KWAME NKRUMAH UNIVERSITY OF SCIENCE AND TECHNOLOGY, KUMASI

COLLEGE OF HEALTH SCIENCES

SCHOOL OF MEDICAL SCIENCES

DEPARTMENT OF ANATOMY

A Preliminary Morphometric Study of Ghanaian Foetal Parameters for Size and Age Estimation

BY

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AUGUST, 2016

A PRELIMINARY MORPHOMETRIC STUDY OF GHANAIAN FOETAL

PARAMETERS FOR SIZE AND AGE ESTIMATION

A THESIS SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF PHILOSOPHY IN HUMAN ANATOMY AND CELL BIOLOGY

IN THE

DEPARTMENT OF ANATOMY, SCHOOL OF MEDICAL SCIENCES, COLLEGE OF HEALTH SCIENCES

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AUGUST, 2016

DECLARATION

The experimental work described in this thesis was carried out at the Department of Anatomy, School of Medical Sciences, Kwame Nkrumah University of Science and Technology. This work has not been submitted for any other degree.

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ACKNOWLEDGEMENTS

I thank the Almighty Yahweh for His abundant grace and love through Christ Jesus. I am very grateful to my supervisor, Prof. Mrs. Chrissie Stansie Abaidoo, for her advice, patience, encouragement and constructive criticisms.

I am indebted to the staff of Sunyani Municipal Hospital and Suntreso Government Hospital especially Mr. Osei Bonsu and Mr. Anastasius Buady, who are certified sonographers.

Special thanks to my parents and siblings for always being there for me.

Finally, I would like to thank my colleagues, Nancy, Rockson, Joshua, Thomas and Ohene-Djan for their support throughout the project.

ABSTRACT

Ultrasonographic foetal biometry has proven to be a reliable tool in the correct estimation of gestational age and assessment of foetal growth. The choice of a reference chart is critical to the proper assessment of foetal biometry due to observed racial differences. Therefore this study was designed to establish foetal biometric standards in Ghanaians. A prospective, cross-sectional study was conducted using a total of 374 pregnant women with known last menstrual period from the Sunyani Municipal Hospital and the Suntreso Government Hospital from October 2015 to March 2016. Measurements of crown-rump length, biparietal diameter, head circumference, abdominal circumference and femur length were obtained via transabdominal sonography. Results of the present study provide for the first time detailed baseline data on foetal biometry in Ghana and show that there is significant disparity between gestational age estimated by the last menstrual period and ultrasound. Head circumference was the best parameter in estimating gestational age in the second and third trimesters of pregnancy with coefficient of determination (R^2) of 96.6% and 84.1% respectively. Combinations of head circumference or biparietal diameter, abdominal circumference and femur length in the third trimester increased the R^2 to 90 or 90.5%. Biparietal diameter was a good predictor of gestational age in the third trimester than previously reported in the literature suggesting normal cephalic indices in the present population. Statistically significant differences in foetal biometry exist between the present population and the American, British and Chinese populations in the literature. This study provides preliminary baseline data for the estimation of gestational age and assessment of foetal growth by sonographers and obstetricians.

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LIST OF ABBREVIATIONS

ABBREVIATIONS	NAME
AC	Abdominal circumference
AIUM	American Institute of Ultrasound in Medicine
APAD	Anteroposterior Abdominal Diameter
ASUM	Australasian Society for Ultrasound in Medicine
BPD	Biparietal Diameter
CI	Cephalic Index
CRL	Crown-Rump Length
EDD	Expected Date of Delivery or Expected Due Date
EFSUMB	European Federation of Societies for Ultrasound in Medicine and Biology
EFW	Estimated Foetal Weight
FL	Femur (diaphysis) Length
FL/AC	Femur length to abdominal circumference ratio
FL/BPD	Femur length to biparietal diameter ratio
FL/HC	Femur length to head circumference ratio

GA	Gestational age
GA_{LMP}	Gestational age estimated by the last menstrual period
GA_{US}	Gestational Age estimated by ultrasound
HC	Head circumference
HC/AC	Head to abdominal circumference ratio
ISUOG	International Society of Ultrasound in Obstetrics and Gynaecology
IUGR	Intrauterine growth restriction
IVF	*in vitro* fertilization
KHz	Kilohertz
LMP	Last Menstrual Period
M1	Mechanical index
MHz	MegaHertz
mm	Millimeter (s)
MSD	Mean gestational sac diameter
SDGs	Sustainable Development Goals
SEE	Standard Error of the Estimate
SEM	Standard Error of the Mean
SFH	Symphysis-fundal height
SGA	Small-for-gestational-age
T1	Thermal index
TAD	Transverse Abdominal Diameter
TAS	Transabdominal sonography

TVS	Transvaginal sonography
UN	United Nation
UNICEF	United Nations Children's Emergency Fund
US	Ultrasound
WHO	World Health Organization

CHAPTER ONE

INTRODUCTION

The estimation of gestational age and the assessment of size and growth of the embryo or foetus are routinely performed during antenatal care (Butt and Lim, 2014). Gestational age is the age of pregnancy (Kalish and Chervenak, 2005). Knowing how long the embryo or foetus is *in utero* is important in predicting the expected date of delivery and hence proper classification of term, preterm and postterm dates (Blondel *et al.*, 2002). Determination of antimalarial drug regime (Rijken *et al.*, 2012) and the scheduling of initiation date for Zidovudine treatment (Traisathit *et al.*, 2006) depend on knowledge of the gestational age. Accurate dating is also paramount to the proper timing of foetal genetic screening (nuchal translucency, chorionic villi sampling and amniocentesis), testing for foetal lung maturity as well as relating the various maternal blood serum (pregnancy-associated plasma protein-A, alpha-fetoprotein, human chorionic gonadotropin, estriol and inhibin-A) levels to risk factors (Kalish and Chervenak, 2005; Neufeld *et al.*, 2006). Virtually all important clinical decisions in obstetrics are dependent on accurate estimation of gestational age (Merritt *et al.*, 1992).

Traditionally the gestational age is estimated from the first day of the last menstrual period (LMP) since the day of conception cannot be accurately known (MacGregor and Sabbagha, 2008; Whitworth *et al.*, 2015). The reliability of LMP-based gestational age estimation however depends on the regularity of a woman's menstrual cycle, accurate recall of LMP, interpretation of bleeding in early pregnancy, lactational amenorrhoea, contraceptives use prior to pregnancy and variations in the timing of ovulation and fertilization (Geirsson, 1991; Nguyen *et al.*, 2000; Salpou *et al.*, 2008). About 11 – 42% of gestational age estimated by LMP are reported as inaccurate

(Nguyen *et al.*, 2000; Whitworth *et al.*, 2015). The symphysis-fundal height (SFH) measurement is also used as a proxy in estimating gestational age and assessing growth abnormalities (foetal growth restriction and macrosomia) (Ogbe *et al.*, 2015; Robert *et al.*, 2015). The detection rates of small-for-gestational-age babies using SFH ranges from 56% - 86% (Robert *et al.*, 2015). The SFH measurement is affected by the technique used, the number of clinicians involved, multiple pregnancies, status of the maternal bladder, maternal position, pre-pregnant weight, molar pregnancy, amniotic fluid level, macrosomia and intrauterine growth restriction (Engstrom *et al.*, 1993; Steingrímsdottir *et al.*, 1995).

In recent years foetal biometry through the use of ultrasound has become indispensable tool for the practice of obstetrics. Ultrasonography is safe, non-invasive, accurate and cost-effective than other diagnostic imaging modalities (Rueda *et al.*, 2014). Ultrasonographic foetal biometry is the measurements of various structures of the foetal anatomy (Shehzad *et al.*, 2006). Ultrasonography has proven to be the best method for estimating gestational age and the expected due date (Salomon *et al.*, 2011; Butt and Lim, 2014). This has reduced expensive hospitalization and unnecessary interventions such as induction of labour and tocolytic treatments due to wrongfully assumed foetal growth abnormality, preterm and post-term labour (Pemberton *et al.*, 2010; Brakohiapa *et al.*, 2012). Ultrasonographic foetal biometry is more useful in estimating foetal weight and diagnosing intrauterine growth restriction (IUGR) and macrosomia than abdominal palpation and symphysis-fundal height (Salomon *et al.*, 2011; Butt and Lim, 2014).

There are two approaches in the study of foetal biometry: a cross-sectional study and a longitudinal study (Loughna *et al.*, 2009). In a cross-sectional study, a foetus is measured only once during gestation. It is appropriate for creating foetal size and age charts. Foetal size charts and foetal age charts are not synonymous (Briceño *et al.*, 2013). In foetal size chart, the foetal parameter is plotted as a function of gestational age whereas in foetal age chart, the gestational age is plotted as a function of the foetal parameter (Loughna *et al.*, 2009). Longitudinal study involves serial measurements of the same foetus for at least three times during pregnancy. It is best used in creating foetal growth charts (Loughna *et al.*, 2009).

Various foetal biometric parameters have been sonographically measured for the creation of foetal age, size and growth charts (Shehzad *et al.*, 2006). They include measurements of mean gestational sac diameter, transverse cerebellar diameter, liver length, kidney length, intra/interorbital diameters, clavicular length, humeral length, scapula length, sacral length and nasal bone length (Shehzad *et al.*, 2006; Butt and Lim, 2014). The commonly measured parameters, sometimes referred to as the gold standard of foetal biometric measurements, are the crown-rump length (CRL), biparietal diameter (BPD), head circumference (HC), femur diaphysis length (FL) and abdominal circumference (AC) (Shehzad *et al.*, 2006). Many clinical decisions depend upon accurate and reproducible measurements of foetal biometry and choice of appropriate reference charts.

1.1 THE PRESENT STUDY

Maternal mortality is unacceptably high across the developing countries, including Ghana. The maternal mortality ratio in 2015 for Ghana was 319 per 100,000 live births and the neonatal mortality in 2013 was 29 per 1,000 live births (UNICEF, 2015). In order to achieve the United Nations Sustainable Development Goals (SDGs) 3.1 and 3.2 of reducing the global maternal mortality ratio to less than 70 per 100,000 live births and neonatal mortality to at least as low as 12 per 1,000 live births by 2030 (UN, 2015) respectively, the role of obstetric ultrasonography cannot be underestimated. An appropriate reference table for ultrasound dating and a reliable reference foetal size chart can improve obstetric management in pregnancy and hence reduce perinatal mortality and morbidity (Lausman *et al.*, 2013; Pay *et al.*, 2015)

Ultrasonographic foetal biometry assumes that the size of an embryo or a foetus is consistent with its age (Butt and Lim, 2014). Different embryos or foetuses of the same biometric measurements can have different gestational ages. Alternatively, different embryos or foetuses of the same gestational age can have the same or different biometric measurements. This indeed is a clinical dilemma since this may suggest normal foetal growth, intrauterine growth restriction (small-for-gestationalage) or macrosomia (large-for-gestational-age). The state of the embryo or foetus can be ascertained by comparing the size or age as the case may be with a reference chart of a specific population derived from low-risk pregnancies. Several reference age and size charts of foetal biometric parameters have been published for populations in Europe (Chitty *et al.*, 1994 a, b, c; Snijders and Nicolaides, 1994; Kurmanavicius *et al.*, 1999 a, b; Paladini *et al.*, 2005; Salomon *et al.*, 2006), America (Deter *et al.* 1982; Hadlock *et al.*, 1982 a, b, c, d), Asia (Lachman and Shen, 1996; Salomon *et al.*, 2006;
Jung *et al.*, 2007) and Africa (Okonofua *et al.*, 1988; Salpou *et al.*, 2008; Mador *et al.*, 2011). These tables and equations have been included in most ultrasound software programme for obstetric use. Since the charts and tables are many, the choice of a reference chart is important in the assessment of foetal biometry (Salomon *et al.*, 2005). An inappropriate reference chart can pose significant clinical implications since this may mislead the obstetrician as to the true state of health or development of

the foetus. Using Z-scores, Salomon *et al.* (2005) observed that the number of foetuses that would have been considered abnormal (below 5th centile and above 95th centile) based on the references by Snijders and Nicolaides (1994), Chitty *et al.* (1994a, b, c) and Kurmanavicius *et al.* (1999a, b) to the French population ranged from 2.6% to 23.6% for BPD, HC and FL. The specificity and sensitivity ranged from 90.1% to 99.7% and 39.6% to 67.1% respectively. None of the references for AC was found to be acceptable to the French population.

Differences in foetal biometry have been attributed to race or ethnicity, maternal age, parity, nutritional status and foetal sex (Davis *et al.*, 1993; Jacquemyn *et al.*, 2000; Leung *et al.*, 2008). Even within a population, Krampl *et al.* (2000) found that geographical changes such as altitude affect foetal size. These have prompted many researchers (Hadlock *et al.*, 1982a, b, c, d, e; Chitty *et al.*, 1994a, b,c; Leung *et al.*, 2008; Westerway *et al.*, 2000; Buscicchio *et al.*, 2008) to develop reference charts that are specific to their populations. Hadlock and coworkers' charts (Hadlock *et al.*, 1982a, b, c, d, e; Hadlock *et al.*, 1984a) that are commonly used in Ghana were developed over 30 years ago from middle class Caucasian women, which are not representative of the Ghanaian population. Also, reference charts over 30 years old were developed using obsolete ultrasound equipment, suboptimal study designs and statistical analyses (Altman and Chitty, 1994). Some researchers (Westerway *et al.*, 2000; Buscicchio *et al.*, 2008) have even called for the revision of older foetal nomograms due to increasing in birthweights in the last decades (Irgens, 2000).

Cross-sectional reference foetal charts and equations from the Ghanaian population using appropriate methods have not previously been published in the literature. Also, there are no standard reference tables and charts for foetal size and foetal age assessment and a number of ultrasound centres are unable to clarify the reference charts and tables they are using. The choice of reference charts have often being based on preference or on the chart that is loaded by default in the software of the ultrasound machine. The present study attempts to establish reference baseline charts and tables in the Ghanaian population for standard foetal biometric parameters using the methods recommended by Altman and Chitty (1994) and Royston and Wright (1998).

1.2 AIM AND OBJECTIVES

1.2.1 AIM

To establish the need for foetal biometric standards for Ghanaians.

1.2.2 OBJECTIVES

1. To determine menstrual-based gestational age and ultrasound-based gestational age.
2. To determine the degree of discrepancy between ultrasound-based gestational age and menstrual-based gestational age.
3. To establish reference charts for foetal age and size estimation based on sonographic measurements of crown-rump length, biparietal diameter, head circumference, abdominal circumference, femur length and their ratios.
4. To compare the foetal size and age charts in the present study with published charts.
5. To determine the best parameter (s) in estimating gestational age in the second and third trimesters of pregnancy.

CHAPTER TWO

LITERATURE REVIEW

2.1 ULTRASONOGRAPHY

2.1.1 Overview of Ultrasonography

Sound is the orderly transmission of mechanical vibrations through a medium (Merritt *et al.*, 1992). Sound above 20 kHz is referred to as ultrasound (Merritt *et al.*, 1992). Diagnostic medical sonography (Ultrasonography) is a medical imaging technique that uses high-frequency sound waves (2 - 18 MHz) to produce dynamic visual images of organs, tissues or blood flow inside the body (Houston *et al.*, 2009). Ultrasound waves are produced by piezoelectric effect (Thornton, 1992). An alternating current applied to piezoelectric crystals within the transducer causes the molecules in the crystals to vibrate creating a mechanical wave which is transmitted into the body (Thornton, 1992). The returning echoes are then converted into electrical signals by the transducer with the strength of the echo being determined by the characteristics of the tissue interface (Thornton, 1992). A computer displays both the strength and position of each echo as real-time two- or three-dimensional image, sonogram or ultrasonogram, on a screen (Houston *et al.*, 2009). These images are usually stored in the form of thermal prints, polaroid pictures, video tape or digital image files. The various modes of ultrasound show the returning echoes in different modes such as the A (amplitude), B (brightness), M (motion), or Doppler modes depending upon desired clinical information (Houston *et al.*, 2009). Transducers come with different frequencies, physical dimensions, footprints (or contact area), shapes and provide different image formats (Szabo and Lewin, 2013).

Diagnostic sonography imaging is the modality of choice in many clinical applications due to its non-invasive nature, convenience, reduced cost, high portability and realtime acquisition compared to other imaging modalities such as X-ray imaging, Computed Tomography or Magnetic Resonance Imaging (Rueda *et al.*, 2014). Ultrasonographic images are known to be affected by artefacts, shadows and speckles, attenuations, missing boundaries and signal dropouts (Rueda *et al.*, 2014). The quality of ultrasound imaging is therefore dependent on the ultrasound equipment, the experience and expertise of the operator, maternal habitus and foetal position (Rueda *et al.*, 2014). Various professional bodies such as the American Institute of Ultrasound in Medicine (AIUM), the International Society of Ultrasound in Obstetrics and Gynaecology (ISUOG), the European Federation of Societies for Ultrasound in Medicine and Biology, the Australasian Society for Ultrasound in Medicine and several others have addressed these challenges by setting up professional standards for minimal training requirements, quality assurance and equipment specifications (Hunter, 2009).

Ultrasonography represents the most significant advance in obstetric diagnosis and clinical management. Since the introduction of ultrasonography there has been significant technological advancements. Diagnostic ultrasonography has moved from transabdominal static A-mode (one-dimensional amplitude imaging) to real-time Bmode (or 2-D mode), low frequency transabdominal sonography to high-frequency transvaginal sonography, Doppler sonography to evaluate the pulsations in the foetal heart and blood vessels and recently static three-dimensional (3-D) and fourdimensional (4-D) (or dynamic 3-D) imaging (Prager *et al.*, 2010). The applications of 3-D or 4-D include geometric modeling, volume contrast imaging, multiplanar imaging, volume measurement, image segmentation, tomographic ultrasound imaging, spatial-temporal image correlation and multiple render modes (Prager *et al.*, 2010). Some investigators believe 3-D or 4-D ultrasound may replace conventional two dimensional (2-D) imaging (Prager *et al.*, 2010). The 3-D or 4-D has improved detailed visualization of certain foetal organ structures like the face and central nervous system, evaluation of foetal lung volumes and foetal echocardiography, improved maternal-foetal psychological bonding and ensured precise volume measurement of organs with irregular shape (Kurjak *et al.*, 2007; Jong-Pleij *et al.*, 2013). 3-D or 4-D has been shown to be superior to conventional 2-D imaging in diagnosing anomalies such as neural tube defects, facial defects (micrognathia, midface hypoplasia and frontal bossing, cleft lip and palate) and clubfoot on low-risk pregnant women (Dimitrova *et al.*, 2006). Ultrasonography has also been used to support interventions such as chorionic villi sampling, amniocentesis, cordocentesis (percutaneous umbilical blood sampling) image-guided biopsy, ultrasound-guided radiotherapy planning and image-guided surgery (Prager *et al.*, 2010).

2.1.2 Obstetric Ultrasonography

Ultrasonographic examination is performed in real-time via transabdominal or transvaginal approach (Kirk and Bourne, 2009). Transabdominal sonography (TAS) is performed by moving across the lower abdomen a low frequency transducer (3 - 3.5 MHz). A gel is applied on the surface of the abdomen to reduce reflection of sound waves. In transvaginal sonography (TVS), a high frequency (5 - 10 MHz) endovaginal probe is covered with a plastic or latex sheath, like a condom, lubricated and inserted in the pregnant woman's vagina (Lohr *et al.*, 2010). Due to the high frequency coupled with proximity of the transducer to pelvic organs, TVS provides higher resolution and greater visualization of early embryonic structures (gestational sac, yolk sac, and embryo), detection of foetal anomalies and ectopic pregnancies (Kirk and Bourne, 2009; Lohr *et al.*, 2010). Achiron and Tadmor (1991) detected anencephaly, exencephaly or acrania and cervical mylemeningocoele undetectable by TAS at 9 - 13 weeks' gestation. Condous *et al.* (2005) found the sensitivity and specificity of detecting ectopic pregnancy using TVS to be 90.9% and 99.9% respectively. Several investigators have also reported similar sensitivity and specificity (Kirk *et al.*, 2007; Kirk and Bourne, 2009). However in pregnancy dating, the accuracy of TAS is same as TVS when the crown-rump length (CRL) is measured from 7 week's gestation (Grisolia *et al.*, 1993; Lohr *et al.*, 2010; Kaur and Kaur, 2011). Whereas in TAS, patients must have a full bladder, TVS can be done instantly as patients need an empty bladder (Nahar *et al.*, 2008). Transvaginal sonography (TVS) can bypass obstacles such as bone, gas filled bowel and extensive pelvic adhesions (Nahar *et al.*, 2008). It can also be performed in obese women and in women with retroverted uterus (Kaur and Kaur, 2011). Problems with TVS include initial unwillingness by patients due to the unorthodox position, limited scanning planes and manoeuvrability of probe and anteverted uterus (Nahar *et al.*, 2008).

Obstetric ultrasonography has become an essential part of antenatal care. First trimester ultrasonography is performed from 6 weeks using transvaginal ultrasonography or from 11 weeks using transabdominal ultrasonography up to 13 weeks 6 days gestation (Salomon *et al.*, 2013). This is to confirm viability of embryo or foetus, to determine gestational age and estimate the expected date of delivery

(EDD), to establish the chorionicity and amnionicity in multiple pregnancy, to evaluate foetal gross anatomy and to measure nuchal translucency as a marker of aneuploidy (trisomy 13, 18 or 21) (Salomon *et al.*, 2013; AIUM, 2013). Foetal viability is confirmed when a yolk sac and an embryo are present in the gestational sac and cardiac activity is detected in M-mode (Tan *et al.*, 2012). First trimester ultrasonography can also be used to evaluate suspected ectopic pregnancy, molar pregnancy and pelvic masses; the cause of vaginal bleeding; to examine the uterus, cervix, adnexa, and cul de sac region and as an adjunct to chorionic villus sampling, embryo transfer, localization and removal of an intrauterine device (AIUM, 2013). In addition to that performed during the first trimester, the International Society of Ultrasound in Obstetrics and Gynaecology (ISUOG) recommends a routine thorough foetal anatomical survey and anomaly detection between 18 to 24 weeks' gestation (Salomon *et al.*, 2013). A third trimester sonography is usually done to evaluate foetal presentation, measure amniotic fluid volume, estimate foetal weight, determine placental location and follow-up evaluation of foetal anomaly (AIUM, 2013).

2.1.3 Safety of Ultrasound

Obstetric ultrasonography has been used for the past 30 years and is generally regarded as safe when performed for medical reasons by a skilled personnel (Doubilet and Benson, 2010). A meta-analysis by Torloni *et al.* (2009) on the adverse effects of ultrasound on the health of pregnant women and their foetuses reported no association between ultrasound and adverse maternal or perinatal outcome, impaired physical or neurological development, increased risk for malignancy in childhood and subnormal intellectual performance or mental diseases. A consistent finding however is a weak association between prenatal ultrasound exposure and subsequent left-handedness in boys (Houston *et al.*, 2009; Torloni *et al.*, 2009). The mechanism for this effect is not yet understood and no firm conclusion has been made (Fowlkes *et al.*, 2008). The existing literature on the safety of ultrasound were obtained using ultrasound machines with less output potential than currently in use today. In 1993, the maximum permissible spatial peak temporal average intensity (SPTA) was increased from 94 to 720 mW/cm^2, allowing higher output potential (Houston *et al.*, 2009). There is therefore insufficient understanding on ultrasound exposure on modern machines. Ultrasound is a form of energy and as such if used impudently can produce harmful effects. The two major mechanisms for potential bioeffects of ultrasound are thermal and non-thermal (mechanical) (Abramowicz *et al.*, 2008). Laboratory studies have demonstrated that ultrasound can raise intracellular temperature depending upon the type of tissue, duration of exposure, beam width, frequency of ultrasound and the ultrasound route (TVS or TAS) (Abramowicz *et al.*, 2008; Houston *et al.*, 2009). Moretti *et al.* (2005) and Edwards (2006) have reported teratogenic effects in humans and different animal species exposed to hyperthermic temperatures *in utero*. Increased maternal temperature, whether from illness or exposure to heat, can produce teratogenic effects (Edwards, 2006). Considering the potential harm of ultrasound exposure from animal studies, a temperature elevation up to 1.5 °C is the upper threshold recommended for clinical use by the World Federation for Ultrasound in Medicine and Biology (Ter Haar, 2011). It further advised that ultrasound exposure that elevates foetal temperature by 4 °C above normal temperature for 5 minutes or more have the potential to induce severe developmental defects (Barnett *et al.*, 2000). In examining 63 Output Display Standard, Sheiner *et al*. (2007) reported mean thermal index (TI) of 1.5 ± 0.5 using pulsed wave Doppler, proving that a high temperature elevation is attainable and hence a clinical evidence of potential bioeffect. In general, temperature elevation becomes progressively greater from B-mode to M-mode, through color Doppler to spectral Doppler mode (Merritt *et al.*, 1992). The AIUM (2013) therefore recommends the use of B-mode and M-mode for all stages of pregnancy. It however advises Doppler ultrasound use in the first trimester only when clinically indicated since a developing embryo or foetus is sensitive to external agents (temperature rise) during this period.

Non-thermal bioeffects result from physical mechanisms such as gas body acoustic (cavitation), radiation pressure and acoustic streaming (Stratmeyer *et al.*, 2008). Cavitation is a term used to describe the interaction between ultrasound waves and gas bubbles within tissues (Stratmeyer *et al.*, 2008). It is now accepted that ultrasound can generate gas bubbles in gas-containing structures like lungs and intestines (O'Brien and Zachary, 1994). This may increase temperature and pressure within the bubble which may mechanically disturb cells within proximity, or result in rapid growth and collapse of those bubbles (Church *et al.*, 2008). There is no evidence in humans suggesting that cavitation occurs during obstetric ultrasonography except when using microbubble contrast agents for hystero-contrast salpingography (Stratmeyer *et al.*, 2008; Church *et al.*, 2008; Fowlkes *et al.*, 2008). The use of gas bubble contrast agents during pregnancy is not recommended since it has the potential of entering foetal circulation through the placenta (Fowlkes *et al.*, 2008).

Due to possible bioeffects of ultrasound an Output Display Standard: thermal index (T1) and mechanical index (MI), were developed to guide the user of the potential for tissue heating and the likelihood and magnitude of non-thermal effects in real-time during ultrasound examination, in order to adjust the length or settings of the examination (Ter Haar, 2011). The thermal index (TI) is further subdivided into indices based upon tissue exposure: thermal index for soft tissue (TIS), thermal index for cranial bone (TIC), and thermal index for bone (TIB). In obstetric ultrasonography, TIS is recommended before 10 weeks' gestation while TIB is recommended at 10 weeks' gestation or later when bone ossification is evident (AIUM, 2013). This is because bones have the highest tendency to heat by absorbing heat energy and by conduction raise the temperature of surrounding tissues, such as the brain and spinal cord (Nelson *et al.*, 2009). Although existing literature on the safety of ultrasound were performed using older ultrasound machines, the risk to human foetuses using modern ultrasound machines can be minimized if diagnostic ultrasound is used only for medical purposes and the radiation protection concept of "As Low As Reasonably Possible" (ALARA) principle is followed. The United States Food and Drug Administration and AIUM discourage the non-medical use of ultrasound for the purpose of sex identification and foetal "keepsake" videos or pictures (Goodnight and Chescheir, 2014). These recommendations have been endorsed nationally and internationally by reputable professional medical and sonographic organizations. Notwithstanding, research is needed using ultrasound machines representative of modern output potential.

2.2 PRENATAL DEVELOPMENT

2.2.1 Summary of Prenatal Development

The prenatal development is divided clinically into two parts: embryonic period and foetal period (Hill, 2007). The period of embryogenesis (or organogenesis) lasts for 8 weeks from the time of fertilization or 10 weeks from the date of the last menstrual period (LMP) (Morin and Van den Hof, 2006). The length of pregnancy (gestation period) is therefore 38 weeks after fertilization or 40 weeks from the day of the LMP (Jukic *et al.*, 2013). During the embryonic period the three germ layers (ectoderm, mesoderm and endoderm) give rise to a number of specific tissues and organs. The ectoderm gives rise to central and peripheral nervous systems; special sensory organs (ear, nose and eye); skin and its appendages; enamel of the teeth; pituitary, mammary and sweat glands (Korones, 2008). The mesoderm gives rise to the vascular system, urogenital system (excluding the bladder), bone, connective tissue, muscle, spleen and cortex of the suprarenal glands (Korones, 2008). Derivatives of the endoderm produces the epithelial lining of the respiratory tract, gastrointestinal tract, urinary bladder, auditory tube and tympanic cavity (Korones, 2008). It also forms the parenchyma of the thyroid, parathyroids, liver, tonsils, thymus and pancreas (Korones, 2008; Sadler, 2011). Over 90% of the more than 4500 designated adult structures develop during this period (O'rahilly, 1979). At the end of the 8th week the embryo acquires a miniature human form. The embryo is most susceptible to teratogens during this period (Hill, 2007). The embryonic period may be divided into 23 Carnegie stages based on morphologic features and not necessarily on the size and age of the embryo, to allow different embryos to be compared with each other (Hill, 2007). Embryonic development visualized by ultrasound closely agrees with the 'developmental time schedule' of human embryos described in the Carnegie staging system (Salomon *et al.*, 2013).

The foetal period begins on day 57 until birth (Korones, 2008). It is characterized by further differentiation, maturation of tissues and organs and rapid growth of the embryo (Hill, 2007; Korones, 2008). The foetus increases rapidly in length during the fourth and fifth months and in weight during the last 2.5 months of pregnancy (Sadler, 2011).

2.2.2 Sonoanatomical Development

The visible ultrasound findings suggesting a potential pregnancy, from the time of fertilization until implantation, are the presence of a thickened hyperechogenic homogenous endometrium (the decidual reaction) and a vascular active corpus luteum with typical peripheral blood flow resembling a ''ring of fire'' on colour Doppler examination (Bottomley and Bourne, 2009). The gestational (chorionic) sac is the first sonographic evidence of a definite intrauterine pregnancy (Tan *et al.*, 2012). This fluid-filled cavity occupies the space between the trophoblast externally and the amnion and exocoelomic (Heuser's) membrane internally (Bottomley and Bourne, 2009). It is detectable by transvaginal sonography (TVS) from day 28-31 when the mean gestational sac diameter (MSD) is 2 to 3 mm and by transabdominal sonography (TAS) from week 5 gestation when the MSD is 5 mm (Timor-Tritsch *et al.*, 1998; Bottomley and Bourne, 2009). The MSD is the average of the three orthogonal measurements (anteroposterior diameter, craniocaudal diameter and transverse diameter) using the inner edges of the sac (Bottomley and Bourne, 2009; Graham, 2010). The gestational age in days, between 5 - 11 weeks, can be calculated by adding 30 to the MSD in millimetres (Graham, 2010). The gestational sac appears as an anechoic center surrounded by an echogenic ring (representing the trophoblasts and decidual reaction), eccentrically located within the decidua, at or near the uterine fundus (Bottomley and Bourne, 2009). Visualization of the gestation sac in a normal pregnancy corresponds with a beta human chorionic gonadotropin level above 1000 mUI (Yigiter, 2011). The MSD increases by 1-1.5 mm daily for the first 50 to 60 days of pregnancy (Lazarus, 2003; Bottomley and Bourne, 2009). A gestational sac without a definite embryo or yolk sac is a pseudo–gestational sac associated with ectopic pregnancies (Tan *et al.*, 2012).

