and Chitty charts for FL had similar performance and were suitable for the study population, but the IG21 charts again demonstrated a pronounced right shifted distribution.

The findings of this research indicate the IG21 growth standards would result in over-diagnosis of LGA and under-diagnosis of SGA and growth restriction if adopted into Australian clinical practice. The population charts currently recommended by ASUM[166] and the NSW Clinical Excellence Commission[210] appear best suited for the population studied in this research, however, the AC distribution at later gestations reveals these charts also have the potential to over-diagnose LGA and under-diagnose SGA and growth restriction. Maternal characteristics of the study cohort revealed slight discrepancies with national data published by the AIHW[235] (namely a higher proportion of overweight participants, a higher proportion of pre-existing or gestational diabetes, and a lower proportion of smokers), indicating the development of new charts based on a wider Australian population is required.

Chapter Five

Fetal growth velocity

5.1 Introduction

Altered growth velocity has been proposed as a method to better define pathologic growth, with particular attention given to reduced growth velocity. How to best measure growth velocity and defining what constitutes a significant change in growth velocity is problematic[17]. The Pregnancy Outcome Prediction (POP) study in 2015 reported reduced abdominal circumference (AC) growth velocity (below the 10th centile) in fetuses with an estimated fetal weight (EFW) below the 10th centile were at increased risk of neonatal morbidity[163]. In 2016, a consensus definition of fetal growth restriction (FGR) was published and included reduced growth velocity of the AC and EFW as a method to identify FGR and defined reduced growth velocity as measurements crossing centiles by more than two quartiles (a centile drop of more than 50)[231]. The Fetal Longitudinal Assessment of Growth (FLAG) study in 2017 reported that newborns with a birthweight in the normal range are more likely to show antenatal features of placental insufficiency (as measured by fetal Doppler) when there was a drop of 30 centiles in customised EFW or AC between 28 and 36 weeks gestational age[257]. More recently, this association was reported between mid-trimester measurements and those performed at 36 weeks gestational age[258]. In 2021 fetal growth velocity standards were published, based on the Fetal Growth Longitudinal Study (Intergrowth-21st project), along with on-line calculators to aid in assessment of growth velocity. Similar to the Intergrowth-21st charts, the fetal growth velocity increments are prescriptive, that is, they define how a fetus should grow in ideal circumstances[259].

Calculation of growth velocity is not a routine feature of third trimester ultrasound, but there is evidence some clinicians use a change in centiles to modify clinical management[260]. How to best incorporate

assessment of reduced growth velocity into clinical practice is unclear. Comparing AC and EFW centiles from ultrasounds performed at different gestations while attractive in its simplicity, may not be the best approach. Assigned centiles in each examination may vary greatly according to which fetal chart was used and the standard deviation of fetal measurements increases with increasing gestational age. Currently, there is no uniformity in the choice of fetal growth chart, and as discussed in chapter 2, this may vary between practices in the same region[260].

Several references for fetal growth velocity have been published for biometric measures of bi-parietal diameter (BPD), head circumference (HC), abdominal circumference (AC) and area (AA), femur length (FL) and estimated fetal weight (EFW) [261-265]. Methodologies used to establish reference ranges vary considerably, and can be broadly described as determination of average growth velocity, where the difference in measurements of fetal size is divided by the time interval, or instantaneous velocity, where the change in measurement is expressed as a function of gestational age. To use reference charts one must first calculate the growth velocity following methods defined by the reference and then compare the result. Comparison of measurement centiles between two time points presents a simpler alternative, however, may not be applicable if the interval between ultrasound examinations differs greatly from that published.

5.2 Literature Review

Employing search terms (fetal or foetal) and (growth velocit* or growth traject* or growth rate), electronic searches for English language articles in CINAHL, PUBMED, Web of Science and The Cochrane Library databases identified 375 potentially relevant publications between 1992 to 2022 on the measurement of fetal growth velocity and/or the relationship between altered growth velocity and clinical outcome. Initial screening of titles and abstracts excluded 225 articles with 153 retrieved for detailed evaluation. A further 72 articles were excluded as shown in figure 1.

Content was summarised in an excel spreadsheet and included author and publication details, study aim and methodology, methods of calculating growth velocity, definitions for reduced or increased growth velocity, and the relationship between altered growth velocity and clinical outcome.

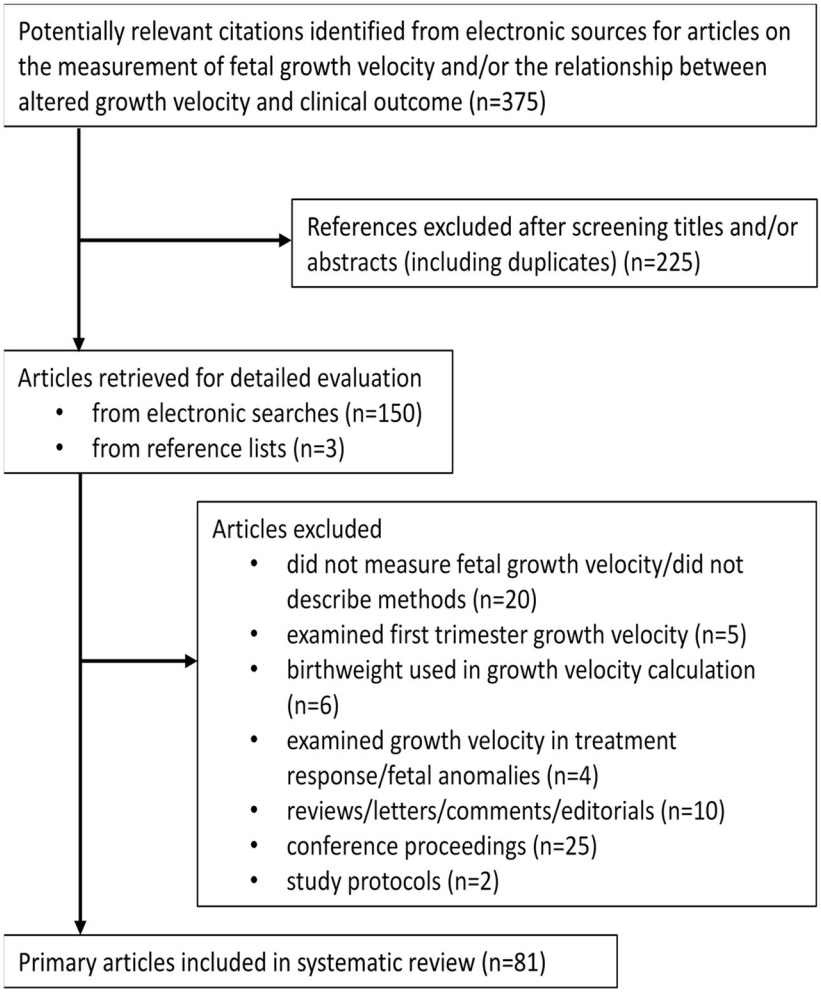

Figure 5.1 *Flow diagram of literature assessment*

5.3 Results

Methods to measure fetal growth velocity varied in complexity and included calculation of instantaneous velocity derived from individual or population growth curves expressed as a regression coefficient, calculation of incremental change in a fetal measurement over time, and calculation of incremental

change in z-score or centile of a fetal measurement over time. In addition to the AC and EFW, some studies also assessed growth velocity of standard fetal measures, namely, the biparietal diameter (BPD, head circumference (HC) and femur length (FL). Some also included humeral length (HL) and fetal thigh circumference (an indicator of fetal fat composition), while studies following methods described by Owen et al[261] used abdominal area (AA) rather than abdominal circumference.

The aim of some articles in the review was to provide charts or reference ranges for growth velocity for fetal biometric parameters[259, 261, 263, 265, 266] , however, most articles explored the relationship between fetal growth rate and maternal characteristics[267-292], neonatal outcomes[24, 163, 293-323], childhood outcomes[324-331], and pregnancy biomarkers[332].

5.3.1 Fetal growth velocity reference charts

Several authors published charts of fetal growth velocity based on low risk populations. In 1996 Owen et al[261] published standards for fetal growth velocity for BPD, FL, abdominal area (AA) and EFW between 26 and 40 weeks based on a prospective longitudinal study of 274 low risk pregnancies. Daily growth rate was determined from paired measurements made 28 days apart and modelled as a function of gestational age using quadratic regression. Growth rate of the BPD and FL gradually decreased until term, while growth rate of the AA and EFW gradually rose until 33 weeks' gestation and gradually decreased until term.

In 2017, Vannuccini et al[263] published a reference range for AC growth velocity between 20 and 36 weeks. This observational study comprised 3334 pregnancies where routine ultrasound examinations were performed at 20 and 36 weeks, and the z-score difference between the two AC measurements was used to formulate an AC growth velocity equation and a reference range. Designed for ease of use in everyday practice, this method may not be suitable for assessment of AC growth velocity at different gestational ages.

Grantz et al[333] published references for fetal growth velocity in 2018 as part of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) fetal growth studies. Growth velocity curves for BPD, HC, AC, HL, FL and EFW were modelled from the mean change in measurement per week of gestational age and centiles were fitted. Data were presented as tables of weekly increments from 11 to 41 weeks for 5th, 10th, 50th, 90th and 95th centiles. BPD, HC, AC, HL and FL velocities peaked in the early second trimester then gradually declined with BPD and HC accelerating again in the mid to late second trimester and AC accelerating in the early third trimester. EFW velocity continued to increase until 35 weeks before gradually decreasing. The authors also provided a formula to assist clinicians calculate EFW growth velocity and the corresponding centile between any set of two gestational ages.

Using data from the Intergrowth 21st project, in 2021 Ohuma et al[259] published growth velocity standards including the BPD, HC, AC and FL from 16 – 40 weeks gestation. This was a multicentre, prospective, longitudinal study comprising 4321 healthy pregnancies. Velocity increments per week were modelled as a function of gestational age using fractional polynomial regression with means and standard deviations modelled separately. The authors found that incremental fetal growth velocity is highest in the early part of the second trimester, then decreases with gestational age for skeletal structures (cranium and femur) while velocity growth for the AC (abdominal organs and subcutaneous fat) was steady across gestational ages.

Wu et al[265] conducted a retrospective longitudinal study in 2021 of 9075 low risk pregnancies to create growth velocity charts for BPD, HC, AC, FL and EFW from 12 to 40 weeks. For each parameter, instantaneous velocity was calculated and expressed as g/week with modelling to produce velocity curves and centiles as a function of gestational age. BPD, HC, AC and FL velocities peaked in the early second trimester then gradually declined with BPD and HC accelerating again in the mid to late second trimester. EFW velocity continued to increase until 35 weeks before gradually decreasing. The authors reported an increase in neonatal complications when the EFW velocity was less than the 10th centile and found AC

velocities less than the 10th centile were associated with small for gestational age (SGA) infants. However, a stronger association with neonatal complications and SGA was observed when EFW and AC measurements were below the 10th centile.

An alternate approach was proposed by Mongelli et al[262], who observed fetal growth in the 3rd trimester is quasi-linear and that average fetal weekly weight could be calculated by dividing the difference between birthweight and the 24 week median weight by the difference in gestational age at birth and 24 weeks. Using a retrospective dataset of 12420 cases, the average fetal weekly weight gain was reported as 175.4g and 5th, 10th, 90th and 95th centiles were modelled.

5.3.2 Individualised growth assessment

A method to estimate individual fetal growth potential was proposed by Deter et al[266] in 2018 whereby serial ultrasound measurements in the second trimester are modelled and used to predict what size the fetus ought to be in the third trimester. Calculations can be performed by accessing the on-line growth analysis software iGAP[334] which generates several growth velocity parameters to identify pathological fetal growth. To be clinically useful, at least two ultrasound examinations in the second trimester are required to model expected third trimester growth, followed by at least two third trimester ultrasounds to assess third trimester growth trajectory. Additionally, familiarity with a new lexicon of growth velocity parameters is necessary for clinicians to understand the results.

5.3.3 Fetal growth velocity and the prediction of small for gestational age and growth restriction

In 2013 Barker et al[51] investigated the growth trajectories of 1116 pregnancies meeting the criteria for FGR and found it was possible to identify two EFW trajectories allowing discrimination between appropriate growth (i.e. constitutionally small fetuses) and pathologic growth (i.e. growth restricted fetuses). Fetuses following a pathologic growth trajectory had higher associations with abnormal Doppler

parameters in the third trimester, maternal pre-eclampsia, perinatal complications, and admission to neonatal intensive care units.

Findings of the Pregnancy Outcome Prediction (POP) study[163] were published in 2015. The aim of this study was to assess the effectiveness of universal third trimester ultrasound to screen for SGA. Growth velocity was defined as the difference in AC Z score between 20 weeks and the last scan before birth and thresholds for the 10th and 90th centiles were defined from the distribution in the study cohort. Key findings of this study were that routine third trimester ultrasound tripled the detection of SGA but with an increased false positive rate, and that in SGA fetuses AC growth velocity in the lowest decile was associated with neonatal complications.

Other studies compared reduced growth velocity to other measures of fetal compromise. Schreiber et al[300] compared reduced growth velocity in the third trimester (defined as below the 10th centile in a study cohort of 246 low risk AGA fetuses) to Doppler assessment of the UA and MCA. They suggested reduced growth velocity and CPR are independent risk factors for an intrapartum non-reassuring fetal heart rate.

Using individualised growth assessment described in section 5.3.2, Deter et al[335] studied growth in fetuses with EFW < 10th centile that were appropriately grown at birth. This study found that up to 40% of the study cohort demonstrated normal growth patterns, while the remainder presented growth patterns consistent with growth restriction. Authors further categorised growth patterns based on iGAP[334] indices as normal pattern, including no growth pathology, minimal growth pathology, and minor growth pathology. Growth restriction patterns were described as early growth restriction, late growth restriction, adaptive growth restriction, and recovering growth restriction.

5.3.4 Fetal growth velocity and maternal diabetes

Maternal diabetes may be pre-gestational, including type 1 diabetes (T1DM) and type 2 diabetes (T2DM), or may present as a complication of pregnancy as gestational diabetes (GDM). All forms are associated

with increased rates of pregnancy complications, although are more common in pre-gestational diabetes. Complications include macrosomia and large for gestational age, respiratory distress syndrome, neonatal hypoglycaemia, neonatal intensive care admission, growth restriction, congenital anomalies, preterm birth and pre-eclampsia[336].

To identify fetuses at risk of neonatal complications, several studies explored the relationship between maternal diabetes and fetal growth velocity, particularly of the AC and EFW. Investigating effects of T1DM, Adamczak et al[267], reported increased fetal growth begins at 23 weeks' gestation. Referencing charts published by Owen et al[261], Wong et al[270] studied 174 mothers with pre-gestational diabetes and found accelerated fetal abdominal growth persisted until 38 weeks' gestation with no significant difference between T1DM and T2DM.

Mulder et al[284] investigated the effect of T1DM on AC growth velocity reporting the time when accelerated AC growth occurred influenced birthweight. Accelerated mid-trimester growth (i.e. at 20 weeks' gestation) was associated with large for gestational age at birth and poor maternal glycaemic control. In a study of infants of mothers with T1DM, Bollepalli et al[274] reported an association between increased AC velocity and neonatal hypoglycaemia. However, Farrell et al[287] and Kernaghan et al[289] did not find EFW or fetal growth velocity useful in predicting neonatal hypoglycaemia or large for gestational age at birth.

The Gestational Diabetes Study [269] was a large multicentre retrospective study investigating AC growth rate in 103377 fetuses and compared the growth rates of fetuses in mothers with or without pre-existing diabetes or gestational diabetes. Data were grouped according to maternal diabetic characteristics and neonatal macrosomia (birthweight above 4000g). Mean AC values for each gestational week were calculated for each group and modelled by linear regression as a function of gestational age. Growth rate for each group was expressed as the regression coefficient. This study found AC growth rate was increased in macrosomic infants of mothers without diabetes and those with GDM between 22 and 30 weeks'

gestation compared to non-macrosomic groups. Macrosomic fetuses of mothers with pre-existing diabetes demonstrated accelerated growth from 30 weeks.

Increased fetal growth rate in maternal diabetes to predict the birth complication shoulder dystocia was investigated by Mourad et al[309], calculating EFW growth rate as the difference in EFW centiles between two ultrasound examinations divided by the time interval. The gestational age at which the ultrasounds were performed was not reported, however, a statistically significant relationship between EFW growth velocity and shoulder dystocia was not found. This finding was not supported by MacDonald et al[310] who reported an association between accelerated EFW and AC growth velocities between 28 and 36 week' gestation and shoulder dystocia in a non-diabetic study cohort. In this prospective study of 347 pregnant women, growth velocity was calculated as the difference in AC and EFW centiles between 28 and 36 weeks divided by the time interval.

Response to insulin pump therapy was assessed by Kernaghan et al[288] in a small prospective cohort of 42 mothers. The difference in EFW reported by ultrasound examinations performed 21 – 35 days apart was calculated and expressed as a z-score. Authors concluded insulin pump therapy offered no benefit in terms of normalising fetal growth velocity, fetal size, birthweight or improving maternal glycaemic control compared to conventional insulin therapy.

5.3.4 Fetal growth velocity and maternal obesity

The relationship between maternal obesity and fetal growth rate was examined by several researchers. Most reported an increase in AC and/or EFW growth velocity from 28 to 30 weeks' gestation[279, 283]. Studies of fetal body composition attributed this to increased fetal abdominal fat[329].

Zhang et al[268] modelled growth curves for BPD, HC, AC, FL and EFW for singleton fetuses of obese and non-obese women enrolled in the National Institute of Child Health and Human Development (NICHD) Fetal Growth Studies. This was a prospective longitudinal study with 468 obese and 2334 non-obese

women. Key findings were that the difference in birthweight between infants of obese mothers and those of normal weight was almost 100g, and that a difference in EFW could be observed from 30 weeks' gestation. Additionally, fetal HC and FL measurements were greater in the obese cohort from 21 weeks' gestation, and the AC was greater from 32 weeks' gestation.

Elhddad et al[290] examined the relationship between maternal weight gain in pregnancy and fetal growth velocity concluding pregnancy weight gain in obese mothers affects fetal growth.

5.3.5 Fetal growth velocity and maternal hypertension

Maternal chronic hypertension is associated with an increased risk of pregnancy complications including pre-eclampsia, Caesarean section, stillbirth, placental abruption, preterm birth and growth restriction[337]. Mateus et al[285] examined the relationship between maternal hypertension and fetal growth velocity in a prospective longitudinal study comparing fetal growth rate between normotensive women, women with hypertension, mild pre-eclampsia, and severe pre-eclampsia. Growth curves for BPD, HC, AC, FL and EFW were generated for each group and compared, demonstrating reduced EFW and AC growth was present at 22 and 23 weeks only in the cohort with severe pre-eclampsia.

Frusca et al[286] used a similar approach in a retrospective study of pregnant women with chronic hypertension. Growth curves for HC, AC and FL were modelled and compared to those of normotensive women. Growth velocity at different gestations was calculated as the derivative of change in size with respect to time and compared to fetal curves of normotensive women to determine the timing of any growth velocity deviations. The study found there were no differences in HC, AC and FL growth velocity at 26 – 28 weeks, but after 30 weeks the growth velocity for AC and FL was actually greater in the chronic hypertension group.

5.3.6 Fetal growth velocity and other maternal conditions and exposures

The effects of assisted reproductive technology on fetal growth velocity in the second and third trimester were investigated by Besharati et al[280]. Pregnancies conceived via ovulation induction, intrauterine insemination, fresh embryo transfer, frozen embryo transfer, and spontaneous conception following infertility were compared with no significant differences in growth trajectories identified.

Reduced fetal growth rate was shown to be associated with maternal malarial infection in pregnancy[271], maternal smoking in pregnancy[273], maternal cannabis use[291], antenatal administration of corticosteroids[282], physically demanding work during pregnancy[275], and high maternal concentrations of bisphenol A (BPA).

No effects on fetal growth velocity were identified with maternal SARS-CoV-2 infection in pregnancy[281], or maternal exposure to household air pollution[292]

5.3.7 Fetal growth velocity and the prediction of large for gestational age

Khan et al[314] examined AC and EFW growth velocity between 32 and 36 weeks in a retrospective study of 14497 fetuses. Growth velocity expressed as Z-score differences between examinations performed at least two weeks apart, divided by the time interval between examinations. The study concluded there was no significant improvement in detection of large for gestational age (LGA) by considering AC or EFW growth velocity. However, the study reported detection of LGA was improved when the ultrasound examination was performed at 36 weeks gestation.

Roeckner et al[294] investigated whether AC and EFW growth velocity improved the prediction of LGA infants in a secondary analysis of the Redefining Fetal Growth Restriction Project. Growth velocity was defined as the difference between AC and EFW Z-scores in measurements performed at 18 – 24 weeks and 26 – 36 weeks. Authors concluded calculation of growth velocity did not improve prediction of LGA when compared to third trimester EFW.

5.3.8 Fetal growth velocity and neonatal outcomes

In a secondary analysis of the Pregnancy Outcome Prediction (POP) Study, an association between reduced FL growth velocity between 20 and 28 weeks and spontaneous preterm birth was reported[305]. Growth velocity was measured by the change in z-scores and fetuses with FL in the lowest decile of growth velocity had a 2 – 3 fold risk of spontaneous preterm birth.

Pacora et al[24] investigated the relationship between reduced growth velocity and antepartum fetal death in 4285 singleton pregnancies. Growth velocity was defined as the change in centile of each parameter per week of gestation as determined by the linear regression slope of centiles as a function of gestational age from 14 – 32 weeks. In cases of antepartum fetal death, the median EFW growth velocity was – 4.53 centiles per week as compared to – 0.14 for controls, demonstrating an association between reduced growth velocity and antepartum fetal death.

The Fetal Longitudinal Assessment of Growth (FLAG) study investigated the relationship between reduced growth velocity in fetuses between 20 and 36 weeks and 28 and 36 weeks and markers of placental insufficiency in a cohort of infants with birthweight considered appropriate for gestational age (AGA) [257, 315]. Fetal growth velocity was calculated as the difference in EFW and AC centiles between ultrasound examinations and was standardised to account for any variability in gestational age at ultrasound. Markers of placental insufficiency included cerebroplacental ratio < 5th centile at 36 weeks (indicating placental resistance and adaptive cerebral redistribution), umbilical artery pH < 7.15 at birth (indicating acidosis post hypoxia during labour), placental weight < 10th centile, and a low neonatal body fat percentage. The studies reported correlations between reduced growth velocity between 28 and 36 weeks and low CPR, acidosis in labour, low neonatal body fat, and low placental weight. Importantly, a similar correlation was found between 20 and 36 weeks, suggesting the routine ultrasound examination at 20 weeks' gestation can be used as a baseline assessment of fetal size suitable for assessing growth velocity in the third trimester.

5.3.9 Fetal growth velocity and childhood outcomes

Bartels et al[329] described the relationship between fetal growth trajectories and maternal and early childhood characteristics. Growth trajectories for AC and EFW were derived from ultrasound measurements at 20 and 34 weeks' gestation and birthweight, and expressed as mm/day. Fast AC and EFW trajectories were associated with increased levels of serum glucose in mothers antenatally, increased childhood adiposity, and increased rates of Caesarean section births.

5.4 Discussion

Findings of the studies in this review support the premise that altered fetal growth velocity is associated with pathological fetal growth and adverse neonatal outcomes. However, significant heterogeneity exists in methods to measure growth velocity and thresholds for defining reduced or increased growth velocity, which affects generalisability and clinical interpretation. Few studies investigating associations of altered fetal growth velocity have used methods described in published reference charts to calculate growth velocity, implying these methods are complex and present data in a way that is difficult to interpret.

To some extent this is reflected in obstetric management guidelines summarised in table 5.1. Vague definitions such as 'a flattening of the growth curve as judged by the clinician'[338] and 'a pattern of slowing growth velocity'[339] are subjective assessments with the potential to misdiagnose clinically significant changes in growth velocity. However, most guidelines define reduced growth velocity as a reduction in measurement centiles (30 to 50 centiles)[6, 13, 20, 210, 340] but typically do not specify the time interval required between the ultrasound examinations. This creates an uncertain landscape for clinicians providing antenatal care and highlights the need for research on how the measurement of growth velocity could be incorporated into clinical practice. The following study seeks to address this issue.

Table 5.1 *Definitions of reduced growth velocity by professional bodies*

	Guideline or statement	Definition of reduced growth velocity
2019	International Society for Ultrasound in Obstetrics and Gynaecology (ISUOG)[20]	AC and/or EFW crossing centiles by more than two quartiles
2021	International Federation of Gynecology and Obstetrics (FIGO)[13]	AC and/or EFW crossing centiles by more than two quartiles
2021	The American College of Obstetricians and Gynecologists[338]	A flattening of the growth curve as judged by the clinician
2023	The Society of Obstetricians and gynaecologists of Canada (SOGC)[340]	AC and/or EFW crossing centiles by more than two quartiles
2023	The Perinatal Society of Australia and New Zealand and Centre of Research Excellence Stillbirth position statement[6]	A decrease in AC or EFW of greater than 30 centiles
2023	Clinical Excellence Commission NSW consensus statement: Choice of Fetal Biometry Charts[210]	A 50 centile reduction in EFW between measures four weeks apart
2024	Royal College of Obstetricians and Gynaecologists (RCOG)[339]	A pattern of slowing growth velocity, particularly a downward trend in AC growth velocity

5.5 The role of growth velocity assessment in clinical practice

A retrospective study was performed to investigate methods of incorporating measures of growth velocity in third trimester ultrasound examinations. All pregnant women in Australia are offered a routine ultrasound examination in the mid trimester (usually performed at 18 – 22 weeks) with a reported uptake of over 90%[341]. Third trimester ultrasound is generally performed selectively but as discussed in chapter 2, the steady increase in the number of third trimester ultrasound examinations performed in Australia suggests most singleton pregnancies will undergo at least one ultrasound in the third trimester. There is no consensus regarding the timing of a 'routine' third trimester ultrasound although the majority are performed between 32 and 36 weeks' gestation[342]. When performed at 36 weeks gestation, the detection of FGR and the prediction of adverse outcomes is reportedly more effective than when performed at 32

weeks[343], therefore, the interval between the routine mid trimester scan and 36 weeks was selected as the period to assess growth velocity in this study. From the many methods described to measure growth velocity described in the literature review, methods that could be most easily adopted into clinical practice were selected. These included calculation of centiles for AC growth velocity using IG21 fetal growth velocity standards published by Ohuma et al[259], the difference between AC and EFW centile between the two ultrasound examinations (as if the clinician were 'eyeballing' reported centiles), and the standardised difference between AC and EFW centiles (correcting for the interval between ultrasound examinations) as described by Kennedy et al[315]. The relationship between reduced growth velocity as determined by these methods and neonatal morbidity was examined to establish which method was most effective.

5.5.1 Study design

The study protocol was approved by ACT Health Human Research Ethics Committee 2021/ETH11858 and is provided in Appendix C. In summary, a retrospective study was conducted to assess fetal growth velocity between the mid trimester ultrasound examination and one performed between 35 and 38 weeks gestation. Birth outcome data was collected to examine the relationship between neonatal morbidity and reduced growth rate.

Clinical measures of neonatal condition included Apgar scores (routine measures at 1 minute and 5 minutes after birth, of baby's colour, heart rate, reflexes, tone, & respiratory effort), and arterial cord blood pH. Markers of neonatal morbidity included one or more of the following: an Apgar score less than 7 at 5 minutes, arterial cord blood pH of less than 7.15 (indicating acidosis), and admission to special care nursery (SCN) or neonatal intensive care unit (NNICU).