The first extraembryonic structure sonographically visible within the gestational sac is the secondary yolk sac (Tan *et al*., 2012). The secondary yolk sac develops from a layer of extraembryonic endoderm and a layer of extraembryonic mesoderm and is located between the chorion and the amnion (Bottomley and Bourne, 2009). The yolk sac provides nutritional, metabolic, endocrine, immunologic and hematopoietic functions during organogenesis until the placental circulation is established (Tan *et al.*, 2012). The presence of yolk sac confirms intrauterine pregnancy as the double decidual sign and intradecidual sign is neither 100% specific nor sensitive as a diagnostic tool for normal intrauterine pregnancy (Doubilet and Benson, 2013). The presence of the yolk sac therefore distinguishes a true gestational sac from a decidual cyst, a pseudogestational sac or an anembryonic pregnancy, as a yolk sac is only seen in an intrauterine pregnancy. The yolk sac is visible with TVS beginning of week 5 when the MSD is 5 to 6 mm, as a round structure with an anechoic center surrounded by a uniformly well-defined echogenic wall. The yolk sac increases in size from 5 to 10 weeks' gestation where it attains its maximum diameter of 6 mm, shrinks around week 9 and eventually disappear by 12 weeks (Bottomley and Bourne, 2009; Butt and Lim, 2014). This degeneration is due to loss of function and hence decrease in vascularity as the placenta takes over the metabolic demands of the rapidly growing embryo (Kurjak and Kupesic, 1998; Lausin *et al.*, 2009). Sometimes, the yolk sac can persist even after 12 weeks' gestation (Tan *et al.*, 2012). The yolk sac is normally measured in three orthogonal planes from its outer borders when the MSD is 8 to 10 mm by TVS and 20 mm by TAS (Timor-Tritsch *et al.*, 1998; Yigiter, 2011). The number of yolk sacs present in the gestational sac is useful in determining the amnionicity of the pregnancy; the number of yolk sacs equal the number of amniotic sacs (Tan *et al.*, 2012). The embryonic pole, about 2 to 3 mm, appears as a linear echogenic structure at the periphery of the yolk sac, detectable with TVS 1 or 2 days after visualization of the yolk sac (Lausin *et al.*, 2009). The yolk sac is connected to the embryo by the vitelline duct (Graham, 2010). This close relationship between the yolk sac and the embryo can be likened to a 'signet ring' (Bottomley and Bourne, 2009). By week 6, the embryo becomes separated from the yolk sac. The embryo is detectable around 1 - 2 mm, and grows by approximately 1 mm per day (Salomon *et al.*, 2013). Its cephalic and caudal ends are distinguishable by day 53 when the diamond-shaped rhomboencaphalon become visible at the caudal ends (Salomon *et al.*, 2013). Within week 7, an echogenic area at the abdominal insertion of the umbilical cord, representing physiological herniation of the gut, can be visualized. Cardiac activity is detected when the embryo measures at least 2 mm, and may not be evident in about 5–10% of embryos measuring between 2 - 4 mm (Salomon *et al.*, 2013). The fluid-filled stomach can be visualized using transvaginal sonography as a small hypoechogenic area by week 8 in the left upper quadrant (Blaas *et al.*, 1995).

2.3 STANDARD SONOGRAPHIC MEASUREMENTS

2.3.1 Crown-Rump Length (CRL)

The true crown-rump length (CRL) is the length of the foetus (around 18 mm) measured from week 8 (Carnegie stage 19), from the tip of the cephalic pole to the tip of the caudal pole when the foetus is in a neutral position (that is neither flexed nor hyperextended) (Bottomley and Bourne, 2009; Papaioannou *et al.*, 2009). Before 7 weeks' gestation (between 4 and 18–22 mm) the crown and rump cannot be visualized, the embryo is extremely flexed so it is the neck-rump length that is measured

(Papaioannou *et al.*, 2009; Pexsters *at al.*, 2010). According to Deter and Harrist (1992), the crown-rump length grows approximately 10 mm per week from weeks 8 to 12 and ranges from 10 mm at 7 weeks to 40 mm at 11 weeks. Foetal flexion or extension and inclusion of yolk sac or lower limb affect the measurements of the CRL (Robinson and Fleming, 1975; Papaioannou *et al.*, 2009). The optimal time to date a pregnancy using CRL is between 8 to 12 weeks.

The crown-rump length is the most accurate and useful method of assessing gestational age in the first trimester (Botttomley *et al.*, 2009). Pregnancy dating by transabdominal static scan of CRL was first described by Robinson and Fleming (1975). Other studies of CRL growth curve using high-frequency transvaginal probe and timed ovulation have shown similar growth pattern (Hadlock *et al.*, 1992; Grisolia *et al.*, 1993). These studies however assumed growth of embryo was uniform regardless of maternal characteristics. Future studies have proven that maternal age and ethnicity affect CRL growth pattern (Botttomley *et al.*, 2009). A smaller than expected foetal CRL in the first trimester has been shown to be associated with an increased risk of miscarriage, growth restriction, preterm delivery and low birthweight (Smith *et al.*, 1998; Reljic, 2001; Mukri *et al.*, 2008).

2.3.2 HEAD MEASUREMENTS

Head measurements include measurements of foetal biparietal diameter (BPD), occipitofrontal diameter (OFD) and head circumference (HC). These measurements reflect foetal head size and brain development (Barbier *et al.*, 2013). The plane for the measurement of OFD, BPD and HC is the level where the continuous midline echo is broken by the cavum septi pellucidi in the anterior third and the thalami (Campbell and Thoms, 1977; Kurmanavicius *et al.*, 1999a). These measurements are used in dating pregnancy, estimating foetal weight and assessing foetal growth (Campbell and Thoms, 1977; Hadlock *et al.*, 1984a; Hadlock *et al.*, 1985a).

2.3.2.1 Biparietal Diameter (BPD)

The biparietal diameter is measured from the outer edge of the proximal parietal bone to the inner edge of the distal parietal bone (outer–inner) or to the outer edge of the distal parietal bone (outer–outer), excluding soft tissues of the scalp (Chitty *et al.*, 1994a). The BPD (outer-iner) reflected the true diameter when A-scan was used and the sound velocity was set to 1600 m/s (Verburg *et al.*, 2008). Modern scanners have an internationally standardized sound velocity of 1540 m/s, making the outer–outer measurement (true diameter) the most preferred method (Verburg *et al.*, 2008). Both measurements of BPD are in use. The BPD (outer-outer) (true diameter) is about 1–5 mm larger than the BPD (outer-inner) measurements (Hadlock *et al.*, 1981; Chitty *et al.*, 1994a; Kurmanavicius *et al.*, 1999a; Leung *et al.*, 2008). The BPD is measured after 11 weeks' gestation (Gameraddin *et al.*, 2014). The reason being that standard landmarks such as septi pellucidi and thalami, which are used to define the standard plane of measurement may not be visible prior to 11 weeks (Lasser *et al.*, 1993). The BPD shows linear growth of 3 mm per week from weeks 14 to 29, with continued mean of approximately 2 mm per week until term (Deter and Harrist, 1992). In the measurement of BPD, the shape of the head is assumed to be ovoid in transaxial view. In cases where head shape is rounded (brachycephaly) or elongated (dolichocephaly) the BPD may be overestimated or underestimated (Hadlock *et al.*, 1981). Abnormal head shape is associated with premature rapture of membranes, breech position and congenital malformations such as hydrocephaly, anencephaly and microcephaly (Salomon *et al.*, 2011). In 1991, Benson and Doubilet developed a formula to correct the head shape to ideal shape called an area-corrected biparietal diameter (BPDa).

The BPDa = $\sqrt{(BPD \times OFD)/1.265}$.

Where OFD = Occipitofrontal diameter.

The OFD is measured in the same plane as BPD between the leading edge of the frontal bone and the outer border of the occiput (Chitty *et al.*, 1994a; Mador, 2014). The value of 1.265 is equivalent to the OFD/BPD ratio (Benson and Doubilet, 1991). This asymmetry in the foetal head shape during development can be objectively assessed by calculating the cephalic index (CI). The cephalic index is the ratio of the biparietal diameter (measured from outer-outer) to the occipitofrontal diameter (measured from outer-outer) (Hadlock *et al.*, 1981). According to Hadlock *et al.* (1981) a normal head shape has a mean of 0.78 (± 2 SD) with normal range of 0.70 - 0.86. A CI of less than 70 is indicative of dolichocephaly while greater than 86 indicates brachycephaly. Where a foetus has an abnormal cephalic index, the BPD may be unreliable in gestational age estimation (Hadlock *et al.*, 1981). Some authors have reported the cephalic index to be independent of gestational age (Hadlock *et al.*, 1981; Tuli *et al.*, 1995) whereas others (Gray *et al.*, 1989; Mador, 2014) have reported changes in cephalic indices with increasing age of the foetus.

2.3.2.2 Head Circumference (HC)

The head circumference (HC) is measured at the same plane as the biparietal diameter (BPD) (Hadlock *et al.*, 1982a). The HC may be calculated from the measurements of the occipitofrontal diameter (OFD) and the BPD (outer-outer) using the equation: HC = 1.57 (OFD + BPD) according to British Medical Ultrasound Society (Chitty *et al.*, 1994a; Snijders and Nicolaides, 1994; Loughna *et al.*, 2009) or 1.62 (OFD + BPD) according to the ISUOG guidelines (Salomon *et al.*, 2011). The HC can also be derived by tracing around the perimeter of outer calvarial margin or automatically derived using the ellipse facility as found in modern ultrasound machines (Salomon *et al.*, 2011). The formula for ellipse has been given as:

$$HC = \pi \sqrt{\tfrac{1}{2}[(OFD)^2 + (BPD)^2]}$$ (Kurmanavicius *et al.*, 1999a),

This has not been internationally agreed since the foetal head is rounded posteriorly and therefore not a true ellipse (Altman and Chitty, 1997; Verburg *et al.*, 2008). The derived methods are less accurate than the ellipse method with a maximum error of 6% (Shields *et al.*, 1987; Chitty *et al.*, 1994a; MacGregor and Sabbagha, 2008). Using the ellipse facility for HC is more reproducible than using the formula. Since the techniques used to obtain the HC may differ, it is important that one chooses the chart for the measurement technique used (Altman and Chitty, 1994; Loughna *et al.*, 2009). The head circumference grows 14 mm per week between 14 to 17 weeks, slowing to 5 mm per week by 38 weeks (Deter and Harrist, 1992).

Sonographic measurements of the HC underestimate actual postnatal HC (Hadlock *et al.*, 1982a; Melamed *et al.*, 2011). This difference increases with increasing gestational age, high cephalic index and large HC. The explanation according to Hadlock *et al.* (1981) is that at term, it may be difficult to distinguish foetal scalp from adjacent soft tissue of the uterus, so that measurements include only the bony calvaria of the foetal skull. There is also difficulty in obtaining the appropriate sonographic plane for HC measurement when the head is engaged (lying in the pelvis) (Melamed *et al.*, 2011). A few studies however found the difference in sonographic HC and actual postnatal HC to be statistically insignificant (Deter *et al.*, 1982). Deter *et al.* (1982) evaluated sonographic HC measurements performed 1–10 days prior to delivery (*n* = 34) and reported the sonographic estimations to be similar to the postnatal measurements of HC (mean difference, 0.46%). The relationship between the size and shape of the foetal head and the pelvic brim is useful in predicting the mode of delivery (Mador *et al.,* 2011). The head circumference can be used to diagnose symmetric or asymmetric growth restriction, microcephaly and macrocephaly (Barbier *et al.*, 2013). It has a similar accuracy as BPD in estimating gestational age and is better than BPD when CI is outside normal range (Hadlock *et al.*, 1981).

2.3.3 Abdominal Circumference (AC)

The foetal abdominal circumference (AC) is measured at the outer skin line on a transverse section through the foetal abdomen as described by Campbell and Wilkin (1975). The plane of section is the level of the liver and stomach, spine and descending aorta and the umbilical vein in the anterior one-third at the level of the portal sinus. The AC can be measured directly by tracing around the perimeter or using the ellipse, or calculated using the formula:

AC = π (TAD + APAD)/2 (Snijders and Nicolaides, 1994).

Where

TAD = Transverse abdominal diameter,

APAD = Anteroposterior abdominal diameter.

The directly measured AC is statistically higher (3.5 - 5%) than the derived measurements throughout gestation (Chitty *et al.*, 1994b; Kehl *et al.*, 2010). Once again, this difference in measuring techniques call for the need for sonographers to be aware of how the circumferences are calculated for the reference charts so that the appropriate chart could be used. Hadlock *et al.* (1982e) however found no statistically significant differences between the two methods. Inclusions of the physiological midgut herniation and the yolk sac can introduce error in measurements (Lasser *et al.*, 1993). The abdominal circumference shows linear growth of 12 mm per week up to 30 week gestation, then 11 mm per week towards term (Deter and Harrist, 1992). It correlates strongly with size of the foetus, hence it is the main parameter used to evaluate growth and estimate foetal weight (Campbell and Wilkin, 1975). The AC is therefore not useful in estimating gestational age since it is mostly affected by abnormal foetal growth (MacGregor and Sabbagha, 2008). A macrosomic foetus has a large AC relative to gestational age and an asymmetrical IUGR foetus has a small AC relative to gestational age (MacGregor and Sabbagha, 2008). This is as a result of the differences in the size of the liver and width of subcutaneous tissue (Campbell and Thoms, 1977; Hadlock *et al.*, 1982b; MacGregor and Sabbagha, 2008). In addition the AC is more challenging to measure than the other parameters since the foetal abdomen has no bone echoes, not always symmetrical and its size can vary with foetal position, oligohydramnios, breathing movements, probe compression and central body flexion or extension (Hearn-Stebbins, 1995; Rusu and Stretean, 2012; Butt and Lim, 2014).

2.3.4 Femur (Diaphysis) Length (FL)

The femur diaphysis length (FL) is the preferred limb measurement included in routine foetal biometry since it is the least moveable, largest and easiest to image (MacGregor and Sabbagha, 2008). The foetal femur ossify early so it can be measured as early as 10 weeks' gestational age (Lachman and Shen, 1996). However, it is best measured after 14 weeks of gestation (Chitty *et al.,* 1994c; Kurmanavicius *et al.,* 1999b) where ossification becomes clearly visible. The femur length is measured from one end of the femoral diaphysis to the other (Chitty *et al.*, 1994c). Technical factors that affect FL measurements include false shortening, excessive gain that falsely extend the diaphysis lengths, inclusion of non-ossified distal femoral epiphysis after 29 to 34 weeks' gestation, artifactual bowing of the femur after 18 weeks and failure to visualize the entire length of the diaphysis (Lessoway *et al.*, 1990; Chitty *et al.*, 1994c; Shipp *et al.*, 2001; MacGregor and Sabbagha, 2008). Also, the angle of the beam relative to the long axis of the bone, the type of probes (linear and convex probes most preferred) and plane of measurement may cause variations in measurement. These necessitate the need to use the technique used to establish the reference chart (Lachman and Shen, 1996; Salomon *et al.*, 2011). A 45-90^{o} angle is recommended by ISUOG (Salomon *et al.*, 2011).

The femur length grows slowly from 3 mm per week during weeks 14 to 27 and 1 mm per week at 38 weeks (Deter and Harrist, 1992). It can be used to predict gestational age from 14 weeks' gestation. Apart from dating, isolated short FL is associated with increased risk of preterm delivery, low birthweight and small-for-gestational-age (SGA) neonates (Weisz *et al.*, 2008; Mailath-Pokorny *et al.*, 2015). Queenan *et al.* (1980) was the first to develop femur length (FL) charts to evaluate foetal growth. A short femur length (< 5th centile or ± 2 SD of the mean) observed at midtrimester ultrasonography may not necessarily be diagnostic of skeletal dysplasia. It could be as a result of inaccurate dating, a normal physiological variation, a feature of SGA, a focal shortening of one femur or an abnormal karyotype (Kurtz *et al.*, 1990; Vergani *et al.*, 2000; Bromley *et al.*, 2002; Zalel *et al.*, 2002). Todros *et al.* (2004) studied a group of 86 foetuses with foetal FL below the 10th percentile of their reference ranges at midtrimester ultrasonography. They found that 32.5% of those foetuses were normal, 46.5% were structurally abnormal and 21% were SGA foetuses. A short femur length has been associated with Down syndrome (Benacerraf, 1996), although according to Shipp *et al.* (2001) might not be clinically significant in some populations due to ethnic variations.

2.4 FOETAL BIOMETRIC RATIOS

The growth of one parameter to another is not synchronous (Hearn-Stebbins, 1995). Hence several authors have calculated ratios of different parts of the body such as head circumference to abdominal circumference (HC/AC), femur length to biparietal diameter (FL/BPD), femur length to abdominal circumference (FL/AC), femur length to head circumference (FL/HC), biparietal diameter to occiptiofrontal diameter (BPD/OFD) to cross-check the validity of foetal measurements, determine abnormal foetal growth and congenital anomalies (Hohler and Quetel, 1981; Hadlock *et al.*, 1981; Hadlock *et al.*, 1983; Benson *et al.*, 1985).

Campbell and Thoms (1977) used the HC/AC ratio to distinguish between symmetric and asymmetric intrauterine growth restriction. The OFD/BPD ratio is used to assess foetal head shape (brachycephaly, dolichocephaly) Hadlock *et al.* (1981). Using a 90% confidence interval microcephaly is suspected when the FL/BPD ratio is greater than 0.87 whereas short-limbed dwarfism is suspected when the ratio is less than 0.71 (Hohler and Quetel, 1981). Where measurement of BPD is unreliable, the FL/HC can be used instead of the FL/BPD ratio (Hadlock *et al.*, 1984b). Foetuses with intrauterine growth restriction have a high FL/AC ratio (> 0.24) due to decreased growth of the AC (Hadlock *et al.*, 1983; Benson *et al.*, 1985). Using a ratio of 0.235 as cut-off, Hadlock *et al.* (1983) correctly identified 19 out of 30 cases of IUGR. Benson *et al.* (1985) also reported sensitivity and specificity of 56% and 74% respectively. Benson *et al.* (1985) however concluded that due to the low prevalence of IUGR in the general population, a high specificity and sensitivity is required in order for the FL/AC ratio to be highly predictive of the condition. A foetus with an FL/AC ratio less than 0.20 may be at risk of macrosomia due to the large AC measurements (Hadlock *et al.*, 1985b).

2.5 FACTORS AFFECTING FOETAL SIZE AND GROWTH

2.5.1 Ethnicity

Studies assessing ethnic or racial variations in foetal biometric parameters have reported conflicting results. A study by Okonofua *et al.* (1988) in Nigeria found the abdominal circumference (AC) and the biparietal diameter (BPD) to be smaller at every gestational age compared to a British population. Gutknecht (1998) and Mador *et al.* (2011) also reported lower BPD values than those in Thailand and Germany respectively. Salpou *et al.* (2008) observed no ethnic differences in biparietal diameter (BPD), head circumference (HC) and femur length (FL) between two ethnic groups (Kirdi and Fulani) in Cameroon between 12-22 weeks' gestational age. In Singapore, a study by Yeo *et al.* (1994) reported no significant racial differences in foetal biometric measurements of HC and AC of Chinese, Malaysian and Indian foetuses from 18 to 40 weeks' gestation. The femur lengths of the Chinese and the Malaysian were similar but both were slightly shorter than the Indian foetuses. This finding was similar to a later study by Raman *et al.* (1996) involving 100 pregnant womens (34 Indian, 33 Malaysian and 33 Chinese) who reported higher FL values of Indians compared to Malaysian and Chinese. Interestingly, a study by Ramli *et al.* (2013) involving 6501 women found no significant difference ($p \geq 0.05$) between the FL values of foetuses of Malaysian and Indian. However FLs of foetuses of Malaysian and Indian were significantly ($p < 0.05$) longer than those of Chinese. This difference from the previous studies may be due to differences in sample size. Several investigators have observed variations in FL among various Asian subpopulations

(Mathai *et al.*, 1995; Shinozuka *et al.*, 1996; Lei and Wen, 1998).

Parker *et al.* (1982) reported no significant differences in CRL and BPD before 20 weeks' gestation between Asian and European. The study had many flaws. The authors failed to report the sample sizes of the populations, estimated gestational age based on LMP which may be unreliable and BPD was measured as early as week 10 of gestation. Prior to 14 weeks the growth of CRL has been reported to be greater in foetuses of black than white or Asian women (Bottomley *et al.*, 2009). A study done by Ruvolo *et al.* (1987) evaluating femur lengths in racially mixed populations found no statistically significant difference in FL between Hispanics, Blacks, Orientals and Caucasians of 19-32 weeks' gestation. The sample size for each group was however small and the chart used to indicate gestational age was not specified. Hadlock *et al.* (1990) found no significant differences in BPD, HC, AC and FL between middle-class white population, African American and Hispanic population from 20-41 weeks. In a study involving 369 Belgian, 78 Moroccan and 77 Turkish between 18-40 weeks, Jacquemyn *et al.* (2000) reported significant interethnic differences in FL, AC, HC but not BPD. Bromley *et al.* (1993) reported a longer femur lengths in blacks than whites between weeks 16-21 and weeks 31-35 from a study of 6082 foetuses. In the same study blacks had slightly larger BPD (0.327 mm, 95% CI 0.030-0.625mm) than whites between weeks 16-21. Davis *et al.* (1993) and Shipp *et al.* (2001) also reported significantly longer foetal FL in black foetuses than in white foetuses from a study of 2831 women and 170 women respectively. Davis *et al.* (1993) however did not specify the gestational age where this was detected and foetuses were measured more than once. Shipp *et al.* (2001) observed this difference from weeks 15-20.

Whereas some authors agree that there are significant ethnic variations in foetal biometric measurements, other studies have suggested that population differences in foetal biometry are negligible. In a study to compare Chinese femur length with Hadlock *et al.* (1982c) chart, Lachman and Shen (1996) found that although the

Chinese femur lengths were shorter than Hadlock's values by average of 0.56 mm between 16-20 weeks, this was equivalent to 2.1 days and therefore not clinically significant. A recent study has reported that variations in foetal biometric measurement may not be attributable to maternal ethnicity (Villar *et al.*, 2014). They argue that foetal growth and newborn length are similar across diverse geographical settings when mothers' nutritional and health needs are met, and environmental constraints on growth are low. This however is far from reality. Altman and Chitty (1994) and Salomon *et al.* (2006) suggested that the limited discrepancies observed between reference charts obtained in Caucasian populations in North America and Europe can be attributed to methodological differences in measurement techniques, study design and statistical methods and not ethnic variation. Ioannou *et al.* (2012) explained that differences in foetal biometry between populations can be attributed to biological variations only when the highest methodological quality are followed uniformly across the different populations.

2.5.2 Maternal Smoking

Maternal tobacco smoke has been associated with increased incidence of intrauterine growth restriction (IUGR), miscarriage, ectopic pregnancies and placenta previa (Bernstein *et al.*, 2005). In the United State, about 13.7% of IUGR is attributed to maternal smoking during pregnancy (Bada *et al.*, 2005). There is a negative correlation between smoking and low birthweight (Ward *et al.*, 2007) and it is strongest during the third trimester (Lieberman *et al.*, 1994; Bernstein *et al.*, 2005). Smoking from early third trimester has been associated with reduction in biparietal diameter, abdominal circumference and femur length measurements (Newnham *et al.*, 1990; Iñiguez *et al.*, 2012). Quitting smoking prior to the late second trimester can significantly reduce the risk of IUGR. MacArthur and Knox (1988) and Cliver *et al.* (1992) observed no statistically significant differences in foetal biometric measurements between women who quit smoking prior to early second trimester and those who never smoked before. Maternal smoking therefore appear to have significant impact in foetal growth in the third trimester.

2.5.3 Foetal Sex

The relationship between foetal sex and foetal growth has provided conflicting results (Smulian *et al.*, 1995; Lampl and Jeanty, 2003; Schwärzler *et al.*, 2004). These conflicting results may be attributed to ethnicity, study design and sample size (Smulian *et al.*, 1995; Pang *et al.*, 2003). Foetal sex has an independent effect on the relationship between standard foetal parameters, their ratios and gestational age. In general, female foetuses weigh less than males (Schwärzler *et al.*, 2004). This has been attributed to differences in sex hormone and maternal–foetal antigenic disparity caused by the Y-chromosome (Schild *et al.*, 2004). Male foetuses are larger than female foetuses at 8-12 weeks' gestation (Bukowski *et al.*, 2007). Others (Bromley *et al.*, 1993; Davis *et al.*, 1993; Lubusky *et al.*, 2006; Ramli *et al.*, 2013; Melamed *et al.*, 2013) have observed larger head measurements (BPD, HC) in male foetuses than female foetuses from second trimester. Davis *et al.* (1993), Schwärzler *et al.* (2004) and Melamed *et al.* (2013) observed sex-related difference in abdominal circumference during the late second and late third trimesters. Most studies found no significance sex difference in femur lengths (Bromley *et al.*, 1993; Raman *et al.*, 1996; Schwärzler *et al.*, 2004; Melamed *et al.*, 2013) whereas few observed statistically small sex difference (Smulian *et al.*, 1995; Ramli *et al.*, 2013). Pang *et al.* (2003) had a quite different observation. In a longitudinal study of 533 Chinese women studied between 24-40 weeks' gestation, the authors found statistically significant sex differences in the femur length, biparietal diameter and head circumference but not abdominal circumference.

There is a mixed view as to whether these observed sex-specific growth pattern for each of the individual foetal biometric indices call for sex-specific reference growth charts. Whilst Smulian *et al.* (1995) and Ramli *et al.* (2013) believe these differences are statistically significant but not clinically significant, Davis *et al.* (1993) and Melamed *et al.* (2013) believe otherwise.

2.5.4 Parity and Maternal Age

Firstborn neonates are smaller than subsequent neonates of the same mother (Ong *et al.*, 2002). Increasing parity is associated with increasing birthweight (Thompson *et al.*, 2001). Infants of primiparous women are shorter, thinner with smaller head circumferences at birth. Advanced maternal age is associated with pre-eclampsia and gestational diabetes, miscarriage, growth restriction and perinatal loss (Jacobsson *et al.*, 2004). A 2-day difference in crown-rump length was reported at 12 weeks' gestation between a woman of 20 years and a woman of 40 years (Bottomley *et al.*, 2009). Parity has significant influence on foetal head and abdominal circumferences whereas maternal age has significant influence on head and abdominal circumferences and biparietal diameter (Pang *et al.*, 2003).

2.5.5 Maternal Diseases

Maternal diseases such as hypertension, diabetes, renal disease, asthma can affect foetal growth (Xiong and Fraser, 2004; Villar *et al.*, 2006; Clark *et al.*, 2007).

Diabetes mellitus, including Type I and Type II diabetes and gestational diabetes, is associated with excessive foetal growth (Xiong and Fraser, 2004). Asthma and hypertension during pregnancy are associated with low birthweights (Clark *et al.*, 2007). In developing foetal charts pregnant women known to have such conditions are excluded from the study.

2.6 METHODS OF ESTIMATING GESTATIONAL AGE

2.6.1 Dating Based On Last Menstrual Period (LMP)

Gestational age (menstrual age) is the age of foetus. It is defined in weeks beginning from the first day of the last menstrual period (LMP) prior to conception (MacGregor and Sabbagha, 2008). This is because the date of ovulation and fertilization cannot be accurately known except in assisted reproductive technologies (MacGregor and Sabbagha, 2008). Gestational age based on the LMP assumes that the average menstrual cycle is 28 days in length with ovulation and fertilization occurring on day 14 and the average length of pregnancy being 280 days from the LMP (Whitworth *et al.*, 2015). Using the Naegele's rule, the EDD is calculated by adding 1 year, substracting 3 months and adding 7 days to the first day of the LMP (Nisbet and De Crespigny, 2002). Naegele's rule can be affected by the number of days in the month, therefore the duration of pregnancy varies between 280 and 283 days (Nisbet and De Crespigny, 2002). About 11 – 42% of gestational age estimated by LMP are reported as inaccurate (Geirsson, 1991; Nguyen *et al.*, 2000; Whitworth *et al.*, 2015). In general many women do not remember their LMP and of those who do about 30% have irregular cycles or are uncertain of their dates. A study by Wilcox *et al.* (2000) reported that only 30% of women with normal 28-day cycles are ''fertile'' between days 10 and 17. Rowland *et al.* (2002) showed that 10% of women have cycles more than 25 days long, 12% between 31-35 days and 3% more than 36 days long. Some women also show digit preference when recalling their LMP (overestimate GA by 2.8 days longer) (Savitz *et al.*, 2002). Even in women with known LMP and regular cycles, bleeding as a result of erosive activity by implanting blastocyst may be mistaken for a delayed menstrual period which may offset the date of LMP by as much as 4 weeks (Ananth, 2007). Bleeding associated with withdrawal from oral contraceptives could also influence the accuracy of LMP-based dating (Lynch and Zhang, 2007). Varying length of the follicular phase can affect the timing of ovulation (Geirsson, 1991; Nguyen *et al.*, 2000). The timing of fertilization relative to ovulation can also affect the accuracy of LMP since spermatozoa can survive up to 7 days in the female reproductive tract and the egg about 24 hours (Lynch and Zhang, 2007). Women with uncertain LMP dates are more likely to be young, primiparous, smokers, unmarried, obese and lower maternal education (Lynch and Zhang, 2007). In Ghana, only 14.6% of dates estimated by LMP matched ultrasound dating exactly (Brakohiapa *et al.*, 2012). Around 18% have been reported by Geirsson and Busby_Earle (1991). Several studies have concluded that even in women with certain date of the LMP, ultrasound dates should be preferred in predicting the actual date of delivery and that knowledge of the LMP should only be used in scheduling dating scan (Gardosi, 1997).

2.6.2 ULTRASOUND DATING

Ultrasonography objectively measure quantitative changes in growth increments of various foetal biometry which are indicative of foetal maturity (Reece *et al.*, 1989). Assessment of gestational age based on ultrasound biometry was first introduced in 1969 by Campbell, and it has become the preferred method for estimating gestational age (GA) and expected date of delivery (EDD) (Butt and Lim, 2014). To calculate gestational age, sonographic foetal biometric measurements are compared with a gestational age-specific reference. The accuracy of gestational age estimation by ultrasound biometry is therefore dependent on the population from which the formula was derived (Mongelli *et al.*, 2003). In gestational age estimation using ultrasound the first scan is used in estimating EDD. Subsequent scans are only used to assess foetal growth (Chervenak *et al.*, 1998; Butt and Lim, 2014).

2.6.2.1 First Trimester Dating

In the first trimester variations in foetal size is small and growth rate is rapid which minimizes the effect of measurement errors (Mongelli *et al.*, 1996). Gestational age is therefore more accurate than later in pregnancy where there is increasing variability in foetal growth (Mongelli *et al.*, 1996; Kalish and Chervenak, 2005; Caughey *et al.*, 2008). The best sonographic measurement recommended in clinical practice for estimating gestational age and hence the expected date of delivery is the crown-rump length (CRL) (Butt and Lim, 2014). A quick way of calculating gestational age in weeks is to add 6.5 to the CRL in centimeters (Kumari *et al.*, 2015). From 7 to 13 weeks' gestation, it is observed to be accurate for dating to within 3 - 7 days (Robinson and Fleming, 1975; Hadlock *et al.*, 1992; Daya, 1993; Verburg *et al.*, 2008; Papaioannou *et al.*, 2009). It becomes unreliable after 14 weeks' gestation due to foetal flexion and extension (Dudley *et al.*, 2004; Bottomley and Bourne, 2009). Other biometric parameters taken to estimate gestational age or assess growth in the first trimester have not proven to be superior to CRL (Taipale and Hiilesmaa, 2001). Hadlock *et al.* (1992) reported that the crown-rump length and biparietal diameter are similar in accuracy between 12-14 weeks' gestation. A study by Taipale and Hiilesmaa (2001) however showed that CRL was more accurate between 8 and 12.5

weeks (CRL < 60 mm). Beyond CRL of 60 mm, they found BPD (from 21 mm) to be more accurate than CRL. The Society of Obstetricians and Gynaecologists of Canada recommends CRL usage up to 84 mm, beyond that the BPD was deemed accurate (Butt and Lim, 2014). The National Institute for Health and Clinical Excellence (NICE) however recommends the use of head circumference (HC) in estimating gestational age when the crown–rump length is above 84 mm (Salomon *et al.*, 2013).

Although dating charts have been established to describe the normal range for yolk sac, gestation sac, heart rate and amniotic sac size observed during the first trimester, they are not used in clinical practice (Grisolia *et al.*, 1993; Papaioannou *et al.*, 2009). They are mostly used in predicting adverse pregnancy outcomes such as miscarriage (Papaioannou *et al.*, 2009). For example, the mean gestational sac diameter was reported by Grisolia *et al.* (1993) to have a prediction error of ± 12 days in estimating gestational age.