The main benefit of a retrospective design was access to a large pool of data with recorded outcomes. Calculating growth velocities retrospectively ensured clinical management was not affected by this information, and furthermore, measurement centiles at the mid trimester scan were not typically

reported. The disadvantage of a retrospective design is that third trimester measurement data is from clinically indicated ultrasound examinations. Broadly speaking, clinical indications for third trimester ultrasound include suspected small for gestation age, suspected large for gestational age, and indications not related to fetal growth, for example, assessment of placental localisation. To help address selection bias, maternal characteristics known to affect fetal growth were recorded. The potential for measurement bias is another consideration as operators are not blinded to the corresponding gestational age or measurement centile during the ultrasound examination. This, however, is reflective of current clinical practice. Lastly, incomplete or missing data is associated with retrospective study design.

The sample size required to assess differences between infants with reduced fetal growth velocity and normal fetal growth velocity was calculated by:

$$n_i = \{p_1(1-p_1) + p_2(1-p_2)\}\left(\frac{Z}{E}\right)^2 \qquad 5.1$$

where:

n_i is the sample size required in each group

The birth outcome of interest was neonatal acidosis as measured by cord artery pH, as a reassuring Apgar score does not completely exclude acidosis. The background rate of neonatal acidosis (cord pH < 7.15) is 7% for births > 37 weeks' gestational age at Canberra Hospital (measured between January 1 and June 30 2021).

p_1 and p_2 are the proportions of acidosis in each group; For a 50% increase in acidosis, p_1=10.5% and P_2 = 7%

Z is the value from the standard normal distribution reflecting the 95th confidence interval = 1.96

E is the margin of error 10.5% - 7% = 3.5%

$$n_i = \{0.105(1-0.105) + 0.07(1-0.07)\}\left(\frac{1.96}{0.035}\right)^2 = 498 \qquad 5.2$$

Data collection

Data were sourced from ultrasound examination performed in 2020 and 2021 from electronic databases routinely used in FMU and was collected by the principal investigator. A search was initiated in the ViewPoint ultrasound database to identify eligible ultrasound examinations, using search terms 'Fetal Growth' , 'singleton', and '35*', '36*', '37*'. Recorded patient identifiers were used to reference antenatal records for mid-trimester ultrasound reports performed by other providers and birth outcome summaries (Clinical Patient Folder (InfoMedix) and/or Birthing Outcome System (v6, MCATS)).

The following inclusion criteria applied:

- Singleton viable pregnancies with ultrasound performed in the 35th week to 37th week of pregnancy (i.e. 35+0 to 37+6 weeks)
- Estimated date of birth (EDB) as confirmed by ultrasound at 8-14 weeks of pregnancy

Exclusion criteria included:

- Pregnancies with a known fetal abnormality
- Pregnancies where EDB was not confirmed by ultrasound at 8-14 weeks of pregnancy
- Multiple pregnancies
- Pregnancies that did not birth at Canberra Hospital

For each patient, the following de-identified data was recorded:

- Gestation (weeks and days) when the mid trimester ultrasound and the third trimester ultrasound was performed
- Fetal measurements from the 35 - 38 week ultrasound
    - Bi-parietal diameter (BPD)
    - Head Circumference (HC)
    - Abdominal circumference (AC)
    - Femur length (FL)

    - Amniotic fluid index
    - Fetal Doppler measurements
- Fetal measurements from the mid-trimester ultrasound (17+0 – 22+0 weeks) sourced from the ViewPoint data base when performed in FMU or from ultrasound reports saved in the digital antenatal records when the examination was performed by other providers
    - Bi-parietal diameter (BPD)
    - Head Circumference (HC)
    - Abdominal circumference (AC)
    - Femur length (FL)
- Maternal characteristics
    - Age
    - Pre-existing diabetes or diabetes in pregnancy
    - Hypertension
    - Smoking
    - History of pre-eclampsia
    - Height
    - Weight
    - Parity
    - Other medical conditions
- Birth outcome data
    - Gestational age at birth
    - Birthweight
    - Sex
    - Method of delivery

- Apgar scores (routine measures at 1 minute and 5 minutes after birth, of baby's colour, heart rate, reflexes, tone, & respiratory effort)
- Arterial cord blood pH (if performed)
- Days of admission to special care nursery (SCN) or neonatal intensive care unit (NNICU)

Data were collated in an Excel spreadsheet (Microsoft® Excel®2016) and datasets were scanned for obvious typographical errors and exclusions such as missing data. In instances where two ultrasound examinations were performed between 35 and 38 weeks, the second dataset was deleted. Following this step, a new unique identifier was assigned to the complete dataset and the patient identifier was deleted.

Assigning centiles for EFW and AC

Gestational age at the time of each ultrasound examination was reformatted from weeks and days to exact weeks (i.e. 36 weeks 2 days was expressed as 36.3 weeks).

Many mid-trimester ultrasound examinations were performed by external providers with measurements sourced from reports stored digitally in antenatal records. In many cases, the EFW was either not reported or the formula used to calculate EFW was not cited. Therefore for consistency, the EFW was calculated using the Hadlock III algorithm[102]:

$$\log_{10} weight = 1.326 - 0.00326AC \times FL + 0.0107 \times HC + 0.0438 \times AC + 0.158 \times FL \qquad 5.3$$

(measurements in cm)

Mid trimester centiles for EFW were calculated according to the Hadlock EFW reference chart (standard deviation 12.7%)[104]. Mid trimester centiles for the AC were calculated according to the Westerway AC reference chart (standard deviation 7.5mm)[172].

Third trimester centiles for EFW were calculated according to the Hadlock EFW reference chart (standard deviation 12.7%)[104]. Third trimester centiles for the AC were calculated according to the Westerway AC reference chart (standard deviation of 15mm 35 to 37 weeks and 17.5mm in the 37th week)[172].

Growth velocity calculation

Growth velocity for AC and EFW was calculated in three ways. The first calculated the difference between third trimester AC and second trimester AC measurements, divided by exact weeks between the examinations, and expressed as mm/week. Centiles for AC growth velocity were assigned using equations from the IG21 fetal growth velocity standards published by Ohuma et al[259].

The second method calculated the difference between AC centiles were calculated by simply subtracting the third trimester measurements from the second trimester measurements as if a clinician were 'eyeballing' reported centiles. This was repeated for EFW centiles. The third method accounted for variation in the interval between the mid trimester ultrasound and third trimester ultrasound. In this cohort, the mid trimester examination was performed between 17 and 23 weeks' gestation and the third trimester ultrasound was performed between 35 and 38 weeks' gestation. Using methods similar to those described by Kennedy et al[315], centiles were standardised by dividing the difference between AC centiles and EFW centiles by the time interval between ultrasound examinations in exact weeks and multiplying by 16 (i.e. the interval in weeks between 20 and 36).

Centiles for third trimester Doppler measurements were assigned using equations published by Ebbing et al[192].

The spreadsheet was then imported into SPSS (IBM SPSS Statistics for Windows, Version 30; IBM Corp., Armonk, NY, USA) for analysis.

5.6 Results

Overall, 402 datasets were excluded from 1044 collected between January 2020 and March 2021 as described in table 5.2. Analysis was performed on 636 complete datasets.

Table 5.2 *Exclusions*

Exclusion criteria	*n*
No mid trimester ultrasound report in medical records	274
Missing measurement data	6
Second third trimester ultrasound performed between 35 and 38 weeks	6
No outcome data (did not birth at Canberra Hospital)	96
Gestational age not confirmed by first trimester ultrasound or known IVF details	12
Significant fetal anomaly	7
Multiple gestation	1
Total	402

Maternal characteristics

Maternal characteristics are summarised in table 5.3. The average maternal age was 32 years and the average BMI was 29.12. Pregnancies complicated by pre-existing or gestational diabetes accounted for 38.7% of the cohort, and pre-existing hypertension accounted for 9.6%. This likely reflects the use of targeted third trimester ultrasound examinations in line with guidelines for management of diabetes in pregnancy[344] and guidelines for management of pregnancies with risk factors for growth restriction[165].

Table 5.3 *Maternal characteristics*

Maternal characteristics		
Average age (years)	32	
Median age (years)	32	
Range (years)	17 – 49	
Average BMI (kg/m^2)	29.12	
Median BMI (kg/m^2)	27.00	
Range (kg/m^2)	16.00 – 66.50	
Medical conditions	*n*	*(%)*
Diabetes (including gestational diabetes)	246	*(38.7)*
Hypertension	61	*(9.6)*
Smoker	13	*(2.0)*
History of pre-eclampsia	23	*(3.6)*
Nulliparous	239	*(37.6)*
Parous	397	*(62.4)*

Birth Outcome data

Birth outcome data are summarised in table 5.4. Overall there were 635 live births and one stillbirth. The average term (> 37 weeks) birthweight at term was 3290g and 18.4% of infants required neonatal intensive care admission.

Table 5.4 *Birth outcome data*

Birth Outcome	>37w *n*	*(%)*	<37w *n*	*(%)*	Total *n*	*(%)*
Live birth	590	*(92.8)*	45	*(7.0)*	635	*(99.8)*
Stillbirth	1	*(0.2)*	0	-	1	*(0.2)*
Male	320	*(50.3)*	25	*(3.9)*	345	*(54.2)*
Female	270	*(42.5)*	21	*(3.3)*	291	*(45.8)*
Birth weight	*g*		*g*		*g*	
Average	3290		2610		3236	
Median	3280		2495		3240	
Range	1990 – 5400		1400 – 3820		1400 – 5400	
Outcome measures	*n*	*(%)*	*n*	*(%)*	*n*	*(%)*
Low birth weight (<2500g)	41	*(6.5)*	23	*(3.6)*	64	*(10.1)*
5 min Apgar < 7	12	*(1.9)*	1	*(0.2)*	13	*(2.0)*
Arterial cord blood* pH <7.15	46	*(10.7)*	3	*(0.7)*	49	*(11.5)*
NNICU/SCN admission	92	*(14.5)*	25	*(3.9)*	117	*(18.4)*

** Arterial cord blood collected in 428/636*

Evaluation of methods to calculate growth velocity

In the study cohort, the mid trimester examination was performed between 17 and 22 weeks' gestation and the third trimester ultrasound was performed between 35 and 38 weeks' gestation. Growth velocity for AC and EFW was calculated in three ways:

- The difference between third trimester AC and second trimester AC measurements was calculated and corrected for the interval between the examinations (expressed as mm/week). Centiles for AC growth velocity were assigned using equations for IG21 fetal growth velocity standards published by Ohuma et al[259].
- The difference between third and second trimester AC centiles determined by Westerway[172] charts (uncorrected for exact interval between examinations) and repeated for EFW centiles determined by Hadlock EFW[104] charts.
- The difference between third and second trimester AC centiles (corrected for exact interval between examinations) determined by Westerway[172] charts and repeated for EFW centiles determined by Hadlock EFW[104] charts. Using methods similar to those described by Kennedy et al[315], centiles were standardised by dividing the difference between AC centiles and EFW centiles by the time interval between ultrasound examinations in exact weeks and multiplying by 16 (i.e. the interval in weeks between 20 and 36).

The AC centile difference (Δ AC) and standardised AC centile difference (Δ AC STD) demonstrated a positive linear relationship as demonstrated by scatterplots in figure 5.2. A similar relationship was observed for EFW centile difference (Δ EFW) and standardised EFW centile difference (Δ EFW STD). Bivariate correlations were examined using Pearson r test demonstrating a strong correlation for Δ AC and Δ AC STD (r 0.997 and 2 tailed significance <0.001) and Δ EFW and Δ EFW STD (r 0.997 and 2 tailed significance < 0.001).

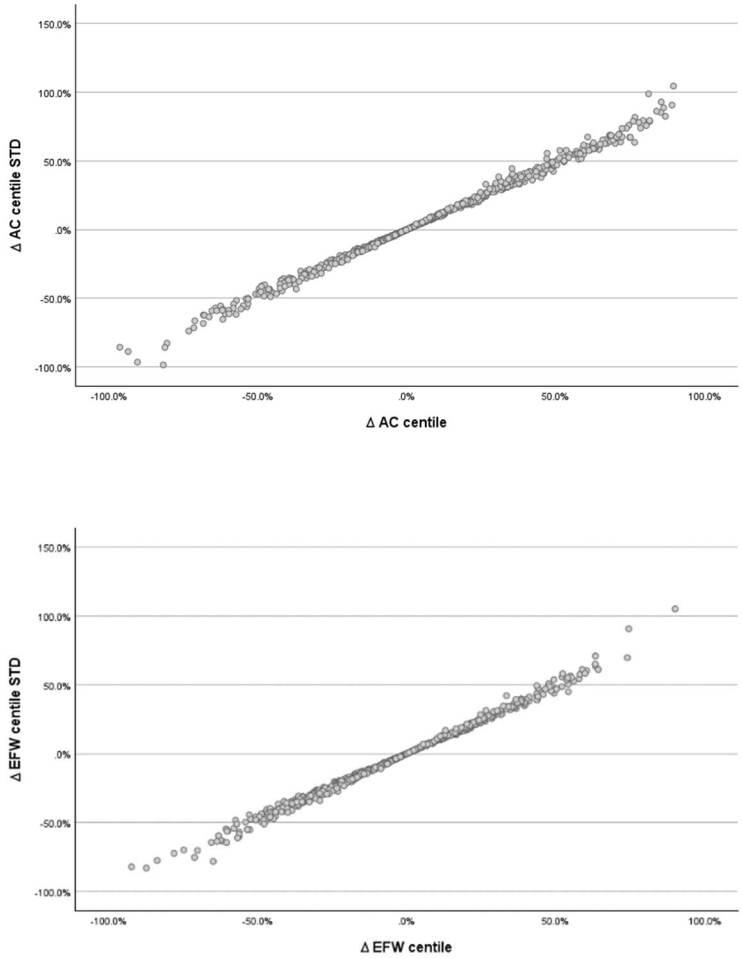

Figure 5.2 *Relationship between absolute centile difference and standardised difference for abdominal circumference (AC) and estimated fetal weight (EFW)*

A positive linear relationship was observed between the difference in AC and EFW centiles and the IG21 AC growth velocity centiles. Both ΔAC and ΔAC STD demonstrated strong correlation with the AC growth velocity centile (IG21 ACV centile) (r 0.812 and 0.818 respectively and 2 tailed significance <0.001). Similarly, ΔEFW and ΔEFW STD were correlated with IG21 ACV centile (r 0.810 and 0.814 respectively and 2 tailed significance <0.001). Scatter plots for the relationship between ΔAC and IG21 ACV centile, and ΔEFW and IG21 ACV centile are shown in figure 5.3.

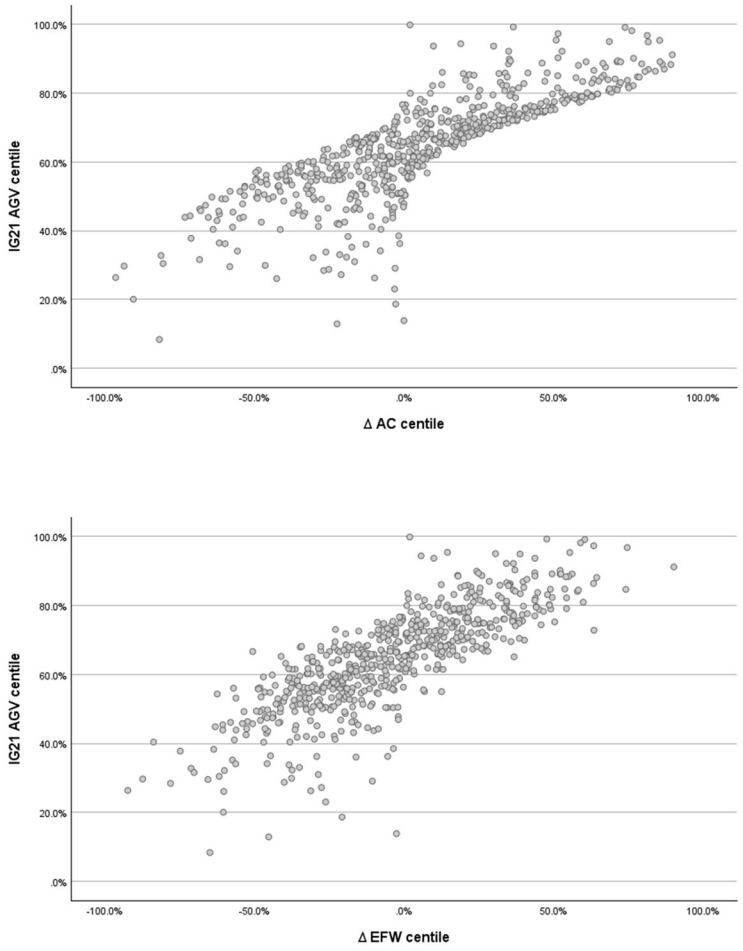

Figure 5.3 *Relationship between absolute centile difference and IG21 growth velocity centile for abdominal circumference (AC) and estimated fetal weight (EFW)*

5.6.1 Growth velocity and neonatal outcome

Birthweight

IG21 ACV strongly correlated with birthweight (r 0.727, p < 0.001) as compared to ΔAC and ΔAC STD, with moderate correlation (r 0.454, p<0.001 and 0.458, p < 0.001 respectively). ΔEFW and ΔEFW STD also demonstrated moderate correlation (r 0.548, p<0.001 and r 0.552, p<0.001 respectively).

Of note, the third trimester AC centile and third trimester EFW centile were strongly correlated with birthweight (r 0.728, p < 0.001 and r 0.778, p< 0.001 respectively) indicating growth velocity calculation did not confer additional information in terms of birthweight.

Arterial cord pH

Analysis of cord blood gas provides an objective measure of fetal metabolic condition at time of birth. The pH of arterial cord blood indicates acidosis that results from fetal hypoxia. In a term newborn, the mean pH is 7.24 to 7.27 and values in preterm newborns are noted to be higher. Cord blood gas is generally performed in high risk births, although some centres perform routine analysis. Uterine contraction during labour results in fetal stress and lower arterial cord pH, and birth via Caesarean section without onset of labour results in higher arterial cord pH. A cord pH less than 7 is associated with adverse neonatal outcomes[345]. Other studies examining the association between reduced growth velocity and neonatal outcome have used a threshold of 7.15[257, 315], therefore, this threshold was used in analysis.

Arterial cord pH was recorded in 427 of 636 cases (67%). Arterial cord pH values were dichotomised to 0 for above 7.15 and 1 for below 7.15 and binary logistic regression was performed to assess the predictive ability of changes in growth velocity to predict this outcome (table 5.5). In all cases odds ratios (exp B) were very close to 1, and all measurements methods with the exception of the IG21 AC velocity centile were not significant. This implies there is no significant relationship between measurement of change in growth velocity and neonatal acidosis.

Table 5.5 *Predictive ability for adverse outcome and markers of fetal compromise*

Cord pH< 7.15 (recorded in 427)						
Variable	**Coef (B)**	**SE**	**OR (exp B)**	**95% CI**		**P value**
				lower	***upper***	
Δ AC centile	0.009	0.004	1.009	1.001	1.018	0.036
Δ AC centile STD	0.009	0.004	1.009	1.000	1.018	0.044
IG21 ACGV centile	0.029	0.011	1.029	1.008	1.052	0.007
Δ EFW centile	0.011	0.005	1.011	1.001	1.022	0.032
Δ EFW centile STD	0.011	0.005	1.011	1.001	1.021	0.035
CPR PI < 5th (recorded in 291)						
Δ AC centile	-1.477	0.545	0.228	0.078	0.665	0.007
Δ AC centile STD	-0.621	0.145	0.538	0.405	0.714	<0.001
IG21 ACGV centile	-6.553	1.230	0.001	0.000	0.016	<0.001
Δ EFW centile	-2.386	0.661	0.092	0.025	0.336	<0.001
Δ EFW centile STD	-2.474	0.688	0.084	0.022	0.325	<0.001
MCA PI <5th (recorded in 291)						
Δ AC centile	-0.004	0.005	0.996	0.987	1.005	0.361
Δ AC centile STD	-0.004	0.153	0.996	0.987	1.005	0.358
IG21 GV centile	-0.033	0.10	0.968	0.949	0.986	0.099
Δ EFW centile	-0.009	0.005	0.991	0.981	1.002	0.099
Δ EFW centile STD	-0.009	0.171	0.991	0.980	1.002	0.102
UA PI > 95th (recorded in 636)						
Δ AC centile	-0.008	0.003	0.992	0.986	0.997	0.004
Δ AC centile STD	-0.009	0.003	0.991	0.985	0.997	0.003
IG21 GV centile	-0.031	0.007	0.969	0.956	0.982	<0.001
Δ EFW centile	-0.014	0.004	0.986	0.980	0.993	<0.001
Δ EFW centile STD	-0.015	0.004	0.986	0.979	0.993	<0.001
NNICU admission (recorded in 636)						
Δ AC centile	0.002	0.003	1.002	0.997	1.008	0.405
Δ AC centile STD	0.002	0.003	1.002	0.966	1.008	0.461
IG21 GV centile	-0.011	0.007	0.990	0.977	1.003	0.119
Δ EFW centile	0.002	0.003	1.002	0.995	1.009	0.595
Δ EFW centile STD	0.002	0.003	1.002	0.995	1.009	0.618
5 min APGAR < 7 (recorded in 636)						
Δ AC centile	0.006	0.006	1.006	0.994	1.018	0.307
Δ AC centile STD	0.007	0.006	1.007	0.995	1.020	0.231
IG21 GV centile	0.038	0.016	1.039	1.007	1.072	0.018
Δ EFW centile	0.010	0.007	1.010	0.996	1.024	0.158
Δ EFW centile STD	0.011	0.007	1.011	0.997	1.026	0.116

Δ AC centile: difference in abdominal circumference centile (third trimester – second trimester)
Δ AC centile STD: standardised difference in abdominal circumference centile (third trimester – second trimester)
IG21 ACGV centile: abdominal circumference growth velocity centile
Δ EFW centile: difference in estimated fetal weight centile (third trimester – second trimester)
Δ EFW centile: standardised difference in estimated fetal weight centile (third trimester – second trimester)
NNICU: neonatal intensive care unit

Cerebroplacental Ratio

The fetus is able to respond to hypoxia and make adaptive adjustments to growth rate. It has been shown that fetuses are able to modify cerebral blood flow and alter the impedance of the middle cerebral artery near term, thus increasing diastolic flow in the middle cerebral artery. This may be more pronounced during episodes of acute hypoxia[23]. The cerebroplacental ratio (CPR) is the ratio of middle cerebral artery pulsatility index (MCA PI) and the umbilical artery pulsatility index (UA PI), and it has been suggested this index is the best predictor of intrapartum fetal compromise[346]. The Fetal Longitudinal Assessment of Growth (FLAG) study in 2017 reported that fetuses with reduced growth velocity (a drop of 30 centiles in customised EFW or AC) between 28 and 36 weeks gestational age were more likely to have a CPR below the 5th centile, indicating placental insufficiency[257]. This association has also been reported between mid-trimester measurements and those performed at 36 weeks gestational age[258].

The cerebroplacental ratio was calculated in 291 of the 636 cases (46%). Values were dichotomised to 0 for above the 5th centile for gestational age and 1 for below. Binary logistic regression was performed to assess the predictive ability of changes in growth velocity to predict this outcome (table 5.5). Change in growth velocity was predictive of CPR below the 5th centile, most notably the IG21 growth velocity centile. Predicted probabilities are presented in figure 5.4.

Middle Cerebral Artery Doppler

The middle cerebral artery Doppler was performed in 291 of the 636 cases (46%). The pulsatility index values were dichotomised to 0 for above the 5th centile for gestational age and 1 for below. Binary logistic regression was performed to assess the predictive ability of changes in growth velocity to predict this outcome (table 5.5). In all cases odds ratios (exp B) were not statistically significant.

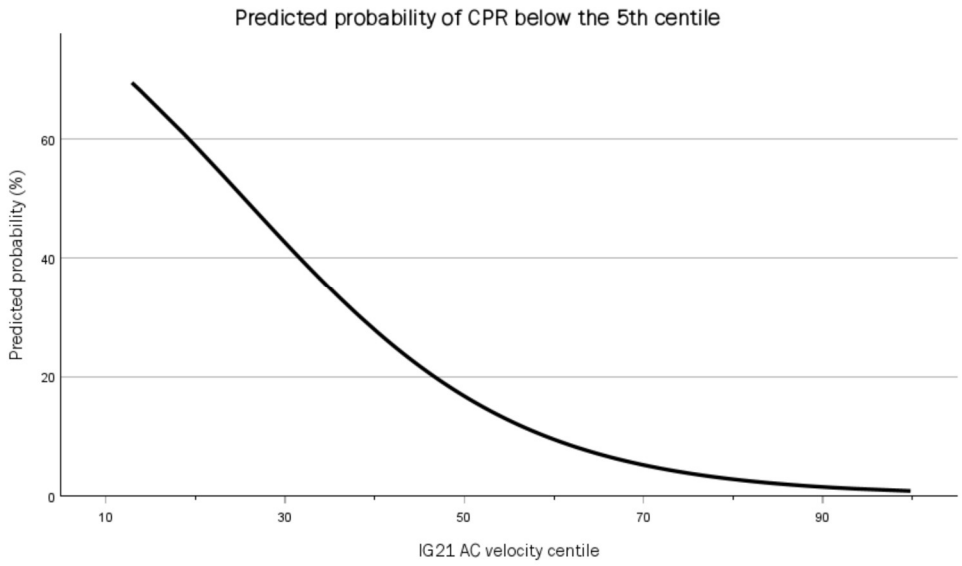

Figure 5.4 *IG21 abdominal circumference growth velocity centile and predicted probability of CPR below the 5th centile*

Umbilical artery Doppler

The umbilical artery Doppler was performed in all 636 cases (46%). Pulsatility index values were dichotomised to 0 for above the 95th centile for gestational age and 1 for below. Binary logistic regression was performed to assess the predictive ability of changes in growth velocity to predict this outcome (table 5.5). In all cases odds ratios (exp B) were statistically significant for small incremental decreases in growth velocity. Assessment of the IG21 growth velocity centile revealed that for an additional incremental change in centile, the odds of an abnormal umbilical artery Doppler increased by 3.1%.

Neonatal intensive care admission

Whether the newborn was admitted to neonatal intensive care was documented in all 636 cases. Admission was dichotomised to 0 for not admitted and 1 for admitted. Binary logistic regression was performed to assess the predictive ability of changes in growth velocity to predict this outcome (table 5.5). In all cases odds ratios (exp B) were not statistically significant.

Apgar scores

Apgar scores are measures of a newborn's physical condition and were originally designed to help identify newborns that may need respiratory support, not as an outcome measure. Therefore, the Apgar score in isolation should not be considered evidence of asphyxia or hypoxia[347]. However, these scores are routinely collected at one and five minutes, unlike arterial cord pH. The score is based on features of the newborn including skin colour, pulse, breathing, muscle tone and reflex. Each parameter is scored 0 – 2 for a total score of up to 10. An Apgar score greater than 7 at 5 minutes indicates the newborn is adapting well, and scores less than 7 indicate possible complications[235]. Apgar scores were recorded in all 636 cases and dichotomised to 0 for above 7.15 and 1 for below. Binary logistic regression was performed to assess the predictive ability of changes in growth velocity to predict this outcome (table 5.5). In all cases odds ratios (exp B) were not statistically significant.

Composite indicators

There were only four cases in this cohort with more than one adverse neonatal finding; one case with NNICU admission and Apgar score < 7.00, and three cases with NNICU admission and arterial cord pH < 7.15. Additional analyses were not performed given the low numbers.