2.6.2.2 Second Trimester Dating

In the second and third trimesters, pregnancy dating is estimated using the biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), femur length (FL) and their combinations (Hadlock *et al.*, 1984a; Butt and Lim, 2014). Second trimester ultrasound prior to 24 weeks' gestation is best for predicting gestational age due to the variability associated with increasing age (Butt and Lim, 2014; Whitworth *et al.*, 2015). Campbell (1969) was the first investigator to estimate gestational age using BPD. The BPD is very reliable up to 26 weeks of gestation, with a variability (± 2 SD) of 7-10 days (Hadlock *et al.*, 1982b). After 26 weeks' gestation, the accuracy decreases and is ± 3-4 weeks (± 2 SD) near term (Altman and

Chitty, 1997). It is less reliable in determining gestational age in abnormal foetal position or variation in head shape. Due to this, the British Medical Ultrasound Society Foetal Measurements Working Party advised that the BPD should not be used in routine clinical practice for the estimation of gestational age or foetal size in later pregnancy (Loughna *et al.*, 2009). Most investigators suggest that in such situations

HC or BPDa (Hadlock *et al.*, 1982a; Benson and Doubilet, 1991; Chervenak *et al.*, 1998) or FL (Hadlock *et al.*, 1982a; Chervenak *et al.*, 1998) should be used in the second trimester. In a total of 152 singleton pregnancies resulting from *in vitro* fertilization, Chervenak *et al.* (1998) found HC to be the best predictor of gestational age between 14 and 22 weeks' gestation. This was also confirmed in a study by Johnsen *et al.* (2006) involving 4179 women who found the median differences between actual and predicted delivery with HC and BPD to be 0.9 and 1.2 days respectively. In a study using 136 singleton IVF foetuses, Mongelli *et al*. (2003) however found the FL to be the best parameter in the second trimester. Hadlock *et al.* (1982c) and Altman and Chitty (1997) reported the variability in estimating GA using FL to be ± 9.5 -10 days between 12 to 23 weeks and ± 19.6 - 22 days between 24 to 40 weeks of pregnancy. The accuracy of using FL to assess gestational age in the second trimester has been found to be equivalent to using the biparietal diameter (BPD) (Hadlock *et al.*, 1982c; Altman and Chitty, 1997; Mongelli *et al.*, 2003; Gameraddin *et al.*, 2014). This is very useful when foetal position makes head measurements unreliable, or in malformed foetal head, or abnormal head shape (dolichocephalic or brachycephalic) (Johnsen *et al.*, 2004).

2.6.2.3 Third Trimester Dating

Gestational age is rarely estimated during the third trimester. Biological variation associated with increasing gestational age makes gestational age estimation in the third trimester less reliable. A 95% confidence interval (CI) of ± 3 weeks or greater have been reported (Doubilet and Benson, 1993; Butt and Lim, 2014). The area-corrected biparietal diameter (BPDa), head circumference (HC) and femur length (FL) are parameters of choice (Benson and Doubilet, 1991) where first-or second-trimester dating are unavailable. The AC alone is not usually used to estimate gestational age because it is difficult to reproduce with exact accuracy (Butt and Lim, 2014). Hadlock *et al.* (1982b) however found the AC (± 18 days) to be slightly more accurate than the BPD (± 25 days) between 36-42 weeks' gestational age. This findings contradicted their later studies in 1984a, where the AC (± 2.96 weeks) was only better than BPD (± 3.08 weeks) between 30-36 weeks.

2.6.2.4 Single versus Multiple Parameters Dating

Biological variability and technical factors limit the use of a single parameter in dating, therefore the use of multiple parameters have been suggested (Hadlock *et al.*, 1987; Hill *et al.*, 1992). Although multiple biometric parameters appear to be superior to using a single parameter beyond 23 weeks (Hadlock *et al.*, 1984a; Benson and Doubilet, 1991; Chavez *et al.*, 2005), the improvement in accuracy has been shown to be clinically negligible especially in larger study populations (Taipale and Hiilesmaa, 2001; Gameraddin *et al.*, 2014). In a total of 152 singleton pregnancies resulting from *in vitro* fertilization at 14 to 22 weeks, addition of AC and FL to HC improved the accuracy of the gestational age by less than 1 day (Chervenak *et al.*, 1998). Butt and Lim (2014) believe that multiple parameters are useful if one parameter is affected by a foetal condition such as achondroplasia on femur length. On the contrary, MacGregor and Sabbagha (2008) believe averaging when a foetus is growth restricted, macrosomic or has congenital anomalies should be avoided. They believe averaging should only be done when the gestational age estimates from the parameters are similar to one another. They cautioned averaging multiple parameters when the estimated gestational age of one or several parameters was more than 2 weeks apart.

2.6.2.5 Combined Menstrual-based and Ultrasound-based Dating

Since the regression equations used for ultrasound dating were based on the last menstrual period (LMP), it is a common practice in most countries to combine the LMP date with ultrasound date in what is known as the 7-day rule or 10-day rule between 12 and 20 weeks' gestation (Dudley *et al.*, 2004; ACOG, 2009). Using the 7-day rule, if the LMP date and ultrasound date are in agreement within 7 days, the LMP date is accepted. On the other hand, if the discrepancy exceeds 7 days, the ultrasound date is preferred. This is widely practiced in the United States, Canada and in Australia (Butt and Lim, 2014). Studies also show that ultrasound biometry performed by an experienced provider has a fairly consistent 8% margin of error at any gestation (Hadlock, 1990; Hunter, 2009). Since the 7-day rule or 10-day rule is applicable for resolving discrepancies when ultrasound is performed before 20 weeks' gestation, this 8% margin of error has been suggested when there is discrepancy between menstrual and ultrasound dating beyond 20 weeks' gestation (Hunter, 2009). This is commonly referred to as the ''Rule of Eights'' (Hunter, 2009). A significant difference between an LMP date and an ultrasound date is an indicator of possible pathology (Butt and Lim, 2014). Several investigators believe that dating using ultrasound biometry in the first half of pregnancy should be given preference than using LMP alone or in combination with ultrasonography (Tunon *et al.*, 1996;

Mongelli *et al.*, 1996; Gardosi, 1997). Ultrasound dating alone improves the accuracy of serum screening for aneuploidy, reduces postdate induction and pregnancies classified as premature (Benn *et al.*, 1997; Blondel *et al.*, 2002; Bennet *et al.*, 2004; Brakohiapa *et al.*, 2012). In a study of 17221 pregnancies, foetal CRL, BPD and FL taken between 8 to 16 weeks' gestation were found to be superior at predicting the spontaneous delivery date by at least 1.7 days compared with known LMP date (Taipale and Hiilesmaa, 2001). The number of postterm pregnancies was 9.1% using known LMP and 2.7% using ultrasound CRL or BPD. A study of 1867 live births reported that ultrasound reduced births classified as postterm than LMP (0.7 % vs. 4.0 %) (Hoffman *et al.*, 2008).

2.6.3 OTHER METHODS OF DATING

Other useful methods of determining gestational age include date of foetal movements (quickening) usually occurring at 19-21 weeks' gestation in nulliparous women and 17-19 weeks' in multiparous women (Mongelli, 2016), foetal heart beat using M-mode ultrasound and symphysis-fundal height (SFH) measurements. Symphysis-fundal height (SFH) measurement is simple, cheap, non-invasive and widely used especially in resource-poor settings. Opinions vary on the usefulness of the measurement of SFH in the assessment of gestational age (Rondo *et al.*, 2003; Neufeld *et al.*, 2006; Adewale and Munir'deen, 2013). The uterine fundus is palpable at the pubic symphysis at week 12, mid-way between pubic symphysis and umbilicus at week 16, umbilicus at week 20 and at the xiphoid process at week 36. Measurement of SFH is affected by the technique used, the number of clinicians involved, multiple pregnancies, status of the maternal bladder, pre-pregnant weight, molar pregnancy, maternal position, macrosomia, polyhydramnios/oligohydramnios and intrauterine growth restriction (Engstrom *et al.*, 1993; Steingrímsdottir *et al.*, 1995). The use of SFH is better in estimating gestational age between 20 - 34 weeks' gestation (Jehan *et al.*, 2010; Ogbe *et al.*, 2015) and hence provide a reasonable alternative when ultrasound is unavailable and the LMP is unknown (Neufeld *et al.*, 2006; White *et al.*, 2012). Variations in SFH across populations have been observed with many calling for local standards for optimal pregnancy dating (Ogbe *et al.*, 2015).

2.7 INTRAUTERINE GROWTH RESTRICTION (IUGR)

Intrauterine Growth Restriction (IUGR) or Foetal Growth Restriction refers to a foetus who has not attained its biologically determined growth potential (Lausman *et al.*, 2013). It is associated with increased risks of morbidity and mortality (Lausman *et al.*, 2013). Small-for-gestational-age (SGA) is often used as a proxy for IUGR (Pay *et al.*, 2015). IUGR and SGA are often used interchangeably (Suhag and Berghella, 2013). However, IUGR, is the pathologic counterpart of SGA. All IUGR infants are SGA but not all SGA infants are IUGR (since some foetuses may be constitutionally small but healthy) (Peleg *et al.*, 1998). The term SGA is used for neonate while IUGR is applied to the foetus (Mandruzzato *et al.*, 2008). Small-for-gestational-age is suspected when the estimated foetal weight (EFW) is below a specific centile for gestational age, usually the 10th percentile (Lausman *et al.*, 2013; Pay *et al.*, 2015). The prevalence of SGA in the general population is about 5-10% (Mandruzzato *et al.*, 2008; Nardozza *et al.*, 2012). After prematurity, IUGR is the second leading cause of perinatal morbidity and mortality (Suhag and Berghella, 2013). The SGA foetus is at a higher risk of adverse effects throughout life. They are at greater risk of stillbirth, birth hypoxia, neonatal complications, perinatal death, impaired neurodevelopment, growth delay and cerebral palsy in childhood (Pallotto and Kilbride, 2006; von Beckerath *et al.*, 2013). They are also at risk of developing hypertension, type 2 diabetes mellitus, obesity, coronary artery disease, stroke and metabolic syndrome in adult life (called Barker's hypothesis) (Barker, 2006). The common risk factors of IUGR include maternal causes (previous history of IUGR, hypertension, progestational diabetes, anemia, cardiopulmonary disease, smoking, renal disease, malnutrition, substance abuse, ethnicity, low pre-pregnancy weight, advanced maternal age), foetal causes (chromosome abnormalities; infections with cytomegalovirus, toxoplasmosis, rubella and syphilis; teratogens, congenital malformations; multiple pregnancies) and placental causes (placental insufficiency, placental infarction, placental abruption, placental previa, velamentous umbilical cord insertion, single umbilical artery) (Figueras and Gardosi, 2011; Suhag and Berghella, 2013). There are two major categories of IUGR: symmetrical and asymmetrical. If the insult occurs early during foetal growth as a result of infection or chromosomal abnormalities, it results in symmetrically small foetus throughout gestation. All foetal biometric parameters are thus small with normal HC/AC and FL/AC ratios (Suhag and Berghella, 2013). In contrast, if the insults happen later during pregnancy, there is disproportionate growth of the foetus. A foetus with asymmetric IUGR has a normal HC and BPD ("Brain-sparing effect") but a small AC due to decreased liver size, thinned limbs (because of decreased muscle mass) and thinned skin (due to decreased subcutaneous fat). This increases the HC/AC and FL/AC ratios (Quinton *et al.*, 2015). Asymmetric IUGR accounts for about 70% of all IUGR and is usually the result of placental insufficiency (Puccio *et al.*, 2013).

There is no cure for IUGR so early recognition is paramount for increased surveillance and early intervention (Ray *et al.*, 2008). General management include treatment of the maternal disease if possible, nutritional interventions and oxygen, institution of bed rest, foetal heart monitoring by cardiotocograph and elective delivery (Peleg *et al.*, 1998). IUGR is diagnosed based on establishment of accurate early dating, assessment of risk factors, symphysis-fundal height measurement and detailed sonographic assessment of the foetus (Suhag and Berghella, 2013). Maternal serum screening such as pregnancy-associated plasma protein-A or human chorionic gonadotropin and uterine artery Doppler assessment is the clinical standard for identifying early onset

IUGR before 34 weeks' gestation (Dugoff *et al.*, 2004, Mayer and Joseph, 2013). The abdominal circumference (AC), biparietal diameter (BPD), femur length to abdominal circumference (FL/AC) ratio, head circumference to abdominal circumference (HC/AC) ratio, estimated foetal weight (EFW) and foetal ponderal index is used to assist the diagnosis of IUGR (Hadlock *et al.*, 1983; Leanza *et al.*, 2014). The AC is the single most sensitive biometric parameter for detecting IUGR/SGA (Leanza *et al.*, 2014**)**. Sensitivity of AC ranges from 48% to 87%, with specificity from 69% to 85% (Figueras and Gardosi, 2011). For estimated foetal weight, sensitivities of 25-100% have been reported with a specificity of 69-97% depending on the foetal parameters incorporated in the foetal weight estimation (Figueras and Gardosi, 2011). The FL/AC and HC/AC ratios have been found to be constant and independent of gestational age (Hadlock *et al.*, 1983; Snijders and Nicolaides, 1994) making it a useful tool in predicting asymmetric IUGR. Asymmetric IUGR is suspected when the HC/AC ratio is greater than 1 from 36 weeks' gestation and FL/AC is more than 0.235 (Hadlock *et al.*, 1985b). Quinton *et al.* (2015) found HC/AC ratio to be a sensitive predictor of SGA even at 28–32 weeks. Their sample size was however small (n =

41). The FL/AC ratio remains constant after 24 weeks at 0.22 ± 0.02 (Hadlock *et al.*, 1983). Asymmetric IUGR is suspected if the FL/AC ratio is more than 0.235 (Hadlock *et al.*, 1983; Hadlock *et al.*, 1985b). Abnormal FL/AC ratio performed before 37 weeks' gestation that return to normal may indicate a severe symmetric IUGR (Hadlock *et al.*, 1983). Several studies have revealed that foetal biometric measurements alone do not clearly predict IUGR/SGA (Baschat *et al.*, 2001; Leanza *et al.*, 2014). Intrauterine growth restriction is undetected in about 30% of routinely scanned cases and incorrectly detected in 50% of cases (Jahn *et al.*, 1998). It is therefore suggested that where growth restriction is suspected, there should be serial biometric measurements every 3 weeks, complete foetal biophysical profile, amniotic fluid volume, non-stress test and doppler assessment of umbilical vessels, ductus venosus and middle cerebral artery weekly (Baschat *et al.*, 2001; Leanza *et al.*, 2014).

2.8 ULTRASOUND ESTIMATION OF FOETAL WEIGHT

Sonographic estimation of foetal weight (EFW) is an integral part of routine antenatal care. It is useful in the detection of foetal growth abnormalities commonly diagnosed using criteria such as low birthweight, small-for-gestational-age (growth restriction) and large for gestational age (macrosomia) (Melamed *et al.*, 2009). Small-forgestational-age is defined as EFW below the 10th percentile and large for gestational age is defined as EFW above the 90th percentile for gestational age. Knowledge of foetal weight has significant bearing on clinical management decisions such as the route, time and place of delivery (Sharma *et al.*, 2014). It provides clue to obstetricians and midwives the possible complications of high-risk pregnancies, especially in case of growth restriction or macrosomia. The two main methods for predicting birthweight are clinical techniques based on abdominal palpation of foetal

parts and measurements of fundal height and imaging techniques via ultrasonography or magnetic resonance imaging. Due to the increasing use of ultrasound in obstetric, foetal sonographic measurement is commonly used to predict foetal weight. Campbell and Wilkin (1975) were the first to estimate foetal weight using measurements of abdominal circumference (AC) alone. Since then, regression models that incorporate other foetal parameters such as abdominal circumference (AC), femur length (FL), biparietal diameter (BPD) and head circumference (HC) have been employed (Melamed *et al.*, 2009). Several studies have shown that the use of multiple parameters, and in particular the combination of head, abdomen and femur length measurements, provide the most adequate estimations of foetal weight (Hadlock, 1990; Melamed *et al.*, 2009). Errors in foetal weight estimation range from 10 – 15% on average (Mayer and Joseph, 2013). This worsens at extreme weights (<1500 g or > 4000 g) (Dudley, 2005; Mayer and Joseph, 2013). This variability is influenced by the variability of foetal volume and density, the nature of the patient population, the formula used for calculation, the gestational age of foetus, the technique and skill of the operator and the resolution of ultrasound images (Peleg *et al.*, 1998). Several foetal weight estimating formulae have been published but the two most popular formulae are that of Shepard *et al.*
(1982) and Hadlock *et al.* (1985a) (Rusu and Stretean, 2012).

CHAPTER THREE

MATERIALS AND METHODS

3.1 STUDY DESIGN AND AREA

A prospective, cross-sectional study on ultrasonographic foetal biometry was conducted from October 2015 to March 2016 at the Sunyani Municipal Hospital and the Suntreso Government Hospital in Sunyani and Kumasi respectively.

3.2 STUDY POPULATION

A total of 110 and 264 pregnant women attending the Sunyani Municipal Hospital and the Suntreso Government Hospital respectively for obstetric ultrasound examination were recruited for the present study. Informed participants' consent and Ethics Committee approval were obtained. Permission as well as cooperation was also obtained from the hospital authorities.

3.3 INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria were women with singleton pregnancy, known last menstrual period (LMP), regular menstrual cycle (28 ± 4 days), no contraceptive use 2 months prior to pregnancy, no hypertension, diabetes, pre-eclampsia and absence of foetal malformations and abnormal foetal karyotype seen at the time of ultrasound examination.

Exclusion criteria were women with multiple pregnancy, unknown last menstrual period (LMP), irregular menstrual cycle, maternal diseases possibly affecting foetal growth such as hypertension, diabetes, asthma and pre-eclampsia. No exclusions were made on the basis of events that occurred after the examinations were done, such as premature birth, pregnancy-induced hypertension or gestational hypertension, preeclampsia and diabetes.

3.4 DATA COLLECTION

Participants who consented provided the following: date of last menstrual period, age, regularity and length of cycle, whether or not they used contraceptives 2 months prior to pregnancy, parity, educational level and maternal medical disorders known to affect foetal growth.

3.4.1 Ultrasonographic Measurements

All the women underwent an ultrasound assessment using two ultrasound machines (Voluson i: GE Healthcare, Zipf, Austria; Toshiba: Nemio XG, Japan) each equipped with 3.5 – 5.0 MHz curvilinear transabdominal probe. Each foetus was measured only once. All measurements were taken in millimeters. Measurements were performed by two trained obstetric sonographers and the investigator. The crown-rump length was obtained between 6-14 weeks, whereas the biparietal diameter (outer-outer), head circumference, abdominal circumference and femur diaphysis length were measured between 14-40 weeks' gestation. All foetal ultrasound scans were performed as per the International Society of Ultrasound in Obstetrics and Gynaecology (ISUOG) practice guidelines (Salomon *et al.*, 2011; Salomon *et al.*, 2013).

The crown-rump length was measured in the mid-sagittal plane with the long axis of the embryo perpendicular to the ultrasound beam. With the embryo or foetus in a neutral position (neither flexed nor extended), measurement calipers were placed on the outer edge of the cephalic pole to the outer edge of the foetal rump, excluding the limbs and yolk sac (Figure 1).

Figure 1: A sonogram showing measurement of crown-rump length at gestational age of 11 weeks 2 days.

The femur length was measured from the outer borders of the edges of the ossified femoral diaphysis excluding the femoral epiphysis (Figure 2). The angle of insonation of the ultrasound beam was 90° with the full length of the bone visualized, unobscured by shadowing from adjacent bony parts.

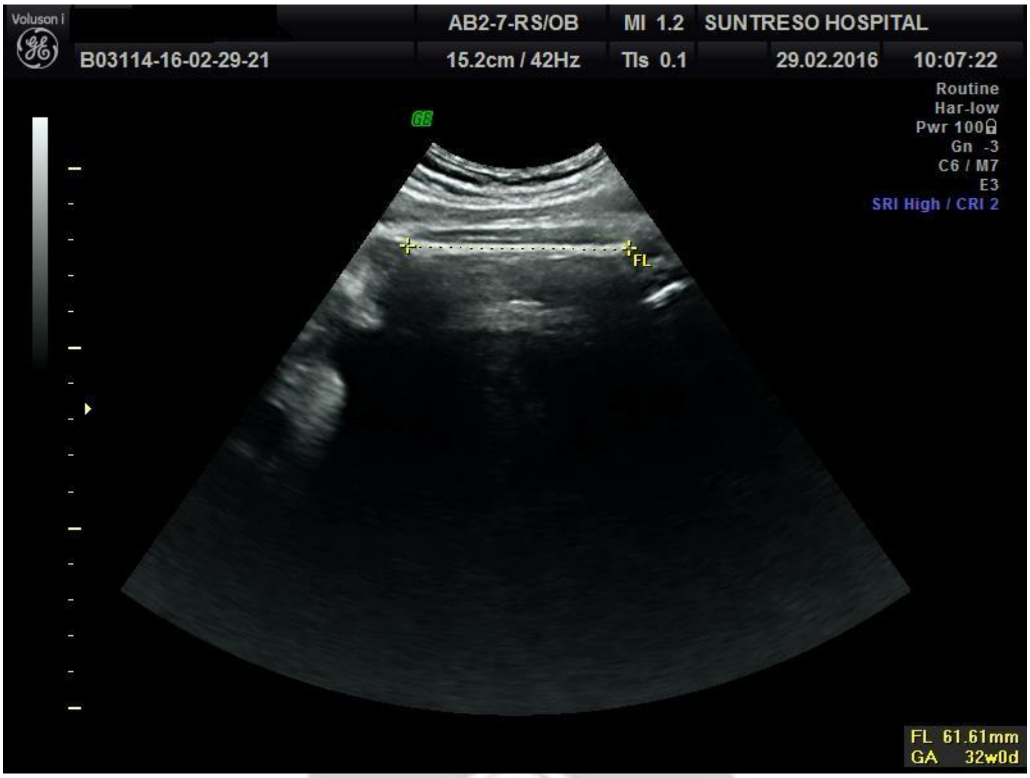

Figure 2: A sonogram showing measurement of femur diaphyseal length at gestational age of 32 weeks.

Foetal head measurements, biparietal diameter and head circumference, were obtained from a transverse axial plane at the level of the thalami showing a central midline echo (falx cerebri) broken in the anterior one-third by the cavum septi pellucidi with the anterior and posterior horns of the lateral ventricle in view. The biparietal diameter was measured perpendicular to the central midline echo, at the widest part of the cranium, from the outer margin of the proximal calvarial wall to the inner margin of the distal calvarial wall (outer-inner) (Figure 3). The foetal head circumference was measured by fitting a computer-generated ellipse to the outer margins of the cranium (Figure 3).

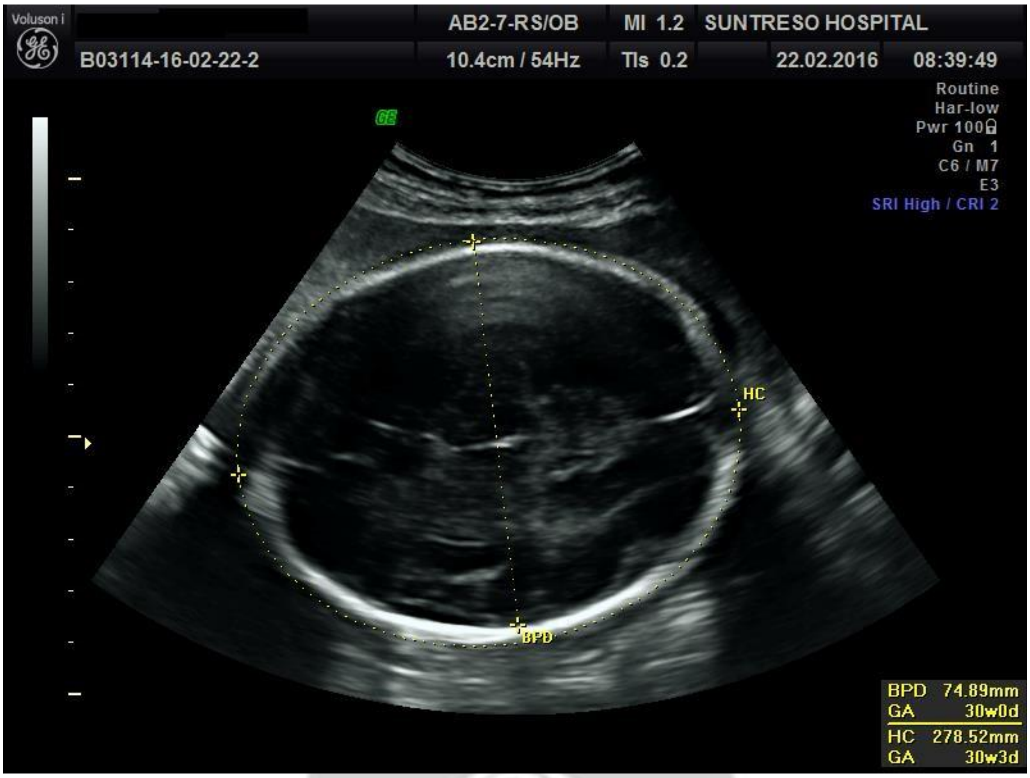

Figure 3: A sonogram showing measurements of biparietal diameter (outer-inner) and head circumference at gestational ages of 30 weeks and 30 weeks 3 days respectively.

The foetal abdominal circumference was measured on a transverse section by fitting a computer-generated ellipse around the outer border of the abdomen (Figure 4). In this plane, the vertebral column, descending aorta, stomach bubble and umbilical vein in the anterior third (at the level of the portal sinus) were visible. The kidneys, heart and urinary bladder were not visible and the vertebral column was positioned laterally to avoid internal shadowing.

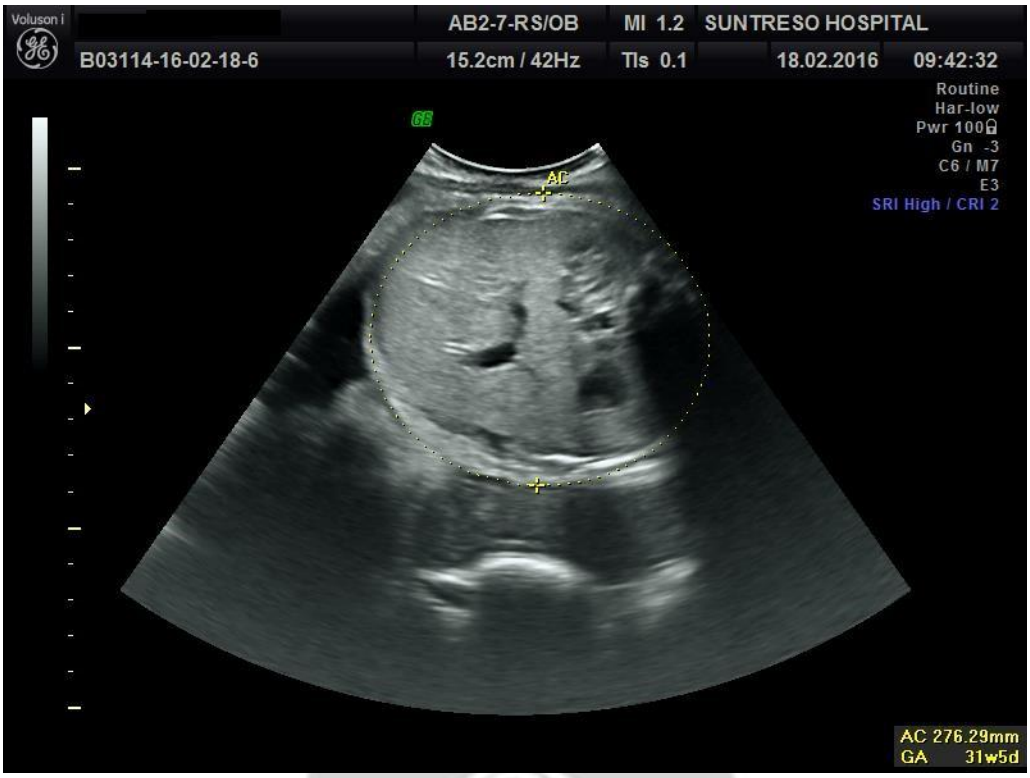

Figure 4: A sonogram showing measurement of abdominal circumference at gestational age of 31 weeks 5 days.

3.4.2 Gestational Age at time of Ultrasound Scanning

The gestational age of a participant was determined using a web-based online calculator (Medi-Mouse, 2015). The cycle length, date of the last menstral period (LMP) and date of ultrasound scanning were inputted and the LMP-based gestational age was generated automatically. The ultrasound gestational age for crown-rump length was determined using Hadlock's chart (Hadlock *et al.*, 1992) whereas the gestational age for biparietal diameter, head circumference, femur length and abdominal circumference were determined using the criteria of Hadlock *et al.* (1984a). The gestational age was calculated in exact weeks and days. Days were converted to a fraction of a week for the regression analysis; that is, a gestational age of 20 weeks

4 days was converted to 20.5714 weeks (Royston and Wright, 1998). In this study all dates are in menstrual age or gestational age, in keeping with the radiologic and obstetric literature, rather than in embryologic age.

3.5 DEVELOPMENT OF FOETAL CHARTS

For the purpose of establishing foetal size and age charts, gestational age was estimated using the date of the last menstrual period (LMP). This is because ultrasound dating assigns gestational age based on foetal size (MacGregor and Sabbagha, 2008). To minimize errors from erroneous LMP dates, foetuses whose LMP-based gestational ages were within 7 days of ultrasound crown-rump length were used in developing the crown-rump length dating equation and table. Also the LMP-based gestational ages that were within 14 days of the mean ultrasound dates were used in developing the foetal size and age charts for biparietal diameter, head circumference, abdominal circumference and femur length. Foetal size charts were also derived for femur length to head circumference (FL/HC) ratio, femur length to abdominal circumference (FL/AC) ratio, head to abdominal circumference (HC/AC) ratio and femur length to biparietal diameter (FL/BPD) ratio.

3.6 STATISTICAL ANALYSIS

Statistical analyses were performed using Microsoft Excel (Version 13. Microsoft Corporation, Redmond, WA, USA) and IBM Statistical Package for the Social Sciences (SPSS) for Windows (Version 22.0. Armonk, NY: IBM Corporation). Consistency checks were performed for each variable. The data were analysed according to the statistical methods described by Altman and Chitty (1994) and Royston and Wright (1998). Centiles were derived based on the assumption that at each gestational age the measurements had a normal distribution. In developing the foetal size charts, for each foetal parameter, fractional polynomial regression models were fitted to the mean as a function of gestational age. The best fitted model was the regression equation that yielded the highest coefficient of regression (R^2), which represents the proportion of variability in the data explained by the model. The standard deviation (SD) was also modelled as a function of gestational age using a simple linear equation. The standard deviations were obtained by calculating the absolute residuals (absolute value of the differences between the fitted mean curve and the original data for each measurement multiplied by a corrective constant of 1.253). From the mean and SD equations, centile curves of the Gaussian distribution for each foetal parameter were calculated using the formula: Centile = $M + K \times SD$, where K is the corresponding centile of the standard normal distribution (± 1.88 for the 3rd and 97th centiles, ± 1.645 for the 5th and 95th centiles and ± 1.28 for the 10th and 90th centiles),

M is the mean and

SD is the standard deviation of the mean of the foetal measurements for each gestational age.

The final check of fit of each model was assessed using normal probability plots of the standard deviation score. This was obtained by subtracting the fitted mean from the observed value and dividing the difference by the fitted SD. The goodness of fit of each model was illustrated by a scatter plot of each measurement with fitted 3rd, 10th, 50th, 90th and 97th centiles against gestational age. The 5th, 50th and 95th centiles for each week of gestation were tabulated. These were compared with published reference charts (Robinson and Fleming, 1975; Hadlock *et al.*, 1982a, b, c, d; Hadlock *et al.*, 1984a; Hadlock *et al.*, 1992; Altman and Chitty, 1997; Kurmanavicius *et al.*, 1999a, b; Leung *et al.*, 2008; Sahota *et al.*, 2009) graphically across the different gestational ages to allow for visual comparison.

The same procedure was followed in developing the foetal age charts for each biometric parameter. In contrast with the foetal size chart, gestational age was plotted as a function of foetal measurements.

The difference in days between gestational age (GA) estimated by ultrasound (GA_{US}) and gestational age estimated from the last menstrual period (GA_{LMP}) was calculated as follows:

$GA = (GA_{LMP} - GA_{US})$.

A positive difference indicated that the LMP date was higher than the corresponding ultrasound estimate, whereas a negative difference indicated that the LMP date was lower than the ultrasound estimate. The proportions of women whose LMP-based gestational age were within ultrasound estimate were determined by cross-tabulation.

Correlation and Regression equations were developed between foetal parameters and LMP-based gestational age in the second trimester, third trimester and both second and third trimesters together.

CHAPTER FOUR

RESULTS

4.1 DESCRIPTIVE CHARACTERISTICS OF STUDY PARTICIPANTS

A total of 374 pregnant women with known last menstrual period (LMP) were enrolled for the study. The mean age of the participants was 28.7 ± 5.4 years with a range of 19-43 years. Out of the 374 women, 4% were between 15-19 years of age, 58.3% were between 20-29 years of age, 34.2% were between 30-39 years of age and 3.5% were between 39-45 years of age. One hundred and eleven (29.7%) of the pregnant women were enrolled in the first trimester (≤ 13 weeks), 89 (23.8%) in the second trimester (14 to 27 weeks) and 174 (46.5%) in the third trimester (≥ 28 weeks). About 55.2% of the participants were primigravida, 18.1% were primiparous and 26.7% were multiparous. Seventy eight (20.8%) had no formal education whereas 34%, 17.1% and 28.1% had basic, secondary and tertiary education respectively. Table 1 shows the characteristics of the participants.

Table 1: Characteristics of the Study Participants.

Characteristic	Frequency	Percentage
Age, years		
15-19	15	4.0
20-29	218	58.3
30-39	128	34.2
40-45	13	3.5
Trimester		
First	111	29.7
Second	89	23.8
Third	174	46.5
Parity		
Nulliparous (Para 0)	206	55.2
Primiparous (Para 1)	68	18.1
Para 2	52	13.9
Para 3	29	7.8
Para 4 or more	19	5.0
Educational Level		
None	78	20.8
Basic	127	34.0
Secondary	64	17.1
Tertiary	105	28.1

4.2 DISCREPANCIES BETWEEN MENSTRUAL-BASED GESTATIONAL AGE AND ULTRASOUND-BASED GESTATIONAL AGE

One hundred and two (90.3%) of the women provided gestational age estimated by the last menstrual period (LMP) that were within the first trimester, whereas 11 gave LMP dates that were within the second trimester. A total of 53 (52.0%) of the women in the first trimester were within the clinical range whereas 49 (48%) were outside the clinical range (Table 2). Only one (9.1%) woman was within the clinical range for the women whose LMP dates showed they were in their second trimester of pregnancy; the rest (90.9%) had their LMP estimated gestational dates being greater than ultrasound CRL dating. In all, the proportion of concordance (± 7 days) between the

LMP-based gestational age and the ultrasound crown-rump length gestational age was 54 (47.8%) with 36 (31.9%) of positive discordances and 23 (20.3%) of negative discordances.

Table 2: Degree of Discrepancy between Last Menstrual Period and Ultrasound Crown-Rump Length Stratified by Trimester of Pregnancy.

Trimester	Acceptable clinical range n (%)	Positive discrepancy n (%)	Negative discrepancy n (%)	Total n (%)
First	53 (52.0)	26 (25.5)	23 (22.5)	102 (100)
Second	1 (9.1)	10 (90.9)	0	11 (100)
Total	**54 (47.8)**	**36 (31.9)**	**23 (20.3)**	**113 (100)**

n = number of observation; % = percentage.

Table 3 shows the difference in gestational age (GA) estimates between the LMP and ultrasound abdominal circumference (AC), head circumference (HC), femur length (FL), biparietal diameter (BPD) and their mean. All the 9 women whose LMP dates showed they were in their first trimester had their ultrasound dates being significantly higher than their LMP dates. Of the 78 women whose LMP dates showed they were in their second trimester of pregnancy, 54 (69.2%) were within the acceptable clinical range of ultrasound HC or FL dates, 52 (66.7%) of ultrasound AC or mean age and 50 (64.1%) of ultrasound BPD date. About 30.8 - 35.9% of these women had their LMP dates outside the acceptable clinical range, with more negative discrepancies (range: 25.6 - 29.5%) than positive discrepancies (range: 3.8 - 6.4%) for gestational age estimated by ultrasound. In the third trimester where 174 women reported for ultrasound dating, the LMP date was within the acceptable clinical range of the ultrasound date in 82.6%, 82.2%, 80.5%, 77.3% and 71.3% respectively for ultrasound

FL, AC, mean, HC and BPD dates. The number of positive discrepancies were more than negative discrepancies in the third trimester. The proportions of positive discrepancies for BPD, mean, HC, FL and AC were 23.0%, 13.8%, 13.4%, 12.8% and 11.5%, whereas their negative discrepancies were 5.7%, 5.7%, 9.3%, 4.7% and 6.3% respectively. In general, of the 261 women whose LMP dates were compared with ultrasound dates, the LMP dates agreed best with the FL dates (75.7%) and this were followed by AC dates (74.7%), HC dates (72.2%) and BPD dates (66.7%). The use of mean GA (73.6%) was only better than that of ultrasound HC and ultrasound BPD dates. About 24.3 - 33.3% had their LMP dates outside the clinical range. Except for BPD, there were more positive discrepancies than negative discrepancies. The proportions of negative discrepancies for ultrasound HC, BPD, AC, mean and FL were 17.4%, 16.1%, 15.7%, 15.7% and 14.7%, whereas their positive discrepancies were 10.4%, 17.2%, 9.6%, 10.7% and 9.6% respectively.

Table 3: Degree of Discrepancy in Gestational Age between the Last Menstrual Period and Ultrasound Foetal Parameters Stratified by the Trimester of Pregnancy.

Foetal Parameter	**Trimester**	**Acceptable clinical range n (%)**	**Positive discrepancy n (%)**	**Negative discrepancy n (%)**	**Total**
Biparietal Diameter	First	0	0	9 (100)	9 (100)
	Second	50 (64.1)	51 (6.4)	23 (29.5)	78 (100)
	Third	124 (71.3)	40 (23.0)	10 (5.7)	174 (100)
	Total	**174 (66.7)**	**45 (17.2)**	**42 (16.1)**	**261 (100)**
Head Circumference	First	0	0	9 (100)	9 (100)
	Second	54 (69.2)	4 (5.1)	20 (25.6)	78 (100)
	Third	133 (77.3)	23 (13.4)	16 (9.3)	172 (100)
	Total	**187 (72.2)**	**27 (10.4)**	**45 (17.4)**	**259** (100)**
Abdominal Circumference	First	0	0	9 (100)	9 (100)
	Second	52 (66.7)	5 (6.4)	21 (26.9)	78 (100)
	Third	143 (82.2)	20 (11.5)	11 (6.3)	174 (100)
	Total	**195 (74.7)**	**25 (9.6)**	**41 (15.7)**	**261 (100)**
Femur Length	First	0	0	9 (100)	9 (100)
	Second	54 (69.2)	3 (3.8)	21 (26.9)	78 (100)
	Third	142 (82.6)	22 (12.8)	8 (4.7)	172 (100)
	Total	**196 (75.7)**	**25 (9.6)**	**38 (14.7)**	**259** (100)**
Mean	First	0	0	9 (100)	9 (100)
	Second	52 (66.7)	4 (5.1)	22 (28.2)	78 (100)
	Third	140 (80.5)	24 (13.8)	10 (5.7)	174 (100)
	Total	**192 (73.6)**	**28 (10.7)**	**41 (15.7)**	**261 (100)**

n = number of observation; % = percentage; mean = the average gestational age of all the ultrasound parameters; ** = Two missing.

Table 4 gives the number of observations per week of gestation for each parameter used in creating the foetal size and age charts and equations for all the measured foetal parameters. For CRL measurements, the highest observation was recorded at week 8 (n = 16) whilst the lowest was recorded at weeks 13 and 14 (n = 1). For BPD, HC, AC and FL, more observations were recorded in the third trimester (n = 117) than in the second trimester (n = 55). The highest observations were from weeks 35 to 38. Most women came at week 38 (n = 18). There was no observation within clinical estimates for week 19.

Table 4: Distribution of Examinations in Completed Gestational Weeks for Foetal Size and Age Creation.

GA in weeks for CRL	**Number of observations**	**%**	**GA in Weeks**	**Number of observations for BPD, HC, AC and FL**	**%**
6	5	7.9	14	4	2.3
7	13	20.6	15	3	1.7
8	16	25.4	16	7	4.1
9	13	20.6	17	5	2.9
10	7	11.1	18	2	1.2
11	4	6.3	20	3	1.7
12	3	4.8	21	3	1.7
13	1	1.6	22	2	1.2
14	1	1.6	23	4	2.3
TOTAL	**63**	**100**	24	4	2.3
			25	6	3.5
			26	6	3.5
			27	6	3.5
			28	7	4.1
			29	6	3.5
			30	7	4.1
			31	3	1.7
			32	8	4.7
			33	6	3.5
			34	6	3.5
			35	11*	6.4
			36	16*	9.3
			37	18	10.5
			38	17	9.9
			39	8	4.7
			40	4	2.3
			TOTAL	**172**	**100**

* One observation was missing for FL and HC; **GA** = Gestational age; **CRL** = Crown rump-length; **AC** = Abdominal circumference; **FL** = Femur length; **BPD** = Biparietal diameter; **HC** = Head circumference; % = Percentage.

4.3 REGRESSION EQUATIONS FOR FOETAL SIZE CHARTS

Regression equations describing the relationships between foetal biometric measurements, their ratios and gestational age in weeks are given in Table 5. A quadratic model was the best fit in generating foetal size equations for the biparietal diameter (BPD), head circumference (HC), femur length (FL), femur length to head circumference (FL/HC) ratio and femur length to abdominal circumference (FL/AC) ratio whilst a linear model was the best fit for the abdominal circumference (AC), head to abdominal circumference (HC/AC) ratio and femur length to biparietal diameter (FL/BPD) ratio. Standard deviations across gestational age were fitted using a linear model. For parameters in the second and third trimesters, the HC recorded the highest coefficient of determination (R^2) since this accounted for 98.1% of the explained variance in foetal size estimation. The lowest was AC, with R^2 of 0.968. For the ratios, the FL/HC ratio gave the highest R^2 of 0.693 whilst the FL/AC ratio recorded the lowest with R^2 of 0.212.

Table 5: Regression Equations for the Mean and Standard Deviation of each Measurements and their Ratios based on Gestational Age in Exact Weeks.

Foetal Biometry	Measurement (mm)	Regression equations	R^2
BPD	Mean	$-27.747 + 4.496\ GA - 0.036\ GA^2$	0.975^{**}
	SD	$2.374 + 0.03\ GA$	
HC	Mean	$-125.694 + 18.622\ GA - 0.173\ GA^2$	0.981^{**}
	SD	$9.049 + 0.022\ GA$	
AC	Mean	$-60.208 + 10.57\ GA$	0.968^{**}
	SD	$2.415 + 0.375\ GA$	
FL	Mean	$-31.874 + 3.772\ GA - 0.027\ GA^2$	0.973^{**}
	SD	$1.852 + 0.031\ GA$	
HC/AC	Mean	$1.383176 - 0.010578\ GA$	0.676^{**}
	SD	$0.079284 - 0.000799\ GA$	
FL/BPD	Mean	$0.525179 + 0.007574\ GA$	0.560^{**}
	SD	$0.08828 - 0.001314\ GA$	
FL/HC	Mean	$0.084958 + 0.006302\ GA - 0.00007247\ GA^2$	0.693^{**}
	SD	$0.059915 - 0.00124\ GA$	
FL/AC	Mean	$0.104926 + 0.008224\ GA - 0.000141\ GA2$	0.212^{**}
	SD	$0.027817 - 0.000443\ GA$	

CRL = Crown rump-length; **BPD** = Biparietal diameter; **HC** = Head circumference; **AC** = Abdominal circumference; **FL** = Femur length; **HC/AC** = Head to abdominal circumference ratio; **FL/BPD** = Femur length to biparietal circumference ratio; **FL/HC** = Femur length to head circumference ratio; **FL/AC** = Femur length to abdominal circumference ratio;

GA = Gestational Age; **SD** = Standard Deviation; **R^2 =** Adjusted coefficient of determination; ******= Significant level ($p < 0.0001$)

Tables 6-10 show the 3rd, 5th, 10th, 50th, 90th, 95th and 97th centiles fitted for BPD, HC, AC and FL with the number of observations (n), mean, standard error of the mean (SEM), standard deviation (SD) and fitted SD. Figure 5 (a-e) illustrates the goodness of fit of the model by showing a scatter plot of each biometric measurement against gestational age with the fitted 5th, 50th and 95th centiles.

4.3.1 Biparietal diameter (BPD)

The biparietal diameter (BPD) showed linear growth of 3 mm per week from weeks 14 to 28, thereafter 2 mm per week until term (Table 6). The mean growth rate was 2.55 mm per week. The standard error of the mean (SEM) ranged from 0.2 to 3 mm, suggesting that the mean BPD in this study was very close to the population mean. The mean BPD of the sample at weeks 18, 22 and 31 were very close to the population mean since they recorded the lowest standard deviation (SD) and SEM. The mean BPD at 14 and 40 weeks' gestation were 29.2 ± 1.8 mm and 93.1 ± 1.9 mm respectively. There was not much variability with increasing gestational age. The fitted SD were constant in most of the weeks, increasing by 0.1 mm every 5 consecutive weeks from 2.7 mm at week 14 to 3.2 mm at week 40. The 95th centile of BPD at 15 and 30 weeks' gestation were 36 mm and 79.6 mm respectively.

Table 6: Fitted Centiles of Biparietal Diameter (BPD) at 14 to 40 exact weeks of Gestation.

					Fitted centiles BPD (mm)							
Weeks	**n**	**Mean**	**SEM**	**SD**	**3rd**	**5th**	**10th**	**50th**	**90th**	**95th**	**97th**	**Fitted SD**
14	4	29.2	0.9	1.8	23.2	23.8	24.7	28.1	33.1	31.5 2.7	32.5	
15	3	31.6	0.9	1.6	26.6	27.2	28.2	31.6	35.0	36.0	36.6	2.7
16	7	35.1	1.7	4.4	29.9	30.5	31.5	35.0	38.4	39.4	40.0	2.7
17	5	42.9	3.0	6.6	33.2	33.8	34.8	38.3	41.8	42.7	43.4	2.7
18	2	45.2	0.2	0.2	36.4	37.0	38.0	41.5	45.0	46.0	46.7	2.7
20	3	47.4	2.8	4.9	42.6	43.2	44.2	47.8	51.3	52.3	53.0	2.8
21	3	51.5	1.9	3.3	45.5	46.2	47.2	50.8	54.4	55.4	56.0	2.8
22	2	58.2	0.1	0.1	48.5	49.1	50.1	53.7	57.3	58.4	59.0	2.8
23	4	57.3	1.3	2.6	51.3	52.0	53.0	56.6	60.2	61.3	61.9	2.8
24	4	60.7	1.3	2.6	54.1	54.7	55.8	59.4	63.1	64.1	64.8	2.9
25	6	63.5	1.3	3.1	56.7	57.4	58.5	62.2	65.8	66.9	67.6	2.9
26	6	66.5	1.3	3.1	59.4	60.1	61.1	64.8	68.5	69.6	70.3	2.9
27	6	66.8	1.1	2.7	61.9	62.6	63.7	67.4	71.1	72.2	72.9	2.9
28	7	71.7	1.0	2.6	64.4	65.1	66.2	69.9	73.7	74.7	75.4	2.9
29	6	72.4	0.9	2.1	66.8	67.5	68.6	72.4	76.1	77.2	77.9	3.0
30	7	74.0	0.4	1.2	69.1	69.8	70.9	74.7	78.5	79.6	80.3	3.0
31	3	79.6	0.2	0.3	71.4	72.1	73.2	77.0	80.9	82.0	82.7	3.0
32	8	81.0	1.2	3.5	73.6	74.3	75.4	79.3	83.1	84.2	84.9	3.0
33	6	84.0	0.8	1.9	75.7	76.4	77.5	81.4	85.3	86.4	87.1	3.0
34	6	85.7	1.5	3.7	77.8	78.5	79.6	83.5	87.4	88.5	89.2	3.1
35	11	86.8	0.8	2.6	79.7	80.5	81.6	85.5	89.4	90.6	91.3	3.1
36	16	89.2	0.9	3.7	81.6	82.4	83.5	87.5	91.4	92.5	93.3	3.1
37	18	90.2	0.7	3.1	83.5	84.2	85.3	89.3	93.3	94.4	95.2	3.1
38	17	90.6	0.9	3.6	85.2	86.0	87.1	91.1	95.1	96.3	97.0	3.1
39	8	95.4	1.1	3.0	86.9	87.7	88.8	92.8	96.9	98.0	98.8	3.2

40	4	93.1	1.0	1.9	88.5	89.3	90.4	94.5	98.6	99.7	100.5	3.2

n = number of foetuses; SEM = Standard error of the mean; SD = Standard deviation.

4.3.2 Head Circumference (HC)

The head circumference (HC) increased by 14 mm from 14 to 15 weeks' gestation (Table 7). This growth rate decreased by 1 mm almost every 3 consecutive weeks, reaching 5 mm per week from week 38 onwards. The mean growth rate was however 9.28 mm per week. Marked variability in HC measurements was seen at weeks 16, 17, 20, 21, 28, 30 and 34 with a range of 11.3 - 13.6 mm. The mean HC at week 18 (167.1 mm) is very close to the population mean, with lowest standard error of the mean (SEM) and standard deviation of 0.4 mm and 0.5 mm respectively. Apart from week 18 which recorded the lowest SEM for head circumference measurements, the rest were more than 2, the highest being 7.9 mm at week 20. This means that at week 20 the mean head circumference of the sample is 7.9 mm different from the population mean. The 97th centile of HC at week 35 was 333 mm. This means that 97% of foetuses at that week had a mean head circumference less than 333 mm while 3% had a mean head circumference greater than 333 mm.

Table 7: Fitted Centiles of Head Circumference (HC) at 14 to 40 exact weeks of Gestation.

					Fitted centiles HC (mm)										
Weeks	n	Mean	SEM	SD	3rd	5th	10th	50th	90th	95th	97th	Fitted SD			
14	4	107.8	3.1	6.3	83.5	85.8	89.1	101.1	9.4	113.1	116.5	118.7			
15	3	120.9	3.1	5.3	97.1	99.3	102.7	114.7	126.7	130.1	132.3	9.4			
16	7	130.0	4.7	12.6	110.3	112.6	115.9	128.0	140.0	143.4	145.6	9.4	17	5	145.5
		5.3	11.8	123.2	125.4	128.8	140.9	152.9	156.4	158.6	9.4				
18	2	167.1	0.4	0.5	135.7	138.0	141.4	153.5	165.5	169.0	171.2	9.4			
20	3	182.3	7.9	13.6	159.7	162.0	165.4	177.5	189.7	193.2	195.4	9.5	21	3	188.6
		7.2	12.4	171.2	173.5	176.9	189.1	201.2	204.7	207.0	9.5				
22	2	221.3	2.5	3.5	182.3	184.6	188.1	200.3	212.5	215.9	218.2	9.5	23	4	215.8
4.2	8.5	193.1	195.4	198.9	211.1	223.3	226.8	229.1	9.6	24	4	226.8	4.0	8.0	203.6
205.9	209.3	221.6	233.8	237.3	239.6	9.6	25	6	233.3	3.3	8.1	213.7	216.0	219.4	231.7
244.0	247.5	249.8	9.6	26	6	248.0	3.8	9.3	223.4	225.8	229.2	241.5	253.8	257.4	259.6
	9.6	27	6	250.9	3.8	9.2	232.9	235.2	238.6	251.0	263.3	266.8	269.1	9.6	
28	7	269.4	4.7	12.4	241.9	244.2	247.7	260.1	272.5	276.0	278.3	9.7			
29	6	269.2	2.6	6.5	250.6	253.0	256.5	268.9	281.3	284.8	287.1	9.7			
30	7	275.7	4.3	11.3	259.0	261.3	264.8	277.3	289.7	293.2	295.5	9.7			
31	3	284.8	2.5	4.4	267.0	269.4	272.9	285.3	297.8	301.3	303.6	9.7			
32	8	295.3	4.8	13.4	274.7	277.1	280.6	293.1	305.5	309.1	311.4	9.8			
33	6	306.1	3.5	8.6	282.1	284.4	287.9	300.4	312.9	316.5	318.8	9.8	34	6	315.1
		4.0	9.9	289.0	291.4	294.9	307.5	320.0	323.6	325.9	9.8				
35	10	320.3	2.7	8.5	295.7	298.0	301.6	314.2	326.7	330.3	332.6	9.8			
36	15	324.5	2.6	10.0	302.0	304.4	307.9	320.5	333.1	336.7	339.0	9.8	37	18	
		330.0	2.4	10.1	307.9	310.3	313.9	326.5	339.1	342.7	345.0	9.9			
38	17	331.4	2.2	8.9	313.5	315.9	319.5	332.1	344.8	348.4	350.7	9.9			
39	8	339.4	3.5	9.9	318.8	321.2	324.8	337.4	350.1	353.7	356.1	9.9			
40	4	337.1	3.2	6.5	323.7	326.1	329.7	342.4	355.1	358.7	361.1	9.9			

n = number of foetuses; SEM = Standard error of the mean; SD = Standard deviation.

4.3.3 Abdominal Circumference (AC)

The abdominal circumference (AC) showed linear growth with a mean of approximately 11 mm per week throughout gestation (Table 8). The mean AC increased from 90.8 ± 6.1 mm at week 14 to 347.2 ± 9.1 mm at 40 weeks' gestation. Variation in the measurements of foetal abdominal circumference at each week was found to be high. Apart from week 21 where the standard deviation (SD) was 0.9 mm, the rest of the weeks recorded SD of more than 4 mm, the highest being 22 mm at week 33. The standard error of the mean (SEM) which tells how accurate the estimate of the mean is likely to be, ranged from 0.9 to 9 mm. At week 33 of gestation, the mean AC was 297 ± 22 mm while the SEM was 9 mm. This means that the difference between the mean AC of the sample of foetuses at week 33 is 9 mm different from that of the population mean at that week. The variability in measurements of AC across gestation increased from 7.1 mm at 14 week to 17.4 mm at 40 week. At 35 weeks' gestation, 5% of foetuses had a mean AC less than 284 mm, whereas 95% had a mean

AC greater than 284 mm.

Table 8: Fitted Centiles of Abdominal Circumference (AC) at 14 to 40 exact weeks of Gestation.

Weeks	n	Mean	SEM	SD	Fitted centiles AC (mm) 3rd	5th	10th	50th	90th	95th	97th	Fitted SD
14	4	90.8	3.1	6.1	73.4	75.2	78.0	87.8	97.6	7.7	100.4	102.2
15	3	98.7	4.4	7.6	83.2	85.1	88.1	98.3	108.6	111.6	113.5	8.0
16	7	108.2	4.7	12.4	93.1	95.1	98.1	108.9	119.7	122.8	124.7	8.4
17	5	122.6	5.2	11.5	103.0	105.0	108.2	119.5	130.7	133.9	136.0	8.8
18	2	136.2	5.6	7.9	112.8	115.0	118.3	130.1	141.8	145.1	147.3	9.2
20	3	158.8	12.1	21.0	132.6	134.9	138.5	151.2	163.9	167.5	169.8	9.9
21	3	178.2	0.5	0.9	142.4	144.8	148.6	161.8	174.9	178.7	181.1	10.3
22	2	197.4	2.9	4.1	152.3	154.8	158.7	172.3	186.0	189.9	192.4	10.7
23	4	190.2	3.2	6.3	162.1	164.7	168.8	182.9	197.0	201.1	203.7	11.0
24	4	194.3	2.0	4.1	172.0	174.7	178.9	193.5	208.1	212.2	214.9	11.4
25	6	208.2	5.0	12.3	181.9	184.6	189.0	204.0	219.1	223.4	226.2	11.8
26	6	225.1	5.9	14.5	191.7	194.6	199.0	214.6	230.2	234.6	237.5	12.2
27	6	222.0	5.8	14.1	201.6	204.6	209.1	225.2	241.2	245.8	248.8	12.5
28	7	239.6	3.6	9.4	211.5	214.5	219.2	235.8	252.3	257.0	260.0	12.9
29	6	247.2	7.1	17.4	221.3	224.5	229.3	246.3	263.3	268.2	271.3	13.3
30	7	256.8	5.5	14.5	231.2	234.4	239.4	256.9	274.4	279.4	282.6	13.7
31	3	294.0	8.1	14.1	241.1	244.4	249.5	267.5	285.4	290.6	293.9	14.0
32	8	281.6	4.4	12.5	250.9	254.3	259.6	278.0	296.5	301.7	305.1	14.4
33	6	297.0	9.0	22.0	260.8	264.3	269.7	288.6	307.5	312.9	316.4	14.8
34	6	306.5	5.4	13.3	270.7	274.2	279.8	299.2	318.6	324.1	327.7	15.2
35	11	319.8	5.5	18.2	280.5	284.2	289.9	309.7	329.6	335.3	339.0	15.5
36	16	331.5	3.9	15.5	290.4	294.1	299.9	320.3	340.7	346.5	350.2	15.9
37	18	330.9	4.0	17.2	300.3	304.1	310.0	330.9	351.7	357.7	361.5	16.3
38	17	346.5	4.1	16.8	310.1	314.0	320.1	341.5	362.8	368.9	372.8	16.7
39	8	359.2	5.0	14.2	320.0	324.0	330.2	352.0	373.8	380.1	384.1	17.0

40	4	347.2	4.6	9.1	329.9	333.9	340.3	362.6	384.9	391.2	395.3	17.4

n = number of foetuses; SEM = Standard error of the mean; SD = Standard deviation.

4.3.4 Femur Length (FL)

The femur length (FL) increased approximately 3 mm per week from 14 to 24 weeks of gestation, thereafter 2 mm per week until term (Table 9). The average growth rate was 2.31 mm per week. Except for week 21, the SEM was less than 2 mm. This means the mean FL of the sample at week 21 is very close to the population mean. The mean FL at week 14 was 15.1 ± 3.1 mm whilst at week 40, it was 78 ± 2.6 mm. Weeks 15 and 22 recorded the lowest SD of 0.5 and 0.4 respectively. The highest SD was 4.5 mm at week 21. The increase in variability of femur length measurements associated with increasing gestational age was very small. The fitted SD increased by just 0.1 mm every 3 consecutive weeks from 2.3 mm at week 14 to 3.1 mm at week 40. Table 11 also shows that at week 15, 5% of foetuses whose femur lengths were measured were less than 14.8 mm whilst 95% were greater than 14.8 mm.

Table 9: Fitted Centiles of Femur Length (FL) at 14 to 40 exact weeks of Gestation.

					Fitted centiles FL (mm)							
Weeks	**n**	**Mean**	**SEM**	**SD**	**3rd**	**5th**	**10th**	**50th**	**90th**	**95th**	**97th**	**Fitted SD**
14	4	15.1	1.5	3.1	11.3	11.9	12.7	15.6	18.6	19.4	19.9	2.3
15	3	20.5	0.3	0.5	14.3	14.8	15.7	18.6	21.6	22.4	23.0	2.3
16	7	21.8	1.4	3.7	17.2	17.7	18.6	21.6	24.6	25.4	26.0	2.3
17	5	26.4	1.5	3.5	20.0	20.5	21.4	24.4	27.5	28.4	28.9	2.4
18	2	30.4	1.2	1.7	22.7	23.3	24.2	27.3	30.4	31.2	31.8	2.4
20	3	36.2	1.6	2.7	28.1	28.7	29.6	32.8	35.9	36.8	37.4	2.5
21	3	36.7	2.6	4.5	30.7	31.3	32.2	35.4	38.6	39.5	40.1	2.5
22	2	40.6	0.3	0.4	33.3	33.9	34.8	38.0	41.3	42.2	42.8	2.5
23	4	42.7	0.9	1.8	35.8	36.4	37.3	40.6	43.9	44.8	45.4	2.6
24	4	45.7	0.6	1.3	38.2	38.8	39.8	43.1	46.4	47.4	48.0	2.6
25	6	47.1	0.9	2.1	40.6	41.2	42.2	45.6	48.9	49.9	50.5	2.6
26	6	50.3	0.8	2.0	42.9	43.6	44.5	47.9	51.3	52.3	52.9	2.7
27	6	50.8	1.0	2.4	45.2	45.9	46.8	50.3	53.7	54.7	55.3	2.7
28	7	54.3	0.6	1.5	47.5	48.1	49.1	52.6	56.1	57.0	57.7	2.7
29	6	57.3	0.7	1.8	49.6	50.3	51.3	54.8	58.3	59.3	60.0	2.8
30	7	55.9	1.1	2.9	51.8	52.4	53.4	57.0	60.5	61.6	62.2	2.8
31	3	59.3	1.4	2.3	53.8	54.5	55.5	59.1	62.7	63.7	64.4	2.8
32	8	61.2	1.4	3.9	55.8	56.5	57.5	61.2	64.8	65.9	66.5	2.8
33	6	65.9	1.2	2.9	57.8	58.5	59.5	63.2	66.9	67.9	68.6	2.9
34	6	66.6	1.0	2.3	59.7	60.4	61.4	65.2	68.9	69.9	70.6	2.9
35	10	67.1	1.0	3.2	61.5	62.2	63.3	67.1	70.8	71.9	72.6	2.9
36	15	72.1	0.8	3.2	63.3	64.0	65.1	68.9	72.7	73.8	74.5	3.0
37	18	71.6	0.8	3.4	65.1	65.8	66.9	70.7	74.6	75.7	76.4	3.0
38	17	73.5	0.8	3.4	66.8	67.5	68.6	72.5	76.4	77.5	78.2	3.0
39	8	75.5	1.0	2.9	68.4	69.1	70.2	74.2	78.1	79.2	79.9	3.1
40	4	78.0	1.3	2.6	70.0	70.7	71.8	75.8	79.8	80.9	81.6	3.1

n = number of foetuses; SEM = Standard error of the mean; SD = Standard deviation.

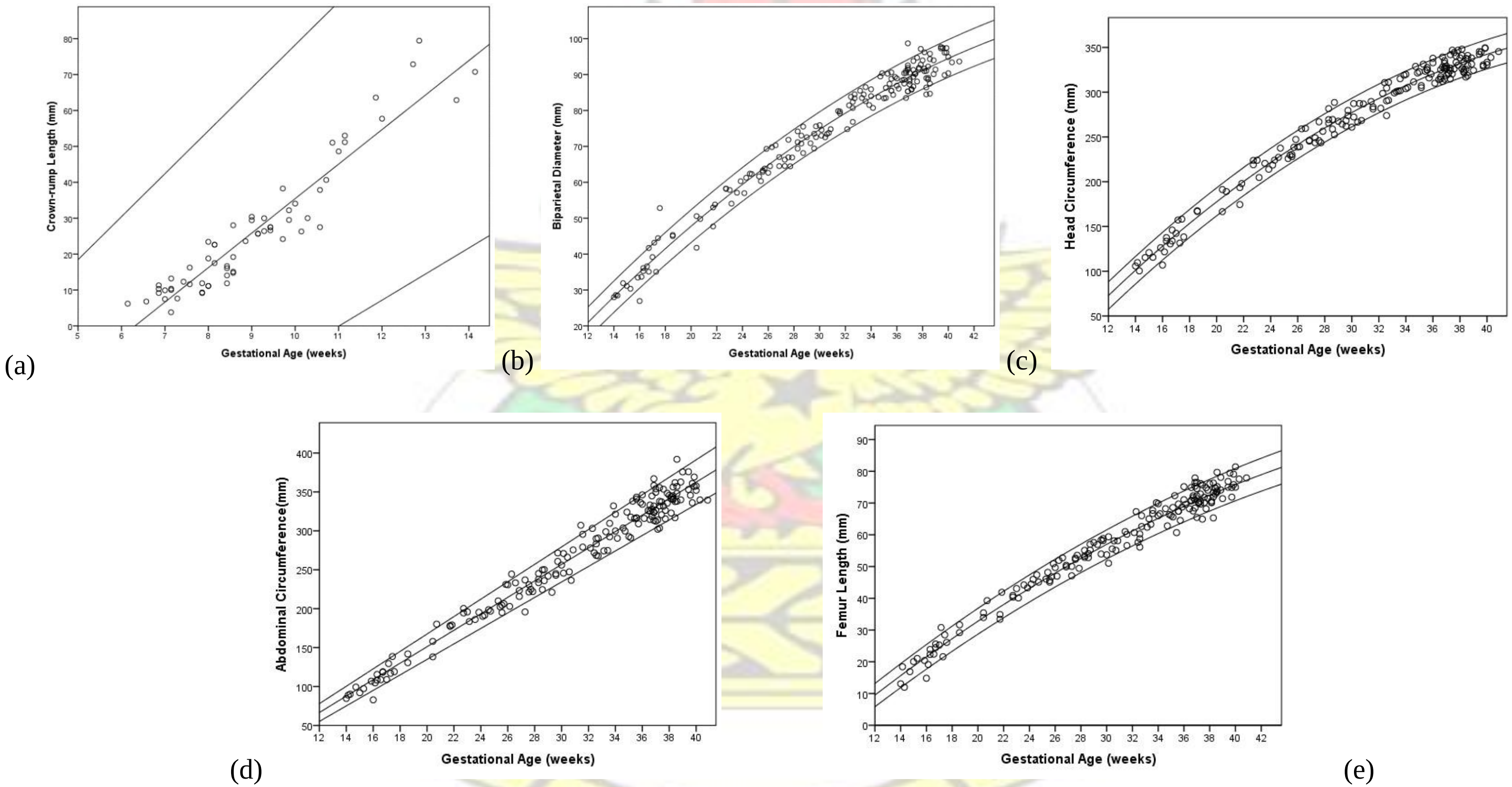

Figure 5: Scatter plots of (a) crown-rump length; (b) biparietal diameter; (c) head circumference; (d) abdominal circumference and (e) femur length against gestational age with fitted 5th, 50th, and 95th centiles.