5.7 Discussion

This study failed to identify a predictive relationship between altered growth velocity and adverse neonatal events. However, a relationship was identified between growth velocity and the cerebroplacental ratio, in keeping with other studies[257, 315, 346]. Morales-Rosello et al suggested the cerebroplacental ratio was a predictor of adverse postnatal outcomes irrespective of fetal weight, and pointed out that many clinical guidelines recommend middle cerebral artery Doppler only in the case of SGA (estimated fetal weight or abdominal circumference below the 10th centile)[248]. Indeed, in the study cohort, middle cerebral artery Doppler was performed in just under half of cases.

The reluctance for adoption of routine middle cerebral artery Doppler in third trimester ultrasound examinations may be due to perceptions regarding false positive results. Periods of increased fetal activity have been shown to affect middle cerebral artery Doppler, in particular, increased peak systolic velocities and end diastolic velocities with resultant reduction in pulsatility index[348].

How to best apply CPR in clinical management is yet to be determined. The DRIGITAT trial reported adverse perinatal outcomes for small for gestational age fetuses was not improved when the intervention was expedited birth[349]. However, the RATIO37 study suggested that for small for gestational age fetuses, planned birth on the basis of CPR did improve outcomes[350] . A recently published randomised control trial (CEPRA) investigated the impact on management of term appropriate for gestational age fetuses presenting with reduced fetal movements. Key findings were that when CPR was calculated and reported to the managing clinician, perinatal outcomes were improved[351]

This research study found abdominal circumference growth velocity centiles calculated from the IG21 fetal growth velocity standards (method 1) demonstrated stronger relationships with outcome measures than did the centile difference between third and second trimester AC and EFW (methods 2 and 3). The relationships between the IG21 AC centile with arterial cord pH< 7.15, CPR PI < 5th centile, UA PI > 95th centile and 5 min APGAR < 7 were statistically significant.

This research study identified strong correlation between standardised and unstandardised differences between third trimester abdominal circumference centiles and estimated fetal weight centiles. This suggests ‘eyeballing’ centile differences may be a reasonable approach for everyday practice, particularly when the interval between ultrasound examinations is substantial. Mongelli et al demonstrated with mathematical modelling that short inter-scan intervals increased the false positive rate for fetal growth restriction by 30.8% for a one week interval and 16.9% for a two week interval[352]. This emphasises the importance of an appropriate interval between observations when assessing growth velocity.

5.8 Chapter Summary

Many studies have demonstrated altered fetal growth velocity is associated with pathological fetal growth and adverse neonatal outcomes. However, significant heterogeneity exists in methods to measure growth velocity and thresholds for defining reduced or increased growth velocity, which affects generalisability and clinical interpretation. Reference charts and centile curves for growth velocity have been published, however methods to quantify fetal growth velocity vary in complexity and often present data in a way that is difficult to interpret.

In this study of retrospective data assessing growth velocity between the mid trimester and the third trimester, a predictive relationship between reduced growth velocity and abnormal cerebroplacental ratio was demonstrated, particularly for abdominal circumference IG21 growth velocity centiles. The cerebroplacental ratio (CPR) is the ratio of the middle cerebral artery pulsatility index (MCA PI) and umbilical artery pulsatility index (UA PI) and a reduced CPR is considered an early marker of placental insufficiency[353] and has the potential to improve prediction of adverse outcomes in growth restricted fetuses[148]. The CEPRA randomised control trial of term (> 37 weeks) AGA fetuses presenting with reduced fetal movements reported improved perinatal outcomes when clinicians were aware of the CPR[351]. However, interobserver reliability of the MCA PI has been questioned (and therefore the CPR), leading to the recommendation that abnormal measurements are repeated to avoid false positive results[148].

The relationship between reduced growth velocity and abnormal CPR is in keeping with other published reports[257, 300, 315], however, how to best apply this finding in clinical practice remains uncertain. This may be due in part to discrepancies in thresholds used to define abnormal, for example, a comparison of five CPR charts demonstrated variability ranging from 15% to 33% in measurements classified as below the 5th (depending on gestational age)[354]. When management decisions are based on the CPR, this has the with the potential to increase induction of labour from 5.6% to 22.3%[354].

As discussed in chapter 3, the survey of current practice in reporting third trimester fetal measurements revealed diverse Doppler practices in Australia and New Zealand, including when Doppler is performed, how it is reported, and the choice of reference charts. The thresholds for the use of fetal and maternal Doppler in third trimester ultrasound varied in terms of the gestational age and estimated fetal weight cut-off. When middle cerebral artery Doppler was performed, the CPR was reported in 55% of cases. Until MCA Doppler is routinely performed in third trimester ultrasound, the CPR remains an underutilised measurement in Australian clinical practice Whether reduced growth velocity is a more sensitive marker of placental insufficiency than CPR or whether the combined predictive value of both markers are more effective in diagnosing placental insufficiency is an area requiring more research.

Chapter Six

Conclusions, implications and recommendations

6.1 Introduction

The aims of this research were to examine the historical development of ultrasound as a tool to measure the fetus, to investigate current practice in performing and reporting third trimester ultrasound in Australia, to assess the suitability of the recently published Intergrowth 21st growth standards for use in the Australian population, and to examine methods of measuring fetal growth velocity and whether this measure can be incorporated into clinical practice.

There were four main areas of enquiry in this thesis:

1. Key to understanding fetal growth measurement is an appreciation of the evolution of ultrasound measurements used in contemporary practice and the circumstances that led to adoption of these particular measurements. Closely linked to this is the development of the many charts of fetal size that these measurements are referenced to, each chart employing different methodologies with the potential to affect suitability for use in different populations.

2. Establishing current Australian practice in performing and reporting third trimester ultrasound is an important element of this research. It is important to understand which reference charts are currently used and to assess areas where practice differs. Potential drivers and barriers to adopting consistent practice must be acknowledged before there can be meaningful improvement.

3. Multiethnic populations such as Australia's present a challenge in identifying suitable fetal measurement charts that can be used nationwide. The Intergrowth 21st (IG21) charts were published in

2014 using a strict methodology and a multi-national population cohort, with the aim of creating international standards for fetal size[38]. These charts are potentially well suited for use in Australia but require validation.

4. Size and growth are not synonymous, and longitudinal assessment of fetal growth via serial measurements of size has been proposed as an alternative method to identify pathologic growth. How to best measure growth velocity and defining what constitutes a significant change in growth velocity is yet to be established[17]. Broadly speaking, there are two main approaches; the simplest is to assess the change in centile of a given parameter over time. Indeed, the consensus definition of fetal growth restriction defines reduced growth velocity as measurements crossing centiles by two quartiles[22]. The second is to assess the incremental change in size of a given parameter over time, and compare this to a reference chart.

6.1.1 The history of fetal growth measurement

Chapter Two described the evolution of the ultrasound parameters that are used to measure fetal size, gestational age, estimate fetal weight, and evaluate fetal wellbeing. Fundamental to fetal measurements were reproducibility and how these parameters related to neonatal measurements. Improvements in ultrasound technology underpinned recognition of anatomical landmarks for fetal measurements, assisting reproducibility of measurements and improving accuracy. Fetal ultrasound measurement was a key factor in the concept of an ultrasonic estimated due date, reinforcing the importance of accurate dating when assessing fetal growth. Technological advances played a critical role in the evolution of Doppler techniques used to assess fetal wellbeing. For each parameter of fetal measurement, researchers developed charts of fetal measurements for the purposes of establishing gestational age, assessing growth, and fetal wellbeing. However, many charts have been published over the years, each developed for different populations. Furthermore, methodologies of chart design vary considerably and have led to the current situation where it is unclear which chart is most suitable for the Australian population. As a

consequence, defining normal and pathological fetal growth and how to best screen for abnormal fetal growth remain contentious issues.

6.1.2 Current practice in reporting third trimester fetal measurements

The diagnosis of abnormal growth is based on differences between the actual measurements and expected measurements for a given gestational age. As fetal growth restriction is associated with increased risk of adverse perinatal outcomes[3, 171], the ability to identify these fetuses allows for increased antenatal monitoring to inform clinical decisions regarding delivery and improve perinatal outcomes[18]. The centile assigned to the estimated weight and/or abdominal circumference plays a critical role in classifying fetal size as appropriate for gestational age, small for gestational age, or as fetal growth restriction. Measurements less than the 10th centile for gestational age or greater than the 90th centile are triggers to change clinical management[17] and measurements below the 3rd centile indicate fetal growth restriction[6]. Of particular concern are the many reference charts with heterogeneous chart methodologies which mean that centiles for a given measurement may vary considerably. The potential for misdiagnosis of growth restriction leading to additional interventions and patient anxiety cannot be underestimated. For example, it is possible for a fetus to be diagnosed as growth restricted by one practitioner, and later that day found to be normally grown by a practitioner using a different reference chart. Consistent use of reliable growth charts is necessary to recognise abnormal fetal growth and inconsistency in current Australian practice highlights issues in adherence to clinical practice guidelines.

A survey was performed to establish current Australian practice in performing and reporting third trimester ultrasound, followed by semi-structured interviews with general radiologists to gain further insights on reporting practices. Findings revealed inconsistent reporting practices persist with four population-based charts for fetal biometry in current use: ASUM[172], Hadlock[79, 180-182], Chitty[99, 183, 184], and Raine (Newnham, personal communication). Some respondents indicated charts derived from different populations were used selectively for different measurement parameters. For the most part, the

estimated fetal weight centile was derived from a fetal weight chart although 14% of respondents indicated customised estimated fetal weight charts were used. Doppler practices are diverse, including when Doppler is performed, how it is reported, and the choice of reference charts. Similar to fetal biometry measurements, Doppler indices are defined as abnormal when certain centile thresholds are exceeded and therefore affected by chart choice. Worryingly, knowledge of which Doppler charts were used was poor.

Comments made by respondents raised concerns regarding the lack of standardisation in how third trimester ultrasound is performed and the potential for diagnostic error. Most acknowledged recommendations and guidelines from professional bodies was an important factor influencing the choice of reference chart, however, inconsistent reporting practices suggest awareness of these recommendations is lacking.

When compared to Australian and New Zealand survey in 2013[34] this study demonstrated some improved consistency regarding choice of fetal biometry charts used in current practice and improved awareness of which chart is used. However, the potential for false positive and false negative diagnosis of fetal growth restriction remains, and it is therefore possible for a fetus to have conflicting diagnoses based on the providers' choice of reference chart. This situation will not change until there is consensus on which reference charts should be used.

6.1.3 Validation of IG21 charts for the Australian population

The Intergrowth 21st growth standards were published in 2014 using a strict methodology and a multi-national population cohort, with the aim of creating international standards for fetal size[38].An observational, prospective, cross-sectional multicentre study was undertaken to assess whether the Intergrowth 21st charts were suitably robust to be adopted into Australian clinical practice.

The distribution of observations from this study were compared to the currently recommended charts (Westerway[172] and Chitty[184] for femur length) and the Intergrowth 21st charts to determine which reference best suited the study population. Assessment of Z-score distribution was the method chosen, the premise being that if the chart is suitable for use in the population, the mean of the Z-score distribution will be 0 with a standard deviation of 1. Four measurement parameters were assessed: the biparietal diameter, head circumference, abdominal circumference and femur length. The Intergrowth 21st charts did not perform well for the study cohort with a significant right-shift in distributions observed for head circumference, abdominal circumference and femur length, suggesting these charts are unsuitable for the Australian population.

In terms of assessing fetal growth, the abdominal circumference has more clinical impact than other parameters as measurements at thresholds below the 3rd centile are used to define fetal growth restriction and measurements below the 10th centile are used to define small for gestational age. Measurements above the 90th and 97th centiles are used to define large for gestational age and macrosomia. The distribution according to the Intergrowth 21st chart would result in a higher proportion of fetuses being classified as large for gestational age or macrosomic, with the clinical consequence of affecting timing and method of birth. Lower proportions below the 3rd and 10th centile have the potential to underdiagnose fetal growth restriction and small for gestational age.

It has been suggested that the 3rd, 10th, 90th and 97th thresholds determined by measurement standards, may not necessarily confer the same interpretation as when these thresholds are applied to population charts[110]. However, using a threshold of below the 3rd centile to define small for gestational age would represent just 0.49% of observations in this study. Similarly, a 97th centile to define large for gestational age would represent 19% of observation in this study.

Assessment of Z-score distributions for currently recommended charts did not demonstrate perfect distributions, however, were a better fit for the study population. The large right shift in distributions demonstrated by the Intergrowth 21st charts makes them unsuitable for adoption in Australian practice.

6.1.4 Fetal growth velocity

Many studies have demonstrated altered fetal growth velocity is associated with pathological fetal growth and adverse neonatal outcomes. However, significant heterogeneity exists in methods to measure growth velocity and thresholds for defining reduced or increased growth velocity, which affects generalisability and clinical interpretation. Broadly speaking, there are two main approaches; the simplest is to assess the change in centile of a given parameter over time. The second is to assess the incremental change in size of a given parameter over time, and compare this to a reference chart.

A retrospective study was performed to assess growth velocity between the mid trimester and third trimester. Growth velocity was calculated by simple assessment of centile change, standardised centile change (adjusting for the exact interval between examinations), and by calculating the incremental growth velocity centile developed from the Intergrowth 21st longitudinal cohort. The predictive ability for these growth velocity measurements to predict adverse neonatal outcome, including markers of placental insufficiency was evaluated.

All methods of measuring growth velocity correlated with birthweight, however the third trimester abdominal circumference centile and estimated fetal weight centile demonstrated stronger correlations, indicating growth velocity calculation did not confer additional advantage in birthweight prediction. No significant relationship between neonatal outcomes (cord pH, Apgar score, intensive care admission) were observed for any method of measuring growth velocity.

A predictive relationship was not observed between the tested methods of measuring growth velocity and abnormal umbilical artery Doppler or middle cerebral artery Doppler, however when considering the

ratio of these Doppler measures (the cerebroplacental ratio), a predictive relationship was demonstrated, particularly for abdominal circumference growth velocity centiles developed from the IG21 longitudinal cohort.

The relationship between reduced growth velocity and abnormal cerebroplacental ratio is keeping with other published reports, however, how to best apply this finding in clinical practice remains uncertain. This may be due in part to discrepancies in thresholds used to define abnormal, and inconsistent use of middle cerebral artery Doppler. As discussed in chapter 3, the survey of current practice in reporting third trimester fetal measurements revealed diverse Doppler practices in Australia and New Zealand, including when Doppler is performed, how it is reported, and the choice of reference charts. The thresholds for the use of fetal and maternal Doppler in third trimester ultrasound varied in terms of the gestational age and estimated fetal weight cut-off. When middle cerebral artery Doppler was performed, the cerebroplacental ratio was reported in 55% of cases. Until middle cerebral artery Doppler is routinely performed in third trimester ultrasound, the cerebroplacental ratio remains an underutilised measurement in Australian clinical practice Whether reduced growth velocity is a more sensitive marker of placental insufficiency than cerebroplacental ratio, or whether the combined predictive value of both markers are more effective in diagnosing placental insufficiency is an area requiring more research.

Assessment of three methods for measuring growth velocity demonstrated formal calculation of an incremental growth centile (Intergrowth 21st growth velocity) had better predictive abilities for adverse outcome than simple assessment of centile change over time. Whether this method warrants adoption into clinical practice requires further evaluation.

6.2 Study strengths and weaknesses

6.2.1 Current practice in reporting third trimester fetal measurements

A survey of ultrasound providers was conducted to investigate reporting practices for third trimester ultrasound and reasons behind the choice of reference charts. The estimated response rate was 15% of eligible RANZCOG members, and 18% of members of the RANZCR Obstetrics and Gynaecology Special Interest Group. Most responses (80%) were from Australian sonologists inclusive of all states and territories, with the majority (70%) practicing in major cities. New Zealand respondents were from major urban areas from seven of the twenty district health boards.

This study demonstrated inconsistent reporting practices persist for third trimester ultrasound, however, when compared to a survey conducted in 2013[34], it was evident that there was improved consistency in biometry charts used and a greater awareness of which chart is used. They way measurements are reported appears to be unchanged with most respondents using the centile for known gestational age. Similarly, awareness of which Doppler charts were used was unchanged from a previous survey[170], with the majority of respondents indicating they were unsure of which chart was used.

New findings revealed by this study include the selective use of charts derived from different populations for different biometry measures reported by 11% respondents, and the extent to which customised charts for estimated fetal weight have been adopted in Australia and New Zealand (14% of respondents). Input from general radiologists via semi-structured interview provided additional insights. There were clear similarities in reporting practices and knowledge of measurement charts used by the interview participants and survey respondents. Interview participants were aware of which fetal measurement charts were used in their practice, but unaware of which Doppler charts were used. A common theme of service provision emerged from the interviews, with participants indicating willingness to adopt reporting practices to align with that of the local tertiary centre or preferences of referring clinicians.

A study weakness is the relatively low response rate for the survey and difficulty engaging general radiologists. Survey distribution was initiated in different stages as it was managed by the professional bodies representing sonologists. While low response rates are typical of medical specialists, the impact of this on interpretation of these findings is unclear as it has been shown response rate is not always predictive of nonresponse bias when the target population is relatively homogenous[217], as is the case in this study. Participant interest in the survey topic is known to influence survey response rates[175], and the exponential increase of literature exploring the topic of fetal growth may have dampened enthusiasm from the obstetric ultrasound community to participate in a survey. Recruitment of general radiologists for interview was difficult and while responses largely echoed that of the survey respondents, this group saw themselves essentially as service providers. Questions regarding choice of fetal measurement chart did not cause as much concern for this group as it does for those in specialist obstetric ultrasound fields,

6.2.2 Validation of IG21 charts for the Australian population

An observational, prospective, cross-sectional multicentre study was conducted to assess fetal biometry in pregnant women in the second and third trimester to assess the performance of the IG21 growth standards in the Australian clinical setting. The findings of this research indicate the IG21 growth standards would result in over-diagnosis of LGA and under-diagnosis of SGA and growth restriction if adopted into Australian clinical practice.

The strengths of this study are the collation of a large dataset of prospectively collected data including ultrasound measurements, maternal characteristics known to influence fetal growth, and neonatal outcomes. Furthermore, the gestational age for all cases were established or confirmed by ultrasound performed between 8 and 14 weeks. Ultrasound measurements were collected following a standardised measurement protocol, made in triplicate, and operators were blinded to the measurements to reduce potential measurement bias.

The timing of prospective data collection unfortunately coincided with the Covid-19 pandemic which contributed to the lower than anticipated recruitment of participating sites and therefore study participants. Data collection was also suspended at different periods during the COVID-19 pandemic as directed by hospital management, and a combination of health workforce shortages and reassignment of staff to critical health areas resulted in one participating site withdrawing from the study. Furthermore, the ACT Human Ethics Research digital platform was upgraded during this period and delayed migration of the study protocol to the new platform and caused significant delays in the recruitment of participating sites. Instead of an Australia-wide study as envisaged, participating sites came from metropolitan and regional New South Wales (NSW) including the Australian Capital Territory (ACT). This raises the question of generalisability for the wider Australian population, as maternal characteristics of the study cohort differed slightly from published national data. Another study weakness is that the sample size of 1642 also fell short of the expected minimum of 2000 plus. This results in less precision in the outer centiles when modelling growth curves from the collected data, for comparison to the Intergrowth 21st curves. Therefore, the data analysis approach chosen was the assessment of Z-score distributions.

6.2.3 The role of growth velocity assessment in clinical practice

A retrospective study was performed to investigate methods of incorporating measures of growth velocity in third trimester ultrasound examinations. In Australia, there is a high uptake of a routine ultrasound examination in the mid trimester[341] (usually performed at 18 – 22 weeks), and while third trimester ultrasound is typically performed selectively, detection of FGR and prediction of adverse outcomes is improved when performed at 36 weeks[343]. The interval between the routine mid trimester scan and 36 weeks was selected as the period to assess growth velocity in this study.

The retrospectively collected dataset included maternal characteristics, second trimester ultrasound measurements, third trimester measurements and neonatal outcomes. The ability to initiate processes to reduce measurement bias were limited by the retrospective nature of the study. Data were sourced from

clinically indicated examinations performed in 2020 and 2021 from a single site. Mid trimester scan reports seldom included measurement centiles at this time, thus limiting the potential for altered growth velocity to change clinical management. Data sourced from a single site may limit generalisability of these findings.

A retrospective design is dependent on consistent high quality record keeping. A high rate of missing data was encountered when compiling the retrospective datasets, possibly due to two upgrades of the ACT hospital record management systems. Similarly, cord blood pH was not always measured or recorded which may raise issues with detection of neonatal acidosis.

6.3 Recommendations and future research

Inconsistent reporting practices persist for third trimester ultrasound, suggesting sonologists may be unaware of current guidelines or that the recommended fetal charts are considered unsuitable for the population. Research in how to best disseminate information regarding the standardisation of third trimester ultrasound would be beneficial in creating awareness new guidelines and acceptance through adoption into clinical practice. The development of new fetal measurement charts using methodologies accepted by the wider obstetric imaging community, would address the issue of chart suitability and also assist with widespread adoption. Different reference charts for fetal Doppler measures also produce different centiles for the same measurement, however, this issue is largely unappreciated. With most ultrasound practitioners unaware of which chart is used in their practice and heterogeneity in reporting practice, comparison of Doppler reference charts in the clinical setting would help inform clinical practice.

The IG21 charts do not appear suitably robust to recommend adoption into clinical practice. The right – shift in distributions for the AC in particular, has the potential to influence timing of birth and may confer neonatal morbidity associated with late gestation prematurity. The development of new fetal

measurement charts using robust methodologies based on an Australian population representative of the county's diversity is required.

There is evidence that reduced growth velocity is predictive of placental dysfunction, as evidenced by the relationship with the cerebroplacental ratio. This was most marked for abdominal circumference growth velocity centiles developed from the IG21 longitudinal cohort. However, a predictive relationship between altered growth velocity and adverse neonatal events was not identified. Growth velocity standardised and unstandardised differences between third and second trimester abdominal circumference and estimated fetal weight centiles had similar predictive performance. This suggests 'eyeballing' centile differences could be a reasonable approach for everyday practice when there is a substantial interval between ultrasound examinations. Future research on the application of fetal growth velocity and cerebroplacental ratio in clinical management is required.

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Appendix A

Pilot survey questionnaire

FETAL MEASUREMENT QUESTIONNAIRE

Thank you for participating in this pilot questionnaire to determine:

- *what is assessed in a standard third trimester ultrasound*
- *which fetal biometry reference charts are used in clinical practice in Australia*
- *methods for reporting fetal measurements in the third trimester*

Information about you and your workplace

1. **Which best describes your workplace? (if you work at multiple practices, select the answer that applies to the practice you are working at today)**

☐ Obstetrician led private practice
☐ Radiologist led private medical imaging practice
☐ Obstetrician led service in public hospital
☐ Radiologist led medical imaging service in public hospital

2. **My qualification in clinical ultrasound is:**

☐ DMU (general)
☐ DMU (obstetric)
☐ University post graduate diploma/masters (sonography)
☐ Other (please specify) _____

3. **I have been practising obstetric ultrasound for:**

☐ Less than 5 years
☐ 5-10 years
☐ More than 10 years

Third trimester ultrasound

4. **In my practice, a standard third trimester ultrasound includes (tick all that apply):**

☐ Bi-parietal diameter (BPD)
☐ Head circumference (HC)
☐ Occipital-frontal diameter (OFD)
☐ Abdominal circumference (AC)
☐ Femur length (FL)
☐ Humerus length (HL)
☐ Amniotic fluid index (AFI)
☐ Umbilical artery Doppler
☐ Middle cerebral artery (MCA) Doppler
☐ Ductus venosus (DV) Doppler

- ☐ Uterine artery Doppler
- ☐ Cervical length assessment
- ☐ Placental localisation
- ☐ Full fetal anatomy assessment (the same as the 18 – 20 week scan)
- ☐ Limited fetal anatomy assessment
- ☐ Biophysical profile
- ☐ Other (please specify) _____

Reporting third trimester ultrasound

5. In my practice, third trimester fetal measurements are usually reported alongside (tick all that apply):

- ☐ An equivalent number of weeks and days
- ☐ A reference range e.g. 5th to 95th centile
- ☐ The centile for this gestational age
- ☐ The number of standard deviations (SDs) below or above the mean
- ☐ The z-score

6. My practice uses the following reference charts for fetal biometry measurements:

- ☐ Do not know
- ☐ ASUM charts [Campbell-Westerway 2000 ANZJOG;40(3): 297-302/ASUM Policy D7 (2000)]
- ☐ Chitty 2002 BJOG 109:919-929
- ☐ Hadlock 1982 Am J Roentgenol 138:875-878
- ☐ Jeanty 1984 J Ultrasound med 1984;3:75-79
- ☐ In house reference range
- ☐ Schulter, Pritchard, Gill 2004 Australasian Radiol 48:480-486
- ☐ Snijders 1994 USOG 4:34-38
- ☐ IG21 [Papageorghiou A, Ohuma E, Altman D et al. 2014 INTERGROWTH-21st Lancet 384: 869–79]
- ☐ Other (please specify)_____

7. All ultrasound machines in my practice have the same reference charts set as the default:

- ☐ Do not know
- ☐ Yes
- ☐ No

8. In my practice, the estimated fetal weight (EFW) is included in the report for third trimester growth scans:

- ☐ Do not know
- ☐ Yes
- ☐ No ***go to question 11***

9. In my practice, the estimated fetal weight (EFW) is usually calculated by:

- ☐ Do not know

- ☐ Hadlock (BPD-HC-AC-FL)
- ☐ Hadlock (BPD-AC-FL)
- ☐ Hadlock (HC-AC-FL)
- ☐ Hadlock (BPD-AC)
- ☐ Hadlock (AC-FL)
- ☐ Warsof (BPD-AC)
- ☐ Shepard (BPD-AC)
- ☐ Schild (Female BPD-AC-FL)
- ☐ Schild (Male BPD-AC-FL)
- ☐ Schild (HC-AC-FL)
- ☐ Birnholz (BPD-TAD)
- ☐ Birnholz (BPD-OFD-TAD)
- ☐ Combs (HC-AC-FL)
- ☐ Other (please specify)_____

10. In my practice, the EFW is usually reported alongside (tick all that apply):

- ☐ Do not know
- ☐ An equivalent number of weeks and days
- ☐ A reference range e.g. 5th to 95th centile
- ☐ The centile for this gestational age
- ☐ The number of standard deviations (SDs) below or above the mean
- ☐ The z-score

11. In my practice, the reference chart used for each fetal biometry measurement and/or EFW are cited in the report:

- ☐ Do not know
- ☐ Yes
- ☐ No

12. In my practice, a fetus is reported as small for gestational age or growth restricted when:

- ☐ Do not know
- ☐ The EFW is below the 10th centile
- ☐ The EFW is below the 5th centile
- ☐ The AC is below the 10th centile
- ☐ The AC is below the 5th centile

13. In my practice, Middle Cerebral Artery Doppler pulsatility index (MCA PI) is included in a third trimester ultrasound assessment:

- ☐ As part of the standard ultrasound examination
- ☐ When the EFW is below the 10th centile
- ☐ When the EFW is below the 5th centile
- ☐ When requested by the referring doctor
- ☐ When requested by the reporting doctor

☐ It is never part of a third trimester ultrasound assessment
☐ Other (please specify) _____

14. In my practice, Ductus Venosus Doppler is included in a third trimester ultrasound assessment:

☐ As part of the standard ultrasound examination
☐ When the EFW is below the 10th centile
☐ When the EFW is below the 5th centile
☐ When requested by the referring doctor
☐ When requested by the reporting doctor
☐ It is never part of a third trimester ultrasound assessment
☐ Other (please specify)_____

15. In my practice, Uterine Artery Doppler is included in a third trimester ultrasound assessment:

☐ As part of the standard ultrasound examination
☐ When the EFW is below the 10th centile
☐ When the EFW is below the 5th centile
☐ When requested by the referring doctor
☐ When requested by the reporting doctor
☐ It is never part of a third trimester ultrasound assessment
☐ Other (please specify)_____

Choice of reference charts

16. Recommendations and guidelines of professional bodies were an important consideration in the choice of reference chart used in my practice

Strongly disagree	Disagree	Neutral	Agree	Strongly agree
○	○	○	○	○

17. Chart methodologies were an important consideration in the choice of reference chart used in my practice

Strongly disagree	Disagree	Neutral	Agree	Strongly agree
○	○	○	○	○

18. Referring practitioner preferences were an important consideration in the choice of reference chart used in my practice

Strongly disagree	Disagree	Neutral	Agree	Strongly agree
○	○	○	○	○

19. The software configuration of the ultrasound machine was an important consideration in the choice of reference chart used in my practice

Strongly disagree	Disagree	Neutral	Agree	Strongly agree
○	○	○	○	○

20. Is there anything you would like to add about how third trimester ultrasound is performed and reported?

_____

_____

_____

_____

_____

Pilot survey interview guide

INTERVIEW GUIDE for Sonologist Interview

Information about you and your practice

1. How long have you been practising obstetric ultrasound?

2. What are your ultrasound qualifications?

Information about reporting fetal growth

3. What are some of the most common clinical indications for third trimester growth ultrasound?

4. Do you know which reference charts for fetal biometry measurements are used in your practice?

   (for example)
   - ASUM charts [Campbell-Westerway 2000 ANZJOG;40(3): 297-302/ASUM Policy D7 (2000)]
   - Chitty 2002 BJOG 109:919-929
   - Hadlock 1982 Am J Roentgenol 138:875-878
   - Jeanty 1984 J Ultrasound med 1984;3:75-79
   - In house reference range
   - Schulter, Pritchard, Gill 2004 Australasian Radiol 48:480-486
   - Snijders 1994 USOG 4:34-38
   - IG21 [Papageorghiou A, Ohuma E, Altman D et al. 2014 INTERGROWTH-21st Lancet 384: 869–79]

5. Why have you chosen these charts?

6. Do you know which formula is used to calculate estimated fetal weight?

   (*for example*)
   - Hadlock (BPD-HC-AC-FL)
   - Hadlock (BPD-AC-FL)
   - Hadlock (HC-AC-FL)
   - Hadlock (BPD-AC)
   - Hadlock (AC-FL)
   - Warsof (BPD-AC)
   - Shepard (BPD-AC)
   - Schild (Female BPD-AC-FL)
   - Schild (Male BPD-AC-FL)

- Schild (HC-AC-FL)
- Birnholz (BPD-TAD)
- Birnholz (BPD-OFD-TAD)
- Combs (HC-AC-FL)

7. Do you know why this method was chosen?

8. How do you report growth measurements?

   (for example)
   - alongside an equivalent number of weeks and days *or*
   - a reference range or
   - centile for gestational age *or*
   - SDs below or above the mean *or*
   - the z-score.