4.3.5 Foetal Proportions

Tables 10-13 show the 3rd, 5th, 10th, 50th, 90th, 95th and 97th centiles fitted for head to abdominal circumference (HC/AC) ratio, femur length to biparietal circumference (FL/BPD) ratio, femur length to head circumference (FL/HC) ratio and femur length to abdominal circumference (FL/AC) ratio respectively together with the number of observations (n) and fitted standard deviation (SD). The HC/AC ratio decreased by 0.01 throughout gestation from 1.24 at week 14 to 0.96 at week 40 (Table 10). The ratio was greater than 1:1 until 36 weeks.

Table 10: Fitted Centiles of Head Circumference to Abdominal Circumference (HC/AC) ratio at 14 to 40 exact weeks of Gestation.

Weeks of gestation	**n**	**3rd**	**5th**	**10th**	**50th**	**90th**	**95th**	**97th**	**Fittted SD**
14	4	1.11	1.12	1.15	1.24	0.07	1.32	1.35	1.36
15	3	1.10	1.11	1.14	1.22	1.31	1.34	1.35	0.07
16	7	1.09	1.10	1.13	1.21	1.30	1.32	1.34	0.07
17	5	1.08	1.10	1.12	1.20	1.29	1.31	1.33	0.07
18	2	1.07	1.09	1.11	1.19	1.28	1.30	1.31	0.06
20	3	1.05	1.07	1.09	1.17	1.25	1.28	1.29	0.06
21	3	1.04	1.06	1.08	1.16	1.24	1.26	1.28	0.06
22	2	1.03	1.05	1.07	1.15	1.23	1.25	1.27	0.06
23	4	1.03	1.04	1.06	1.14	1.22	1.24	1.25	0.06
24	4	1.02	1.03	1.05	1.13	1.21	1.23	1.24	0.06
25	6	1.01	1.02	1.04	1.12	1.19	1.22	1.23	0.06
26	6	1.00	1.01	1.03	1.11	1.18	1.20	1.22	0.06
27	6	0.99	1.00	1.02	1.10	1.17	1.19	1.21	0.06
28	7	0.98	0.99	1.01	1.09	1.16	1.18	1.19	0.06
29	6	0.97	0.98	1.00	1.08	1.15	1.17	1.18	0.06
30	7	0.96	0.97	1.00	1.07	1.14	1.16	1.17	0.06
31	3	0.95	0.97	0.99	1.06	1.13	1.14	1.16	0.05
32	8	0.94	0.96	0.98	1.04	1.11	1.13	1.15	0.05
33	6	0.93	0.95	0.97	1.03	1.10	1.12	1.13	0.05
34	6	0.93	0.94	0.96	1.02	1.09	1.11	1.12	0.05
35	11	0.92	0.93	0.95	1.01	1.08	1.10	1.11	0.05
36	16	0.91	0.92	0.94	1.00	1.07	1.09	1.10	0.05
37	18	0.90	0.91	0.93	0.99	1.06	1.07	1.09	0.05
38	17	0.89	0.90	0.92	0.98	1.04	1.06	1.07	0.05

39	8	0.88	0.89	0.91	0.97	1.03	1.05	1.06	0.05
40	4	0.87	0.88	0.90	0.96	1.02	1.04	1.05	0.05

n = number of foetuses; SD = Standard deviation.

The normal range of FL/BPD ratio was found to be 0.73 ± 0.1 (Table 11). The ratio increased slowly throughout gestation from 0.631 at week 14 to 0.828 at 40 weeks' gestation.

Table 11: Fitted Centiles of Femur Length to Biparietal Diameter (FL/BPD) ratio at 14 to 40 exact weeks of Gestation.

Weeks of Gestation	n	3rd	5th	10th	50th	90th	95th	97th	Fitted SD
14	4	0.500	0.516	0.542	0.631	0.7[illegible]	0.746	0.763	0.070
15	3	0.510	0.526	0.551	0.639	0.727	0.752	0.768	0.069
16	7	0.520	0.536	0.560	0.646	0.732	0.757	0.773	0.067
17	5	0.530	0.545	0.570	0.654	0.738	0.762	0.778	0.066
18	2	0.540	0.555	0.579	0.662	0.744	0.768	0.783	0.065
20	3	0.560	0.575	0.597	0.677	0.756	0.779	0.793	0.062
21	3	0.570	0.584	0.607	0.684	0.762	0.784	0.798	0.061
22	2	0.580	0.594	0.616	0.692	0.768	0.789	0.803	0.059
23	4	0.590	0.604	0.625	0.699	0.774	0.795	0.809	0.058
24	4	0.600	0.614	0.634	0.707	0.780	0.800	0.814	0.057
25	6	0.610	0.623	0.644	0.715	0.785	0.806	0.819	0.055
26	6	0.620	0.633	0.653	0.722	0.791	0.811	0.824	0.054
27	6	0.630	0.643	0.662	0.730	0.797	0.817	0.829	0.053
28	7	0.640	0.653	0.671	0.737	0.803	0.822	0.834	0.051
29	6	0.650	0.662	0.681	0.745	0.809	0.827	0.839	0.050
30	7	0.661	0.672	0.690	0.752	0.815	0.833	0.844	0.049
31	3	0.671	0.682	0.699	0.760	0.821	0.838	0.849	0.048
32	8	0.681	0.691	0.708	0.768	0.827	0.844	0.854	0.046
33	6	0.691	0.701	0.718	0.775	0.833	0.849	0.860	0.045
34	6	0.701	0.711	0.727	0.783	0.839	0.854	0.865	0.044
35	11	0.711	0.721	0.736	0.790	0.844	0.860	0.870	0.042
36	16	0.721	0.730	0.745	0.798	0.850	0.865	0.875	0.041
37	18	0.731	0.740	0.755	0.805	0.856	0.871	0.880	0.040
38	17	0.741	0.750	0.764	0.813	0.862	0.876	0.885	0.038
39	8	0.751	0.760	0.773	0.821	0.868	0.881	0.890	0.037
40	4	0.761	0.769	0.782	0.828	0.874	0.887	0.895	0.036

n = number of foetuses; SD = Standard deviation.

The FL/HC ratio increased slowly throughout gestation from 0.159 at week 14 to 0.221 at week 40 (Table 12). From week 25 until term the normal range of FL/HC was 0.21 ± 0.01.

Table 12: Fitted Centiles of Femur Length to Head Circumference (FL/HC) ratio at 14 to 40 exact weeks of Gestation.

Weeks of Gestation	n	3rd	5th	10th	50th	90th	95th	97th	Fitted SD
14	4	0.079	0.089	0.105	0.159	0.213	0.229	0.239	0.043
15	3	0.086	0.095	0.110	0.163	0.216	0.231	0.241	0.041
16	7	0.092	0.101	0.116	0.167	0.219	0.233	0.243	0.040
17	5	0.098	0.107	0.121	0.171	0.221	0.235	0.244	0.039
18	2	0.104	0.113	0.127	0.175	0.223	0.237	0.246	0.038
20	3	0.116	0.124	0.137	0.182	0.227	0.240	0.248	0.035
21	3	0.122	0.130	0.142	0.185	0.229	0.241	0.249	0.034
22	2	0.127	0.135	0.147	0.189	0.230	0.242	0.250	0.033
23	4	0.133	0.140	0.151	0.192	0.232	0.243	0.251	0.031
24	4	0.138	0.145	0.156	0.194	0.233	0.244	0.251	0.030
25	6	0.143	0.150	0.160	0.197	0.234	0.245	0.252	0.029
26	6	0.148	0.154	0.164	0.200	0.235	0.245	0.252	0.028
27	6	0.153	0.159	0.168	0.202	0.236	0.246	0.252	0.026
28	7	0.157	0.163	0.172	0.205	0.237	0.246	0.252	0.025
29	6	0.162	0.167	0.176	0.207	0.237	0.246	0.252	0.024
30	7	0.166	0.171	0.180	0.209	0.238	0.246	0.251	0.023
31	3	0.170	0.175	0.183	0.211	0.238	0.246	0.251	0.021
32	8	0.174	0.179	0.187	0.212	0.238	0.246	0.250	0.020
33	6	0.178	0.183	0.190	0.214	0.238	0.245	0.250	0.019
34	6	0.182	0.186	0.193	0.215	0.238	0.245	0.249	0.018
35	11	0.186	0.190	0.196	0.217	0.238	0.244	0.248	0.017
36	16	0.189	0.193	0.198	0.218	0.237	0.243	0.247	0.015
37	18	0.193	0.196	0.201	0.219	0.237	0.242	0.245	0.014
38	17	0.196	0.199	0.203	0.220	0.236	0.241	0.244	0.013
39	8	0.199	0.202	0.206	0.221	0.235	0.240	0.242	0.012
40	4	0.202	0.204	0.208	0.221	0.234	0.238	0.240	0.010

n = number of foetuses; SD = Standard deviation.

The FL/AC ratio increased from 0.19 at week 14 to 0.21 at week 18, attained a constant value of 0.22 from weeks 21 to 37, and then decreased to 0.21 until term (Table 13). The normal range of FL/AC ratio after 15 weeks was 0.21 ± 0.01.

Table 13: Fitted centiles of Femur length to Abdominal Circumference (FL/AC) ratio at 14 to 40 exact weeks of Gestation.

Weeks of Gestation	**n**	**3rd**	**5th**	**10th**	**50th**	**90th**	**95th**	**97th**	**Fitted SD**
14	4	0.152	0.157	0.165	0.192	0.220	0.228	0.233	0.022
15	3	0.157	0.162	0.169	0.197	0.224	0.231	0.236	0.021
16	7	0.161	0.166	0.174	0.200	0.227	0.235	0.239	0.021
17	5	0.166	0.171	0.178	0.204	0.230	0.237	0.242	0.020
18	2	0.170	0.175	0.182	0.207	0.233	0.240	0.245	0.020
20	3	0.177	0.182	0.189	0.213	0.237	0.244	0.249	0.019
21	3	0.181	0.185	0.192	0.215	0.239	0.246	0.250	0.019
22	2	0.184	0.188	0.194	0.218	0.241	0.247	0.252	0.018
23	4	0.186	0.190	0.197	0.219	0.242	0.248	0.253	0.018
24	4	0.189	0.193	0.199	0.221	0.243	0.249	0.253	0.017
25	6	0.191	0.195	0.201	0.222	0.244	0.250	0.254	0.017
26	6	0.193	0.197	0.203	0.223	0.244	0.250	0.254	0.016
27	6	0.194	0.198	0.204	0.224	0.244	0.250	0.254	0.016
28	7	0.196	0.199	0.205	0.225	0.244	0.250	0.254	0.015
29	6	0.197	0.200	0.206	0.225	0.244	0.249	0.253	0.015
30	7	0.197	0.201	0.206	0.225	0.243	0.249	0.252	0.015
31	3	0.198	0.201	0.206	0.224	0.242	0.248	0.251	0.014
32	8	0.198	0.201	0.206	0.224	0.241	0.246	0.249	0.014
33	6	0.198	0.201	0.206	0.223	0.240	0.244	0.248	0.013
34	6	0.198	0.201	0.205	0.222	0.238	0.243	0.246	0.013
35	11	0.197	0.200	0.204	0.220	0.236	0.240	0.243	0.012
36	16	0.196	0.199	0.203	0.218	0.233	0.238	0.241	0.012
37	18	0.195	0.197	0.202	0.216	0.231	0.235	0.238	0.011
38	17	0.193	0.196	0.200	0.214	0.228	0.232	0.234	0.011
39	8	0.191	0.194	0.198	0.211	0.225	0.229	0.231	0.011

40	4	0.189	0.192	0.195	0.208	0.221	0.225	0.227	0.010

n = number of foetuses; SD = Standard deviation.

Figure 6 (a-d) illustrates the goodness of fit of the model by showing scatter plots of the ratios against gestational age with the fitted 3rd, 5th, 50th, 95th and 97th centiles.

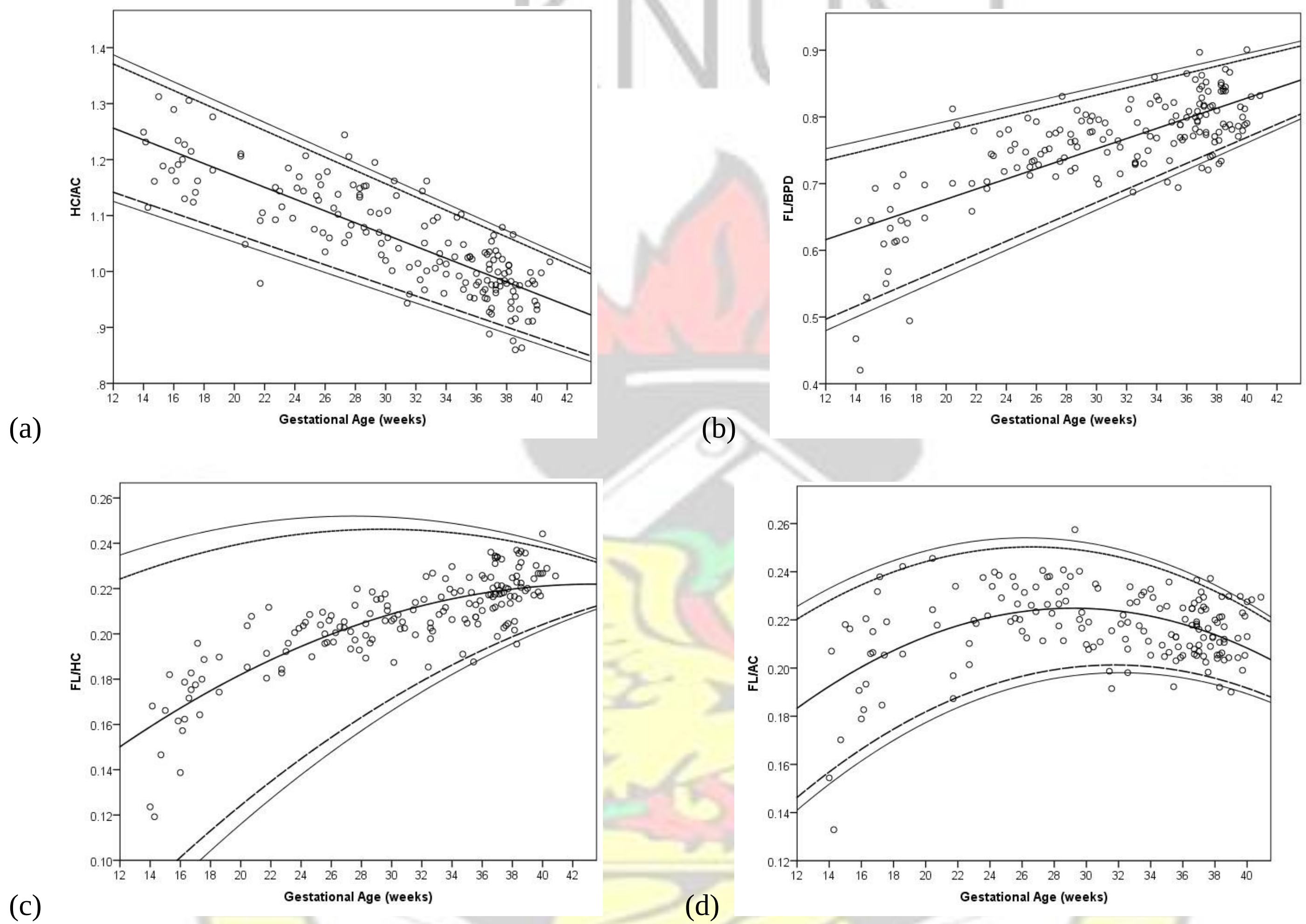

Figure 6: Scatter plots of (a) head to abdominal circumference (HC/AC) ratio, (b) femur length to biparietal diameter (FL/BPD) ratio, (c) femur length to head circumference (FL/HC) ratio and (d) femur length to abdominal circumference (FL/AC) ratio against gestational age with fitted 3rd, 5th, 50th, 95th and 97th centiles.

4.4 COMPARISON OF FOETAL SIZE CHARTS OF THE PRESENT STUDY WITH OTHER REFERENCE CHARTS

The foetal size charts of the present study were compared with other published charts. Figures 7-10 show the comparison of the foetal size chart for abdominal circumference (AC) in the present study with those from Hadlock *et al.* (1982b), Hadlock *et al.* (1984a), Chitty *et al.* (1994b), Leung *et al.* (2008) and Kurmanavicius *et al.* (1999b). The 5th, 50th and 95th centiles of AC in the present study were significantly higher than the Chinese chart by Leung *et al.* (2008) throughout gestation, especially in the early second trimester and late third trimester (Figure 7). At week 15, the 5th, 50th and 95th centiles of AC in the present study were 4 mm, 6 mm and 9 mm bigger than the respective centiles of the Chinese chart. This increased to a difference of 14 mm, 15 mm and 17 mm respectively at week 38. The 50th and 95th centiles of the Chinese chart were much narrower than their 5th centile in comparison with the present study.

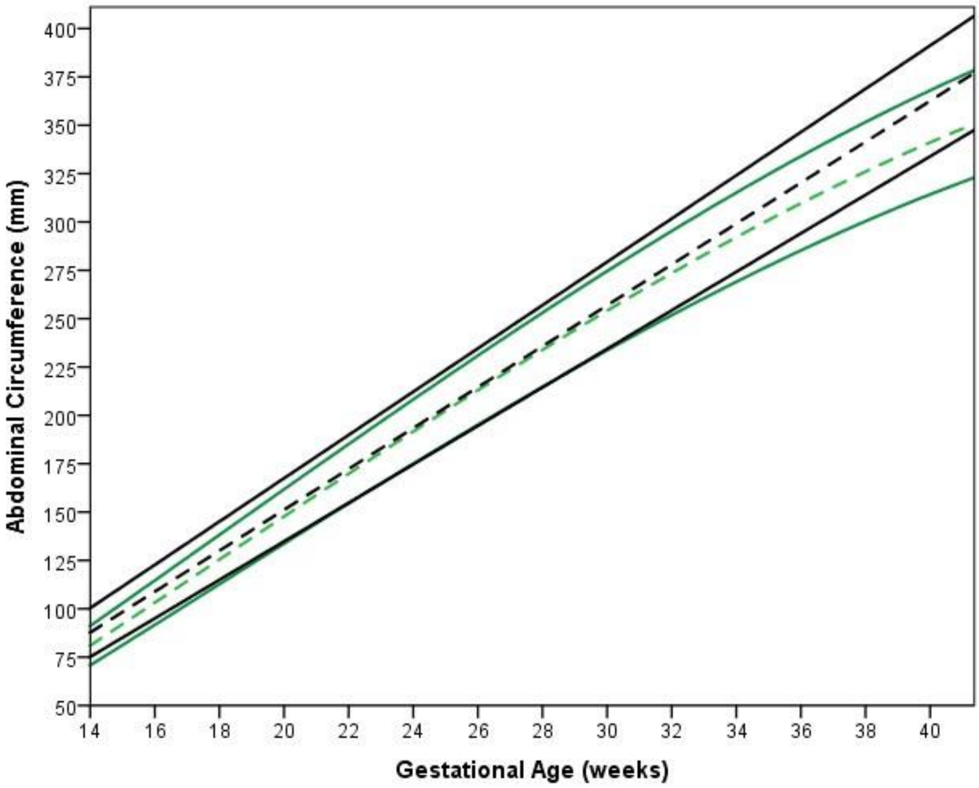

Figure 7: Comparison of the 5th, 50th and 95th centiles for abdominal circumference in the present study (black lines) with Leung *et al.* (2008) (green lines). The dashed lines represent the 50th centile.

The observed differences between the charts of AC in the present study and the Chinese by Leung *et al.* (2008) were similar to that observed between the present study and that from Kurmanavicius *et al.* (1999b). The 5th and 50th centiles of AC by Kurmanavicius *et al.* (1999b) were much narrower than their 95th centile in comparison with the present study (Figure 8).

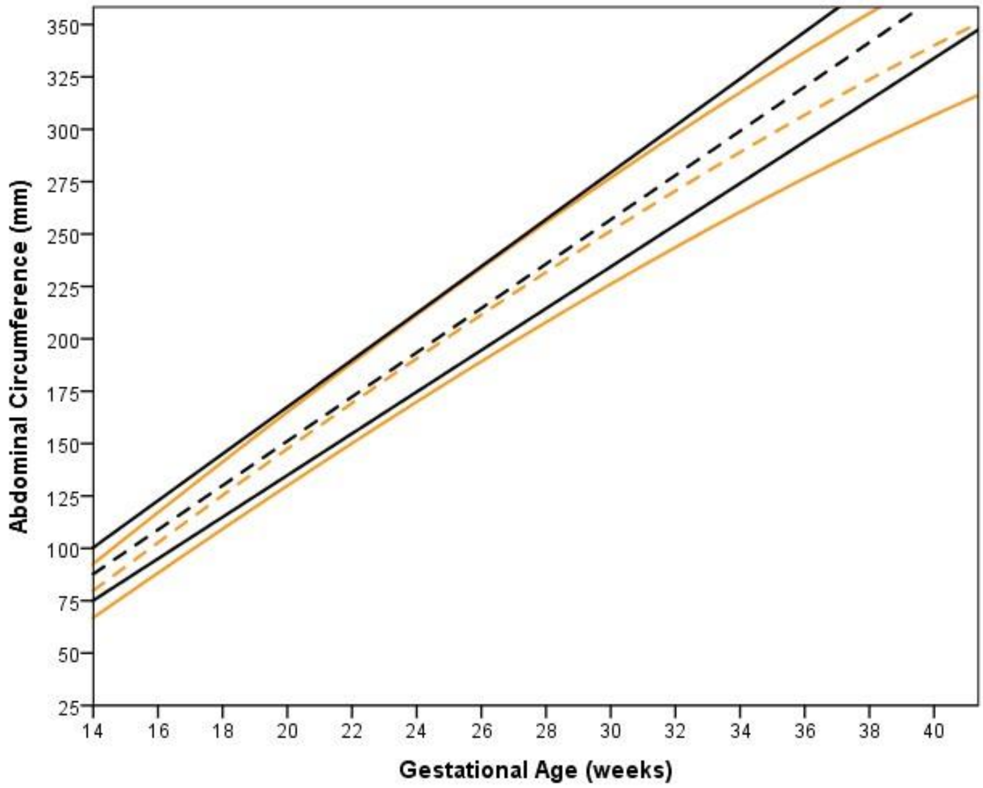

Figure 8: Comparison of the 5th, 50th and 95th centiles for abdominal circumference in the present study (black lines) with Kurmanavicius *et al.* (1999b) (yellow lines). The dashed lines represent the 50th centile.

The AC chart of the present study was also compared with similar charts by Hadlock *et al.* (1982b) and Hadlock *et al.* (1984a) from middle class Caucasians women (Figure 9). The 5th centile of the present study was bigger up to week 21 and week 40 but smaller between weeks 23-39 in comparison with Hadlock *et al.* (1982b) chart. Compared to the AC chart by Hadlock *et al.* (1984a), the present study was bigger up to week 24 and after week 36 but smaller between 25-36 weeks' gestation. The 50th centile was also significantly wider in the early second trimester and late third trimester but were significantly narrower between weeks 20-34. In both the 5th and 50th centiles, Hadlock *et al.* (1984a) chart was much narrower than Hadlock *et al.* (1982b) chart. The 95th centile of the present study was significantly narrower from week 18 but significantly wider after week 31 compared to the two charts by Hadlock and coworkers (Hadlock *et al.,* 1982b; Hadlock *et al.,* 1984a). The 95th centile of Hadlock *et al.* (1984a) was narrower up to week 22 but higher afterwards in comparison with Hadlock *et al.* (1982b) chart. The AC chart by Hadlock *et al.* (1984a) was obtained from 361 foetuses of middle class Caucasians women between 14-42 weeks, by tracing the outer perimeter of the abdomen directly from Polaroid images using an electronic digitizer or by calculation using the formula for the circumference of a circle [AC = 1.57(TAD + APAD)]. In the 1982 chart (Hadlock *et al.,* 1982b), the circumference was obtained solely by tracing the outer boundaries of the abdomen of 400 foetuses between 15-41 weeks' gestation.

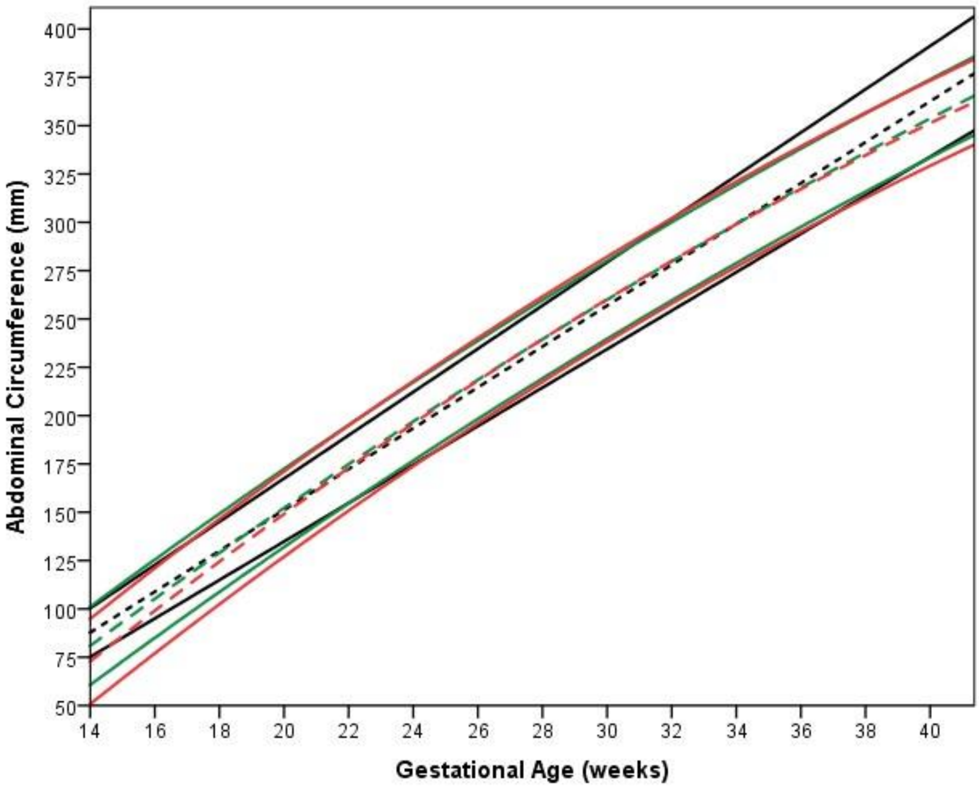

Figure 9: Comparison of the 5th, 50th and 95th centiles for abdominal circumference in the present study (black lines) with Hadlock *et al*. (1984a) (red lines) and Hadlock *et al*. (1982b) (green lines). The dashed lines represent the 50th centile.

The British chart from Chitty *et al.* (1994b) followed a similar trend with Hadlock *et al.* (1982b). The abdominal circumference (AC) was obtained by tracing around the perimeter of 610 foetuses between 12-42 weeks. Values for the AC from Chitty *et al.* (1994b) were significantly narrower in early second trimester (50th and 95th centiles) and late third trimester (5th and 50th centiles) (Figure 10). Interestingly a similar chart by Chitty *et al.* (1994b) using the formula for AC from 425 foetuses showed a statistically significantly lower centiles throughout gestation, especially the early second and late third trimesters.

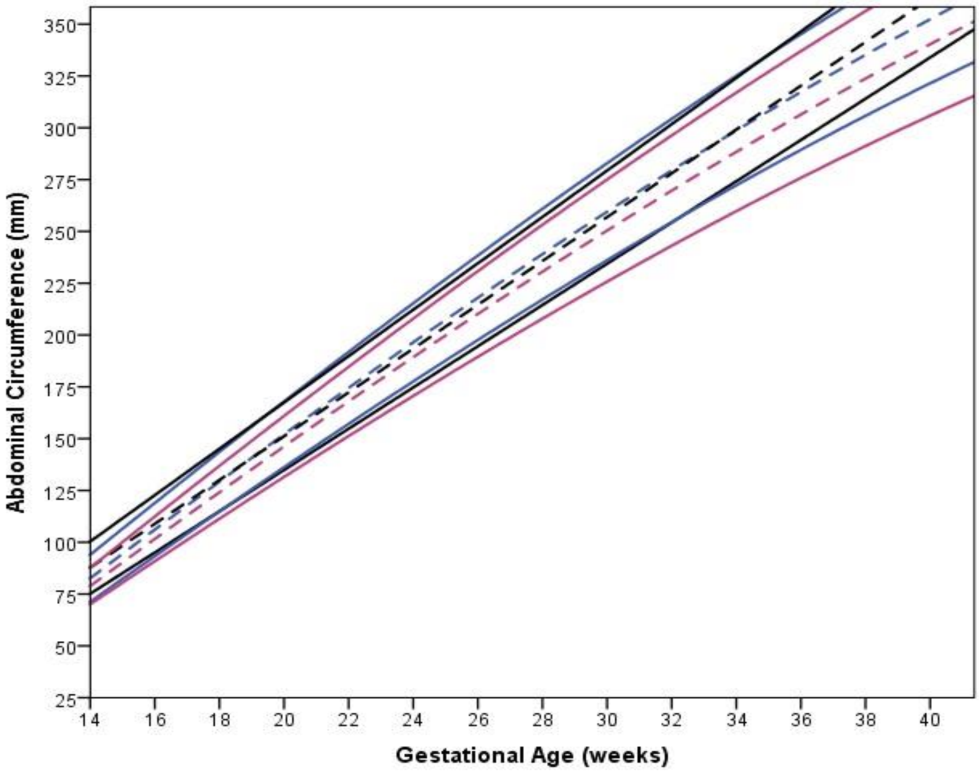

Figure 10: Comparison of the 5th, 50th and 95th centiles for abdominal circumference in the present study (black lines) with Chitty *et al*. (1994b) (blue lines: measured AC; pink lines: calculated AC). The dashed lines represent the 50th centile.

The foetal femur lengths of the present study were significantly longer than the femur lengths of the Chinese (Leung *et al.*, 2008), across all gestations (Figure 11). The difference was 2 mm, 3 mm and 4 mm for the 5th, 50th and 95th centiles respectively**.** The femur length chart of Leung *et al.* (2008) was obtained from 708 foetuses between

12-40 weeks.

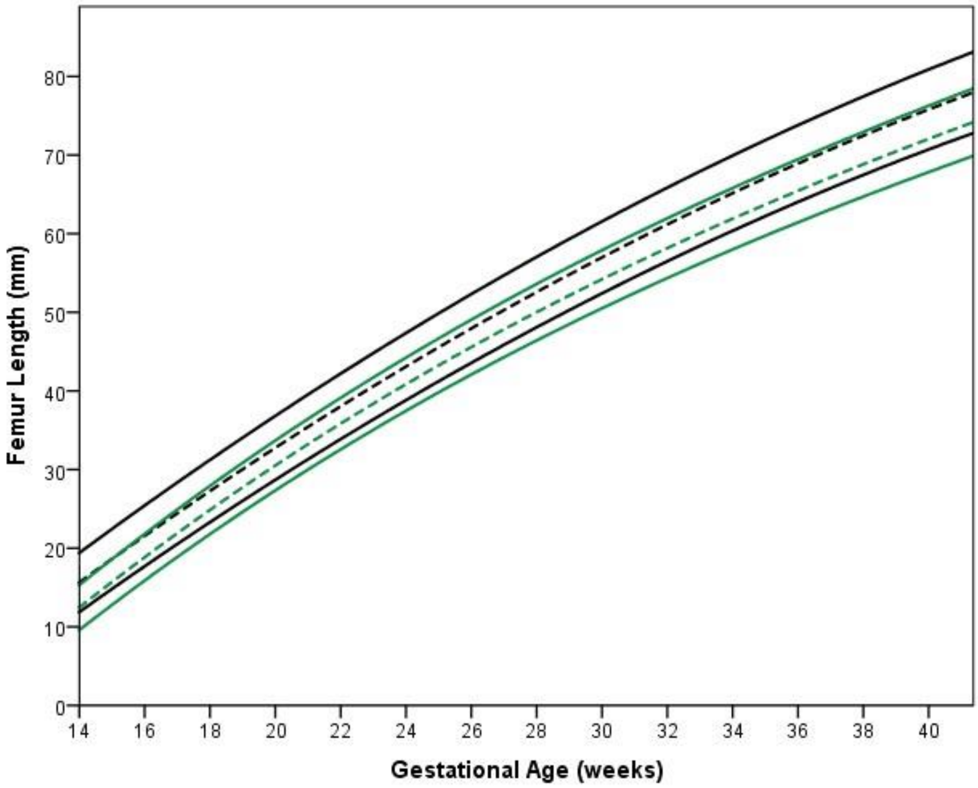

Figure 11: Comparison of the 5th, 50th and 95th centiles for femur length in the present study (black lines) with Leung *et al*. (2008) (green lines). The dashed lines represent the 50th centile.

The foetal femur lengths of the present study were also compared with the American charts by Hadlock *et al.* (1982c) and Hadlock *et al.* (1984a) (Figure 12). The 5th and 50th centiles of the femur length in the present study were significantly longer than Hadlock *et al.* (1984a) up to 20 weeks' gestation but were significantly shorter afterwards. However the 95th centile of the present study was significantly shorter than Hadlock *et al.* (1984a) throughout gestation. The 5th and 50th centiles of femur lengths of the present study were 2 mm longer at week 16, but 2 mm shorter at week 38 compared to Hadlock *et al.* (1984a). The same trend was observed between the present study and Hadlock *et al.* (1982c) chart. However, the FL of Hadlock *et al*. (1982c) was approximately 1 mm longer up to week 23 and 1 mm shorter from week 35 in comparison with Hadlock *et al*. (1984a).

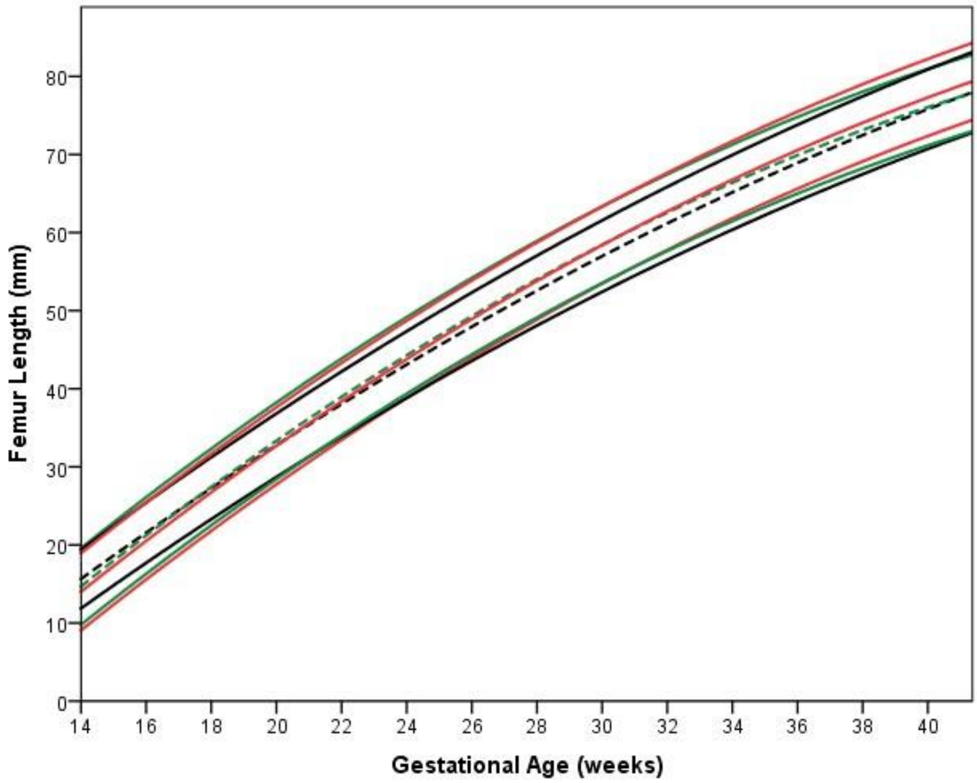

Figure 12: Comparison of the 5th, 50th and 95th centiles for femur length in the present study (black lines) with Hadlock *et al*. (1984a) (red lines) and Hadlock *et al*. (1982c) (green lines). The dashed lines represent the 50th centile.

Centiles for the femur lengths derived from the present study were also compared with those reported by Chitty *et al.* (1994c) and Kurmanavicius *et al.* (1999b) who measured the femoral diaphyseal lengths of 649 and 5860 foetuses respectively between 12-42 weeks' of gestation (Figure 13). The mean femur lengths of both Kurmanavicius *et al.* (1999b) and Chitty *et al.* (1994c) were significantly shorter than the femur lengths of the present study at all centiles. In early second and late third trimesters their femur lengths were 1-2 mm shorter than the present study. There were slightly more deviation between the femur lengths of the present study with Chitty *et al.* (1994c) chart than with Kurmanavicius *et al.* (1999b) chart.

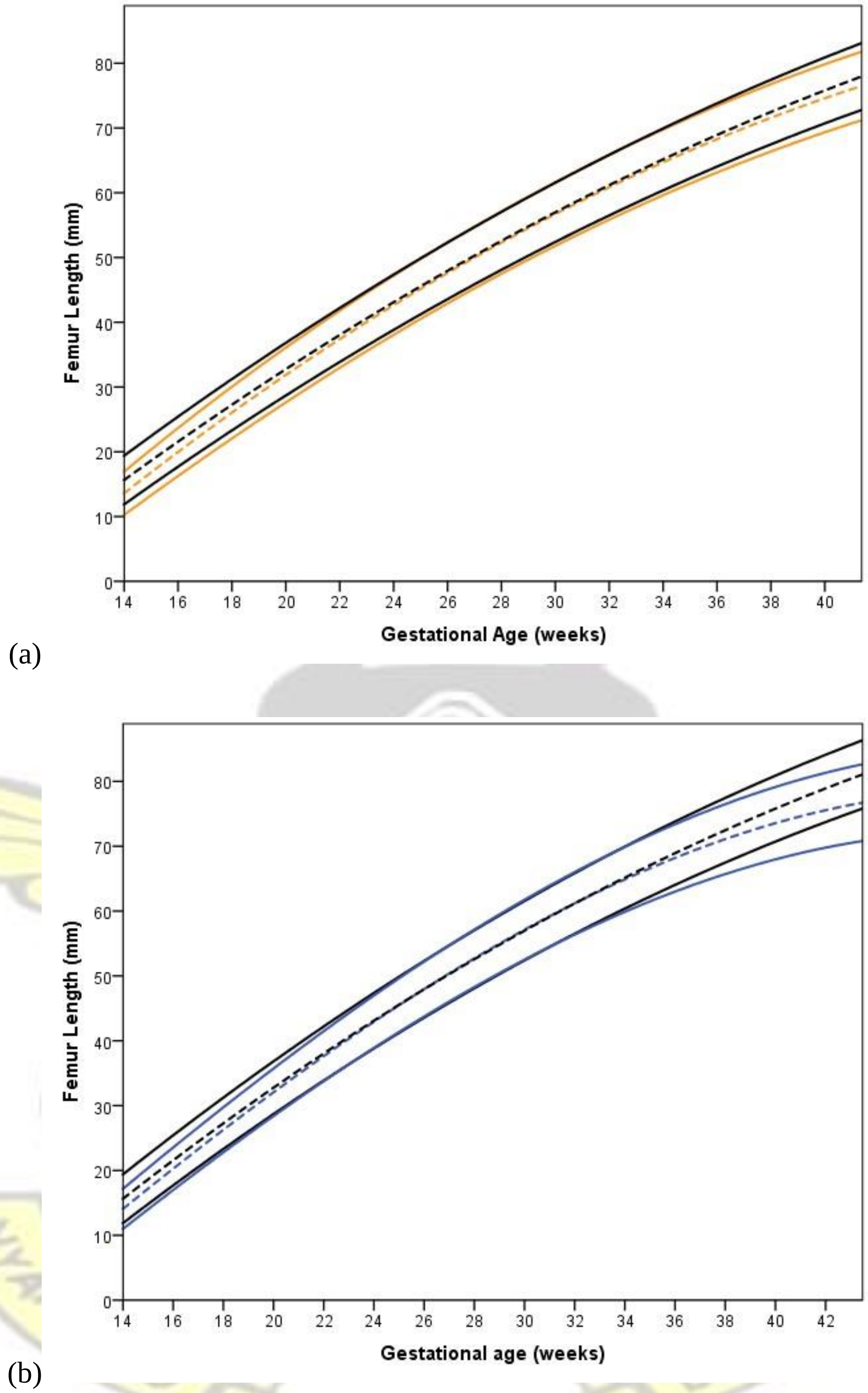

Figure 13: Comparison of the 5th, 50th and 95th centiles for femur length in the present study (black lines) with (a) Kurmanavicius *et al*. (1999b) (yellow lines) and (b) Chitty *et al.* (1994c) (blue lines). The dashed lines represent the 50th centile.

Figure 14 shows the comparison of the reference BPD chart of the present study with that of Kurmanavicius *et al.* (1999a) who measured the BPD of 6217 foetuses via outer-outer from 12 to 42 weeks. Centiles of BPD (outer-outer) chart by Kurmanavicius *et al.* (1999a) were significantly bigger than the present study throughout gestation, increasing with gestational age. Their 5th, 50th and 95th centiles at week 36 were respectively 4 mm, 5 mm and 7 mm bigger than the present study.

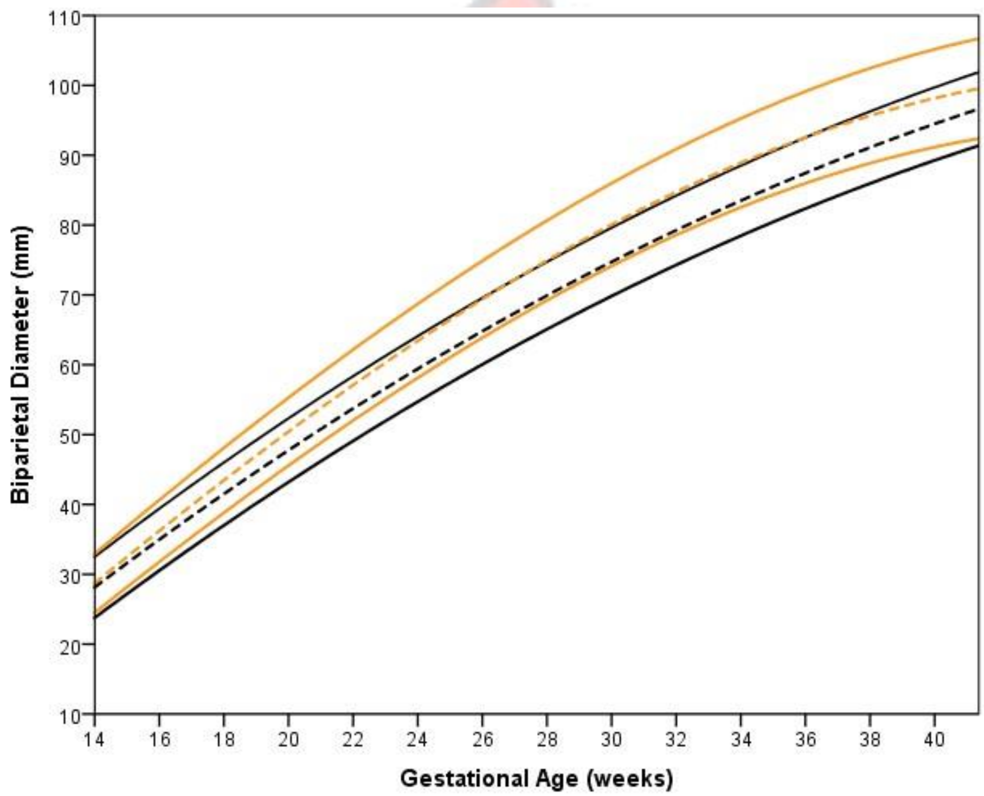

Figure 14: Comparison of the 5th, 50th and 95th centiles for biparietal diameter in the present study (black lines) with Kurmanavicius *et al.* (1999a) (yellow lines). The dashed lines represent the 50th centile.

The 5th, 50th and 95th centiles chart of BPD by Chitty *et al.* (1994a) were all significantly smaller (2-3 mm**)** up to 24 weeks' gestation in comparison with the present study (Figure 15). Beyond week 24 only the 50th and 95th centiles were significantly bigger than the present study. Chitty *et al.* (1994a) derived the BPD chart from 594 foetuses between 1242 weeks by measuring the BPD from the outer-inner of the calvarial wall. The outerinner BPD chart of the present study was also compared to the outer-outer BPD chart by Chitty *et al.* (1994a) (Figure 15). Chitty's outer-outer BPD chart (Chitty *et al.*, 1994a) was significantly bigger from week 16 than the outer-inner BPD chart of the present study.

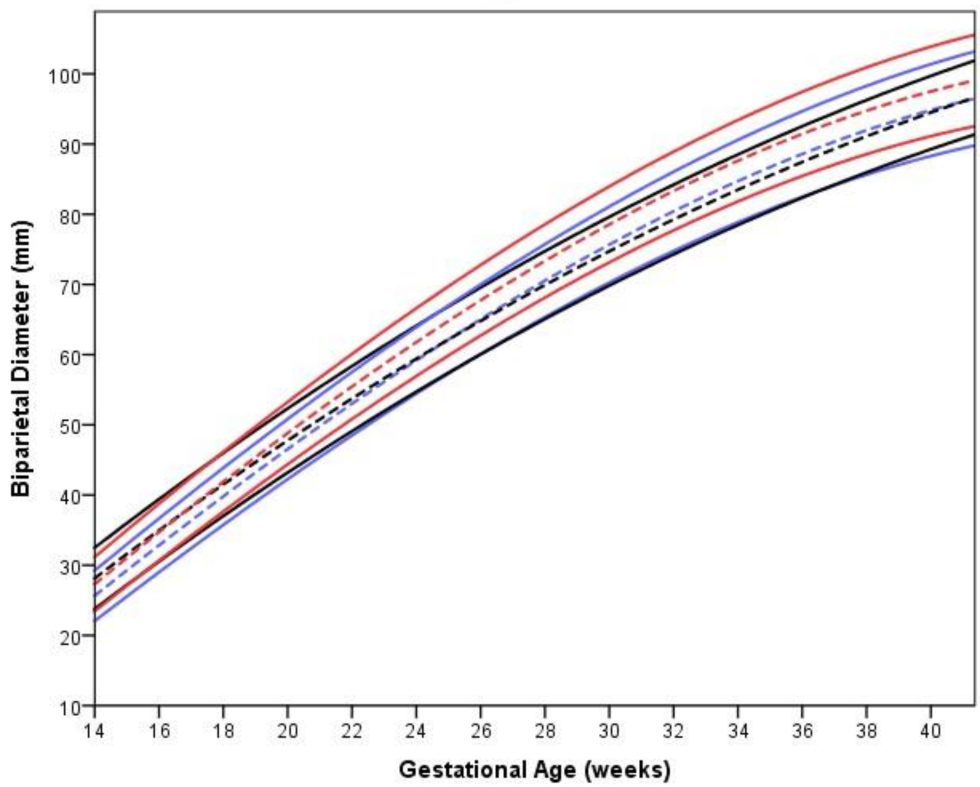

Figure 15: Comparison of the 5th, 50th and 95th centiles for biparietal diameter in the present study (black lines) with Chitty *et al.* (1994a) (outer-inner: blue lines; outer-outer: red lines). The dashed lines represent the 50th centile.

The outer-inner BPD measurements of Hadlock *et al.* (1982d) from 533 middle-class whites women between 14-40 weeks were significantly smaller in the second trimester but significantly bigger in the third trimester (except 95th centile) in comparison with the present study (Figure 16). A similar trend was observed in comparison with the Hadlock *et al.* (1984a) chart. However, the BPD chart of Hadlock *et al.* (1984a) was approximately 1-2 mm smaller up to week 18 but 1 mm bigger between weeks 23-36, compared to the Hadlock *et al.* (1982d) chart.

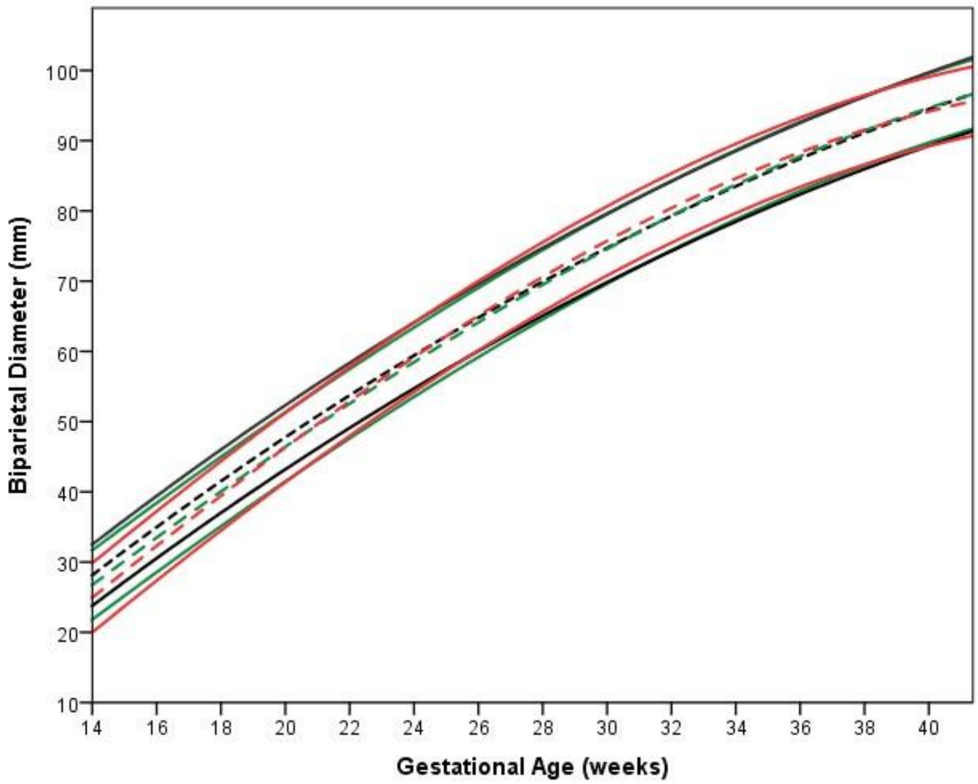

Figure 16: Comparison of the 5th, 50th and 95th centiles for biparietal diameter in the present study (black lines) with Hadlock *et al*. (1984a) (red lines) and Hadlock *et al*. (1982d) (green lines). The dashed lines represent the 50th centile.

The outer-inner BPD chart of the present study was also compared with the outer-inner BPD chart of 708 Chinese foetuses between 12-40 weeks' gestation. Centiles of the Chinese chart by Leung *et al.* (2008) were significantly lower in the second trimester but significantly higher in the third trimester in comparison with the present study (Figure 17). The 50th centile of BPD in the present study at week 16 was 2 mm bigger than the

Chinese chart by Leung *et al.* (2008). At week 32 however, the 50th centile of the present study was 2 mm smaller.

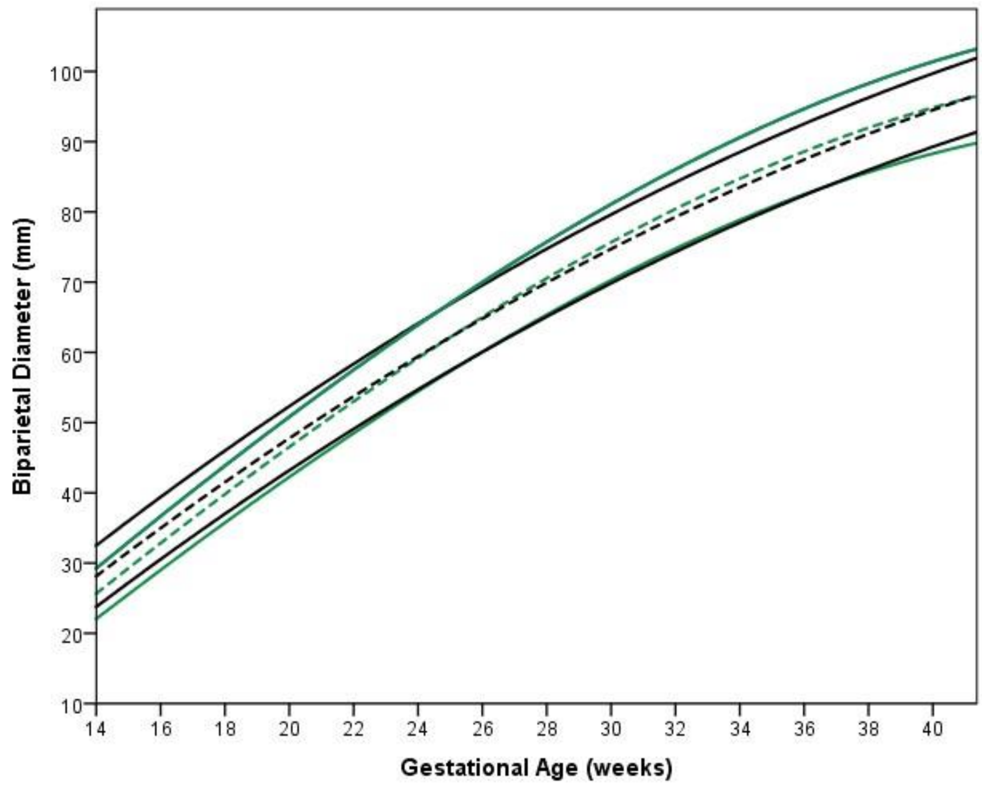

Figure 17: Comparison of the 5th, 50th and 95th centiles for biparietal diameter in the present study (black lines) with Leung *et al.* (2008) (green lines). The dashed lines represent the 50th centile.

The mean head circumference (HC) measurements in the present study were significantly larger than those from Hadlock *et al.* (1982a) in the second trimester up to week 25 but significantly smaller from week 27 of gestation. At week 16 however the median value of HC in the present study was 4 mm greater than Hadlock *et al.* (1982a). This can be seen in figure 18 where at week 38 the present study recorded HC value of 332 mm at the

50th centile whereas Hadlock *et al.* (1982a) recorded 335 mm. Except weeks 14-15, the centiles of HC by Hadlock *et al.* (1984a) was significantly larger than that of Hadlock *et al.* (1982a). The HC of Hadlock *et al.* (1982a) was derived from 400 foetuses of middle class Caucasian women between 15-41 weeks by tracing around the outer perimeter of the calvarium. The 1984a HC chart by Hadlock and coworkers was drawn from the same population with a sample size of 361. However, the circumference was obtained by using both the formula for the circumference of a circle and by tracing the outer margin of the calvarial wall directly from Polaroid images using an electronic digitizer.

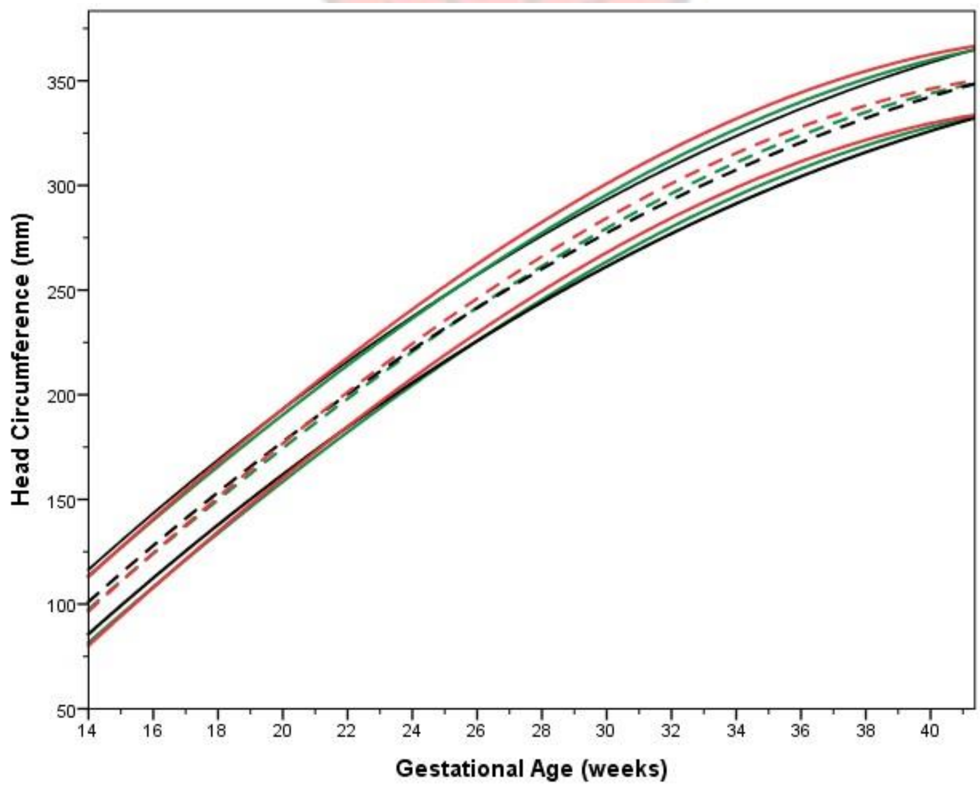

Figure 18: Comparison of the 5th, 50th and 95th centiles for head circumference in the present study (black lines) with Hadlock *et al.* (1982a) (green lines) and Hadlock *et al.* (1984a) (red lines). The dashed lines represent the 50th centile.

In comparison with the chart from Kurmanavicius *et al.* (1999a) who derived the HC from

5462 foetuses using the measurements of the occipitofrontal diameter (OFD) and BPD (outer-outer), the 5th centile of the present study was very slightly smaller in the second trimester but significantly larger in the third trimester (Figure 19). The 50th centile of Kurmanavicius *et al.* (1999a) was slightly smaller up to 20 weeks and after 36 weeks, but slightly larger from weeks 21-35 compared to the present study. Their 95th centile were slightly smaller before week 21 but larger after week 21 in comparison with the present study.

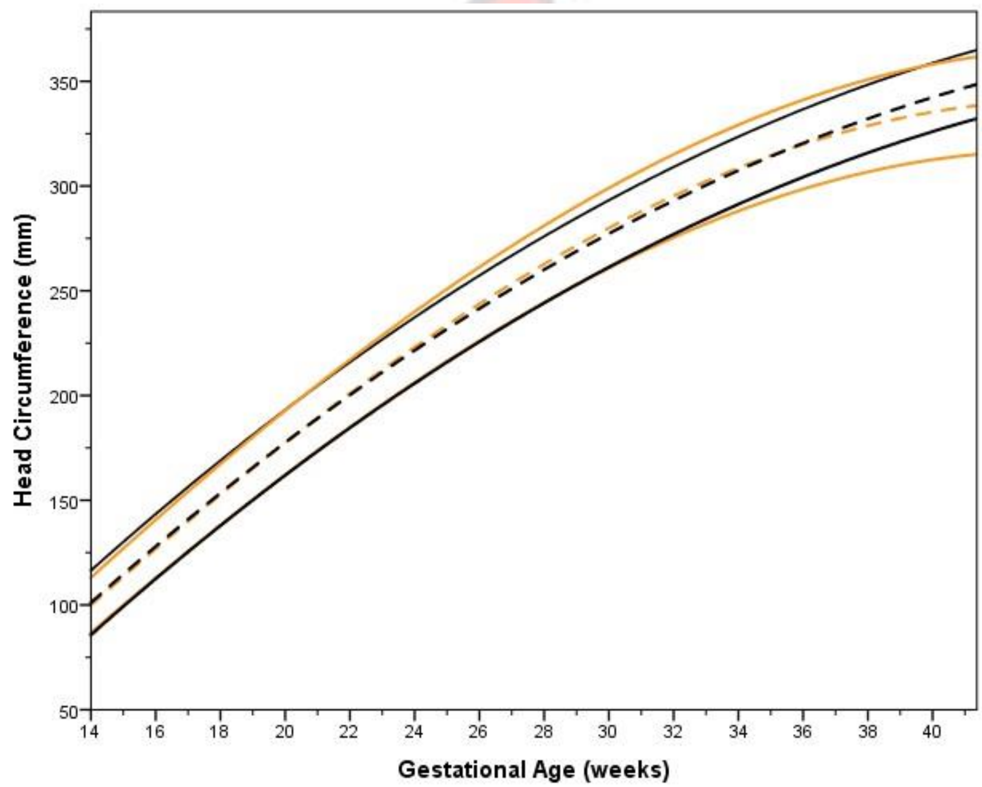

Figure 19: Comparison of the 5th, 50th and 95th centiles for head circumference in the present study (black lines) with Kurmanavicius *et al.* (1999a) (yellow lines). The dashed lines represent the 50th centile.

The head circumference chart by Leung *et al.* (2008) was derived using the ellipse facility from 706 Chinese foetuses. There were much wider deviation in the second trimester and late third trimester between the present study and the Chinese study. The 5th and 50th centiles of the the Chinese chart were significantly smaller than the present study except between weeks 30-34 (Figure 20). Their 95th centile was however smaller throughout gestation. At weeks 16 and 38, the 50th centile of the Chinese HC was 8 mm and 6 mm smaller than the present study respectively.

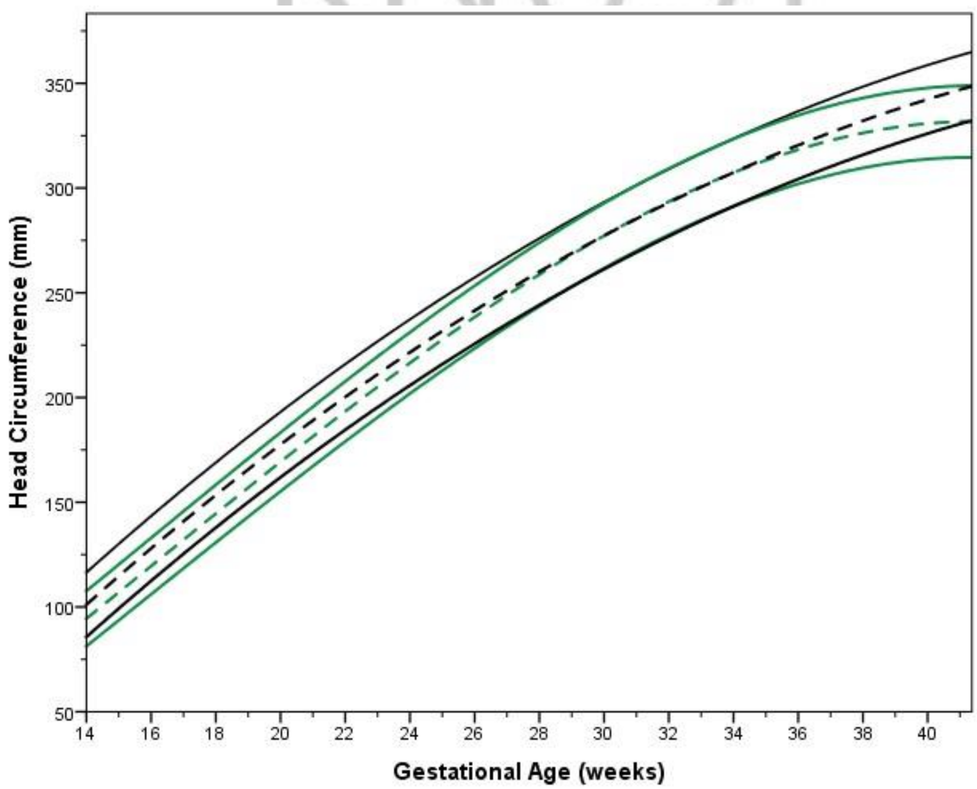

Figure 20: Comparison of the 5th, 50th and 95th centiles for head circumference in the present study (black lines) with Leung *et al.* (2008) (green lines). The dashed lines represent the 50th centile.