9. Why have you chosen this method of reporting?

10. Do you provide graphical information in your reports?

11. What cut-offs do you use to report a fetus as small for gestational age or growth restricted?

12. Do you ask the sonographer to perform additional Doppler measurements when the biometry suggests growth restriction?

13. What do you write in the conclusion when biometry suggests growth restriction?

Adopting new fetal biometry reference charts

14. What do you know about IG21 charts published in 2014?

15. If ASUM recommended the adoption of a difference chart, would your practice adopt the new charts?

16. Do you see any potential barriers in implementing new charts?

17. Is there anything else you would like to add about how fetal growth is measured by ultrasound?

Final questionnaire

Section 1: Information sheet and electronic consent

Participant Information Sheet

Third trimester ultrasound and fetal measurements questionnaire

Researcher:

My name is Debra Paoletti,

I am a part time research student at the Australian National University (ANU) Medical School. My PhD research topic is *Fetal Growth Measurement*. As part of this research I would like to determine which fetal biometry reference charts are in current use and how third trimester ultrasound is reported. I am also a practising sonographer, however, this research is not part of my current employment duties. I am writing to invite you to voluntarily participate in a study by completing a questionnaire about fetal biometry reference charts and third trimester ultrasound.

Project Title:

Current Australian and New Zealand practice in third trimester ultrasound and measuring fetal growth.

General Outline of the Project:

The purpose of this research is to determine how fetal growth is reported, the reference charts currently used in Australian and New Zealand practices, and the factors that influenced the choice of reference chart.

Ultrasound practitioner members of the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG), the Royal Australian and New Zealand College of Radiologists (RANZCR), and the Australasian Society for Ultrasound in Medicine (ASUM) are invited to complete a questionnaire about fetal biometry reference charts and third trimester ultrasound.

Participant Involvement:

Participation is voluntary and you do not have to complete the questionnaire. As you will not be asked to give identifying details on the questionnaire, it will not be feasible to withdraw from the study once the questionnaire is submitted. The questionnaire will take approximately 10 - 15 minutes. It has been made available via the web-based survey tool Qualtrics.

Information provided by this questionnaire could be used to assist with strategies to achieve consistency in the way fetal growth is measured and reported.

Confidentiality:

Your questionnaire responses do not include any personal identifiers. Your questionnaire responses will be sent to a link at Qualtrics.com where data will be stored in a password protected electronic format. Qualtrics does not collect identifying information such as your name, email address, or IP address. Therefore, your responses will remain confidential. No one will be able to identify you or your answers, and no one will know whether or not you participated in the study.

Privacy Notice:

In collecting your personal information within this research, the ANU must comply with the Privacy Act 1988. The ANU Privacy Policy is available at https://policies.anu.edu.au/ppl/document/ANUP_010007 and it contains information about how a person can:

- Access or seek correction to their personal information;
- Complain about a breach of an Australian Privacy Principle by ANU, and how ANU will handle the complaint.

Data Storage:

Data will be stored on a password protected ANU computer. Data backup will include external hard-drive and ANU OneDrive. Data will be stored for a minimum of five years from the date of any publication arising from the research.

Queries and Concerns:

If you have any further questions on the research project or require additional information I can be contacted at u6146524@anu.edu.au or by phone at 02 51247357

This research partially fulfils the requirements for a PhD under the supervision of Prof. Michael Peek. If you have any questions or concerns about this research please contact Prof. Peek michael.peek@anu.edu.au

Ethics Committee Clearance:

The ethical aspects of this research have been approved by the ANU Human Research Ethics Committee (Protocol 2017/418). If you have any concerns or complaints about how this research has been conducted, please contact:

Ethics Manager

The ANU Human Research Ethics Committee

The Australian National University

Telephone: +61 2 6125 3427

Email: Human.Ethics.Officer@anu.edu.au

Electronic consent:

Please select your choice below. You may print a copy of this consent form for your records.

Clicking on the "Agree" button indicates that

- You have read the above information
- You voluntarily agree to participate

○ Agree

○ Disagree

Section 2: Demographics

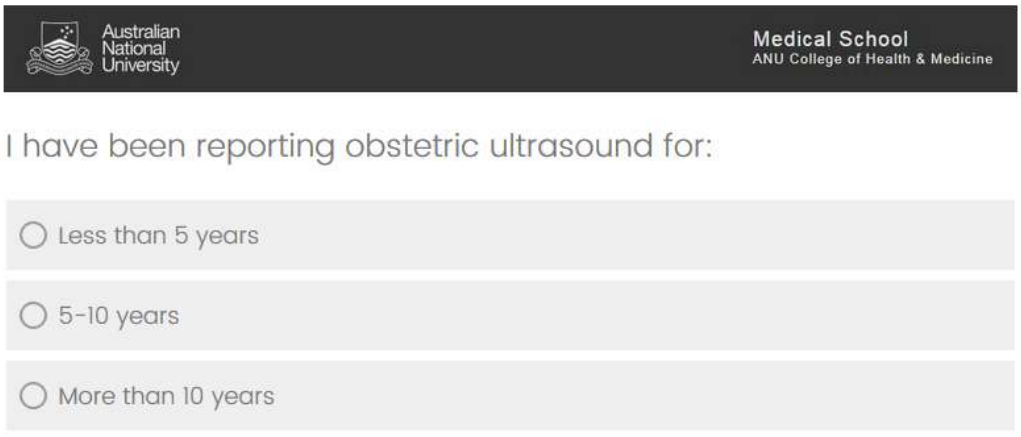
About you & your Workplace

Which best describes your workplace? (if you work at multiple practices, select the answer that applies to the practice you are working at today)

- ○ Obstetrician led private practice
- ○ Radiologist led private practice
- ○ Obstetrician led service in a public hospital
- ○ Radiologist led medical imaging service in a public hospital
- ○ Other (please specify)

The postcode for my practice is:
(if you work at multiple practices, select the answer that applies to the practice you are working at today)

- ○ Australia
- ○ New Zealand



Section 3: Reporting third trimester ultrasound

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Reporting third trimester ultrasound

At this practice, I usually report third trimester fetal measurements alongside:
(please select all that apply)

- [ ] An equivalent number of weeks and days e.g. AC 270mm, 31w1d
- [ ] A reference range e.g. AC 270mm, 30w3d - 32w0d
- [ ] The measurement and standard deviation e.g. AC 270mm +/- 2SD
- [ ] The percentile for the known gestational age e.g. AC 270mm, 90th percentile
- [ ] The z score e.g. AC 270mm, z = 1.28
- [ ] Other (please specify)

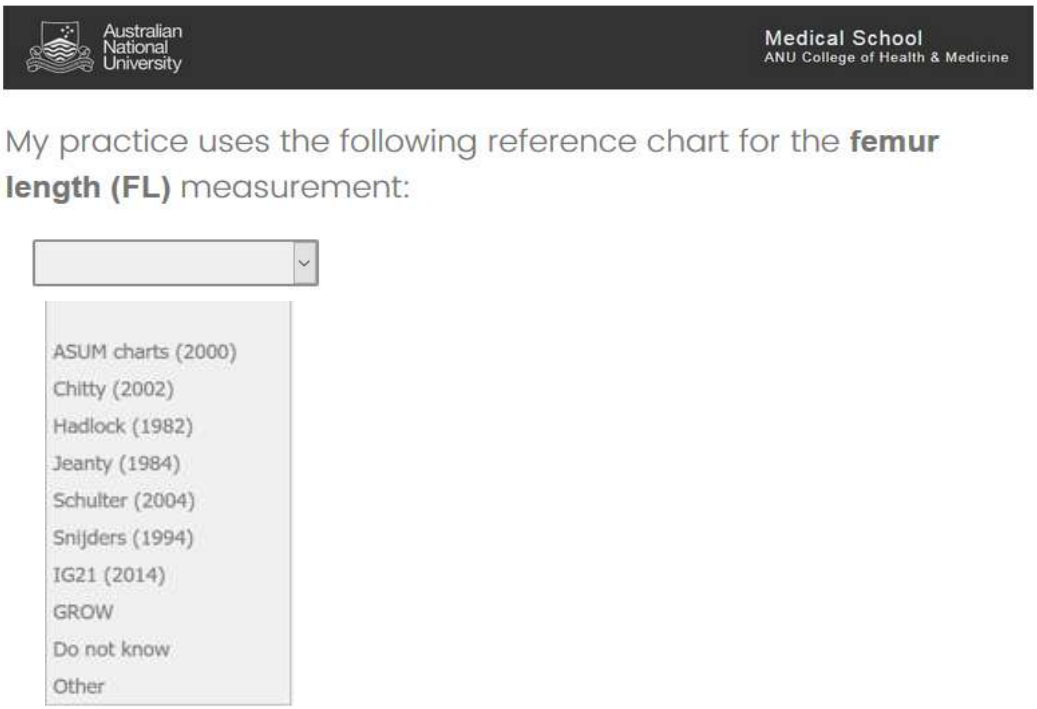
My practice uses the following reference chart for the **biparietal diameter (BPD)** measurement:

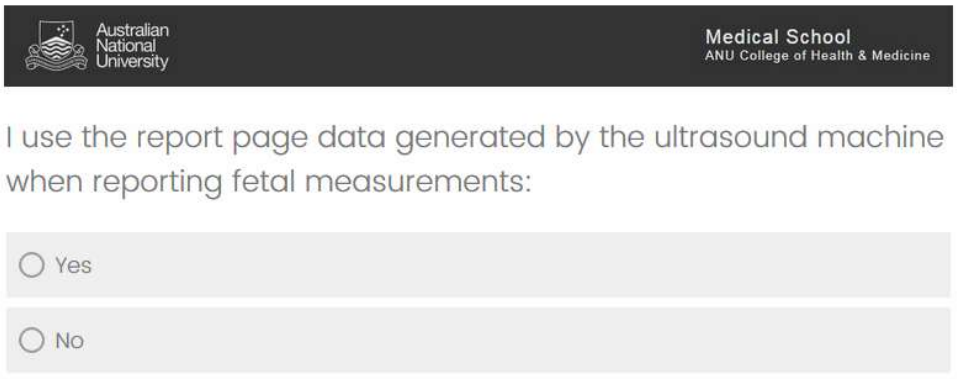
My practice uses the following reference chart for the **head circumference (HC)** measurement:

- ASUM charts (2000)
- Chitty (2002)
- Hadlock (1982)
- Jeanty (1984)
- Schulter (2004)
- Snijders (1994)
- IG21 (2014)
- GROW
- Do not know
- Other

My practice uses the following reference chart for the **abdominal circumference (AC)** measurement:

- ASUM charts (2000)
- Chitty (2002)
- Hadlock (1982)
- Jeanty (1984)
- Schulter (2004)
- Snijders (1994)
- IG21 (2014)
- GROW
- Do not know
- Other





Display logic is used for the next two questions:

YES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All ultrasound machines in my practice are configured with the same reference charts:
Yes
No
Do not know

NO


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In my practice, measurements are reported using:
A digital reporting tool (e.g. ViewPoint or Astraia)
A customised chart

In my practice, the **estimated fetal weight (EFW)** is calculated by:

- Hadlock (BPD-HC-AC-FL)
- Hadlock (BPD-AC-FL)
- Hadlock (HC-AC-FL)
- Schild (sex specific BPD-AC-FL)
- Shepard (BPD-AC)
- IG21 (HC-AC)
- Combs (HC-AC-FL)
- Do not know
- Other

I usually report **EFW** alongside:

- ○ The percentile for the known gestational age e.g. 1481g, 71st percentile
- ○ The percentage error of the estimation e.g. 1481g +/- 15%
- ○ The error of the estimation in grams e.g. 1481g +/- 222g
- ○ The z score e.g. 1418g, z=0.58
- ○ Nothing - I just report the EFW in grams
- ○ Other (please specify)

The reference charts used for each measurement (BPD, HC, AC, FL) and EFW are cited in my reports:

- ○ Yes
- ○ No

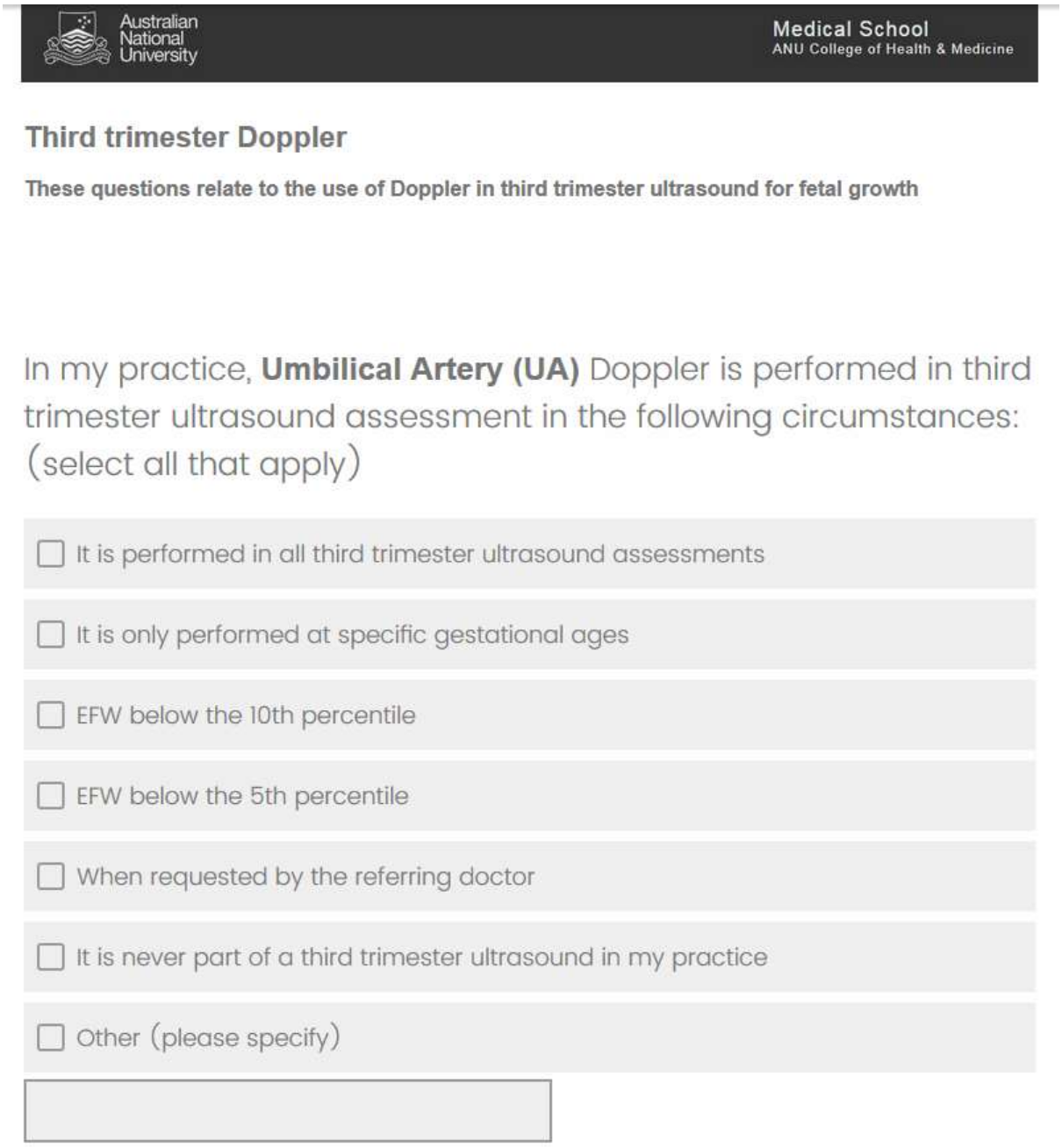
Reference charts used by this practice differ from those used by other practices I have worked at:

- ○ Yes
- ○ No
- ○ Do not know
- ○ I have not worked at other practices

I comment the fetus may be small for gestational age or growth restricted at the following cut-off:
(select all that apply)

- [ ] EFW below the 10th percentile
- [ ] EFW below the 5th percentile
- [ ] AC below the 10th percentile
- [ ] AC below the 5th percentile
- [ ] Both EFW and AC below the 10th percentile
- [ ] Both EFW and AC below the 5th percentile
- [ ] I don't comment on small for gestational age or growth restriction
- [ ] Other (please specify)

Section 4: Third trimester Doppler



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Third trimester Doppler

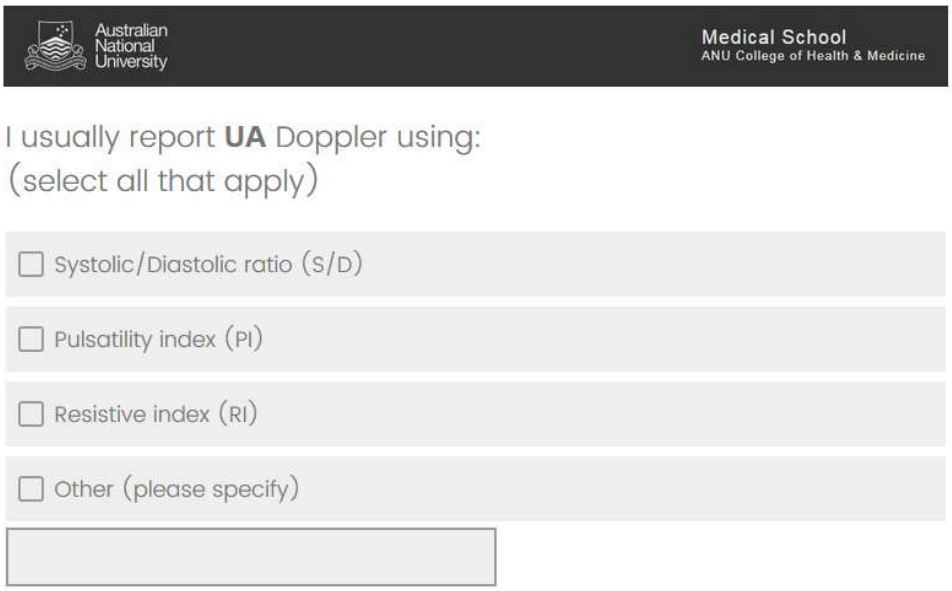
These questions relate to the use of Doppler in third trimester ultrasound for fetal growth

In my practice, **Umbilical Artery (UA)** Doppler is performed in third trimester ultrasound assessment in the following circumstances: (select all that apply)

- ☐ It is performed in all third trimester ultrasound assessments
- ☐ It is only performed at specific gestational ages
- ☐ EFW below the 10th percentile
- ☐ EFW below the 5th percentile
- ☐ When requested by the referring doctor
- ☐ It is never part of a third trimester ultrasound in my practice
- ☐ Other (please specify)

Skip logic is used to skip the next three questions when 'It is never part of a third trimester ultrasound in my practice' is selected.

Display logic is used for the next question when 'It is only performed a specific gestational ages' is selected.



My practice uses the following reference chart for **UA** Doppler:

- Trudinger (1985)
- Arduini (1990)
- Baschat (2003)
- Acharya (2005)
- Medina Castro (2006)
- Ebbing (2007)
- Parra-Cordero (2007)
- Do not know
- Other

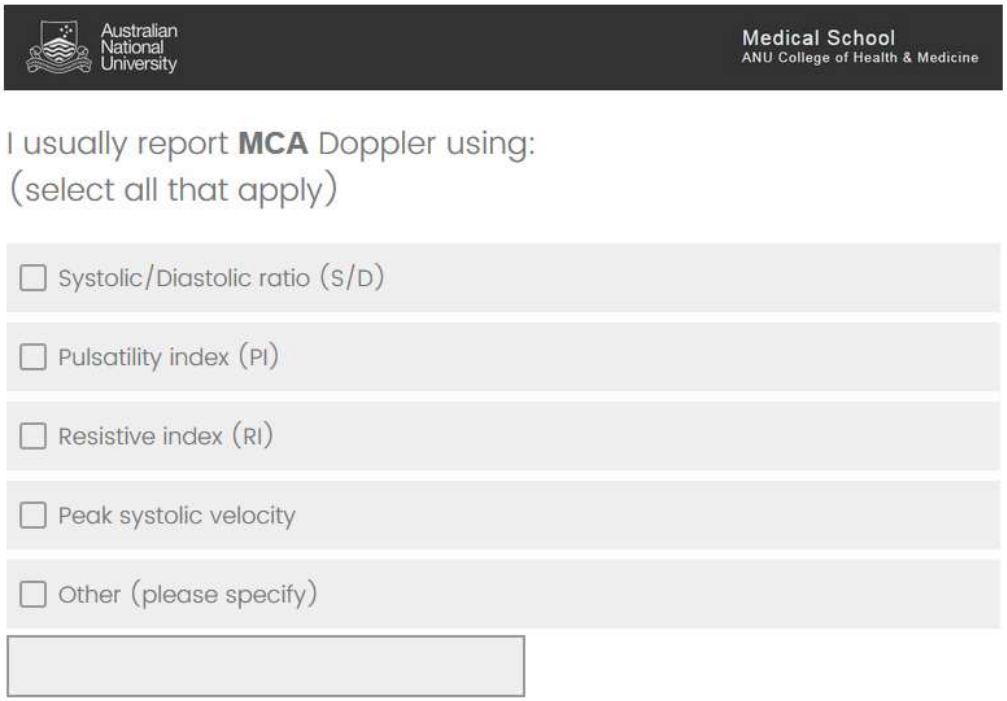
In my practice, **Middle Cerebral Artery (MCA)** Doppler is performed in third trimester ultrasound assessment in the following circumstances:
(select all that apply)

- ☐ It is performed in all third trimester ultrasound assessments
- ☐ It is only performed at specific gestational ages
- ☐ EFW below the 10th percentile
- ☐ EFW below the 5th percentile
- ☐ When the UA Doppler is abnormal
- ☐ When requested by the referring doctor
- ☐ It is never part of a third trimester ultrasound in my practice
- ☐ Other (please specify)

Skip logic is used to skip the next six questions when 'It is never part of a third trimester ultrasound in my practice' is selected.

Display logic is used for the next question when 'It is only performed a specific gestational ages' is selected.

Please specify the gestational ages at which **MCA** Doppler is performed:



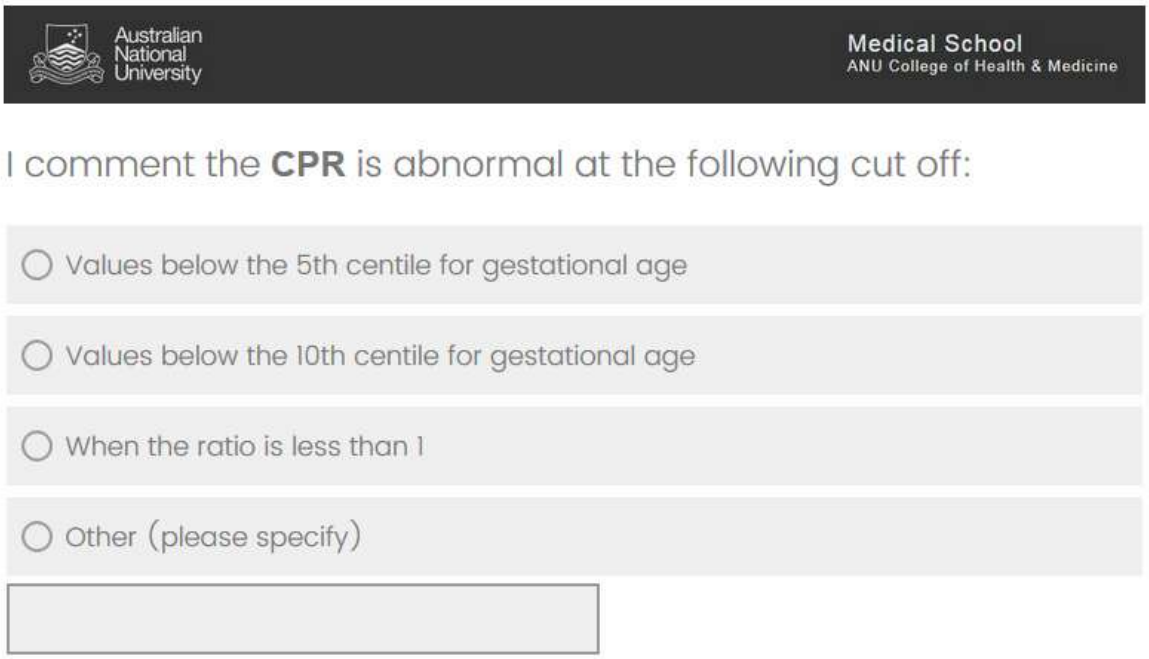
My practice uses the following reference chart for **MCA** Doppler:

- Kurmanavicius (2001)
- Baschat (2003)
- Medina Castro (2006)
- Ebbing (2007)
- Bahlmann (2012)
- Ayoola (2016)
- Do not know
- Other

In my practice, the **Cerebroplacental ratio (CPR)** is reported:

- ○ Yes
- ○ No

Skip logic is used to skip the next two questions when 'no' is selected: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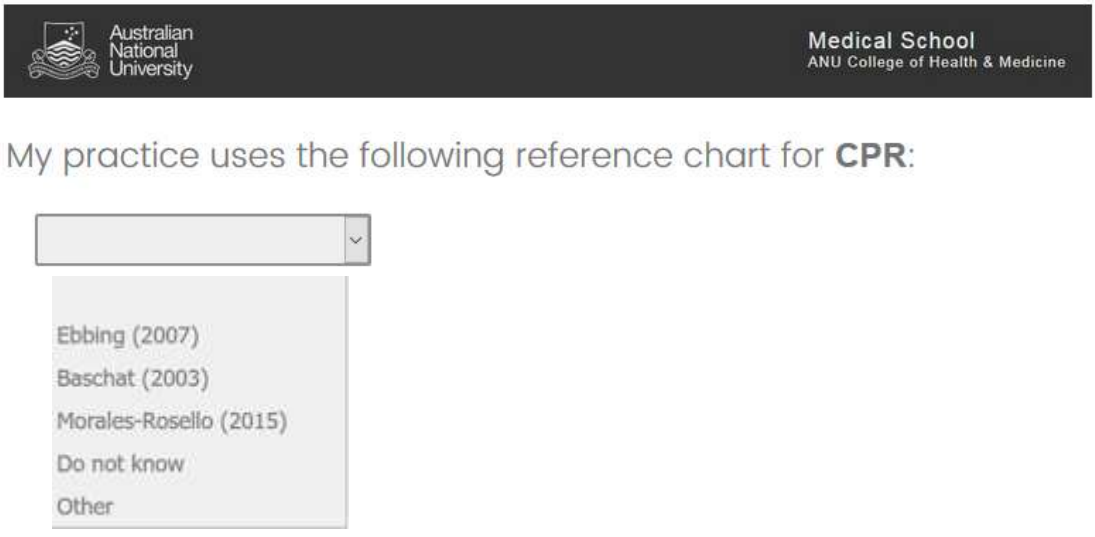
I comment the CPR is abnormal at the following cut off:
Values below the 5th centile for gestational age
Values below the 10th centile for gestational age
When the ratio is less than 1
Other (please specify)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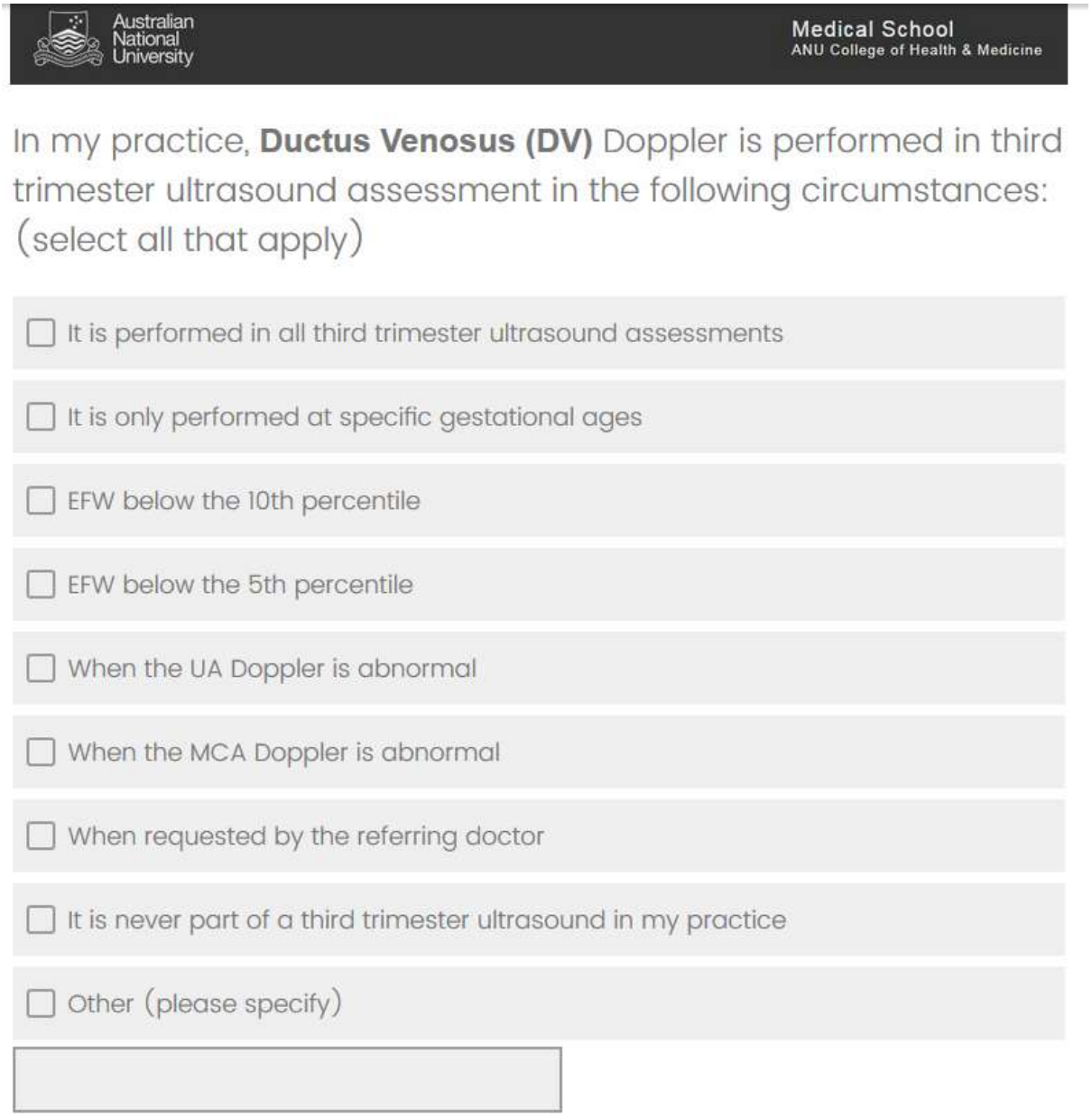
My practice uses the following reference chart for CPR:
Ebbing (2007)
Baschat (2003)
Morales-Rosello (2015)
Do not know
Other



Skip logic is used to skip the next three questions when 'It is never part of a third trimester ultrasound in my practice' is selected.

Display logic is used for the next question when 'It is only performed a specific gestational ages' is selected.

Please specify the gestational ages at which **DV** Doppler is performed:

I usually report **DV** Doppler using:
(select all that apply)

- ☐ Systolic/Diastolic ratio (S/D)
- ☐ Pulsatility index (PI)
- ☐ Pulsatility Index for Veins (PVIV)
- ☐ Resistive index (RI)
- ☐ Peak systolic velocity
- ☐ Other (please specify)

My practice uses the following reference chart for **DV** Doppler:

- Hecher (1994)
- Kessler 2006
- Tongprasert (2012)
- Turan (2015)
- Do not know
- Other

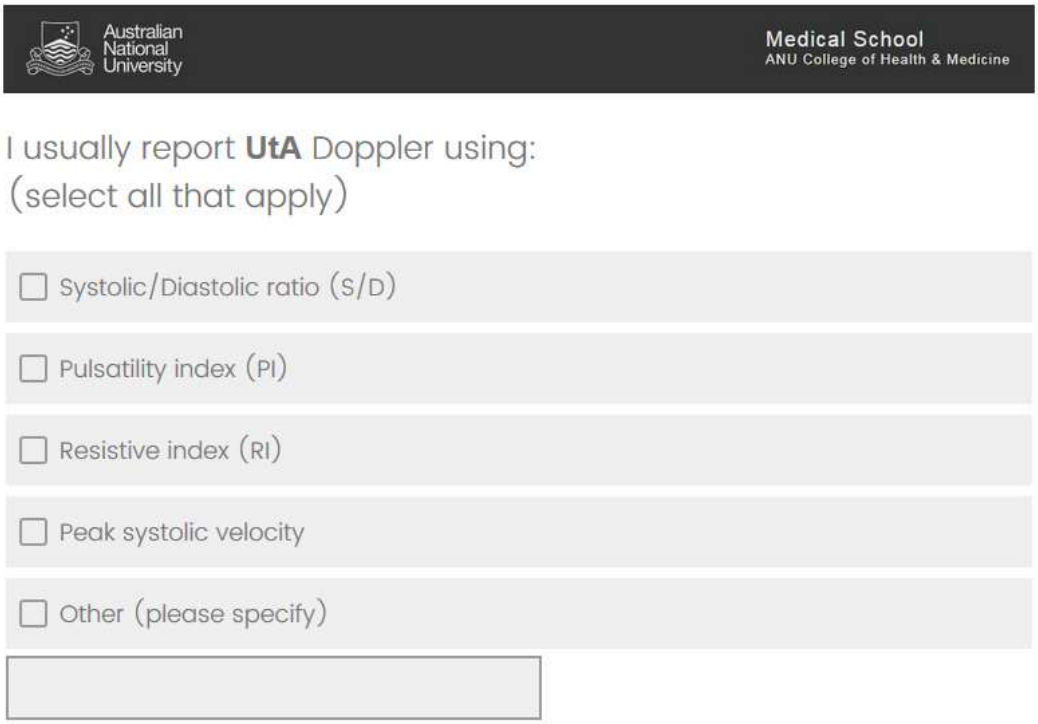
In my practice, **Uterine Artery (UtA)** Doppler is performed in third trimester ultrasound assessment in the following circumstances: (select all that apply)

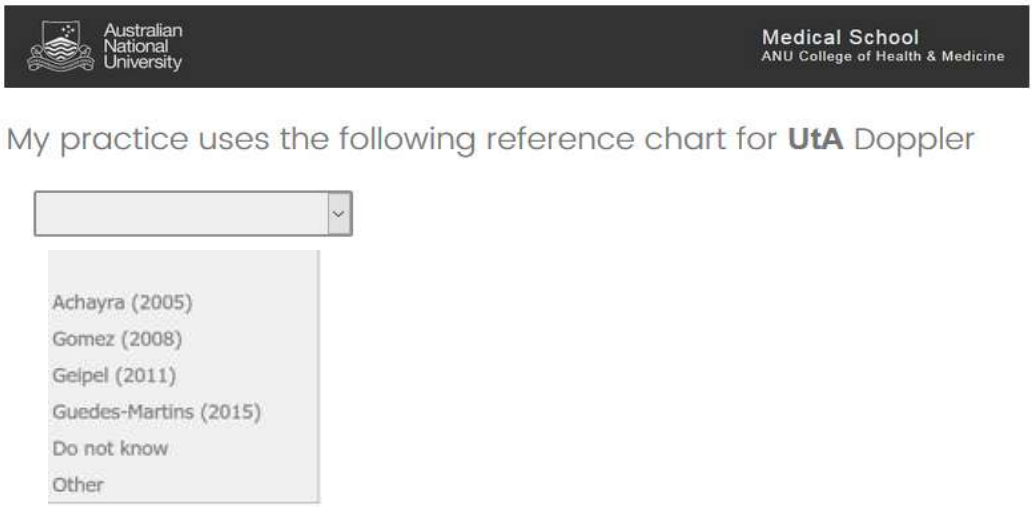
- [ ] It is performed in all third trimester ultrasound assessments
- [ ] It is only performed at specific gestational ages
- [ ] EFW below the 10th percentile
- [ ] EFW below the 5th percentile
- [ ] When requested by the referring doctor
- [ ] It is never part of a third trimester ultrasound in my practice
- [ ] Other (please specify)

Skip logic is used to skip the next three questions when 'It is never part of a third trimester ultrasound in my practice' is selected.

Display logic is used for the next question when 'It is only performed a specific gestational ages' is selected.

Please specify the gestational ages at which **Ut** Doppler is performed:




Australian National University
Medical School
ANU College of Health & Medicine
My practice uses the following reference chart for UtA Doppler
Achayra (2005)
Gomez (2008)
Gelpel (2011)
Guedes-Martins (2015)
Do not know
Other

Section 5: Choice of reference chart

Choice of reference chart

To what extent do you agree that the following factors are important considerations in the choice of reference charts?

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
Recommendations and guidelines of professional bodies	○	○	○	○	○
Chart methodologies	○	○	○	○	○
Referring practitioner preferences	○	○	○	○	○
The software configuration of the ultrasound machine	○	○	○	○	○

Under which circumstances would you consider changing the reference charts used at your practice?

	Extremely likely	Somewhat likely	Neither likely nor unlikely	Somewhat unlikely	Extremely unlikely
ASUM recommendation	○	○	○	○	○
RANZCR recommendation	○	○	○	○	○
RANZCOG recommendation	○	○	○	○	○

Is there anything you would like to add about how third trimester ultrasound is performed and reported?

Interview Guide for Radiologist Interview

My name is Deb Paoletti. Thank you for participating in this interview.

Before we begin, can I confirm you have received the participant information sheet and consent form for the interview, and are happy for the audio of this interview to be recorded? Can you please email me the signed the consent form?

To remind you, I am a part time research student at the Australian National University (ANU) Medical School. My PhD research topic is Fetal Growth Measurement. As part of this research I would like to determine which fetal biometry reference charts are in current use and how third trimester ultrasound is reported in Australian and New Zealand practice. I am also a practising sonographer, however, this research is not part of my current employment duties. I am inviting you to voluntarily participate in an interview about fetal biometry reference charts and third trimester ultrasound.

The project title is Current Australian and New Zealand practice in third trimester ultrasound and measuring fetal growth.

The purpose of this research is to determine how fetal growth is reported, the reference charts currently used radiology practices, and the factors that influenced the choice of reference chart.

Participation is voluntary and you can withdraw participation at any time until the work is prepared for thesis and publication. If you decide to withdraw your data will be destroyed and not used.

The interview will take approximately 30 minutes, but may be longer if you wish. The questions are not invasive but if there is a question you do not wish to discuss we can skip it. Importantly, there are no right or wrong answers.

There is a very small risk of third party identification. To minimise this, you will not be asked any personal identifying information in the interview. Interviewees will be coded as Radiologist (1,2,3…) Responses

which inadvertently contain identifiable information will be removed during transcription. Data used in thesis and future publication will describe participating radiologists according to this code and will not refer to geographic location which could potentially identify the interviewee.

In collecting your personal information within this research, the ANU must comply with the Privacy Act 1988. The ANU Privacy Policy is available at https://policies.anu.edu.au/ppl/document/ANUP_010007 and it contains information about how a person can:

- Access or seek correction to their personal information;
- Complain about a breach of an Australian Privacy Principle by ANU, and how ANU will handle the complaint

Data, including the recorded interview will be stored on a password protected ANU computer. Data backup will be on ANU OneDrive. Data will be stored for a minimum of five years from the date of any publication arising from the research. After this time, recorded interviews will be destroyed. De-identified data will be archived electronically and retained by the principal researcher.

If you have any further questions on the research project or require additional information I can be contacted at debra.paoletti@anu.edu.au or by phone at 02 61747357

This research partially fulfils the requirements for a PhD under the supervision of Prof. Michael Peek. If you have any questions or concerns about this research please contact Prof. Peek michael.peek@anu.edu.au

The ethical aspects of this research have been approved by the ANU Human Research Ethics Committee (Protocol 2017/418). If you have any concerns or complaints about how this research has been conducted, please contact:

Ethics Manager

The ANU Human Research Ethics Committee

The Australian National University

Telephone: +61 2 6125 3427

Email: Human.Ethics.Officer@anu.edu.au

Information about you and your practice

1. Is your workplace a private medical imaging practice or a public hospital service?

2. What is the postcode of your practice?

3. Please tell me how long have you been reporting obstetric ultrasound?

4. Did you complete an ultrasound qualification in addition to your radiology qualification?

Information about third trimester obstetric ultrasound and reporting fetal growth

5. Can you estimate what proportion of your practice's workload is made up of third trimester growth scans?

6. What are some of the most common clinical indications for third trimester growth scans?

The following questions refer to routine fetal biometry measurements, the BPD, HC, AC, FL and EFW

7. Tell me how you report third trimester fetal measurements.

Prompts:

- Do you refer to the report page generated by the US machine when reporting the fetal measurements and estimated fetal weight?
- Do you report a centile for the known gestational age?
- Do you report the error in measurement?
- What charts are used in your practice?
    - for example ASUM, Chitty, Hadlock, Jeanty, IG21
- Do you cite the chart in the report?
- Do you know which formula is used to calculate estimated fetal weight?
    - for example, Hadlock (BPD-HC-AC-FL), Hadlock (BPD-AC-FL), Hadlock (HC-AC-FL), Hadlock (BPD-AC), Hadlock (AC-FL)
- Do you know which reference chart is used for EFW ?
    - for example Hadlock, Australian National Birthweight Chart
- What cut-offs do you use to report a fetus as small for gestational age or growth restricted?

8. Please tell me why these particular reference charts and EFW formula used at your practice?

Prompts:

- Is your equipment configured with the same charts?
- Are these charts the same as ones you have used when working at other practices?

The following questions refer to the use of Doppler in the third trimester

9. Please describe under what circumstances Doppler is used in the third trimester and how these measurements are reported.

Prompts:

- Which Doppler index/indices do you report?
- Why is that particular one reported?/What are the reasons for co-reporting Doppler indices?
- Do you know which Doppler charts are used at your practice?
- What cut-offs do you use to report abnormal Doppler parameters?
- Under what circumstances would additional Doppler measurements be performed?
    - (for example) Middle cerebral artery (MCA), Ductus venosus (DV), Uterine artery (UtA)

Adopting new fetal biometry reference charts

10. What are your thoughts regarding the adoption of new reference charts?

Prompts:

- If professional bodies (RANZCR,ASUM) recommended the adoption of a difference chart, would your practice adopt the new charts?
- Do you see any potential barriers in implementing new charts?

11. Is there anything that I have not covered that you would like to discuss about third trimester ultrasound?

Transcripts of general radiologist interviews

Radiologist 1
Can you estimate what proportion of your practice's workload is made up of third trimester growth scans? Um, ok in terms of average working day working week sort of thing? *Yeah, whatever is easier to estimate.* Probably about, I'd say, let me think, probably somewhere between sort of 5 – 10% sort of thing would be growth scans and then we've got probably similar sort of morphs and first trimesters. We cover a big region obviously and plus we do a lot of the most of the public outpatient work still, so yeah. *So without putting words in your mouth would it be fair to say about a third of your obstetric workload would be made up of third trimester growth scans?* Yeah, yeah
What are some of the most common clinical indications for third trimester growth scans? Um, listen the whole range. It might be small fundal height, it might be um you know some problem in a previous pregnancy, it might be, ah, a low PAPP-A, I mean it might be decreased fetal movements. I would say that it's probably more and more it's becoming because of past history, some sort of problem in the past with a pregnancy, but there's also lots of reasons when people set up for an antenatal visit there's a relatively low threshold these days just to get an ultrasound I think to make sure everything's OK, and you know, check growth and liquor and Dopplers and those sorts of things. So um, yeah, how does that sound?
Tell me how you report third trimester fetal measurements. Sorry, just to add to that you now see of course you get referrals (the business has slowly been growing over the years) people are doing their own scans, they then sort of say they think they've seen something slightly abnormal in their own scan so they're getting you to do the formal scan to check. So that's the other one to throw in the mix. But as I say, there's no dominant referral, it's a whole bunch of those different things. So sorry…
That's fine. We get those ones too. The next question was how you report third trimester fetal measurements? Ok so I've got a very standard way. Once there's an accepted EDD I always lead off with that and sort of say that based on the EDD the pregnancy should be that size, normally in so many weeks and days, so that is stated and obvious that that's the EDD used for the pregnancy and with respect to and centiles that get discussed, and then I say whether or not there's a fetal heartbeat and so on. Then I give the measurements, and we still routinely just give the classics of ASUM for you know, BPD, head circumference, AC and femur length for pretty much every pregnancy, and, ah, it would be every pregnancy, and once we get to the third trimester and there is an agreed EDD I only then give centiles I don't give the weeks and days – I'd only do that if say there wasn't an established EDD and there'd been no prior studies and this was the first for the pregnancy (obviously that's rare). Usually by then 90 – 95% of patients have had you know at least 2 or God knows how many more. Um, hopefully there is an agreed EDD, but what I find fascinating is that these days how infrequently that's put on a referral.

Anyway, you go back and check and go it looks like clearly this is the agreed EDD because there was a dating scan that correlated with the NT scan so in that case that's the assumed EDD but not put on the referral by the obstetrician or GP obstetrician, so I say the assumed EDD so that anyone reading my report knows OK well, that's the EDD being used and that correlates therefore with the centile. And, so as I say I give those percentiles for those 4 measurements and then I put the EFW, estimated fetal weight, and then I put in brackets Hadlock 3 so it's clear which algorithm I'm using um so if people want to compare apples with apples they go oh well he used Hadlock 3 - and all the machines in our practice are set to Hadlock 3 including our machines in XXX [rooms in regional town, part of same imaging group] and we've encouraged XXX [level 2 hospital], not that we run that any more to have the same so that everything's comparable, know what I mean?

Yeah, totally

I put in brackets Hadlock 3, I give the estimated, then I give the +/- which is… now I'm not too sure if you can change the setting for that in the machine, you probably can um I'm trying to remember if that's adjustable but from memory that's around 12% I think, and then I give +/- and say it sits on the x centile, and then if they have had a previous third trimester scan (I never go back and compare it with the morph, I think that's not relevant) but if they've had a third trimester scan I note that 2 weeks ago or 4 weeks ago or whatever, the AC was on x centile and EFW was on z centile so that they can see what the trend is (although we also obviously produce trend charts they can look at), but actually written in the report they've got that written in there to actually read if that makes sense.

Yep, that's very thorough I must say.

Please tell me why these particular reference charts and EFW formula used at your practice?

Good question – let me open the case I've got here, 'cause over the years and we've obviously tried to link in with you guys so we're trying to use the same charts. For the BPD, HC, AC and FL we use ASUM and as I say for EFW we use Hadlock 3

And for your EFW do you also use the Hadlock birthweight chart or are you using the Australian standard birthweight chart?

Ah, OK, now you got me.

That's alright, it is a bit complex

Yeah, I'm just looking at it and it's got here author name Hadlock 3, um I'm not too, yeah so, and it's got here looks like setting A, whatever A is on a Tosh machine, so sorry I can't tell you that

No, that's OK. When you're writing the last bit of your report to you report a fetus as being small for gestational age or growth restricted, and if you do, what cut offs do you use?

Um, so yes I do. I give, um, er, with respect to liquor I always give a subjective assessment, AFI if it's a singleton pregnancy and deepest pocket, so all three sort of assessments or measurements, if you like, and if everything's normal, everything's in the normal range, I don't necessarily have a comment or impression or conclusion, or anything not necessarily, unless there was something written on the referral that seemed to show a level of anxiety of whoever wrote it, um, or if there's a specific question to answer if you know what I mean, um, but, um, if there was um ah but if it's otherwise I will put its small or large for dates and the cut off I use for that is the 10th centile of either, you know, AC and EFW, no sorry, EFW. So yeah 10th centile of 90th I'll say large or small for days but if it's the AC centile and that's the only abnormality and EFW's in the normal range, I'll just say AC's on x centile and no other adverse feature identified, you know, if there was low liquor or there was abnormal Doppler or something like that I'd often document that. Does that make sense?

Yeah. On the report too do you say which charts you've used? Do you say these centiles are ASUM centiles for instance?

Well, um, no, we don't. No. I mean, that's something we've informed our local referrers about, and 'cause we go to fortnightly O&G ultrasound meeting. But actually, on the report itself we don't say that BPD, HC, AC, FL follow ASUM charts, apart from mentioning Hadlock 3. In terms of how that Hadlock measurement correlates with a centile, and again, I've forgotten which centile chart we use for that, but anyway… I don't actually have it in there

That's fine. Interestingly, different papers have called different Hadlock charts different things, would you believe, so is Hadlock 3 the 4 parameter one from your point of view?

No, no. So that's HC, AC, and FL .

OK perfect.

Not BPD, because as we know the BPD can be small if the head's a bit doliocephalic and so on, so.

Absolutely. I personally agree with you, but that's not the purpose of what my interview's about. It's just to work out what people are doing. The next question was about why these charts but I understand from what you've already said was that it was based on being uniform and with discussion with your referrers etc .

Yeah, we wanted uniformity across the practice and was the thing we always do both here and in XXX and like if you add up all our machines there'd be about 10 machines or something. Um, making sure that they're all set to the same charts and whatever so that is the patient comes in on a different machine it shouldn't make any difference, because we've had those problems you know a machine gets serviced or you get a new machine and suddenly all your presets are gone and you find the most bizarre things going which includes… it's something we are very forceful with 'cause we've got Tosh, or Canon as they now are, and as I say in the past we used to provide a service to XXX and we ensured there was conformity there, and it's now another practice there, at least we encourage them to have the same as us as we do most of their antenatal clinic stuff, their outpatient stuff, so if they get measured when they're in hospital then at least there's uniformity. Um, and it's also something we discuss at that fortnightly O&G meeting. Um and ah and so that people are aware and if for whatever reason they want to come back to us and say well, every few years you get a new obstetrician comes to town and says 'why are you using Hadlock 3 or whatever?' and you go through it. Anyway, know what I mean?

Yeah, totally. That's good. I've only got a couple more things left to ask you if you're still with me.

Sure

Please describe under what circumstances Doppler is used in the third trimester and how these measurements are reported.

OK, so we routinely always do the umbilical artery. But we only do the MCAs, and this is something I've really been strong about is that we only use it when there is justification because there is the theoretical risk proven on vitro of micro cavitation and micro heating and um there's strong pulsed waves, so if any of the following are present after 22 weeks AC less than 10th centile, EFW less than 10th centile, AC and/or EFW crossing more than 2 quartiles of centiles, AFI less than 5cm or deepest pocket less than 2cm. or the umbilical artery average PI greater than the 95th centile.

Very comprehensive!

(laughter)

Which index would you report for the umbilical artery then?

I'll just get to that because…I just have to bring this up. I have it on my computer and I bring it up every time. Um, and again it's the one we got from you guys in Canberra and so once again it's so that we've got that uniformity so if a patient goes to Canberra hopefully everything's been measured the same way. Let's see… Ebbing C, Rasmussen S from Ultrasound OG 2007.

Awesome. Do you…

Do you still use that one?

Yeah, yeah. Do you report the PI only or do you add in other indices for your referrers?

We report the PI only unless you're doing it because the PSV's relevant obviously. If it's just in the setting of a concern about growth, I just give the PI. Now, how do I report MCAs. OK, it's like I report umbilical artery Dopplers. I say, in the normal setting, I say, there's normal diastolic flow in the umbilical arteries and then I say the average PI x and I don't give a centile, because I sort of think, I'm still old fashioned, I still believe that normal is normal and it's only abnormal if it's abnormal, you know what I mean? And with the MCAs I say something like there's no reactively increase diastolic flow in the MCA and PI x centile, no, PI whatever it is the value and a lot more lately I've been sort of saying it lies between the 50th and 75th centile or something like that. I don't know why I'm doing that, it seems to be pressure, everyone seems to want to have these numbers but it just worries me that medicine's become this, you know, 'medicine by numbers' rather than sort of if it's clearly normal; in the past I used to say 'which is well above the 5th centile' or something like that but now I tend to give them a maybe a bit of an idea of where it sits. Does that make sense?

Totally. Do you ever do ductus venosus or uterine artery in the third trimester?

Ah, no, very rarely. We used to do ductus venosus but now we do the MCA. We sort of feel, our feeling is that if you then need to use the ductus venosus the baby's probably sick enough if it sort of needs that justification it shouldn't be in XXX etc so we very rarely do that unless specifically asked. And the same with uterine artery. By the time we're in the third trimester …no we don't routinely do uterine arteries, we only do when asked, usually earlier in the pregnancy.

What are your thoughts regarding the adoption of new reference charts?