Figure 21 shows a comparison of the foetal head circumference chart of the present study with that of Chitty *et al.* (1994a) where the HC was obtained from 594 foetuses between 12-42 weeks using both the plotted (or ellipse) method and the derived (or calculated) method. The 50th and 95th centiles of their HC (plotted or derived) were significantly smaller in the early second trimester but significantly bigger after week 23 in comparison with the present study. The 5th centile of their plotted HC was significantly bigger throughout gestation, whereas their derived HC was only significantly bigger between weeks 26-35 in comparison with the present study. There were much deviation in the present study with the derived HC chart of Chitty *et al.* (1994a) than with their plotted HC chart in the early second trimester. In the third trimester however there were much deviation in the present study with the plotted HC chart by Chitty *et al.* (1994a) than with their derived HC chart.

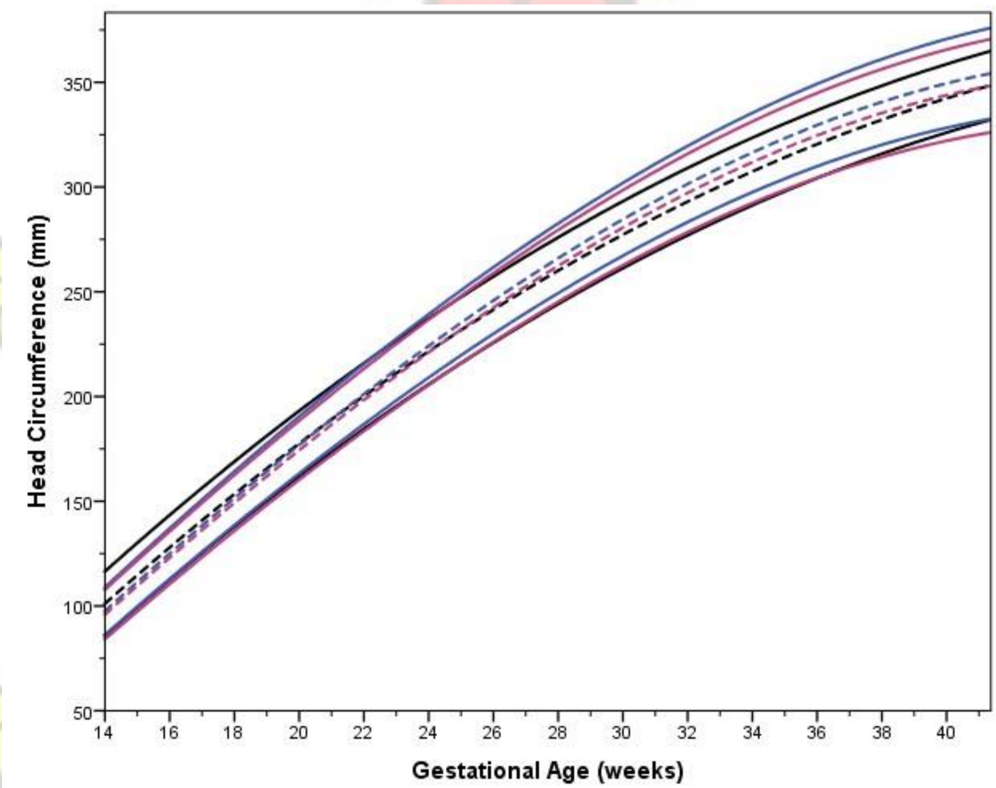

Figure 21: Comparison of the 5th, 50th and 95th centiles for head circumference in the present study (black lines) with Chitty *et al*. (1994a) (plotted: blue lines; derived: pink lines). The dashed lines represent the 50th centile.

4.5 CORRELATION AND LINEAR REGRESSION ANALYSIS BETWEEN FOETAL PARAMETERS

There was a very strong positive correlation between foetal parameters: biparietal diameter (BPD), head circumference (HC), femur length (FL) and abdominal circumference (AC) (Table 14). A stronger correlation was observed in the second trimester than in the third trimester. Pearson's correlation coefficient between each pairwise combination of the measured sonographic parameters in the second trimester was high, ranging from r = 0.969 between AC and BPD, r = 0.977 between FL and BPD, r = 0.980 between FL and AC, r = 0.983 between BPD and HC and also between AC and HC to r = 0.989 between FL and HC (all correlations yielded P < 0.01). In the third trimester, Pearson's correlation coefficient between each pairwise combination of foetal parameters ranged from r = 0.880 between FL and HC, r = 0.869 between FL and BPD, r = 0.892 between AC and BPD, r = 0.894 between AC and HC, r = 0.900 between FL and AC to r = 0.951 between HC and BPD (all correlations yielded P < 0.01). Table 14: Pearson's Correlation between Foetal Parameters

		Biparietal diameter	Head circumference	Abdominal circumference	Femur length
Biprietal Diameter		1			
		1			
Head Circumference	**r2**	0.983^{**}	1		
	r3	0.951^{**}	1		
Abdominal Circumference	**r2**	0.969^{**}	0.983^{**}	1	
	r3	0.892^{**}	0.894^{**}	1	
Femur length	**r2**	0.977^{**}	0.989^{**}	0.980^{**}	1
	r3	0.869^{**}	0.880^{**}	0.900^{**}	1

r2 = coefficient of correlation in the second trimester; **r3** = coefficient of correlation in the third trimester; **= Significant level (p < 0.01).

Table 15 shows the regression equations for predicting the value of an unknown foetal measurement when of one foetal parameter is known. The best regression equation is the equation with the largest adjusted coefficient of determination (R^2) and the smallest standard error of the estimate (SEE). Based on this the second trimester equations could predict better the values of an unknown measurement in the second trimester than their corresponding third trimester equations. The FL could explain the prediction of a foetus's BPD by 95.3% with SEE of just 3.00 mm in the second trimester. In the third trimester the R^2 reduced to 77.1% and the SEE increased to 3.59 mm. The HC could also explain the prediction of a foetus's BPD by 96.6% with SEE of just 2.54 mm in the second trimester. In the third trimester the R^2 reduced to 90.4% and the SEE decreased to 2.32 mm.

Table 15: Regression Equations for Predicting Measurements between Foetal Parameters

Trimester	**Regression equation (mm)**	**SEE (mm)**	**R^2**
Second	BPD = 12.310 + 1.070 FL	3.00	0.953*
	HC = 41.770 + 4.072 FL	7.81	0.977*
	BPD = 1.522 + 0.262 HC	2.54	0.966*

	$AC = 24.823 + 3.886\ FL$	10.15	0.959*
	$AC = -13.682 + 0.947\ HC$	9.19	0.966*
	$AC = -13.551 + 3.508\ BPD$	12.44	0.938*
Third	$BPD = -55.011 + 3.388\ FL - 0.019\ FL^2$	3.59	0.771*
	$HC = -210.451 + 12.96\ FL - 0.076\ FL^2$	11.15	0.800*
	$BPD = -4.136 + 0.286\ HC$	2.32	0.904*
	$AC = -274.051 + 12.992\ FL - 0.063\ FL^2$	16.83	0.815*
	$AC = -126.934 + 1.401\ HC$	17.57	0.798*
	$AC = -534.509 + 15.535\ BPD - 0.065\ BPD^2$	17.30	0.802*
Both Second and Third	$BPD = 7.120 + 1.353\ FL - 0.003\ FL^2$	3.64	0.963*
	$HC = 17.829 + 5.477\ FL - 0.016\ FL^2$	11.29	0.972*
	$BPD = -0.952 + 0.276\ HC$	2.43	0.983*
	$AC = 29.511 + 3.322\ FL + 0.012\ FL^2$	15.59	0.963*
	$AC = 35.018 + 0342\ HC + 0.002\ HC^2$	15.60	0.963*
	$AC = -45.305 + 4.166\ BPD$	17.18	0.955*

BPD = Biparietal diameter; **HC** = Head circumference; **AC** = Abdominal circumference; **FL** = Femur length; **mm** = Millimeters; **R^2 =** Adjusted coefficient of determination; *= Significant level ($p < 0.0001$); **SEE** = Standard error of the estimate.

4.6 REGRESSION EQUATIONS FOR ULTRASOUND DATING

Table 16 shows the regression equations for the mean and the standard deviation (SD) for each foetal biometric measurement as a function of gestational age. Except for the abdominal circumference (AC) where a linear model was the best fit, a quadratic model was the best fit for the crown-rump length (CRL), biparietal diameter (BPD), head circumference (HC) and femur length (FL). The standard deviations across gestation were regressed using a linear model. Each parameter recorded a high adjusted coefficient of determination (R^2). The values of R^2 were 0.973, 0.968, 0.968, 0.967 and 0.903 for HC, FL, BPD, AC and CRL respectively.

Table 16: Regression Equations for the Mean and Standard Deviation of each Measurement based on Gestational Age in Exact Weeks.

Foetal biometry (mm)	**GA (weeks)**	**Regression equation**	**R^2**
CRL	Mean	$6.188 + 0.1252\ CRL - 0.000428\ CRL^2$	0.903^{**}
	SD	$0.47 + 0.00339\ CRL$	
BPD	Mean	$7.153 + 0.206\ BPD + 0.00139\ BPD^2$	0.968^{**}
	SD	$0.393 + 0.012\ BPD$	
HC	Mean	$9.549 + 0.029\ HC + 0.000166\ HC^2$	0.973^{**}
	SD	$0.07 + 0.00417\ HC$	
AC	Mean	$6.532 + 0.091\ AC$	0.967^{**}
	SD	$0.4 + 0.00351\ AC$	
FL	Mean	$8.686 + 0.315\ FL + 0.0011\ FL^2$	0.968^{**}
	SD	$0.75 + 0.00991\ FL$	

CRL = Crown rump-length; **BPD** = Biparietal Diameter; **HC** = Head Circumference; **AC** = Abdominal Circumference; **FL** = Femur Length; **GA** = Gestational Age; **SD** = Standard Deviation; **R^2 =** Adjusted coefficient of determination; ******= Significant level ($p < 0.0001$).

Tables 18–23 show the 5th, 50th and 95th gestational age centiles for each foetal biometric measurement and the 'uncertainty' of predictions (the difference in days between the 50th centile and the 95th centile) for a given foetal size. Table 17 shows the gestational age (weeks + days) of crown-rump length (CRL) within a range of 4 to 80 mm. Gestational age using first trimester CRL increased from 6 weeks 5 days with CRL of 4 mm to

13 weeks 2 days with CRL of 80 mm. The error in predicting gestational age using CRL was ± 5 days and this was constant throughout the range of measurements.

Table 17: Gestational age Assessed by Crown-Rump Length (CRL)

CRL	Gestational Age (weeks + days)			Uncertainty	CRL	Gestational Age (weeks + days)			Uncertainty
(mm)	50th	5th	95th	(± days)	(mm)	50th	5th	95th	(± days)
4	6 + 5	5 + 6	7 + 3	5	**44**	10 + 6	10 + 1	11 + 5	5
6	6 + 6	6 + 1	7 + 5	5	**46**	11 + 0	10 + 2	11 + 6	5
8	7 + 1	6 + 3	8 + 0	5	**48**	11 + 1	10 + 3	12 + 0	5
10	7 + 3	6 + 4	8 + 1	5	**50**	11 + 3	10 + 4	12 + 1	5
12	7 + 4	6 + 6	8 + 3	5	**52**	11 + 4	10 + 5	12 + 2	5
14	7 + 6	7 + 1	8 + 4	5	**54**	11 + 5	10 + 6	12 + 3	5
16	8 + 1	7 + 2	8 + 6	5	**56**	11 + 6	11 + 1	12 + 4	5
18	8 + 2	7 + 4	9 + 1	5	**58**	12 + 0	11 + 2	12 + 6	5
20	8 + 4	7 + 5	9 + 2	5	**60**	12 + 1	11 + 3	13 + 0	5
22	8 + 5	8 + 0	9 + 4	5	**62**	12 + 2	11 + 4	13 + 1	5
24	9 + 0	8 + 1	9 + 5	5	**64**	12 + 3	11 + 5	13 + 2	5
26	9 + 1	8 + 3	10 + 0	5	**66**	12 + 4	11 + 6	13 + 3	5
28	9 + 3	8 + 4	10 + 1	5	**68**	12 + 5	12 + 0	13 + 3	5
30	9 + 4	8 + 5	10 + 2	5	**70**	12 + 6	12 + 1	13 + 4	5
32	9 + 5	9 + 0	10 + 4	5	**72**	13 + 0	12 + 1	13 + 5	5
34	10 + 0	9 + 1	10 + 5	5	**74**	13 + 1	12 + 2	13 + 6	5
36	10 + 1	9 + 3	10 + 6	5	**76**	13 + 2	12 + 3	14 + 0	5
38	10 + 2	9 + 4	11 + 1	5	**78**	13 + 2	12 + 4	14 + 1	5
40	10 + 4	9 + 5	11 + 2	5	**80**	13 + 3	12 + 5	14 + 2	5
42	10 + 5	9 + 6	11 + 3	5					

Table 18 shows the gestational age estimates of biparietal diameter (BPD) from 26 to 98 mm. The estimated gestational age with BPD of 26 mm was found to be 13 weeks 3 days with a prediction error of ± 8 days. The error in prediction increased to ± 13 days at 23 weeks 5 days (BPD = 58 mm), reaching ± 18 days at 40 weeks 5 days (BPD = 98 mm).

Table 18: Gestational age Assessed by Biparietal Diameter (BPD)

BPD (mm)	Gestational Age (weeks + days) 50th	5th	95th	Uncertainty (± days)	BPD (mm)	Gestational Age (weeks + days) 50th	5th	95th	Uncertainty (± days)
26	13 + 3	12 + 2	14 + 4	8	**64**	26 + 0	24 + 1	28 + 0	13
28	14 + 0	12 + 6	15 + 1	8	**66**	26 + 6	24 + 6	28 + 5	14
30	14 + 4	13 + 2	15 + 6	9	**68**	27 + 4	25 + 4	29 + 4	14
32	15 + 1	13 + 6	16 + 3	9	**70**	28 + 3	26 + 2	30 + 3	14
34	15 + 5	14 + 3	17 + 1	9	**72**	29 + 1	27 + 1	31 + 2	14
36	16 + 3	15 + 0	17 + 5	9	**74**	30 + 0	27 + 6	32 + 1	15
38	17 + 0	15 + 4	18 + 3	10	**76**	30 + 6	28 + 5	33 + 0	15
40	17 + 4	16 + 1	19 + 0	10	**78**	31 + 5	29 + 3	33 + 6	15
42	18 + 2	16 + 5	19 + 5	10	**80**	32 + 4	30 + 2	34 + 5	16
44	18 + 6	17 + 3	20 + 3	11	**82**	33 + 3	31 + 1	35 + 5	16
46	19 + 4	18 + 0	21 + 1	11	**84**	34 + 2	31 + 7	36 + 4	16
48	20 + 2	18 + 5	21 + 6	11	**86**	35 + 1	32 + 6	37 + 3	16
50	20 + 6	19 + 2	22 + 4	11	**88**	36 + 0	33 + 5	38 + 3	17
52	21 + 4	20 + 0	23 + 2	12	**90**	33 + 0	34 + 4	39 + 3	17
54	22 + 2	20 + 4	24 + 0	12	**92**	37 + 6	35 + 3	40 + 2	17
56	23 + 0	21 + 2	24 + 6	12	**94**	38 + 6	36 + 2	41 + 2	18
58	23 + 5	22 + 0	25 + 4	13	**96**	39 + 5	37 + 1	42 + 2	18
60	24 + 4	22 + 5	26 + 2	13	**98**	40 + 5	38 + 1	43 + 2	18
62	25 + 2	23 + 3	27 + 1	13					

In Table 19, the range at which gestational age using HC could be determined from the present study was 100 to 350 mm. The error in predicting the gestational age increased from ± 6 days at 14 weeks 1 day (HC = 100 mm) to ± 11 days at 24 weeks (HC = 220 mm). It then increased gradually to ± 18 days at 40 weeks (HC = 350 mm).

Table 19: Gestational age Assessed by Head Circumference (HC)

HC (mm)	Gestational Age (weeks + days) 50th	5th	95th	Uncertainty (± days)	HC (mm)	Gestational Age (weeks + days) 50th	5th	95th	Uncertainty (± days)
100	[illegible]	[illegible]	[illegible]	[illegible]	**235**	25 + 4	23 + 6	27 + 2	12
105	14 + 3	13 + 4	15 + 2	6	**240**	26 + 0	24 + 2	27 + 6	12
110	14 + 5	13 + 6	15 + 4	6	**245**	26 + 4	24 + 6	28 + 3	13
115	15 + 1	14 + 1	16 + 0	6	**250**	27 + 1	25 + 2	29 + 0	13
120	15 + 3	14 + 3	16 + 3	7	**255**	27 + 5	25 + 6	29 + 4	13
125	15 + 5	14 + 6	16 + 5	7	**260**	28 + 2	26 + 3	30 + 1	13
130	16 + 1	15 + 1	17 + 1	7	**265**	28 + 6	27 + 0	30 + 6	14
135	16 + 3	15 + 3	17 + 4	7	**270**	29 + 3	27 + 4	31 + 3	14
140	16 + 6	15 + 6	18 + 0	8	**275**	30 + 1	28 + 1	32 + 1	14
145	17 + 2	16 + 1	18 + 2	8	**280**	30 + 5	28 + 5	32 + 5	14
150	17 + 4	16 + 3	18 + 5	8	**285**	31 + 2	29 + 2	33 + 3	14
155	18 + 0	16 + 6	19 + 1	8	**290**	31 + 6	29 + 6	34 + 0	15
160	18 + 3	17 + 2	19 + 5	8	**295**	32 + 4	30 + 3	34 + 5	15
165	18 + 6	17 + 4	20 + 1	9	**300**	33 + 1	31 + 0	35 + 3	15
170	19 + 2	18 + 0	20 + 4	9	**305**	33 + 6	31 + 4	36 + 0	15
175	19 + 5	18 + 3	21 + 0	9	**310**	34 + 3	32 + 2	36 + 5	16
180	20 + 1	18 + 6	21 + 3	9	**315**	35 + 1	32 + 6	37 + 3	16
185	20 + 4	19 + 1	22 + 0	10	**320**	35 + 6	33 + 4	38 + 1	16
190	21 + 0	19 + 4	22 + 3	10	**325**	36 + 4	34 + 1	38 + 6	16
195	21 + 4	20 + 0	23 + 0	10	**330**	37 + 1	34 + 6	39 + 4	17
200	22 + 0	20 + 4	23 + 3	10	**335**	37 + 6	35 + 3	40 + 2	17
205	22 + 3	21 + 0	24 + 0	11	**340**	38 + 4	36 + 1	41 + 0	17
210	23 + 0	21 + 3	24 + 4	11	**345**	39 + 2	36 + 6	41 + 6	17
215	23 + 3	21 + 6	25 + 0	11	**350**	40 + 0	37 + 4	42 + 4	18
220	24 + 0	22 + 2	25 + 4	11					
225	24 + 3	22 + 6	26 + 1	12					
230	25 + 0	23 + 2	26 + 5	12					

For abdominal circumference (AC), the range of measurements for GA estimation was 80-390 mm (Table 20). The prediction error increased slowly from ± 8 days at week 14 to ± 12 days at 23 weeks' of gestation. By week 40 the error had reached ± 20 days.

Table 20: Gestational age Assessed by Abdominal Circumference (AC)

AC (mm)	Gestational Age (weeks + days)			Uncertainty (± days)	AC (mm)	Gestational Age (weeks + days)			Uncertainty (± days)
	50th	5th	95th			50th	5th	95th	
80	13 + 6	12 + 5	15 + 0	8	**245**	28 + 6	26 + 5	30 + 6	15
85	14 + 2	13 + 1	15 + 3	8	**250**	29 + 2	27 + 1	31 + 3	15
90	14 + 5	13 + 4	15 + 6	8	**255**	29 + 5	27 + 4	31 + 6	15
95	15 + 1	14 + 0	16 + 3	8	**260**	30 + 1	28 + 0	32 + 2	15
100	15 + 4	14 + 3	16 + 6	9	**265**	30 + 5	28 + 3	32 + 6	15
105	16 + 1	14 + 6	17 + 2	9	**270**	31 + 1	28 + 6	33 + 2	16
110	16 + 4	15 + 2	17 + 6	9	**275**	31 + 4	29 + 2	33 + 6	16
115	17 + 0	15 + 5	18 + 2	9	**280**	32 + 0	29 + 5	34 + 2	16
120	17 + 3	16 + 1	18 + 6	9	**285**	32 + 3	30 + 1	34 + 5	16
125	17 + 6	16 + 4	19 + 2	10	**290**	32 + 6	30 + 4	35 + 2	16
130	18 + 3	17 + 0	19 + 5	10	**295**	33 + 3	31 + 0	35 + 5	17
135	18 + 6	17 + 3	20 + 2	10	**300**	33 + 6	31 + 3	36 + 2	17
140	19 + 2	17 + 6	20 + 5	10	**305**	34 + 2	31 + 6	36 + 5	17
145	19 + 5	18 + 2	21 + 2	10	**310**	34 + 5	32 + 2	37 + 1	17
150	20 + 1	18 + 5	21 + 5	11	**315**	35 + 1	32 + 5	37 + 5	17
155	20 + 4	19 + 1	22 + 1	11	**320**	35 + 5	33 + 1	38 + 1	18
160	21 + 1	19 + 4	22 + 5	11	**325**	36 + 1	33 + 4	38 + 4	18
165	21 + 4	20 + 0	23 + 1	11	**330**	36 + 4	34 + 0	39 + 1	18
170	22 + 0	20 + 3	23 + 4	11	**335**	37 + 0	34 + 3	39 + 4	18
175	22 + 3	20 + 6	24 + 1	12	**340**	37 + 3	34 + 6	40 + 1	18
180	22 + 6	21 + 2	24 + 4	12	**345**	37 + 6	35 + 2	40 + 4	19
185	23 + 3	21 + 4	25 + 1	12	**350**	38 + 3	35 + 5	41 + 0	19
190	23 + 6	22 + 0	25 + 4	12	**355**	38 + 6	36 + 1	41 + 4	19
195	24 + 2	22 + 3	26 + 0	12	**360**	39 + 2	36 + 4	42 + 0	19
200	24 + 5	22 + 6	26 + 4	13	**365**	39 + 5	37 + 0	42 + 4	19
205	25 + 1	23 + 2	27 + 0	13	**370**	40 + 1	37 + 3	43 + 0	20
210	25 + 4	23 + 5	27 + 4	13	**375**	40 + 5	37 + 6	43 + 3	20
215	26 + 1	24 + 1	28 + 0	13	**380**	41 + 1	38 + 2	44 + 0	20
220	26 + 4	24 + 4	28 + 3	13	**385**	41 + 4	38 + 5	44 + 3	20

225	27 + 0	25 + 0	29 + 0	14	**390**	42 + 0	39 + 1	45 + 0	20
230	27 + 3	25 + 3	29 + 3	14					
235	27 + 6	25 + 6	30 + 0	14					
240	28 + 3	26 + 2	30 + 3	14					

The uncertainty in estimating gestational age using the femur length (FL) was initially high (± 10 days) but increased gradually to ± 18 days by week 40 (Table 21). The range for gestational estimation for FL in the present study was 11-82 mm.

Table 21: Gestational age Assessed by Femur Length (FL)

FL	**Gestational Age (weeks + days)**			**Uncertainty**	**FL**	**Gestational Age (weeks + days)**			**Uncertainty**
(mm)	**50th**	**5th**	**95th**	**(± days)**	**(mm)**	**50th**	**5th**	**95th**	**(± days)**
11	12 + 2	10 + 6	13 + 5	10	**47**	25 + 6	23 + 6	27 + 6	14
13	13 + 0	11 + 4	14 + 3	10	**49**	26 + 5	24 + 5	28 + 6	14
15	13 + 5	12 + 1	15 + 1	10	**51**	27 + 4	25 + 4	29 + 5	14
17	14 + 3	12 + 6	15 + 6	11	**53**	28 + 3	26 + 3	30 + 4	15
19	15 + 0	13 + 4	16 + 4	11	**55**	29 + 2	27 + 1	31 + 3	15
21	15 + 6	14 + 1	17 + 3	11	**57**	30 + 2	28 + 0	32 + 3	15
23	16 + 4	14 + 6	18 + 1	11	**59**	31 + 1	28 + 6	33 + 2	15
25	17 + 2	15 + 4	18 + 6	11	**61**	32 + 0	29 + 5	34 + 2	16
27	18 + 0	16 + 2	19 + 5	12	**63**	32 + 6	30 + 4	35 + 1	16
29	18 + 5	17 + 0	20 + 3	12	**65**	33 + 6	31 + 4	36 + 1	16
31	19 + 4	17 + 5	21 + 2	12	**67**	34 + 5	32 + 3	37 + 0	16
33	20 + 2	18 + 4	22 + 0	12	**69**	35 + 5	33 + 2	38 + 0	17
35	21 + 0	19 + 2	22 + 6	13	**71**	36 + 4	34 + 1	39 + 0	17
37	21 + 6	20 + 0	23 + 5	13	**73**	37 + 4	35 + 1	40 + 0	17
39	22 + 5	20 + 5	24 + 4	13	**75**	38 + 3	36 + 0	41 + 0	17
41	23 + 3	21 + 4	25 + 2	13	**77**	39 + 3	37 + 0	42 + 0	17
43	24 + 2	22 + 2	26 + 1	14	**79**	40 + 3	37 + 6	43 + 0	18
45	25 + 1	23 + 1	27 + 0	14	**81**	41 + 3	38 + 6	44 + 0	18
					82	41 + 6	39 + 2	44 + 3	18

Table 22 compares the prediction error at specific range of gestations. The prediction error increased for each parameter throughout gestation. Head circumference (HC) recorded the lowest prediction error throughout gestation. The error in predicting HC was ± 6.8 days between 12-18 weeks, and this increased to ± 17.1 days from 36-41 weeks. Up to week 23, the prediction errors of HC, AC, BPD and FL were ± 8.3 days, ± 9.9 days, ± 10.3 days and ± 11.7 days respectively. Though AC was a better predictor than FL up to week 29, this was not so in late gestational period (36-41 weeks).

Table 22: Prediction error (in days) at Specific range of Gestations

Measurement	Weeks of gestation				
	12-18	**18-24**	**24-30**	**30-36**	**36-41**
Biparietal diameter (BPD)	9.1	11.4	13.6	15.6	17.4
Head circumference (HC)	6.8	9.7	12.6	15.1	17.1
Abdominal circumference (AC)	8.7	11.1	13.7	16.3	18.8
Femur length (FL)	10.7	12.6	14.3	15.8	17.2

4.7 CORRELATION BETWEEN GESTATIONAL AGE AND FOETAL PARAMETERS

There was a strong positive correlation between gestational age and the crown-rump length with correlation coefficient (r) of 0.948 ($p < 0.001$). Table 23 shows Pearson's correlation between gestational age and abdominal circumference (AC), biparietal diameter (BPD), head circumference (HC) and femur length (FL) in the second and third trimesters of pregnancy. Correlations between gestational age and foetal parameters were stronger in the second trimester than in the third trimester. In the second trimester, HC correlated strongly with gestational age with correlation coefficient (r) of 0.983, followed by FL (r = 0.979), AC (r = 0.975) and then BPD (r = 0.969). The correlation coefficient between gestational age and foetal parameters in the third trimester showed that the best correlation was still HC (r = 0.918), followed by BPD (r = 0.916) and the least correlation was AC (r = 0.913). When both the second and third trimesters were considered, the correlation coefficients (r) were 0.984, 0.983, 0.982 and 0.982 for AC, FL, BPD and HC respectively.

Table 23: Pearson's Correlation between Gestational Age and Foetal Parameters.

Foetal Parameter (mm)	**Second trimester (N = 55)** r	**Third trimester (N = 117)** r	**Both second and third trimesters** r
BPD	0.969**	0.916**	0.982**
HC	0.983**	0.918**	0.982**
AC	0.975**	0.913**	0.984**
FL	0.979**	0.914**	0.983**

** = Correlation is significant ($p < 0.01$); **r** = coefficient of correlation; **BPD** = Biparietal diameter; **HC** = Head circumference; **AC** = Abdominal circumference; **FL** = Femur length

4.8 STEPWISE MULTIPLE REGRESSION ANALYSIS FOR GESTATIONAL AGE PREDICTION

Table 24 shows regression equations for predicting gestational age using individual parameters and the combinations of parameters in the second and third trimesters of pregnancy. The best equation for estimating gestation age is the one with the highest adjusted coefficient of determination (R^2) and the lowest standard error of the estimate (SEE). In the second trimester, the best equation was the one involving head circumference (HC) alone with an R^2 of 0.966. This was followed by the formula involving femur length (FL) alone, abdominal circumference (AC) alone and then biparietal diameter (BPD) alone with R^2 of 0.958, 0.949 and 0.938 respectively. Combinations of FL and AC yielded an R^2 of 0.964, which was slightly better than using FL, AC and BPD alone. In the third trimester however, although HC was still the best parameter in estimating gestational age with R^2 of 84.1%, AC was the least with R^2 of 83.1%. The biparietal diameter with R^2 of 83.7% was slightly higher than FL with R^2 of 83.5%. Addition of FL to HC explained an additional 5% of variation in gestational age. Also, the addition of AC to HC and FL increased the R^2 by 1%. Combinations of HC, FL and AC therefore accounted for 90.0% of the variance in gestational age estimation. The best regression equation involving three predictor variables (BPD, FL and AC) accounted for 90.5% of the variance in gestational age estimation.

When both the second and third trimesters were considered, the R^2 for each regression equation was higher compared to the equations in the third trimester. The abdominal circumference (AC) significantly predicted gestational age and accounted for 96.7% of the explained variance in gestational age when all other variables remained constant. The biparietal diameter (BPD) explained an additional 1% of variation in gestational age whereas the addition of FL to AC and BPD explained an additional 0.3% of the variance. Together the AC, BPD and FL accounted for 97.9% of the variance in gestational age estimation with SEE of 1.09 weeks. When the BPD was replaced with HC, the R^2 was still 97.9%. However the SEE slightly reduced by 1.08 weeks.

Table 24: Stepwise Multiple Regression Analysis for Predicting Gestational Age

Trimester	Regression equation (mm)	SEE (weeks)	R^2
Second	GA = 4.952 + 0.087 HC	0.84	0.966*
	GA = 7.617 + 0.220 FL + 0.035 AC	0.87	0.964*
	GA = 8.485 + 0.356 FL	0.94	0.958*
	GA = 6.593 + 0.089 AC	1.03	0.949*
	GA = 4.961 + 0.322 BPD	1.14	0.938*
Third	GA = -4.053 + 0.125 HC	1.36	0.841*
	GA = -0.207 + 0.414 BPD	1.38	0.837*
	GA = 7.318 + 0.413 FL	1.39	0.835*
	GA = 10.239 + 0.080 AC	1.40	0.831*
	GA = -0.671 + 0.069 HC + 0.214 FL	1.13	0.891*
	GA = 1.285 + 0.052 HC + 0.153 FL + 0.023 AC	1.08	0.900*
	GA = 1.221 + 0.109 BPD + 0.147 FL + 0.020 AC	1.05	0.905*
Second and third	GA = 6.532 + 0.091 AC	1.35	0.967*
	GA = 6.486 + 0.423 FL	1.37	0.966*
	GA = 1.774 + 0389 BPD	1.42	0.964*
	GA = 1.240 + 0.108 HC	1.43	0.963*
	GA = 4.691 + 0.121 BPD + 0.035 AC + 0.133 FL	1.08	0.979*
	GA = 4.637 + 0.032 HC + 0.038 AC + 0.127 FL	1.09	0.979*
	GA = 3.799 + 0.050 HC + 0.050 AC	1.14	0.977*

GA = 4.023 + 0.050 AC + 0.182 BPD	1.14	0.977*
GA = 6.266 + 0.209 FL + 0.047 AC	1.15	0.976*
GA = 4.012 + 0.184 BPD + 0.227 FL	1.19	0.975*
GA = 3.878 + 0.050 HC + 0.233 FL	1.23	0.973*

BPD = Biparietal diameter; **HC** = Head circumference; **AC** = Abdominal circumference; **FL** = Femur length; **GA** = Gestational age; **R^2 =** Adjusted coefficient of determination; *****= Significant level ($p < 0.0001$); **SEE** = Standard error of the estimate.