Well, only if there is good justification for it. And given we're a community based practice, um, screening and tend not to be involved with really sick early third trimester pregnancies, there's no point in adopting anything suitable for that range of patients. That's why we stick to Hadlock 3 (used to be Hadlock 4, but now Hadlock 3). Um, but it's a question of I guess what's the evidence to justify the change and also what are other people using because there's no point in us changing if everyone else is still using what's been used in the past, conversely, no point in using what we've got if everyone else is changing to some more national, or whatever. If you guys in Canberra said to us look we've changed to x then yeah. Does that make sense?

Yeah. If the professional bodies got their act together though, like RANZCR, ASUM, RANZCOG made an agreement and put out a guideline, do you reckon your practice would adopt their recommendations?

Oh yes definitely, we'd certainly discuss it and probably adopt it. If all three of them said, you know, these are the charts you should be using for these reasons, you know, and we could see others were as well. As I say, it's just that uniformity. Most of our patients don't tend to move around, but you do get patients that move around and that's why I always mention at least that it's Hadlock 3, not that I don't necessarily say what percentile the chart is, but yeah, at least the actual figure is there,

Is there anything that I have not covered that you would like to discuss about third trimester ultrasound?
Um, no. I'm glad you didn't ask me about CPR, we never report the CPR, even when asked usually 'cause we think that if it's something that someone want to calculate they can themselves, but I believe it's role is at the very least controversial and once again I think it's medicine by numbers. I've had some new obstetrician in town here says 'what's he CPR?' and on the basis of a CPR even if everything else is pretty much in the normal range the obstetrician might deliver early and I think it's scary. So anyway. I'm glad you didn't ask me that.
(laughter)

Radiologist 2

Can you estimate what proportion of your practice's workload is made up of third trimester growth scans?
Percentage of ultrasounds or total workload including MRs, CT, Xray, procedures?
Well, whatever is easiest for you to estimate. So if we can work off your ultrasound workload if you like.
2%
So not doing that many then? Or do you think you're doing a lot?
How many…I'd say one or two a day. Because we do a lot of other things, that's why – not obstetrics we're talking about here, only third trimester correct?
That's right
Yeah, so that's pretty much it yes.

What are some of the most common clinical indications for third trimester growth scans?
Basically, there's always like small for growth baby, large for growth baby, or reduced movements. Very late sometimes you get some unusual PV spotting and also you know, low lying placenta, clear now, query progress, and diabetes you know macrosomia, query macrosomia. We have that kind of stuff, mainly growth scans.

Tell me how you report third trimester fetal measurements.
So mainly, in my mind there are three categories, so one is growth rate. Growth rate is concentrating more on the abdominal circumference and then obviously BPD, femur length and, ah, these are the things, then measurements of oligohydramnios, poly, amniotic volume. Then there are Dopplers, so umbilical artery Doppler and if there is a problem then MCA Doppler. And, ah, so these are the main fetal growth, maternal wellbeing, Dopplers, and ah, and they're done… fetal growth is Hadlock charts are used. Why they're used. I don't know, it's in the software in the machines. Now how Chitty is superior to Hadlock or how Hadlock is superior to Chitty, I never got into it that way and neither I think it's going change what I do or it will have an impact on the patients because that's why I didn't get too much deep into it.

Is that Hadlock for everything or just the estimated fetal weight?

Ah, estimated fetal weight and pretty much everything.

OK

I don't think we use Chitty at all.

When you report a measurement, do you report a centile for the known gestational age or do you report differently?

So I report centile and also I report the gestation according to that.

When you do the reports do you say which charts you've used?

No

When it comes to the estimated fetal weight do you compare the calculation that's done by the machine to a birthweight chart, do you know?, or do you use a fetal growth chart for that?

It's a fetal growth chart and it just comes up with a +/- 15%. And if it is abnormal then I go into detail of it, but if it's in the normal range then I pretty much [unintelligible]

What cut-offs do you use to report a fetus as small or large for gestational age?

It depends on the whole picture. So not only abdominal circumference is the main thing in my head I really want to be very very cautious about and is it's getting to somewhere around 5% or less than 5% of what it should be, 5 percentile, then I get worried and try to look into the causes, you know, maternal cause, fetal cause or placental cause, so things like that. So for your absolute number which I get worried or convinced is 5th percentile, that's like a gross scenario and obviously then…that's pretty much it if you're asking about the number.

Would you comment? So only comment when we've got numbers around the 5th centile, or do you comment…

I would comment if we're getting around 10th percentile.

OK

So 10th percentile, and there is no associated oligohydramnios, umbilical Dopplers are normal blah blah. No structural deformities seen, no oligohydramnios. This is likely, you know, and probably we can monitor in…ongoing monitoring is suggested. Something along those lines.

OK. With the charts on the machines, it's just how they came? You don't know why they were picked in particular?

That's correct. I have worked in 3 practices in the ACT region, private, and they all used Hadlock as far as I remember. There is no direct appreciation of which charts we're going to use, it's all, ah, a very low level activity if you like. Pretty much whatever came with the software that's pretty much good enough for us and our staff – we don't do too much high end cases.

No worries. So all your machines are the same, aren't they?

Same manufacturer, because when you buy from one it just makes logistic sense to buy everything all machines from same vendor because you can use the same probe, like a small probe, MSK probe into the other room and start, and also the software to get it into PACS system.

Then you don't have to buy 2 or 3 softwares so if you have a Toshiba machine versus say a Philips machine then you have to have 2 software maintenance contracts and whatever.

Yeah

So, logistically it's a nightmare, so all our machines are all the same, Samsung.

And they're all set up the same way too, aren't they?

Same rooms, same bed set up, same set out, same probes, everything the same

Please describe under what circumstances Doppler is used in the third trimester and how these measurements are reported.

OK, so 3 types of Doppler are reported practically in clinical practice. So one is umbilical artery and MCA and if things are not looking good, then ductus venosus. So with the umbilical artery we routinely measure, right, it's a part of the examination, so but if it's not looking good then progress on to MCA Doppler and then ductus venosus to comment on fetal wellbeing, fetal anaemia, fetal distress and then umbilical artery Doppler obviously you want to know the pulsatility index and you want to know diastolic flow, you want to make sure it is a low resistance flow and some diastolic flow, you don't want to see reversal of diastolic flow which means there is a significant amount of fetal resistance going, and if it's abnormal, there is a chart it's normally plotted on, and according to the gestation, the pulsatility index, then I report on the number of the pulsatility index – we're talking about umbilical artery?

Yeah, yep

Diastolic flow, normal, reduced or reversed, and then obviously then that's about it then we go to the MCA Dopplers and you want to see pulsatility index, high resistance flow. But if there is brain sparing circulation, so I comment on obviously flow, pulsatility index. And then I like to calculate a CPR or ratio, and then if it's less than 5% it makes me worried more. Ductus venosus deep A wave, that's like when the delivery should be happening generally so that's the staircase in my head when I go from worried, more worried, very worried. So then that's how it comes.

If the umbilical artery's normal would you stop there, or is MCA part of your normal practice?

In growth, I think MCA we will do it.

You said you report the PIs, do you know which charts you use for Doppler?

No, I don't know the name. I always thought that there's only one chart. I don't know the name. And variations of the chart – there was one growth chart we were using from the time you taught us and I thought it was the only one. There is gestation on one side and PI on one side and X axis and Y axis and I never got into the detail of what are the benefits, what is this one and what are the other ones.

Yeah, no worries. Would you ever consider doing uterine artery Doppler in the third trimester?

Uterine artery Doppler I would do it in the first trimester. Always. There are other issues with history of pre-eclampsia, or a history of drug abuse, taking vasoconstrictors, predict placental circulation, then looking at the notching wave form. Then I would use uterine artery Dopplers. Third trimester I would, I think I would not use uterine artery Doppler routinely…definitely first trimester because they can predict early pre-eclampsia, that's what my understanding is. Then that's I would not use it in third trimester routinely.

I've only got one last topic to cover.

What are your thoughts regarding the adoption of new reference charts? I don't have the in-depth knowledge like to comment on you know, strength of one versus the other, and that's why… I don't have the in depth knowledge to give you an honest and correct answer for this. What is happening is if somebody proves to me look, you know, your growth charts, the one that you use is potentially causing some bad outcome or the reports are not good enough. Because the patient is getting a little bit of under reporting or the charts which I am currently using are affecting patient management in an adverse way, then of course we have to progress… and do whatever for the patient part. If it's just for the change of it then, you know, it just gets hard to, Because that change is not easy, change involves changing my practice, which is not that hard you know. I can sit with you and in 3, 4 hours in a couple of sessions you can teach me and then I'll get the gist of it. But then teaching my sonographers then changing the protocols changing the reporting templates. Then also educating the referrers that is an important part of it and difficult part of it. Like obstetricians they are very set in their ways. I see that this would be forthcoming challenges in that picture if we were to change. So, do I want to change, yes, if somebody can prove that the new charts are going to change and revolutionise patient care and increase and better their outcome. Definitely I can try, but these are the challenges I've outlined I think then I think it would be very difficult to make a case for a change
If professional bodies (RANZCR, ASUM and RANZCOG) recommended the adoption of a difference chart, would you be likely to follow that? Yeah, but they don't … yes that's true but they don't do that unless the current ones are not doing the job or there's a significant difference in the outcome of the patient. Yeah sure, we're obviously, it's like asking yourself. You change the times and thus you ask yourself whatever latest is available and then obviously and then it becomes more easy to convey to your staff that's what we need to use and that's what our radiology college say and then also the reference come on board more easily than, you know, based on my opinion to change it, the radiology college, this about outcomes because everyone wants to do better for the patient. So if it comes from the radiology college then of course if they make it change I'll obviously change.
Is there anything that I have not covered that you would like to discuss about third trimester ultrasound? For instance, do you get adequate information on the request form? That is very referrer dependent. It's very patchy… there's not much information we require it always will be query SGA, query LGA, just compare with previous. But obviously more information is there the better it is but sometimes we do not get much. More will be good, but sometimes we just don't get it.

Radiologist 3
What proportion of your workload is made up of third trimester growth scans? In today's practice probably less than 1%. I'm not often rostered to the other hospital, so it's not common at all. *What are some of the most reasons in your practice that a third trimester scan is requested?* Are we answering for my main job or my subspecialty jobs? I do them every Friday in private [private, metropolitan]. *That might make more sense.* So growth and wellbeing, placental localisation, growth and wellbeing, yeah
Tell me how you report third trimester fetal measurements. We report the absolute number for the measurement, um, on our machines we have the ASUM percentiles on to the machine so the sonographers while scanning will look at those percentiles and be influenced by what they're seeing on their measurements while they're measuring. We then plot them on the Raine study data which is different and annoyingly our PACS which is ViewPoint has a different population entirely to both of those other two for their percentiles, and so when it come to me to sign of a report, in the work flow in private which is sonographer directed where scans are done, worksheets are done and all typed up to be efficient and I've got to double check it, um, the typist may type helpfully the percentile which is not the ASUM population or the plotted Raine population. I can't remember how it came to this, but a few weeks ago I was like 'why is this percentile marker different to the other ones in the same study?', and so we had three different populations all at the same time. *That's complicated, super complicated.* Yeah, especially when you're suddenly calling something small or an outlier *On your Raine charts, is that for all biometry or…* It's for head circumference, AC, and femur length. That's what everyone around Perth is used to seeing and plots on, so we just plot that on a hardcopy piece of paper for consistency for everyone *OK, so patients will come with a piece of paper and a graph and you just…* No, we provide that *OK* And it goes back to the obstetrician
I know that there's a Raine estimated fetal weight chart as well – you don't use that one? No, we report the estimated fetal weight which is one of the Hadlock ones, I can't remember which one though. That's what we report, which is why sometimes you're like oh it's estimated percentile is nice but it plots really small. *Hadlock's really quite complicated, because he's got his formula for calculating the weight and then there's a Hadlock fetal weight chart, as opposed to an Australian birthweight chart, and I know that there's a Raine birthweight chart as well…* I'm not familiar with the Raine birthweight chart

So you have a very complex set up. So you'll do the numbers, just to clarify, report the absolute numbers and the percentiles, and plot it as well.

No, we don't report the percentiles

Ah, you don't…

We just say the AC is x. So the report is the biometry is plotted, AC, FL, head circumference, and then we give them the plot, which is Raine, but sometimes in our reports when things are trending downwards or something, we do put, the AC percentile was the 50th and now this, and those percentiles are not the Raine plotted ones, it's a different population.

Well…

Everyone seems to be quite comfortable with that, like what is plotted is not the same percentile as what we're saying is the percentile, unless no-one's noticed.

Do you know why those charts were used?

Why Raine as a plotted chart?

Well, I'm assuming that's because that's your population.

It's because that's what they're used to seeing and change is difficult, so the easiest thing would be to use one population as a reference for the same patient in every one. Yeah, that's what happens.

Do you do Doppler in all of your third trimester scans?

Um, so we do the umbilical artery and MCA Dopplers and images are save in private for every single scan, but we don't report them. Um, we're kind of, floated by XXX, where the local practice is that you only report the umbilical artery if the AC's under the 10th centile, and only do the MC if this one is like that and if the moon came up in a year and you were turning left, and so what we report is suppressed in private, but we do take measurements on everyone in case someone says 'what was it?' but it's only reported if it's part of that algorithm.

Do you ever do extended Doppler like ductus venosus or uterine artery?

Curiously no. I've not had to report a ductus in the last 5 years. Um, yeah.

This will be an interesting question. What are your thoughts regarding the adoption of new reference charts?

[Laughter] Well no, I mean, I do a lot of different specialties like I do breast, I do obstetrics, there's reference charts and things for everything and things are forever changing. So it would be like 'oh, God, something else has changed'. Um, but for me the main issue is inconsistency using 3 different populations in the one report which are all discordant, like I think say there was a new wiz-bang Australian – this is the chart to use, like Intergrowth was meant to be but hasn't happened, in our clinical practice at least, that would be really useful 'cause it would take away a lot of confusion and inconsistencies.

We've pretty much covered everything. Is there anything that I have not covered that you would like to discuss about how third trimester ultrasound's reported?

I think it's really quite curious. In private, the culture is because of the direction from tertiary hospitals, mainly XXX, that we only report the umbilical Doppler if something's small and then only the next one, and then what that means is that we're not reporting the comprehensive

study that's actually been done. Like, you're referring someone to me for an ultrasound and we're measuring how long the leg is, we're measuring what this waveform looks like. From my point of view, we should be reporting every bit of information from that 100-point check that we did of the baby, and then my interpretation should say, you know, this is a normally grown fetus and the amniotic fluid's normal and the weird outlier umbilical artery trace is probably normal for this baby, it just happens to be that normals defined by 5th to 95th percentile and this baby happens to have a number that's an outlier. But, you know, we can disregard that, because then, we'd be used to seeing numbers that are sometimes out of range, because GPs do that all the time. You look at a blood test and half of them are red because they're outside the normal range, because that's what a normal range is defined by, and for you it's probably clinically not relevant. So, when we don't report them all the time, like sometimes you have an outlying number and everyone freaks out. Bit like maybe it would be useful if it was consistently reported all the time, and then we considered whether it was an outlier number, or an abnormal number, like shown as abnormal, but that's just a difference of clinical opinion. We're very much don't report it, and that's what the practice is.

Just to follow on from that, do you ever comment that a fetus might be small for gestational age or growth restricted?

Yeah, so, I've started to stop making comments like that as well because it becomes a big thing. So when I came back from my fellowship I was very junior, and just go well this number's under this 10 threshold, I'm gonna call it IUGR, and then like once you've labelled something people get very excited by that, and I probably over-called and over-labelled, because I was just using a protocol that I learnt from an exam, because in private you work for sub-specialists, I generally, we have the numbers, we put them there, and we'll report whether it's appropriate growth on a trend, rather than whether it's small or large. I think I'd just favour saying it's a small for gestational age if it was under 10th, and I'd only report IUGR now if the AC was dropping. But it kind of waxes and wanes depending on what case you've just had that was like overcalled or when you've had people say you're not being sensitive enough in what you're reporting.

That's interesting. How much of a drop?

Aw!

I'm just curious – this isn't a test.

Good point, so when is it crossing centiles? You know, I'm like it's a very tiny pixel of a square on the growth chart on a hard copy thing to say it's crossing. If you can kind of out it away from your face and it looks like it's sort of going up… probably two small squares.

So it's a visual call for you, or a numerical call.

Visual. If it's starting to be a bit more flat. But that said, we've had a few lately in private that are growth and wellbeing that have had previous small size where obviously the mum's small, eg Indian, and they're going to be small compared to the population and we're following it up, um, where we report the percentiles from ViewPoint, which isn't ASUM or Raine, I don't remember which population it is, and I just report the percentile today is this was this. It's the same population percentile and what it is, but for me there's a lot of variability in how we measure it, we could remeasure a little bit more generously and then we make it not look so bad. But like…I'm not…

No, no, that's fine

It's the measurement, if there's a big difference in your measurement

Radiologist 4
Can you estimate what proportion of your practice's workload is made up of third trimester growth scans? Probably nearly a third Is that a third of all or a third of obstetrics? Ah, right, a third of obstetrics
What are some of the most common clinical indications for third trimester growth scans? It just usually says growth and Dopplers and AFI. Sometimes previous SGA, sometimes just patting them on their…a feel good one. And obviously occasionally twins, but mostly they don't say why, *That's interesting. Do you find that to be an issue at all?* Ah, not really, but obviously the more information they give us the better our reports can be to reflect what they want. Obviously as long as we have a template that covers everything that they should want it's OK but it would be better if they told us what the issue was, yes.
Tell me how you report third trimester fetal measurements. I do weeks and days and a centile, and then I give an estimated fetal weight on a centile as well, not a grams. *When you're getting your data for the report, do you refer to the report page on the ultrasound machine?* Usually yes *Do you ever report the error in the estimation?* No, That's why I leave it as a percent rather than, you know, 300g +/- whatever. No.
This is the interesting question; do you know which charts are used in your practice? A lot of different ones. Some are ASUM, some are Hadlock, some are Chitty, and there's probably a 4th one and I can't think of its name. When you write your report do you say which charts the measurements have been based on? No
With the estimated fetal weight, do you know which formula's used? I think it's Hadlock, but I don't know the formula. Some are ASUM and some are Hadlock. So, Hadlock actually has 4 charts just to make life interesting. Then no, I haven't seen a 1,2,3 or 4 on it Do you know which weight chart is used to generate the centile? Again, on the thing it's often mixed, which is a bit strange. Sometimes obviously if they've got Chitty leg length and Hadlock 2 or 3 then obviously somehow they work it out, but I don't exactly know how. Then, there aren't four Hadlock measurements and then a Hadlock estimated fetal weight. But when it's comparing that weight to a reference chart for the centile, it's either going to be a fetal weight chart or something like the Australian birthweight charts. It's generated off the ultrasound machine so no, I don't know that background whether which chart it's using.

Do you ever report a fetus as being small for gestational age or growth restricted?

Occasionally.

What cut-off do you tend to use?

10% or the newer ones, the other thing we use is if the abdominal circumference has decreased, um, I can't remember what factor it's by. I don't know, if it drops a certain number of centiles. I have it in my yellow book. I can't remember exactly

I gather, but I don't want to put words in your mouth, you might not be sure why those particular charts and formula are used.

I would presume they're standard across the practice but then again I don't know exactly, and but I know they're probably different than the NSW guidelines that have just come out. Obviously XXX and XXX will maybe sort that out and if they don't I will…I'm sure they've been sent that stuff but I don't know if our machines are using the same data and whether they've been upgraded to use the same data as NSW Health guidelines. Because they obviously, they took the 4 measurements as you know and worked out the Australian data for like 10 000 people from NSW that they ultrasounded and then they picked the best fit. And so they're not all the same and I, because we don't do a lot of NSW stuff I haven't chased that up through XXX hospital or XXX hospital. I do have the piece of paper here somewhere though.

It's actually not on their website yet either which doesn't make it that easy. Do you know, are all your machines configured the same way, although you sort of alluded to that…

You'd hope so, but then again, no I don't know. Some may use different data, it doesn't seem to always be the same data.

Please describe under what circumstances Doppler is used in the third trimester and how these measurements are reported.

Ah, we've started reporting…one it depends. They've started asking for Dopplers and AFI and we do that, otherwise it's a growth scan and Dopplers. Um, they'll do the umbilical artery, used to be SD ratio, now we're tending to quote the PI and that's been shifted slowly, and then if they're abnormal you do the middle cerebral artery, and if that's abnormal then you calculate a CPR ratio

Do you know which charts are used?

No

And with cut-offs for Doppler, at which point to you decide the umbilical artery is abnormal.

I think it's on the 95th centile, I think. Ah, there are graphs there but it's very hard to see on the graphs whether they're on the 95th or 92nd 97th centile. I'd say 95th. I'm sure that's on the chart that's written on the sonographer's tick sheet. The cut-off's the 95th centile.

And for middle cerebral artery?

Middle cerebral artery is definitely less that the 5th centile.

Sorry, I think I missed what you said before about the CPR. Is it calculated every time you do an MCA, or…

No, no. Only when it's less than the 5th centile.

Do you ever do additional fetal Doppler like ductus venosus or maybe uterine artery?

Yes, they've started doing it. It's not, I don't think it's on every scan yet. They do tend, no, sorry, that's XXX [an interstate hospital the practice provides remote reporting for], they do uterine arteries on every third trimester I think and they do a ductus. I don't think we do it that often in practices in XXX [local imaging group]

What are your thoughts regarding the adoption of new reference charts?
I think it's really good, because truly, a lot of our reference charts come from England or America and they been tweaked over the years and these days, I mean, we're all different body shapes, we're all different weights. I don't know if the babies are getting bigger. I don't know if the babies are getting bigger because we're all overweight and we've all got borderline gestational diabetes.
Possibly.
We tend to scan more people of large for gestational age than small for gestational age, Definitely they're a larger number of, gestational diabetes scans, rather than growth retardation of the fetus.

So if the professional bodies, like RANZCR & ASUM recommended adopting a different chart…
Yeah
Do you think your practice would be in that?
I think…here we go, fetal biometry charts. Yes. This was all from NSW Health. I'm sure you've seen it, or I can easily email it to you.
No, no I have seen it.
Look, I think it's a good idea. Honestly, you might as well use the local bell shaped curve, and then, yeah so that. And it was quite interesting to see when they looked at the spread of the numbers when they did Hadlock, Chitty and ASUM and IG21. What we always used to say was ASUM was for whatever, they basically now make Chitty for femoral length because it fits a lot better. So I think that's very good and they scanned a lot, they obviously, oh no they scanned 6500 people.
So that was all done retrospectively I think, but it's still a very big cohort. It's interesting isn't it how the femur length chart is different but I guess if you think about it, you might not remember, but back in the old days with the sector widths, the lines of sight on the sectors at the margins were spaced further apart, so… That's where the difference comes in I think.

So anyway, do you see any potential barriers to implementing the new charts?
I presume it depends on the vendors, 'cause I can tell you from the radiologists reporting perspective whatever's there on the machine is what we report. So, it will depend on the vendors. I haven't always seen Chitty on the machines, and I don't know if we've, you know I've seen a mixture of Hadlock and ASUM. I haven't necessarily seen Chitty on some of the machines. So, yeah. I presume the vendors can do all of it but I don't know.
Yes, I'm not certain. I was gonna have a look, and then if we weren't doing it suggest to XXX maybe he could look at it, because obviously he, XXX is head of the ultrasound. You don't really want to step on people's toes

Is there anything that I have not covered that you would like to discuss about third trimester ultrasound?
Ah, I suspect AFI. We've gone from a percentile and saying it looks OK and then the deepest pocket and that was interesting reading and obviously all of that stuff if you're in obstetrics is known, whereas if it's kind of your general reporting things. When they stared doing it at XXX hospital, and you're kind of going oh! Why are they doing that, so you google it, and it's been around obviously for quite a while, it's just that if you're not really up on why they use the deepest pocket to stop the early Caesarean sections, then you didn't really know why they changed it. And likewise, I don't actually know why they changed from SD to pulsatility index, um, but these things happen and they obviously correlate better with outcomes and so we start reporting different things.

Do you feel like you're getting enough guidance from professional bodies, or do you feel like you sort of have to work it all out for yourself?
Ah, you have to work it out for yourself. Um, I suspect, you know it's all there if you google it and if you were on the working panel and things like that. And they're probably sitting somewhere on all the obstetric college websites and guidelines, but obviously we are on the other side in radiology, and um, yeah they probably do need to send out emails when, you know, we go from SD ratio to PI. Whereas you guys, probably all the sonographer and obstetric world probably get that because they're a member of you know, the Australian Society of Ultrasound or Obstetrics College, who would then keep them informed of that type of stuff.
Yeah, I think, correct me if I'm wrong, I think, doesn't RANZCR just say refer to ASUM?
They probably do, but just in the sense they don't send out a newsletter. So therefore, we don't know the guidelines have been updated. So a lot of it is just going to conferences and listening to whoever is the latest person who's interested in say obstetrics or, you know, you go to a conference and you hear Emmeline from Perth talk. So then you find out they've now got an updated criteria for polycystic ovaries, things like that. So you basically rely on whatever you read that feeds through the internet and um conferences, because we're such generalists. We just can't keep up.
It is a problem, isn't it?
Yep, yep so we truly do rely on the sonographers who get fed this information and then it gets disseminated to us at some stage.

Appendix B

Research protocol for Validation of Intergrowth 21 charts for the Australian population

"Validation of Intergrowth 21 charts for the Australian population"

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Contents

1. Synopsis

The diagnosis of abnormal fetal growth is based on differences between the actual measurements and expected measurements as determined by a reference chart for a given gestational age. There is no consistent use of any one fetal growth chart in Australian ultrasound practices leading to potential misdiagnosis of abnormal fetal growth and unnecessary interventions. In 2014 the Intergrowth21 (IG21) charts were published as international standards for fetal growth and may be well suited for use in Australia's multi-ethnic population. The aim of this research is to provide evidence to allow adoption of a consistent way to measure and report fetal growth and, in particular, to help reach a consensus about implementation of IG21 charts in Australian practices.

An observational, prospective, cross-sectional, multicentre study is proposed to collect fetal biometry data from women presenting for second and third trimester ultrasound. These measurements will be referenced to the IG21 chart to validate the Intergrowth21 fetal measurement charts as they relate to the 3rd, 10th & 97th centiles for an Australian population.

2. Abbreviations and Acronyms

AC	*Abdominal Circumference*
ACT	*Australian Capital Territory*
ANU	*Australian National University*
ASAR	*Australian Sonographer Accreditation Registry*
ASUM	*Australasian Society of Ultrasound in Medicine*
BPD	*Bi Parietal Diameter*
DIAS	*Diagnostic Imaging Accreditation Scheme*
EDB	*Estimated Date of Birth*
FGR	*Fetal Growth Restriction*
FL	*Femur Length*
HC	*Head Circumference*
HREC	*Human Research Ethics Committee*
IG21	*Intergrowth21*
JCSMR	*John Curtin School of Medical Research*
NSW	*New South Wales*
NNICU	*Neonatal Intensive Care Unit*
PAPP-A	*Pregnancy Associated Plasma Protein A*
PlGF	*Placental Growth Factor*
RANZCOG	*Royal Australian and New Zealand College of Obstetricians and Gynaecologists*
SGA	*Small for Gestational Age*

3. Introduction/Background

The diagnosis of abnormal fetal growth is based on differences between actual and expected measurements for a given gestational age. Most fetal measurement charts assume a normal distribution of variability in fetal size; this makes is easy to define the 10th, 5th and 3rd centiles based on measures that are a set number of standard deviations from the mean. Each of these cut-offs can be defined as the point which defines a sub-group of fetuses that are 'small for gestational age' (SGA). However, only a fraction of these will be due to pathologic processes that may result in fetal growth restriction (FGR). Furthermore, some fetuses where the measured size is above the 10th centile may in fact be growth restricted. FGR is associated with an increased risk of neonatal morbidity and mortality, and undiagnosed FGR is the strongest risk factor for stillbirth [3].

Which fetal measurement reference chart to use for the Australian population has been a contentious issue in Australian ultrasound practices for the past two decades. In 2001 the Australasian Society of Ultrasound in Medicine (ASUM) recommended the use of the Campbell Westerway charts for fetal biometry which were formulated from an Australian population [172]. Despite this, there are currently at least eight fetal growth charts in clinical use in Australia [34]. The potential for misdiagnosis of fetal growth restriction leading to additional interventions and patient anxiety cannot be underestimated. Similarly, the opportunity for timely interventions may be missed by underdiagnoses of fetal growth restriction. For example, it is possible for a fetus to be diagnosed as small for gestational age (SGA) by one practitioner, and later that day found to be normally grown by a practitioner using a different reference chart. Comparison of three fetal measurement reference charts has demonstrated up to a six-fold increase in measurements classified as below the 5th centile [29]. Consistent use of reliable growth charts is necessary to recognise abnormal fetal growth and inconsistency in current Australian practice highlights issues in adherence to clinical practice guidelines. The 2013 survey of Royal Australian and New

Zealand College of Obstetricians and Gynaecologists (RANZCOG) revealed inconsistencies in fetal biometry reference charts used to report fetal growth [34].

Differences in median values and percentile curves of published fetal measurement reference charts can be attributed to racial and biological characteristics of the study population, differences in study design, and methods of data analysis [154]. In 2014 the Intergrowth21 (IG21) charts were published [38]. IG21 are international standards formulated from data collected from over 4,300 'normal' low risk pregnant women collected in eight international centres. The charts are based on the premise that all fetuses, regardless of ethnicity or country of birth, have the potential to grow at the same rate throughout gestation. These standards may be well suited for use in Australia's multi-ethnic population, however it is necessary to determine whether the Australian population 'fits' these charts before they are implemented in clinical practice.

4. Objectives

The primary aim of this research is to provide evidence to allow adoption of a consistent way to measure and report fetal growth and, in particular, to help reach a consensus about implementation of IG21 charts in Australian practices.

Secondary aims are to determine whether growth restricted neonates demonstrated evidence of fetal growth restriction at the time of the prenatal ultrasound, and whether maternal risk factors for fetal growth restriction were identified in the pregnancy.

5. Hypothesis

Intergrowth21 charts are suitably robust to identify abnormal fetal biometry and growth in the Australian population to recommend implementing these charts in clinical practice.

6. Study Methodology

An observational, prospective, cross-sectional multicentre study is proposed to assess fetal biometry in pregnant women in the second and third trimester. Ultrasound measurements will include bi-parietal diameter (BPD), head circumference (HC), abdominal circumference (AC) and femur length (FL). These measurements form part of a routine ultrasound assessment of fetal size and will be reported in the usual way.

Published studies that have compared local populations to the IG21 charts have used retrospective data collection [220, 355] and prospective data collection [222]. Collecting data prospectively has several advantages. Measurements can be made in triplicate to reduce random error [223], and sonographers can be blinded to the measurements to reduce operator bias [224]. Ultrasound measurements can be standardised to reduce random error and measurement bias. While it has been shown that both intra and inter-observer variability is similar [223, 356], standardisation exercises are shown to further improve quality and consistency of ultrasound measurements [225]. This is important when ultrasound measurements will be performed by a mix of experienced and less experienced sonographers. Additionally, data on maternal characteristics known to influence fetal growth and risk factors for abnormal fetal growth [226-228] can be collected at the time of the ultrasound examination, instead of relying on retrospective assessment of patient files.

Cross-sectional data, that is, the measurements from one ultrasound examination will be collected for the purposes of this study. Data used in this study will be sourced from clinically indicated ultrasounds. In Australia, routine ultrasound examinations are performed at 11 to 14 weeks for first trimester screening, and at 18 to 22 weeks for fetal morphology assessment. Ultrasound assessment of pregnancy is not routinely performed after 22 weeks unless clinically indicated [357], a recent audit of current practice in an Australian hospital reported over 50% of singleton pregnancies have at least one third trimester growth scan [37]. While inclusion of data from clinically

indicated ultrasounds has the potential to be a source of bias, it is an aim of this research to assess the performance of the IG21 charts in the Australian clinical setting.

Currently, Australian charts of fetal biometry are based on a local or state populations [172, 358-360]. It is the aim of this research to compare the IG21 charts to fetal measurements from a truly representative sample of Australian pregnant women by inviting participation from institutions across Australia.

There are both statistical and practical considerations in determining an appropriate sample size. If the sample size for this study is too small, results will not be generalizable, and an overly large sample size will unnecessarily extend the time for data collection.

In general, fetal measurements approximate a normal distribution [155, 229] and the sample size for this study can be determined by calculations for demonstrating equivalence [230].

The 3rd centile is generally considered to be clinically significant, and AC measurements less than the 3rd centile form part of the criteria to diagnose late onset FGR [231] and increase clinical surveillance or intervention. Considering standard error in the estimation of the 3rd centile, if a 50% error was acceptable, then 4.5% of the population would be misclassified as representing the lower 3% of the population. If the null hypothesis is that the Australian population is the same as the IG21 population, 1-sample equivalence testing with power is 0.9 and type 1 error, α is 0.025 (half of that required in a 2 sided test for equivalence), a sample size of 510 is required per site.

Ideally, observations should be spread evenly across each week of pregnancy, and it is acknowledged that by sourcing data from clinically indicated ultrasound examinations this will be unlikely. Even in published cross sectional fetal measurements charts, an even spread of observations across each week of pregnancy is not usually achieved. For example, while the Westerway charts achieved representation at all gestational weeks from 11 weeks to 40 weeks, numbers varied from a peak of 769 at 18 weeks to 49 at 40 weeks [172]. Charts published in 2004

by Schluter [359] similarly achieved representation at all gestational weeks from 11 weeks to 41 weeks but numbers represented at each gestational age varied from 2 at 11 weeks and 6409 at 19 weeks. Therefore, each participating site will aim for an even number of observations at gestation 'windows' between 14 and 17 completed weeks, 18 and 22 completed weeks, 23 and 27 completed weeks, 28 and 32 completed weeks, 33 and 36 completed weeks, and 37 and 41 completed weeks.

A further consideration is data that may be excluded during the study, lost to follow up, or withdrawn following participant's request. It is estimated that this may be as high as 6% [38].

Taking these factors into consideration, a minimum of 2000 observations in total with a minimum of 500 observations from each participating site will be collected for this study.

7. Study population

A minimum of 2000 participants will be invited to take part in this study. It is anticipated six centres across Australia will each contribute data from approximately 500 pregnant women to this study. Pregnant women presenting to participating ultrasound practices for clinically indicated second and third trimester ultrasound assessments will be invited to participate in this study. Written information will be provided upon arrival at the ultrasound department describing the study and inviting participation.

Inclusion criteria:

- Singleton viable pregnancies with an estimated date of birth (EDB) as confirmed by ultrasound at 8-14 weeks of pregnancy.

Exclusion criteria:

- Pregnancies with a known fetal abnormality
- Pregnancies with significant maternal disease (eg cancer, renal disease)
- Pregnancies where EDB was not confirmed by ultrasound at 8-14 weeks of pregnancy

- Multiple pregnancies

8. Study procedure

Each participating centre will nominate a lead sonographer or clinician to oversee data collection at their site. The lead will:

- Be responsible for local or institutional ethics and governance as applicable
- Oversee data collection
- Complete Participating Centre Details form
- Ensure safe storage of completed Data Collection Sheets
- Be the contact person for the principal researcher
- Be the contact person for any participating patient queries

Pregnant women presenting to participating ultrasound practices will be invited to participate in this study. Written material will be provided explaining the aim of the study and the nature of the data requested. Translations of written material will be made available as required. Signed, written consent will be obtained for permission to use ultrasound measurements in this study, record maternal characteristics, and for birth outcome data to be collected from institutional databases (appendix 1). Prior to the ultrasound examination, the patient will be asked to complete a brief questionnaire to record possible maternal risk factors for abnormal fetal growth and maternal characteristics that may also influence fetal growth (appendix 2).

These include:

- Pre-existing diabetes or diabetes in pregnancy
- Hypertension
- Smoking
- History of pre-eclampsia
- Height

- Weight
- Ethnicity
- Previous pregnancy history
- Other medical conditions
- Family history of disease

Data collected on the day of the ultrasound examination by the sonographer performing the ultrasound includes:

- A patient identifier to allow birth outcome data to be collected at a later date
- Gestational age at the time of ultrasound examination
- First trimester PAPP-A (if known)
- Fetal biometry as measured by ultrasound which form part of a routine obstetric ultrasound assessment:
    - bi-parietal diameter (BPD)
    - head circumference (HC)
    - abdominal circumference (AC)
    - femur length (FL)

The ultrasound measurement protocol (appendix 3) includes:

- Standardised measurement planes, with additional BPD measurements with calipers placed at the outer edges of the parietal bones as described in the IG21 chart methodology (designated BPDi). This measurement differs from current practice where measurement calipers are placed on the outer edge of the nearest parietal bone to the inner edge of the farthest. *The imaging plane is identical, which means BPDi can be measured on the same frozen image as the BPD and HC.*
- Measurements performed in triplicate (three measurements from each parameter from three separate images).
- Operator blinding, that is, the bottom corner of the ultrasound monitor where measurements are displayed with the equivalent gestational age in weeks and days will be covered during the ultrasound examination.

Institutional birth outcome data will be collected by the principal researcher with assistance from the nominated site lead sonographer/sonologist from other participating centres as applicable (appendix 4). This will include:

- Recorded birth outcome data on birth outcome summary:
- Gestational age at birth
- Birthweight
- Method of delivery
- Apgar scores (routine measures at 1minute and 5 minutes after birth, of baby's colour, heart rate, reflexes, tone, & respiratory effort)
- Cord gases (if this was performed)
- Days of admission to special care nursery (if this occurred)
- Days of admission to neonatal intensive care unit (NNICU) (if this occurred)

After birth outcome data has been linked to data collected in the study, a new unique identifier will be assigned to the complete dataset. De-identified data from the research data sheets will be transferred to an excel spreadsheet for analysis.

Participation is voluntary, and participants can withdraw from the study up until such time the data is de-identified for analysis. Data collection sheets for participants who withdraw before data is de-identified will be destroyed. The number of participants that withdraw from the study will be recorded.

There are no benefits to participants for taking part in this study, however, data collected may benefit pregnant women in the future by providing evidence to allow adoption of IG21 charts in Australian practices.

9. Data Management

Confidentiality will be preserved as far as possible for the participants, however, it is necessary to record a patient identifier (hospital record number) on the data collection sheet to enable birth outcome data to be collected after the baby's birth and linked to the data collected on the day of the ultrasound examination.

Until this time, paper copies will be stored in a locked filing cabinet in:

- the office of the Director of Obstetrics and Gynaecology, Centenary Hospital for Women Youth & Children, Canberra Hospital, or
- the office of the Department Director of a participating centre

A digital backup will be kept on a password-protected computers at:

- the Canberra Hospital, or
- the participating institution

Only nominated researchers will have access to data provided by the participants. After birth outcome data has been linked to data collected in the study, a new unique identifier will be assigned to the complete dataset. De-identified data from the research data sheets will be transferred to an excel spreadsheet for analysis.

Patients participating in this study will not be identifiable in thesis or publications. Sonographers involved in data collection will be assigned a unique code. No personal identifiers will be included data analysis or data presentation.

De-identified data used for analysis will be stored on a password protected ACT Health/ANU computer and backed up on ANU OneDrive. It is an ANU requirement to also have external hard-drive back up. The data collection sheets and external hard drive will be stored in a locked filing

cabinet in the office of the Director of Obstetrics and Gynaecology, Centenary Hospital for Women Youth & Children, Canberra Hospital. Data will be stored for a minimum of seven years from the date of any publication arising from the research. After this time, paper data collection sheets will be destroyed. De-identified data will be archived electronically and retained by the principal researcher.

10. Adverse Event Reporting

There are no adverse events in this observational low risk study.

11. Statistical Analysis

The aim is to pool data from all sites involved in the study. Site means, standard deviations and fitted centiles from data analysis will be calculated and compared to corresponding values from the pooled data. Differences of < 0.5 SD between values for a single site and the pooled data will be considered acceptable.

Assessment of data distribution will be assessed by plotting observations on IG21 charts for BPD, HC, AC and FL for visual assessment of the spread of data points within the 95% confidence band

Quantile regression will be applied to the collected data to produce new curves for the mean, 3rd, 10th, 90th and 97th centiles.

Z-scores for each biometric parameter will be calculated to allow comparison with IG21 data.

The impact of adopting IG21 charts will be assessed by calculating the mean and standard deviation of the Z scores based on IG21 charts and the ASUM recommended charts.

The proportion of fetuses below the 3rd and 10th centile and above the 90th and 97th centile using IG21 charts and ASUM recommended charts will be calculated.

Birth outcome data will be analysed to determine the number of cases of growth restriction in the study population to determine:

- if this was predicted by the fetal measurements in pregnancy
- if this was predicted by identified risk factors for fetal growth restriction

Statistical analysis will be performed by the principal researcher under supervision of Prof Stephen Haslett with advice from the John Curtin School of Medical Research (JCSMR).

12. Quality assurance, monitoring & safety

Data from clinically indicated ultrasound examinations performed by credentialed sonographers in accredited practices will be used in this study.

Ultrasound equipment used in this study will comply with the Diagnostic Imaging Accreditation Scheme (DIAS) requirements for performance, age and maintenance.

A standardised measurement protocol will be used in this study (appendix 3), presented in person or via webinar to participating centres (appendix 5). The lead sonographer or clinician at each site will oversee data collection.

A quality assurance program (appendix 6) will monitor image quality and measurement consistency during data collection. Quality assurance programs are typically lacking in methodologies used to develop charts of fetal size [154], and are especially important when measurements will be performed by multiple sonographers in multiple centres.

Audit of image quality is currently performed for combined first trimester screening [361], but not for images used for fetal biometry in the second and third trimester. This will be performed in accordance with principles described by several authors [362-365].

For quality assurance purposes, sonographers participating in this study will be assigned a unique identifier (appendix 6). The following data from participating centres will be collected:

- Years of experience for each sonographer involved in data collection
- Number of ultrasounds performed in this study
- Make, model and age of ultrasound equipment used in this study

The quality assurance program will include:

- Qualitative image assessment
- Calculation of intra-observer variability
- Calculation of inter-observer variability

13. Ethical Issues

Pregnant women presenting to participating ultrasound practices for clinically indicated second and third trimester ultrasound assessments will be invited to participate in this study. Written material will be provided explaining the aim of the study and the nature of the data requested. Signed, written consent will be obtained for permission to use ultrasound measurements in this study, record maternal characteristics, and for birth outcome data to be collected from institutional databases.

There are no dual relationships, coercion or inducements identified.

All ultrasound examinations will be performed by accredited sonographers [233].

Ethics review includes ACT HREC, ANU HREC, and institutional ethics review for participating centres as applicable.

14. Finance and resource use

There is no funding for this project.

15. Dissemination of Results and Publication policy

The results will form part of the PhD thesis of the principal investigator and be written up for

publication in scientific journals and presentation at international meetings.

16. References

17. Appendices

Appendix 1. Participant Information Sheet and Consent Form

Participant Information Sheet

Validation of Intergrowth 21 charts for the Australian population

You are being invited to take part in a research study. Before you decide to take part it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Please ask the study team any questions you have and request any further information you need.

Why is this study being done?
The purpose of the study is to find out more about the different patterns of growth among babies before birth. We assess the growth by comparing ultrasound measurements of the size of your baby's head, abdomen and limbs with reference charts. The information obtained from this study will enable us to compare our current ultrasound reference charts with a new international chart before the new chart is used in Australia.

What is involved in the study?
If you agree to take part in the study it means that we can use the measurements we take of your baby at today's ultrasound and compare them on different reference charts. After you baby is born we will look up hospital birth records or call you and record baby's birth weight, the gestation reached when baby was born, baby's sex, and baby's health scores.

There is a short questionnaire for you to fill in asking information about things that are known to influence how a baby grows during pregnancy. If you have any questions about these, the sonographer performing your ultrasound will be happy to answer them.

Why have I been chosen?
You have been invited to participate in this study because you have been referred for an obstetric ultrasound examination in the second or third trimester of pregnancy.

Do I have to take part?
Participation in this study is voluntary. It is completely up to you whether or not you participate. If you decide not to participate, it will not affect the treatment you receive now or in the future. Whatever your decision, it will not affect your relationship with the staff caring for you.

Are there any risks?
There will be no change to your pregnancy management. There will be no change to how your ultrasound

examination is reported or when the results are available.

Are there any benefits?
The information obtained from this study will enable us to compare our current ultrasound reference charts with a new international chart and potentially improve the ability to detect abnormal growth of babies in pregnancy. Your participation may help others in the future, but will not directly benefit you.

What are the costs?
There will be no cost to you for participating in this study.

Access to the results of the study
Results will be written up for publication in scientific journals and presentation at international meetings. In any publication, information will be provided in such a way that you cannot be identified. Results will be provided to you, if you wish. Keep this information sheet for the researcher's contact details.

What about confidentiality?

Your participation in this study is confidential. It will be necessary to record an identifier (your hospital ID number) on the data collection sheet to link birth outcome data. Only the researchers named below will have access to your details and results that will be held securely in a locked filing cabinet in the office of the Director of Obstetrics and Gynaecology, Centenary Hospital for Women Youth & Children, Canberra Hospital. Electronic copies will be kept on a password protected ACT Health computer. After data has been linked, your identifier will be deleted before any data analysis. No personal details will be used in data analysis and no individual participant will be identified when the results of the study are published.

If you have any questions please contact the research team

Contact at ***name of site/institution***:

Principal researcher: Debra Paoletti, Senior Sonographer, Fetal Medicine Unit, Canberra Hospital u6146524@anu.edu.au phone 02 61747357

This research partially fulfils the requirements for a PhD under the supervision of Prof. Michael Peek. If you have any questions or concerns about this research please contact Prof. Peek at michael.peek@anu.edu.au

Should you have any problems or queries about the way in which the study is conducted, and do not feel comfortable communicating with the staff conducting this survey, please contact: ACT Health Human Research Ethics Committee (ACTH-HREC), Level 6, Building 10, Canberra Hospital, Telephone: (02) 6174 7968 or ethics@act.gov.au *or name of institutional ethics committee*

Consent Form for Participation in a Research Project.

I, _____ *(name of participant)*

of _____ *(address)*

have been asked to consent to participation in a research project entitled:

Study title

In relation to this study I have read the Participant Information Sheet and have been informed of the following points:

1. Approval has been given by the ACT Health Human Research Ethics Committee.
2. The aim of the study is to compare your baby's ultrasound measurements to a different reference chart
3. The results obtained from the study may or may not be of direct benefit to me
4. The study will involve using ultrasound measurements of my baby, some details about me that are known to influence how a baby grows in pregnancy, and some birth outcome details after my baby is born. The data collection sheet will be kept in locked storage for 7 years before being destroyed. Electronic copies will be archived on a password protected ACT Health/ANU computer and will be backed up. No personal details will be used in data analysis and I won't be identified when the results of the study are published.
5. Should I have any problems or queries about the way in which the study was conducted, and I do not feel comfortable contacting the research staff, I am aware that I may contact the ACT Health Human Research Ethics Committee Secretariat, Canberra Hospital, Yamba Drive, Garran ACT 2605 (ph: 6174 7968)
6. I can refuse to take part in this project or withdraw from it at any time without giving a reason
7. I understand that while the results of the research will be made accessible my involvement and my identity will not be revealed.

After considering all these points, I accept the invitation to participate in this study.

Name: (please print) _____**Date:** _____

Signature (Participant) _____

Investigator: (please print) _____**Date:** _____

Signature (Investigator) _____

Appendix 2. Data Collection Sheet

Coding (for research purposes) _____

FETAL MEASUREMENT DATA COLLECTION SHEET

CENTRE CODE: _____

DATE OF ULTRASOUND EXAMINATION _____/_____/_____

ESTIMATED DATE OF BIRTH _____/_____/_____

For birth outcome data:
Hospital ID: _____planned place of birth _____

For participant to complete:
MATERNAL CHARACTERISTICS

Date of birth	
Height in cm	
Weight in kg (most recent)	
Ethnic background	
Do you have pre-existing diabetes or diabetes in pregnancy?	Y / N
Do you have high blood pressure (hypertension)?	Y / N
Are you a smoker?	Y / N If **Yes**, how many cigarettes per day? _____
Did you have pre-eclampsia in a previous pregnancy?	Y / N / NA
Do you have any other health conditions? (if **Yes**, please specify)	Y / N
Is there a family history of disease? (If **Yes**, please specify)	Y / N
Are you currently taking medication? (if **Yes**, please specify)	Y / N

PTO

PREGNANCY HISTORY

On-going pregnancies	Weeks pregnant at time of delivery	Weight of baby	Complications (eg. Stillbirth, birth defect)
1			
2			
3			
4			

Number of miscarriages	
Number of terminations	
Number of ectopic pregnancies	

For sonographer/researcher to complete:

SONOGRAPHER/SONOLOGIST CODE: _____

PREGNANCY DETAILS

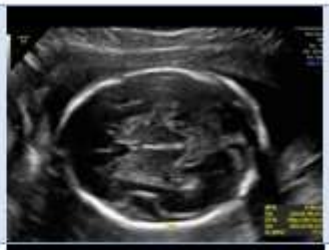
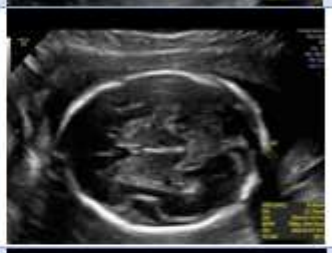
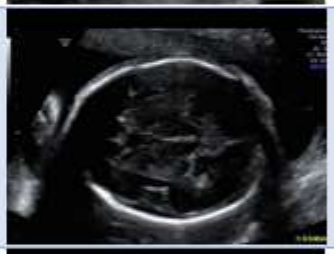
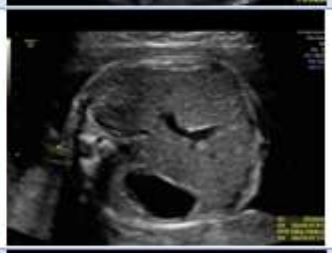
Gestational Age on day of examination	weeks	days
EDB determined by first trimester US	Y / N / NA	
PAPP-A MoM	PlGF MoM	

ULTRASOUND MEASUREMENTS

Parameter (cm)	1	2	3	
BPD 2 outer to outer				
BPD 1 outer to inner				
HC				
AC				
FL				

Appendix 3. Ultrasound Measurement Protocol

FETAL MEASUREMENT STANDARDS IG21 VALIDATION PROJECT

Parameter	Imaging plane	Measurement	Image
BPD	**Axial plane through the fetal head** • image well magnified • head horizontal, oval and symmetrical • centrally positioned falx cerebri • CSP in the anterior third • thalami located symmetrically	Callipers placed at the maximal diameter from the outer edge of the nearest parietal bone to the inner edge of the farthest	
HC	**Identical plane to BPD**	The ellipse should follow the outer perimeter of the bony skull (not overlying skin)	
BPDi	**Identical plane to BPD**	Callipers should be placed at the maximal diameter on the **outer edges** of the parietal bones	
AC	**Axial plane through the fetal abdomen** • image well magnified • circular section with spine lateral • stomach bubble visible • short segment of umbilical vein at the level of the portal sinus visible	The ellipse should be as close to the skin as possible and include the fetal fat layer	
FL	**Length of femoral diaphysis** • image well magnified • femur closest to the transducer should be measured • as close as possible to horizontal across screen • longest axis can be determined by the strong acoustic shadow and visualisation of both cartilaginous ends	Callipers should be placed on the outer edges of the diaphysis at the junction of bone and cartilage	

Appendix 4. Outcome Data Collection Sheet

Coding (for research purposes) _____

BIRTH OUTCOME DATA SHEET

GA at birth					
Method of delivery	NVD	Instrumental delivery	IOL	Elective CS	Emergency CS
Birthweight					
Sex					
APGAR scores					
Special care nursery admission	Y / N				
NNICU admission	Y / N				
Other (eg. cord gases)					

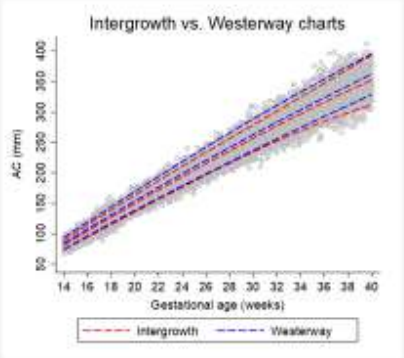
Appendix 5. Standardised Measurement Protocol Presentation

VALIDATION OF INTERGROWTH 21 CHARTS FOR THE AUSTRALIAN POPULATION

Principal researcher: Debra Paoletti PhD candidate
Supervisor: Prof Michael Peek
Supervisory Panel: Prof Jon Hyett, A/Prof Sue Campbell Westerway, Prof Stephen Haslett

AIM & STUDY DESIGN

- To assess the suitability and implications of adopting the Intergrowth21 charts in Australia
- Prospective, cross sectional, multicentre study
- Sample size at least 2000
  - 500 per site



WHAT DOES PARTICIPATION IN THIS STUDY INVOLVE?

- Nominating a lead sonographer or clinician to:
  - Responsibility for institutional ethics approval
  - Oversee data collection
  - Ensure safe storage of completed *Data Collection Sheets*
  - Be the contact person for the principal researcher
  - Be the contact person for any participating patient queries
- Data collection includes:
  - Gaining signed consent from study participant
  - Checking/completing maternal characteristics recorded on data collection sheet
  - During the ultrasound measuring an additional BPD measurement **outer to outer**
  - Recording the ultrasound measurements on the data collection sheet
  - Participating in a Quality Assurance program

RECRUITMENT

- Women presenting for ultrasound examinations will be invited to participate in the study & sign consent
- Inclusion criteria:
  - Singleton pregnancies with an estimated date of birth (EDB) as confirmed by ultrasound at 8-14 weeks of pregnancy
- Exclusion criteria:
  - Pregnancies with a known fetal abnormality
  - Pregnancies where EDB was not confirmed by ultrasound at 8-14 weeks of pregnancy
  - Multiple pregnancies
- Data collection sheet to record maternal characteristics & pregnancy history

DATA COLLECTION SHEET

For participant to complete:
MATERNAL CHARACTERISTICS

Date of birth	
Height in cm	
Weight in kg (most recent)	
Ethnic background	
Do you have pre-existing diabetes or diabetes in pregnancy?	Y / N
Do you have high blood pressure (hypertension)?	Y / N
Are you a smoker?	Y / N If Yes, how many cigarettes per day? _____
Did you have pre-eclampsia in a previous pregnancy?	Y / N / NA
Do you have any other health conditions? (If Yes, please specify)	Y / N
Is there a family history of disease? (If Yes, please specify)	Y / N
Are you currently taking medication? (If Yes, please specify)	Y / N

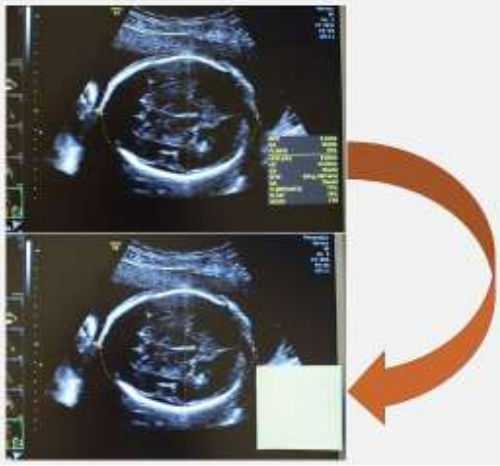
PREGNANCY HISTORY

On-going pregnancies	Weeks pregnant at time of delivery	Weight of baby	Complications (eg. Stillbirth, birth defect)
1			
2			
3			
4			

Number of miscarriages	
Number of terminations	
Number of ectopic pregnancies	

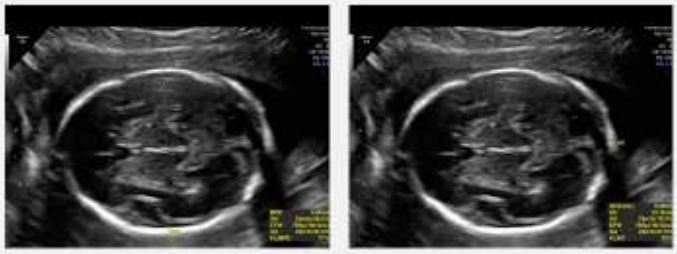
ULTRASOUND MEASUREMENTS

- Blinded measurements by covering bottom corner of ultrasound screen
- 3 measurements from 3 separate images for:
- BPD & HC
  - BPD (outer to inner – the standard measurement)
  - BPDi (outer to outer – the IG21 measurement)
- AC
- FL



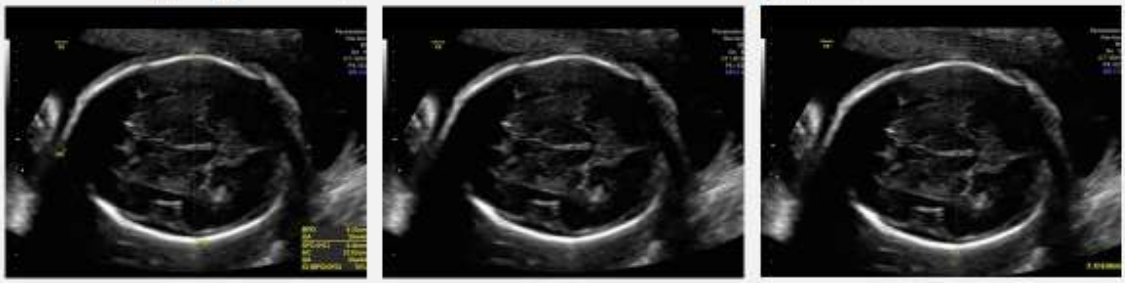
BPD & HC IMAGING PLANE

- Axial plane through fetal head
- Image well magnified
- Head horizontal, oval & symmetrical
- Centrally positioned falx cerebri
- CSP in anterior third
- Thalami located symmetrically



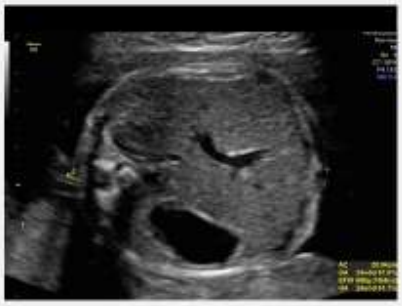
BPD & HC TECHNIQUE

- Measure BPD using Calculation Package and placing calipers at the maximal diameter on the outer edge of the nearest parietal bone to the inner edge of the farthest parietal bone
- Measure HC using Calculation Package and placing ellipse at the outer perimeter of the bony skull (not the overlying skin)
- *Before unfreezing the image, clear calipers*
- *Measure BPDi by placing distance calipers at the maximal diameter on the* ***outer edges*** *of the parietal bones*



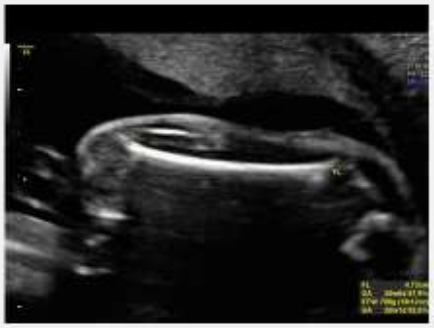
AC IMAGING PLANE AND TECHNIQUE

- Axial plane through the fetal abdomen
- Image well magnified
- Circular section with spine lateral
- Stomach bubble visible
- Short segment of umbilical vein at the level of the portal sinus visible
- The ellipse should be as close to the skin as possible and include the fetal fat layer

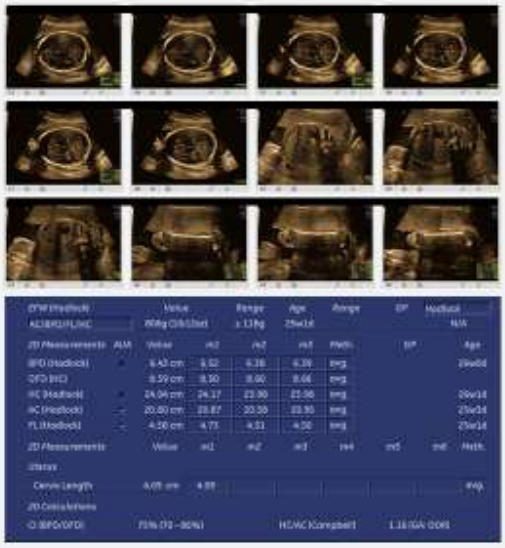


FL IMAGING PLANE AND TECHNIQUE

- Length of femoral diaphysis
- Image well magnified
- Femur closest to the transducer should be measured
- As close as possible to horizontal across screen
- Longest axis can be determined by the strong acoustic shadow and visualisation of both cartilaginous ends
- Calipers should be placed on the outer edges of the diaphysis at the junction of bone and cartilage



DATA COLLECTION SHEET



For sonographer/researcher to complete:

SONOGRAPHER/SONOLOGIST CODE: AS

PREGNANCY DETAILS

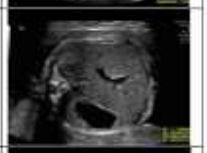
Gestational Age on day of examination	25 weeks	1 days
EDB determined by first trimester US	(Y) N / NA	
PAPP-A MoM 0.98	PlGF MoM 1.18	

ULTRASOUND MEASUREMENTS

Parameter (cm)	1	2	3	
BPD 2 outer to outer	6.55	6.41	6.41	
BPD 1 outer to inner	6.52	6.38	6.39	
HC	24.17	23.98	23.98	
AC	20.87	20.58	20.95	
FL	4.73	4.51	4.50	

QUALITY ASSURANCE

- Image quality
  - Image audit and quality scoring
- Assessment of
  - Intra observer variability
  - Inter observer variability

Parameter	Image Scoring	Image
BPD, HC & BPD	**Axial plane through the fetal head (5 points)** • head occupies at least 50% of the image • symmetrical, horizontal plane, falx centrally placed • thalami visible • CSP visible • calipers/ellipse placed correctly	
AC	**Axial plane through the fetal abdomen (5 points)** • abdomen occupies at least 50% of image • symmetrical, circular section, spine lateral • stomach bubble visible • portal sinus visible • calipers/ellipse placed correctly	
FL	**Length of femoral diaphysis (4 points)** • length of femur occupies at least 50% of image • angle of femur <30° • both ends of bone clearly identified • callipers placed correctly	

OUTCOME DATA

- Principal researcher will liaise with lead sonographer/clinician to arrange this
- Participating centres will be acknowledged in any publications
- Sonographers involved in data collection will be acknowledged in any publications (if they consent)

ANY QUESTIONS, COMMENTS OR QUERIES

Deb Paoletti debra.paoletti@act.gov.au & u6146524@anu.edu.au

Phone: 02 61747357

Appendix 6. Quality Assurance Program

PARTICIPATING CENTRE DETAILS

Coding (for research purposes) _____

SONOGRAPHER/SONOLOGIST DETAILS

Sonographer/sonologist Code	US experience (years)	Number of examinations performed in this study*

*to be completed by researcher when data collection has been completed

EQUIPMENT DETAILS

Ultrasound machine	Make and model	Year of manufacture	Transducer details	Transducer details
1				
2				
3				
4				
5				
6				

Image quality assurance

1. Three (3) from 3 different cases for each measurement parameter are to be submitted for audit
    a. 3 images of BPD and HC (BPD calipers and HC ellipse may be on the same image)
    b. 3 images of BPDi
    c. 3 images of AC
    d. 3 images of FL
2. Each image will be assessed on the criteria listed in the table below
3. Images will be considered satisfactory when:
    a. 4 of the assessment criteria are met for BPD & HC
    b. 4 of the assessment criteria are met for BPDi
    c. 4 of the assessment criteria are met for AC
    d. 3 of the assessment criteria are met for FL
4. Submission guidelines
    a. Images are to be submitted to the lead sonographer within 6 months of commencement of the study, and annually thereafter
    b. Images must be de-identified and imported into a powerpoint presentation labelled with sonographer ID

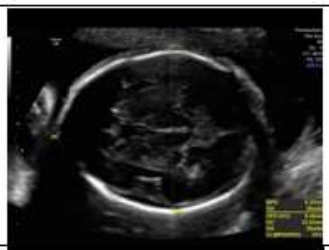
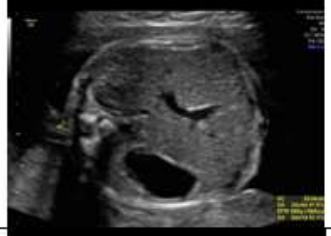
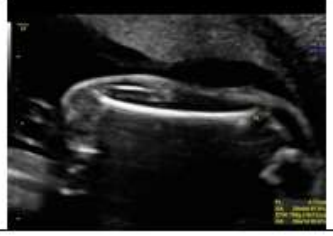
Parameter	Image Scoring	Image
BPD, HC & BPDi	**Axial plane through the fetal head (5 points)** • head occupies at least 50% of the image • symmetrical, horizontal plane, falx centrally placed • thalami visible • CSP visible • calipers/ellipse placed correctly	
AC	**Axial plane through the fetal abdomen (5 points)** • abdomen occupies at least 50% of image • symmetrical, circular section, spine lateral • stomach bubble visible • portal sinus visible • calipers/ellipse placed correctly	
FL	**Length of femoral diaphysis (4 points)** • length of femur occupies at least 50% of image • angle of femur <30° • both ends of bone clearly identified • callipers placed correctly	

IMAGE ASSSESSMENT SHEET

OPERATOR ID _____DATE_____

Axial plane through fetal head (✓criteria met ×criteria not met) BPD HC BPDi must each meet criteria Satisfactory = 4/5 criteria met						
Image no.	Image size	Symmetrical & horizontal section	Thalami visible	CSP visible	Caliper/Ellipse placement	S/NYS
1						
Comments						
2						
Comments						
3						
Comments						

Axial plane through fetal abdomen (✓criteria met ×criteria not met) Satisfactory = 4/5 criteria met						
Image no.	Image size	Symmetrical & circular section	Stomach visible	Portal sinus visible	Caliper/Ellipse placement	S/NYS
1						
Comments						
2						
Comments						
3						
Comments						

Length of femoral diaphysis (✓criteria met ×criteria not met) Satisfactory = 3/4 criteria met					
Image no.	Image size	Horizontal	Both ends of bone clearly defined	Caliper placement	S/NYS
1					
Comments					
2					
Comments					
3					
Comments					

Appendix C

Study protocol: The role of fetal growth velocity assessment in clinical practice

The role of fetal growth velocity assessment in clinical practice

Principal investigator:

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Institution responsible for the running of the study:

The Canberra Hospital

Contents

Synopsis

The diagnosis of abnormal fetal growth is based on differences between the actual measurements and expected measurements as determined by a reference chart for a given gestational age. Measurements less than the 10th percentile or greater than the 90th percentile tend to be triggers to change clinical management. However, measurements in the outer centiles are not necessarily pathological, and a single third trimester ultrasound provides an assessment of fetal size at a single time point that may not necessarily reflect the process of growth. Altered growth velocity has been proposed as a method to better define pathologic growth, but there are different views on what constitutes a significant change in growth velocity.

The aim of this research is to define thresholds for suboptimal fetal interval growth relevant to clinical practice by retrospective analysis of fetal growth velocity in a cohort of pregnancies referred for third trimester ultrasound examinations.

Abbreviations and Acronyms

AC	Abdominal Circumference
ACT HREC	Australian Capital Territory Human Research Ethics Committee
AFI	Amniotic fluid index
ANU	Australian National University
BPD	Bi Parietal Diameter
CPR	Cerebral Placental Ratio
EDB	Estimated Date of Birth
EFW	Estimated Fetal Weight
FGR	Fetal Growth Restriction
FL	Femur Length
FLAG	Fetal Longitudinal Assessment of Growth
FMU	Fetal Medicine Unit
HC	Head Circumference
MCA PI	Middle Cerebral Artery Pulsatility Index
NNICU	Neonatal Intensive Care Unit
POP	Pregnancy Outcome Prediction
SCN	Special Care Nursery
SPSS	Statistical Package for the Social Sciences
UA PI	Umbilical Artery Pulsatility Index

Introduction/Background

Abnormal fetal growth and fetal growth restriction (FGR) in particular, is associated with increased risk of adverse perinatal outcomes[3, 171]. Prenatal identification allows for increased fetal monitoring to inform clinical decisions regarding delivery, and has been shown to improve perinatal outcomes[18].

The role of ultrasound in the measurement of fetal biometry and estimation of fetal weight is well established, with the identification of abnormal growth based on comparison with expected measurements for a given gestational age derived from a reference chart. Measurements less than the 10th percentile for gestational age or greater than the 90th percentile for gestational age tend to be triggers to change clinical management. However, measurements in the outer centiles are not necessarily pathological. Furthermore, a single third trimester ultrasound provides an assessment of fetal size at a single time point that may not necessarily reflect the process of growth, and a fetus with abnormal growth may have measurements that fall within the 10th or 90th percentiles.

Altered growth velocity has been proposed as a method to better define pathologic growth, with particular attention given to reduced growth velocity[51]. Defining what constitutes a significant change in growth velocity is difficult[17]. The Pregnancy Outcome Prediction (POP) study in 2015 reported reduced abdominal circumference (AC) growth velocity (below the 10th percentile) in fetuses with an estimated fetal weight (EFW) below the 10th percentile were at increased risk of neonatal morbidity[163]. In 2016, a consensus definition of FGR was published that included reduced growth velocity, namely, fetal abdominal circumference (AC) measurements or estimated fetal weight (EFW) crossing percentiles by more than two quartiles (a percentile drop of more than 50)[231]. The Fetal Longitudinal Assessment of Growth (FLAG) study in 2017 reported that babies with a birthweight in the normal range are more likely to show features of placental insufficiency (as measured by fetal Doppler) when there was a drop of 30 percentiles in customised EFW or AC between 28 and 36 weeks gestational age[257]. More recently, this association was reported between mid-trimester measurements and those performed at 36 weeks gestational age[258]. In 2020 fetal growth velocity standards were published, based on the Fetal Growth Longitudinal Study (Intergrowth-21st project), along with on-line calculators to aid in assessment of growth velocity. Similar to the Intergrowth-21st charts, the fetal growth velocity increments are prescriptive, that is, they define how a fetus should grow in ideal circumstances[259].

Calculation of growth velocity is not a routine feature of third trimester ultrasound, but there is evidence some clinicians use a change in percentiles to modify clinical management[260]. How to best incorporate assessment of reduced growth velocity into clinical practice is unclear. Comparing AC and EFW percentiles from ultrasounds performed at different gestations while attractive in its simplicity, may not be the best approach. Assigned percentiles in each examination may vary greatly according to which fetal chart was used and the standard deviation of fetal measurements increases with increasing gestational age. Currently, there is no uniformity in the choice of fetal growth chart, and this may vary between practices in the same region[260].

Research Aims

The overall aim of this research is to define thresholds for suboptimal fetal interval growth relevant to clinical practice.

The following will be examined:

- if findings of the FLAG study can be applied to clinically indicated third trimester ultrasound examinations (is a reduction of 30 percentiles between the mid trimester and third trimester ultrasound associated with markers of placental insufficiency)
- if reduced growth velocity (determined from longitudinal studies) can be applied to cross-sectional fetal growth charts that are commonly used in Australia
- is growth velocity calculated by the Intergrowth-21st on-line calculator useful in clinical practice

Findings from this research may help provide evidence to inform methods of incorporating measures of growth velocity in third trimester ultrasound examinations.

Methodology

We propose a retrospective study to calculate fetal growth velocity from fetal measurements made at ultrasound examinations performed in the 35th week to 37th week of pregnancy in the Fetal Medicine Unit (FMU), Canberra Hospital, and fetal measurements performed at the routine mid trimester scan (performed at 18-22 weeks). Birth outcome data will be collected to examine the relationship between neonatal morbidity and reduced growth rate.

Clinical measures of neonatal condition include Apgar scores (routine measures at 1 minute and 5 minutes after birth, of baby's colour, heart rate, reflexes, tone, & respiratory effort), and arterial cord blood pH. Markers of neonatal morbidity include one or more of the following: an Apgar score less than 7 at 5 minutes, arterial cord blood pH of less than 7.15 (indicating acidosis), and admission to special care nursery (SCN) or neonatal intensive care unit (NNICU).

The main benefit of a retrospective design is access to a large pool of data with recorded outcomes. The FMU performs approximately 6000 ultrasounds per year, of which 67% are performed in the third

trimester (yet only a proportion will be performed between 35 and 37 weeks). There are approximately 3500 singleton births at Canberra Hospital annually. Calculating growth velocities retrospectively ensures clinical management was not affected by this study.

The disadvantage of a retrospective design is that third trimester measurement data will come from clinically indicated ultrasound examinations. Although many pregnancies in Australia will have a third trimester ultrasound, unlike the mid trimester scan, it is not a routine examination [37]. Broadly speaking, clinical indications for third trimester ultrasound include suspected small for gestation age, suspected large for gestational age, and indications not related to fetal growth, for example, assessment of placental localisation. To assess possible selection bias, maternal characteristics known to affect fetal growth and the indication for the examination will be recorded. The retrospective design also has the potential for measurement bias due to lack of operator blinding, however, this is reflective of current clinical practice (i.e. when a measurement is made during an ultrasound examination, the operator is typically able to see the corresponding gestational age or measurement percentile). Another concern associated with retrospective design is incomplete/missing data. To minimise this, two elements of the inclusion criteria are that the ultrasound examination was performed in the FMU and infants were born at the Canberra Hospital.

Study population

The study population will comprise of singleton pregnancies where a third trimester ultrasound was performed in the FMU between 35 and 37 weeks in infants born at the Canberra Hospital. Within this population, there will be a group of infants that demonstrated normal fetal growth velocity in utero, and a group that demonstrated reduced fetal growth velocity. While the main focus of this research the group with reduced fetal growth velocity, it is acknowledged that there will be a third group of infants demonstrating increased fetal growth velocity. Figure 1 represents the study population profile.

Inclusion criteria:

- Singleton viable pregnancies with ultrasound performed in the 35th week to 37th week of pregnancy
- Estimated date of birth (EDB) as confirmed by ultrasound at 8-14 weeks of pregnancy

Exclusion criteria:

- Pregnancies with a known fetal abnormality
- Pregnancies where EDB was not confirmed by ultrasound at 8-14 weeks of pregnancy
- Multiple pregnancies
- Pregnancies that did not birth at Canberra Hospital

Sample size

The sample size required to assess differences between infants with reduced fetal growth velocity and normal fetal growth velocity can be calculated by:

$$n_i = \{p_1(1-p_1) + p_2(1-p_2)\}\left(\frac{Z}{E}\right)^2$$

where:

n_i is the sample size required in each group

The birth outcome of interest is neonatal acidosis as measured by cord artery pH, as a reassuring Apgar score does not completely exclude acidosis[366]. The background rate of neonatal acidosis (cord pH < 7.15) is 7% for births > 37 weeks' gestational age at Canberra Hospital (measured between January 1 and June 30 2021).

p_1 and p_2 are the proportions of acidosis in each group; For a 50% increase in acidosis, p_1=10.5% and P_2 = 7%

Z is the value from the standard normal distribution reflecting the 95th confidence interval = 1.96

E is the margin of error 10.5% - 7% = 3.5%

$$n_i = \{0.105(1 - 0.105) + 0.07(1 - 0.07)\}\left(\frac{1.96}{0.035}\right)^2 = 498$$

To obtain the required sample size, interim analysis of data will be performed to identify infants with reduced fetal growth velocity and to assess differences in outcome between the groups. If no statistically significant difference is detected between the groups, it may be necessary to increase the sample size to improve power.

Procedure

Data for this study will come from the three password protected electronic databases routinely used in the Fetal Medicine Unit (FMU) and will be collected by the principal investigator. These include:

- ViewPoint
    - Ultrasound reports (studies performed in FMU)
    - Maternal characteristics (age, diabetes, hypertension, history of pre-eclampsia, height, weight, parity, other medical conditions associated with abnormal fetal growth)
- Clinical Patient Folder
    - Ultrasound reports (studies not performed in FMU, i.e. the mid-trimester scan may have been performed by a different ultrasound provider)
- Birthing Outcomes System
    - Birth outcome data as recorded in birth outcome summary

A search will be initiated in ViewPoint to identify eligible ultrasound examinations, using search terms 'Fetal Growth' and '35*', '36*', '37*'. Patient identifiers in ViewPoint will be used to reference Clinical Patient Folder and Birth Outcome System for outcome data.

For each patient, the following de-identified data will be recorded:

- Gestation when the ultrasound was performed
- Indication for the ultrasound examination
- Fetal measurements from the 35 - 37 week ultrasound and mid-trimester ultrasound
    - This includes:
        - Bi-parietal diameter (BPD)
        - Head Circumference (HC)
        - Abdominal circumference (AC)
        - Femur length (FL)
        - Amniotic fluid index
        - Fetal Doppler measurements (if performed)
            - Umbilical artery pulsatility index (UA PI)
            - Middle cerebral artery pulsatility index (MCA PI)
    - Measurements rather than percentiles will be recorded as the use of fetal growth charts is not consistent between ultrasound providers; percentiles will be calculated during analysis
    - Estimated fetal weight (EFW) calculation is not consistent between ultrasound providers; EFW will be calculated during analysis
    - Fetal Doppler measures and amniotic fluid index are indicators of placental insufficiency
- Maternal characteristics
    - Possible risk factors for abnormal fetal growth
        - Age
        - Pre-existing diabetes or diabetes in pregnancy
        - Hypertension
        - Smoking
        - History of pre-eclampsia
        - Height
        - Weight
        - Parity
        - Other medical conditions

- Birth outcome data
    - Gestational age at birth
    - Birthweight
    - Sex
    - Method of delivery
    - Apgar scores (routine measures at 1 minute and 5 minutes after birth, of baby's colour, heart rate, reflexes, tone, & respiratory effort)
    - Cord blood (if performed)
    - Days of admission to special care nursery (SCN) or neonatal intensive care unit (NNICU) (if this occurred)

Data Management

The principal investigator will be responsible for data collection, and has password protected access to ViewPoint, Clinical Patient Folder, and Birthing Outcomes System.

Export data from the ViewPoint search will be directly imported as an Excel spreadsheet and will include a patient identifier (hospital record number) to enable outcome data to be referenced from Clinical Patient Folder and Birthing Outcomes System. The spreadsheet will be stored on a password protected computer at the Canberra Hospital.

Patient identifiers will be deleted when outcome data for each dataset has been recorded. Only de-identified data will be used for analysis. Each case will be issued a sequential number (1,2,3 etc.). Data used for analysis cannot be re-identified. The de-identified spreadsheet used for analysis will be stored on a password protected computer at the Canberra Hospital and backed up on the Australian National University (ANU) OneDrive.

Analysis will be performed by the principal investigator at the Canberra Hospital and at ANU.

Data will be stored for a minimum of seven years from the date of any publication arising from the research, then archived electronically and retained by the principal researcher.

Adverse Event Reporting

There are no adverse events in this retrospective low risk study.

Statistical Analysis

Each dataset in the Excel spreadsheet will consist of:

- Gestational age (weeks and days) when the ultrasounds were performed
    - Third trimester fetal measurements (35 – 37 weeks)
        - Bi-parietal diameter (BPD)
        - Head Circumference (HC)

        - Abdominal circumference (AC)
        - Femur length (FL)
        - Amniotic fluid index (AFI)
        - Fetal Doppler measurements (if performed)
            - Umbilical artery pulsatility index (UA PI)
            - Middle cerebral artery pulsatility index (MCA PI)
    - Second trimester fetal measurements (18 – 22 weeks)
        - Bi-parietal diameter (BPD)
        - Head Circumference (HC)
        - Abdominal circumference (AC)
        - Femur length (FL)
- Maternal characteristics
    - Age
    - Pre-existing diabetes or diabetes in pregnancy
    - Hypertension
    - Smoking
    - History of pre-eclampsia
    - Height
    - Weight
    - Parity
    - Other medical conditions
- Birth outcome data
    - Gestational age at birth
    - Birthweight
    - Sex
    - Method of delivery
    - Apgar scores (routine measures at 1 minute and 5 minutes after birth, of baby's colour, heart rate, reflexes, tone, & respiratory effort)
    - Cord blood (if performed)
    - Days of admission to special care nursery (SCN) or neonatal intensive care unit (NNICU) (if this occurred)

For each dataset, the following will be calculated:

- Gestational age in days
- EFW (Hadlock HC-AC-FL and Hadlock BPD-HC-AC-FL algorithm) and corresponding z-scores and percentiles (referenced to commonly used EFW charts)
- AC z-scores and percentiles (referenced to commonly used charts)
- Growth velocity (percentile differences between time points for AC and EFW)
- AC conditional velocity z-score (Intergrowth 21st on-line calculator)
- UA PI and MCA PI percentile (referenced to commonly used charts)
- Cerebral placental ratio (CPR) (MCA PI/UA PI) percentile (referenced to commonly used charts)

- Amniotic fluid index (AFI) (low < 5, high >24)
- Birthweight percentile (referenced to commonly used charts)

Data will be transferred from the Excel spreadsheet for analysis in SPSS.

The relationship between growth velocity calculated from percentile differences between time points for AC and AC conditional velocity score (Intergrowth 21st on-line calculator) will be examined visually (scatter plots and Bland-Altman plots).

Regression analysis will be used to examine the relationship between calculated growth velocities and prenatal markers of placental insufficiency (abnormal Doppler measures, low AFI) and postnatal markers (low birthweight, umbilical artery pH <7.15).

Quality assurance, monitoring and safety

The data for this study will come from ViewPoint, Birthing Outcome Systems, and Clinical Patient Folder. The principal investigator has password protected access to these databases and has received appropriate training to use these databases. Regular access to these systems is required for FMU staff to operate in a paperless environment.

As an image archive and reporting system for obstetric ultrasound, ViewPoint accepts direct import of image and measurement data from the ultrasound device. This virtually eliminates the risk of transcription error.

Birthing Outcomes System records all birth outcomes for the Canberra Hospital. Birth outcome data recorded in is entered contemporaneously and rechecked at patient discharge.

Clinical Patient Folder stores medical records for each patient, including diagnostic test results for ultrasound examinations. This database will be accessed to view mid-trimester ultrasound reports for studies that were not performed in the Fetal Medicine Unit.

Data collection will be performed by the principal investigator on site in FMU and stored in ACT government password protected computers. Only de-identified data will be used in analysis; data used for analysis cannot be re-identified.

Ethical Issues

Ethical review by ACT HREC.

Finance and resource use

There is no funding for this project.

Dissemination of Results and Publication policy

The results will form part of the PhD thesis of the principal investigator and be written up for publication in scientific journals and presentation at international meetings.

References