4.9 COMPARISON OF DATING CHARTS FOR THE PRESENT STUDY WITH OTHER PUBLISHED CHARTS

Figure 22 shows a comparison of gestational age estimates of the crown-rump length (CRL) at the 50th centile in the present study with the dating charts from Robinson and Fleming (1975), Hadlock *et al.* (1992) and Sahota *et al.* (2009). In comparisons with the three CRL dating charts, the present study overestimated gestational age during early CRL measurements but underestimated gestational age for CRL greater than 21 mm. Robinson and Fleming (1975) and Hadlock *et al.* (1992) charts gave a 3-day underestimation whereas Sahota *et al.* (2009) chart gave a 1-day underestimation of gestational age for CRL measuring 8 mm. All the three dating charts gave a 2-day overestimation for CRL between 50-70 mm. However, for CRL between 4-6 mm, the dating chart of the present study overestimated gestational age on the average by 6 days, 4 days and 3.5 days in comparision with the dating charts of Robinson and Fleming (1975), Hadlock *et al.* (1992) and Sahota *et al.* (2009) respectively.

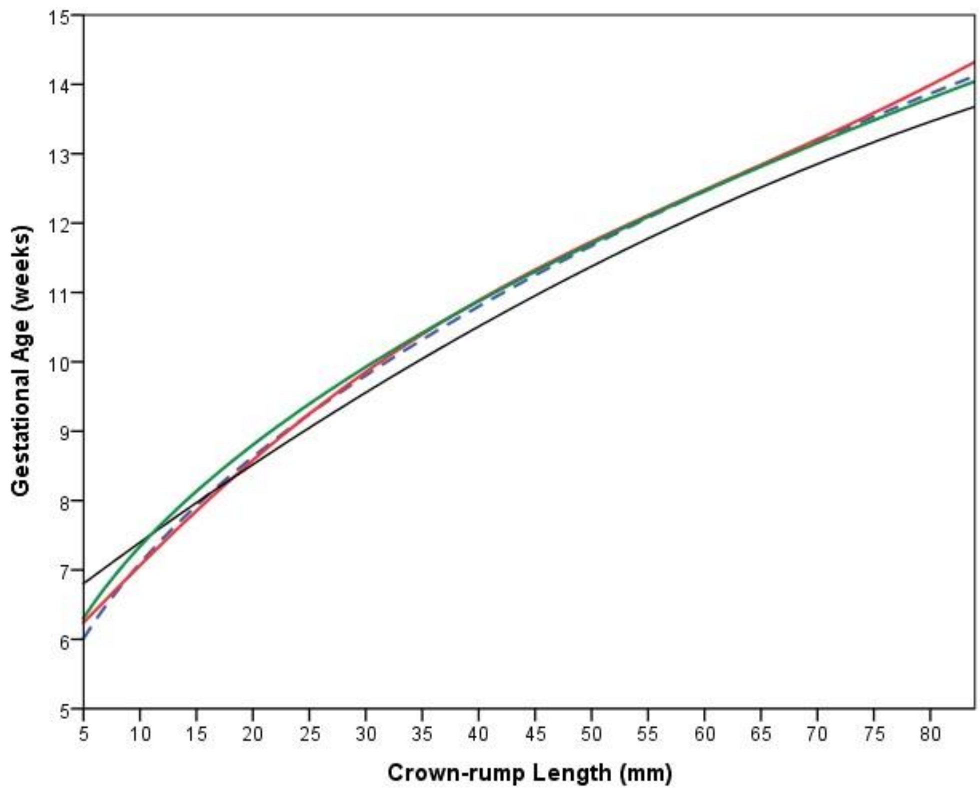

Figure 22: Comparison of the 50th centile for crown-rump length in the present study (solid black line) with Robinson and Fleming (1975) (dashed blue line), Hadlock *et al.* (1984a) (solid red line) and Sahota *et al.* (2009) (solid green line).

The chart for dating using BPD in the present study was compared with those of Hadlock *et al.* (1982d), Hadlock *et al.* (1984a), Altman and Chitty (1997) and Leung *et al.* (2008) (Figure 23). In comparisons between the gestational ages of the present study and the gestational age estimates from the reference equations of Altman and Chitty (1997) (outerinner), the present study underestimated GA by 4 to 5 days for BPD less than 39 mm but overestimated gestational age by 4 to 9 days for BPD > 76 mm. The BPD dating chart of the present study was nearly the same as the dating chart of Altman and Chitty (1997) (outer-outer) with a difference of ± 1 day up to BPD of 42 mm. However, for BPD greater than 42 mm, the present study overestimated gestational age significantly, reaching a difference of more than 2 weeks for BPD above 86 mm (this corresponds to GA of

35 weeks 1 day). The dating chart of the present study was very close to Hadlock *et al.* (1982d) chart than with Hadlock *et al.* (1984a) chart. Hadlock *et al.* (1982d) overestimated GA by maximum of 3 days for BPD less than 42 mm, thereafter the difference was just -2 to 0 days. Hadlock *et al.* (1984a) chart however overestimated GA by more than 3 days (BPD < 46 mm) reaching 1 week at early second trimester but underestimated GA by 3-4 days for BPD > 76 mm in comparison with the present study. The difference between the dating curve of the present study and the Chinese curve by Leung *et al.* (2008) was almost similar to the difference between the dating curve of the present study and Hadlock *et al.* (1984a) curve. In the second trimester of pregnancy, the difference was slightly smaller with Leung *et al.* (2008) chart than with Hadlock *et al.* (1984a) chart.

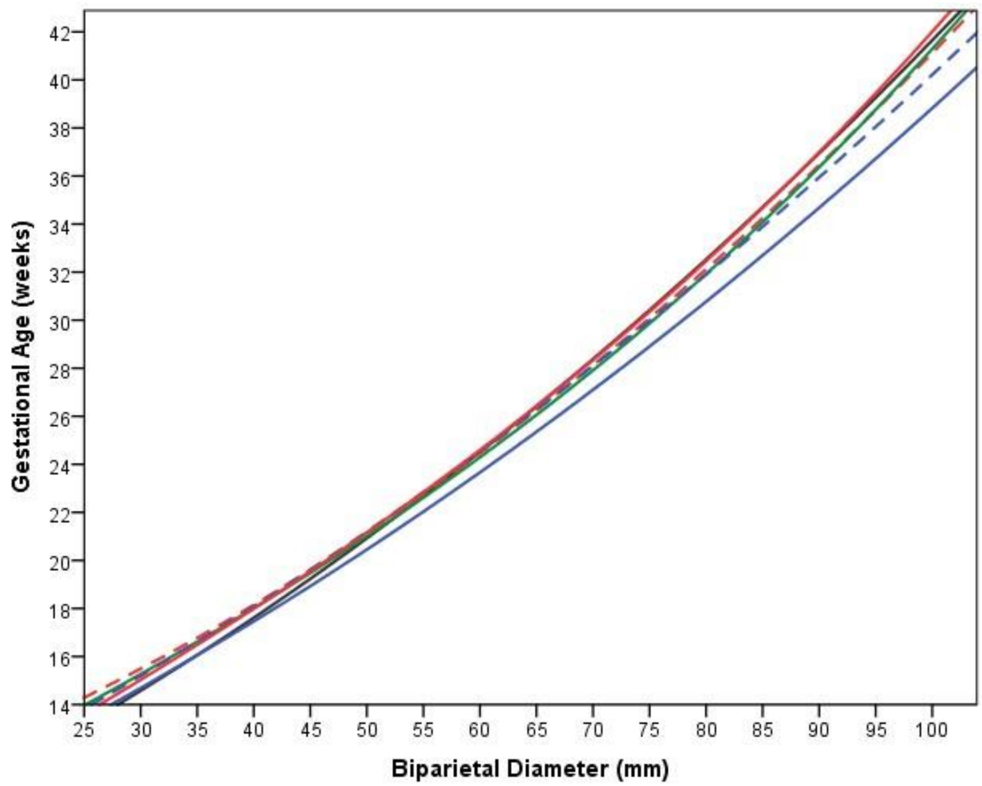

Figure 23: Comparison of the 50th centile for biparietal diameter (outer-inner) derived in the present study (black) with Hadlock *et al.* (1982d) (solid red line), Hadlock *et al.* (1984a) (dashed red line), Altman and Chitty (1997) (outer-inner: dashed blue line; outer-inner: solid blue line) and Leung *et al.* (2008) (solid green line).

The dating chart for head circumference (HC) in the present study was also compared with charts from Hadlock *et al.* (1982a), Hadlock *et al*. (1984a), Altman and Chitty (1997) and Leung *et al*. (2008) as shown in figure 24. Both Hadlock *et al.* (1982a) and Hadlock *et al.* (1984a) curves were nearly the same as the present study with ± 2 days difference except for HC less than 155 mm where there was constant 3 days overestimation of GA in comparison with the present study. Hadlock *et al.* (1982a) curve was comparatively closer to the present study than with Hadlock *et al.* (1984a) except HC between 210-320 mm. In comparison with the British chart by Altman and Chitty (1997) where the HC was measured by tracing around the perimeter, the present study underestimated gestational age by a maximum difference of 3 days for HC between 110-195 mm. In the late second to mid-third trimesters however, the present study overestimated gestational age by 5 to 9 days for HC between 240-330 mm corresponding to 26 weeks 2 days to 37 weeks 5 days. A similar trend was observed when the present study was compared with Altman and Chitty's HC chart (1997) where the HC was derived from the measurements of the occipital-frontal diameter (OFD) and the BPD (outer-outer) using the formula: π (OFD + BPD)/2. However, the present study underestimated GA by up to 4 days and overestimated GA by up to 6 days for the same range in which the HC was measured by tracing around the perimeter of the outer calvaria.

In comparison with the Chinese chart (Leung *et al*., 2008), the present study underestimated GA throughout gestation except HC values between 260 to 285 mm where there were no difference. The maximum observed underestimation was 3 days, except for HC values less than 195 mm and above 325 mm where a 4 to 6 days underestimation was seen. In comparisons with all the reference charts, the present study agreed best with the British chart for HC less than 120 mm.

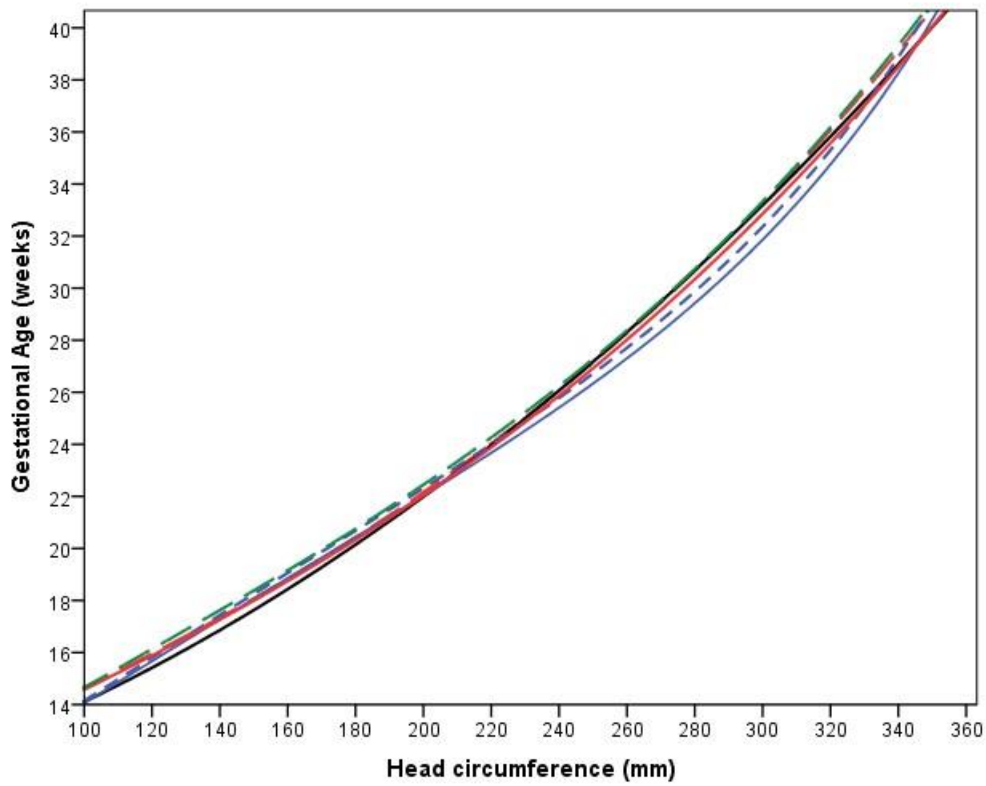

Figure 24: Comparison of the 50th centile for head circumference derived in the present study (solid black line) with Hadlock *et al*. (1982a) (solid red line), Hadlock *et al*. (1984a) (dashed red line), Altman and Chitty (1997) (HC measured-solid blue line; HC derived-dashed blue line) and Leung *et al.* (2008) (dashed green line).

Figure 25 shows the dating chart for abdominal circumference (AC) based on the present study in comparison with the charts from Hadlock *et al*. (1982b) and Hadlock *et al*. (1984a). Except for AC less than 120 mm, the gestational age estimates of the present study were very close to Hadlock *et al*. (1984a) chart than with Hadlock *et al*. (1982b) chart. A ± 2 days difference in gestational age was observed between the present study and Hadlock *et al*. (1982b) chart for AC less than 315 mm, that is, up to 35 weeks.

Thereafter the present study increasingly underestimated GA up to term by 3 - 11 days.

A similar trend was observed when the present study was compared with Hadlock *et al*.

(1984a) chart. However, for AC less than 105 mm there was 3-4 days underestimation and a significant but slightly lower underestimation towards term by Hadlock *et al*.

(1984a) compared to Hadlock *et al*. (1982b) chart.

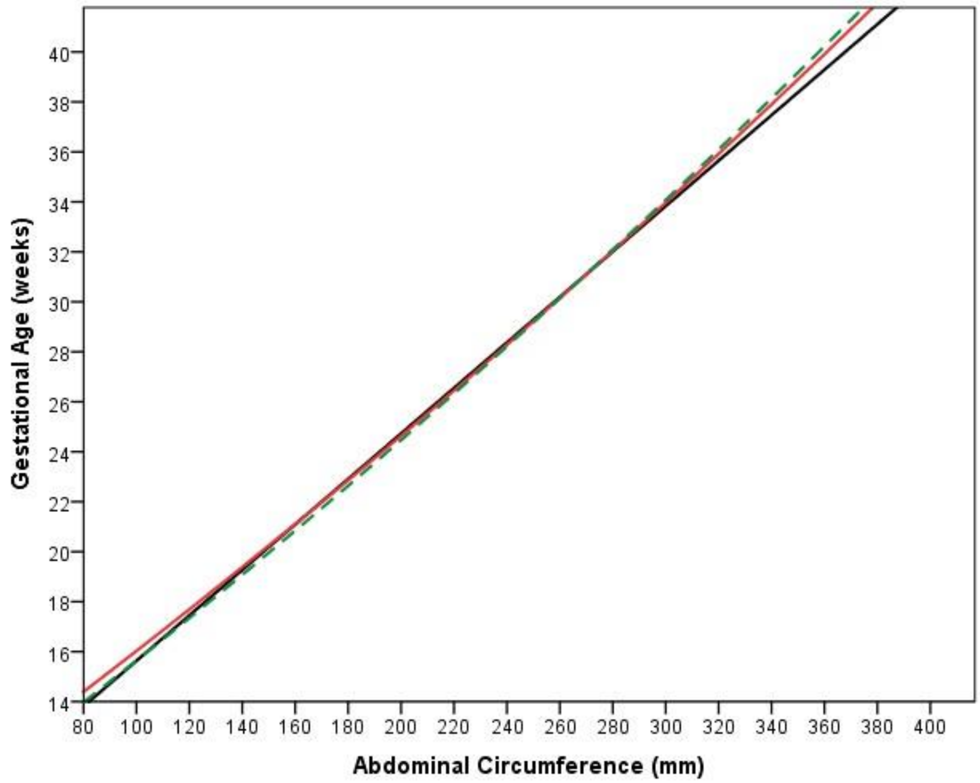

Figure 25: Comparison of the 50th centile for abdominal circumference derived in the present study (solid black line) with Hadlock *et al.* (1982b) (dashed green line) and Hadlock *et al.* (1984a) (solid red line).

In Figure 26, the gestational age estimates of femur length (FL) from the present study were less than the gestational age estimates of the Chinese (Leung *et al.*, 2008) across gestation. The difference was slightly more than 3 days, but this increased to more than 1 week for FL less than 20 mm (< 15 weeks) and greater than 46 mm (> 25 weeks). Compared to Hadlock *et al.* (1984a) curve, the present study underestimated gestational age by 3-7 days for FL below 24 mm, thereafter gestational age estimates were virtually the same up to term with ± 2 days difference. With respect to Hadlock *et al.* (1982c) chart, a 3-6 day underestimation of GA was observed for FL less than 19 mm whilst a 3-4 day overestimation was recorded for FL between 35-69 mm. Outside those ranges, Hadlock *et al.* (1982c) chart was nearly the same as the present study. Comparatively Hadlock *et al.* (1984a) chart was very close to the present study than Hadlock *et al.* (1982c) chart. The British chart by Altman and Chitty (1997) overestimated GA by 3-10 days in comparison with the present study for FL less than 24 mm and greater than 66 mm. No significant difference was observed for FL between 24-66 mm. In early second trimester, the FL chart of the present study performed worse in comparison with all the reference charts. For FL measuring 12 mm, the GA estimate of the present study was 6, 7, 7 and 10 days less than the GA estimate of Hadlock *et al.* (1982c), Hadlock *et al.* (1984a), Altman and Chitty (1997) and Leung *et al.* (2008) respectively.

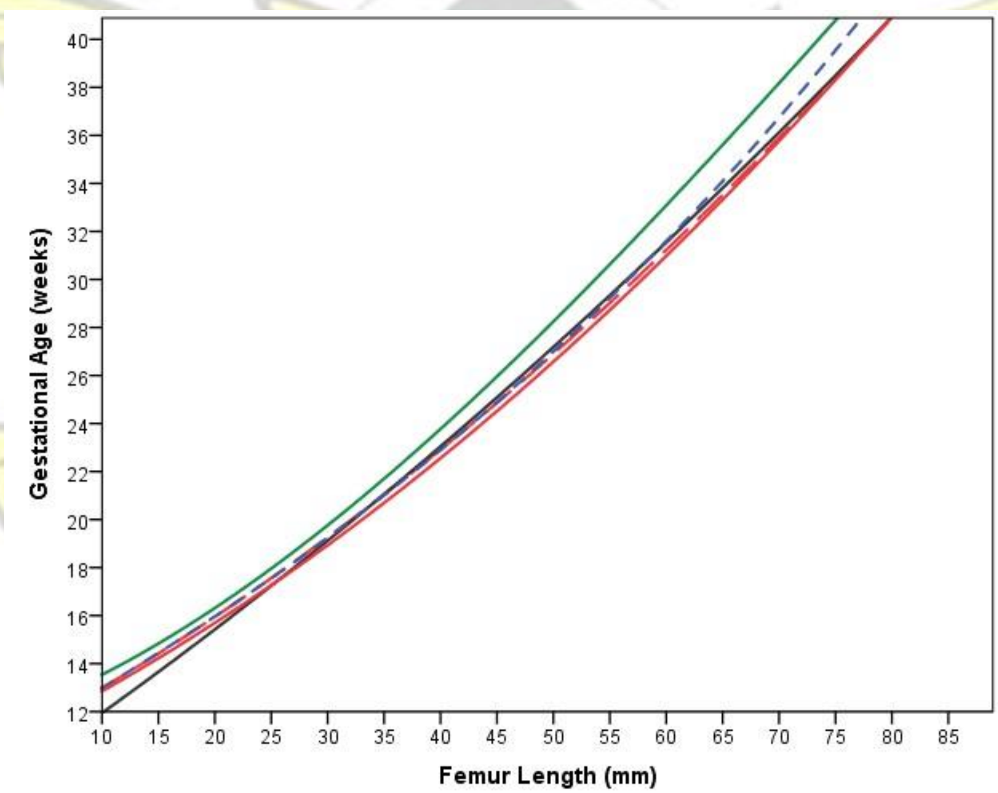

Figure 26: Comparison of the 50th centile for femur length derived in the present study (solid black line) with Hadlock *et al*. (1982c) (solid red line), Hadlock *et al*. (1984a) (dashed red line), Leung *et al.* (2008) (solid green line) and Altman and Chitty (1997) (dashed blue lines).

CHAPTER FIVE

DISCUSSION

5.1 COMPARISON BETWEEN MENSTRUAL-BASED AND ULTRASOUND-BASED GESTATIONAL AGE ESTIMATION

There was significant discrepancy between gestational age estimated by the last menstrual period (GA_{LMP}) and gestational age estimated by ultrasound (GA_{US}). For women in their first and second trimesters of pregnancy whose LMP dates were known, approximately 47.8% were within the acceptable clinical range of ultrasound crown-rump length (CRL) estimates. The clinical range according to the American College of Obstetricians and Gynaecologists (ACOG), the American Institute of Ultrasound in Medicine (AIUM) and the Society for Maternal-Foetal Medicine for which menstrual date could be used to estimate the due date is when the GA_{LMP} is within ± 5 days for up to 8 completed weeks and ± 7 days between 9 to 13 completed weeks (ACOG, 2014). Fifty nine (52.2%) of the women would have had their GA_{LMP} re-dated using ultrasound CRL. For comparison between dating by the use of LMP and ultrasound biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), femur length (FL) and their combination, the study found that all the 9 women whose LMP dates suggested first trimester gestation would have had their GA reassigned since these were dated as second trimester according to ultrasound estimates. Women in their second trimester (according to LMP-based dating) recorded a lower (64.1-69.2%) acceptable clinical range of ultrasound estimates than those in their third trimester (71.3-82.6%). This may be due to differences in the clinical ranges used. In the second trimester the acceptable range between weeks 14 -15 is ± 7 days, weeks 16-21 is ± 10 days and finally weeks 22-27 is ± 14 days (ACOG, 2014). For the third trimester however, the range is ± 21 days. The wider range in the third trimester is due to the high variability associated with foetal growth rate at that period. Consequently gestational age estimated by ultrasound is more likely to vary giving unreliable estimates of ± 3-4 weeks (Brakohiapa *et al.*, 2012). Ultrasound dating is superior to LMP dating up to 24 weeks of gestation in predicting the expected date of delivery (EDD) (Reddy *et al.,* 2014). A reliable LMP dating might therefore provide a better estimate of EDD than ultrasound dating after 24 weeks of gestation (Verburg *et al.*, 2008).

In a retrospective study of 2072 women by Brakohiapa *et al.* (2012) on the discrepancy between GA_{LMP} and GA_{US}, they reported a 67.8% acceptable clinical range of ± 2 weeks in the first trimester, 57.2% in the second trimester and 59.4% in the third trimester. Their proportion of women in the first trimester was higher than the present study of 47.4% probably due to the differences in the clinical ranges. In the third trimester more women fell within the wider acceptable range of ± 21 days adopted in the present study than the range of ± 14 days by Brakohiapa *et al.* (2012). However when the LMP reported second trimester dates were compared with ultrasound CRL and BPD dates, the proportion of women within the acceptable range was the same (57%) for the present study and Brakohiapa *et al.* (2012). This might be due to the same range used (± 14 days). This is in contrast with the 94% (n =171) reported in an earlier study by Neufeld *et al.* (2006)

between 15-24 weeks' gestation. This relatively high percentage was because pregnant women were trained by nurses and midwives to use memory aids to recall their LMPs. Brakohiapa *et al.* (2012) also reported a higher positive discrepancy of more than two weeks than negative discrepancy in each trimester. This was in contrast with the present study where a higher positive discrepancy was recorded only in the third trimester. An LMP-based gestational age greater than ultrasound-based gestational age has been associated with preterm delivery, low birthweight and stillbirth (Smith *et al.*, 1998; Nguyen *et al.*, 2000; Larsen *et al.*, 2000; Morin *et al.*, 2005). This is due to the high number of presumed postterm deliveries, unnecessary induction of labour and emergency caesarean sections. In a study of 3397 embryos by Smith *et al*. (1998), ultrasound CRL dates that were more than 2 days younger than the LMP were associated with low birthweights. A similar finding was reported by Larsen *et al.* (2000). However Larsen *et al.* (2000) used 16387 singleton pregnancies between 12-20 weeks whose gestational ages estimated by BPD were more than 7 days younger than expected from the LMP date. Ultrasound dates shorter than LMP dates have been attributed to delayed ovulation, inaccurate recall of the last menstrual period, missed miscarriage and slower growth rate of foetuses (Larsen *et al.*, 2000; Morin *et al.*, 2005). Slower early growth rate of embryos or foetuses is related to placental dysfunction which may result in increased risk of intrauterine growth restriction. Maternal obesity, short stature, heavy smoking, severe pre-eclampsia and abnormal karyotype affect foetal growth, hence such foetuses are smaller than expected at ultrasound examination than by the LMP (Morin *et al.*, 2005). Maternal obesity has been linked to delayed ovulation and irregular menstrual cycles (Morin *et al.*, 2005). In the present study, the unusually high discrepancy (52.2%) between gestational age estimated by LMP and gestational age estimated by ultrasound CRL could be attributed to poor recollection, although this was difficult to accept due to the short interval between the date of the LMP and the day of ultrasound scanning.

First trimester crown-rump length has been acclaimed as the most reliable method of estimating GA up to 13 weeks 6 days having low intra and inter-observer errors and a low prediction error of ± 3-7 days (ACOG, 2014). As a result, due date predicted using ultrasound CRL is normally not changed even where subsequent scans from other foetal parameters give different dates (Butt and Lim, 2014). Usually such discrepancies are suggestive of growth abnormalities (ACOG, 2014). The reliability of dating using CRL is because biological variation in the first trimester is minimal compared to the third trimester where there is increased variability with increasing gestational age (Salomon, 2010). Embryologists have observed a uniform growth pattern of the human embryo with small variability in size and age in early pregnancy, with foetal sex and racial differences having very little effect in the first trimester (Parker *et al.,* 1982; Grisolia *et al.,* 1993). When ultrasound date is higher than the LMP date, there is a higher risk of caesarean section. Grewal *et al.* (2010) reported a 10% and 60% increased risk of caesarean section for nulliparous women with GA_{LMP} lower than GA_{US} by 4 days and 21 days respectively. A significantly lower GA_{LMP} compared to GA_{US} may result in higher occurrences of presumed preterm deliveries and unnecessary preparation and expensive hospitalization towards labour (Brakohiapa *et al.,* 2012).

The reliability of LMP-based gestational age estimation depends on the regularity of a woman's menstrual cycle, accurate recall of the LMP, interpretation of bleeding in early pregnancy, lactational amenorrhoea or contraceptive use 2 months prior to pregnancy (which could influence the timing of ovulation and fertilization) (Salomon, 2010; Ogbe *et al.*, 2015). Poor recollection may be due to digit preference due to cultural beliefs or illiteracy (Ogbe *et al.*, 2015).

Ultrasonography has been reported to be the method of choice in predicting the day of delivery and pregnancy outcomes (Tunon *et al.*, 1996; Taipale and Hiilesmaa, 2001; Savitz *et al.*, 2002). Tunon *et al.* (1996) selected a population of 15241 women to determine whether ultrasound BPD measured between 15 and 22 weeks predicted the day of delivery better than the GA_{LMP}. These authors found that ultrasound estimate predicted the day of delivery in 52% of the women as compared to 46% predicted by welldocumented LMPs. Moreover, the proportion of estimated postterm births was 10% using the LMP date and 4% using ultrasound BPD date. Taipale and Hiilesmaa (2001) also reported 10.3% of postterm deliveries using LMP compared to 2.7% using ultrasonography. Although ultrasonography has been found to be superior to LMP in estimating gestational age and due date, where discrepancies in ultrasound and menstrual based gestational ages exist, the underlying discrepancy should be evaluated since chromosomally malformed (eg. triploidy and trisomy 18) and growth restricted foetuses are smaller than expected at ultrasound examination than by the LMP (Morin *et al.*, 2005; Saltvedt *et al.*, 2006). Midwives and obstetricians should therefore make efforts to assist pregnant women to recall the date of their last menstrual period.

Studies comparing the GA_{LMP} with GA_{US} either used the ultrasound date of one of the foetal parameters or the mean date. The present study observed that the proportions of women whose LMP dates were within clinical range differed depending on which ultrasound foetal parameter was used for dating. Higher proportions of women were within the clinical range when the GA_{LMP} were compared with ultrasound FL date (75.7%) than for ultrasound AC date (74.7%), ultrasound mean date (73.6%), ultrasound HC date (72.2%) and ultrasound BPD date (66.7%). This reflects the inherent accuracy level of each biometric foetal parameter. Smaller proportions of women with known LMP dates were within the clinical estimate of ultrasound BPD date. This is in agreement with the findings of many investigators (Hadlock *et al.*, 1981; Salomon *et al.*, 2011) about the unreliability of dating using biparietal diameter in the third trimester due to variation in foetal head shape, premature rapture of membranes and breech presentation.

5.2 CHARTS FOR FOETAL SIZE ESTIMATION

The average growth rate of biparietal diameter (BPD) in the present study (2.55 mm/week) was slightly smaller than the reference studies from 14-40 weeks: 2.61 mm/week (Hadlock *et al.*, 1982d), 2.66 mm/week (Chitty *et al.*, 1994a), 2.58 mm/week (Leung *et al.*, 2008) and 2.67 mm/week (Kurmanavicius *et al.*, 1999a). The growth rate of BPD decreased with increasing gestational age. The head circumference (HC) in the present study grew at a rate of 9.28 mm/week which is slightly smaller than the mean growth rate of 9.48 mm/week (Hadlock *et al.*, 1982a), 9.69 mm/week (Chitty *et al.*, 1994a) but slightly higher than 9.09 mm/week (Leung *et al.*, 2008) and 9.06 mm/week (Kurmanavicius *et al.*, 1999a). The HC also decreased with increasing gestational age. The present study confirms the accelerated growth of the head circumference in early gestation due to increasing size of the brain, and decreasing growth rate towards term before flattening at week 38. The mean growth rate of femur length (FL) in the present study (2.31 mm/week) is similar to Kurmanavicius *et al.* (1999b) (2.35 mm/week) but slightly different from Hadlock *et al.* (1984a) (2.43 mm/week), Chitty *et al.* (1994c) (2.29 mm/week) and Leung *et al.* (2008) (2.29 mm/week) from 14-40 weeks.

The median growth rate of abdominal circumference (AC) from 14-40 weeks in the present study was 10.6 mm/week and this is similar to the mean growth rate of 10.5 mm/week by Hadlock *et al.* (1982b), 10.4 mm/week by Chitty *et al.* (1994b) but slightly higher than the 10.0 mm/week reported by both Leung *et al.* (2008) and Kurmanavicius *et al.* (1999b). Whereas the AC in all the reference studies decreased slightly reaching around 8 mm/week in late third trimester, the present study observed a constant growth rate of 10.6 mm/week throughout gestation, probably due to the linear relationship observed between foetal abdominal circumference and gestational age. The growth rate of 10.6 mm/week was however similar to a longitudinal study by Deter and Harrist (1992), who observed a mean growth rate of 12 mm/week from 14-29 weeks, thereafter a constant 11 mm/week to term. The high growth rate of abdominal circumference compared with other foetal parameters in the third trimester accounts for the increasing weight gain of the foetus in the last 2.5 months of pregnancy (Sadler, 2011). Hence AC is a useful parameter in assessing foetal growth abnormalities.

Although foetuses in the present study were larger in comparison with the reference studies, they were not near the cut-off point for macrosomia. Foetuses at risk of macrosomia have a mean growth rate greater than 12 mm per week (Hadlock *et al.*, 1985b) and AC measuring more than 350 mm in the late third trimester (Chaabane *et al.,* 2013; Buikema *et al.*, 2014). The head to abdominal circumference (HC/AC) ratio and femur length to abdominal circumference (FL/AC) ratio obtained in this study were normal suggesting proportionate growth (neither growth restricted nor macrosomic). Since AC is the single most important parameter in estimating foetal weight, foetuses in the present study may have slightly higher birthweights than the reference studies. Using the FL/AC ratio below the 10th centile (or FL/AC < 0.205) by Hadlock *et al.* (1985b) as cut-off point, foetuses in the present study would have falsely been identified to be at risk of macrosomia (Hadlock *et al.*, 1985b). Macrosomic infants have an increased risk for shoulder dystocia, placenta praevia, asphyxia, postpartum haemorrhage, brachial plexus injury, prolonged labour, meconium aspiration, traumatic midforceps and cephalopelvic disproportion (Salomon, 2010; Mayer and Joseph, 2013). The foetal size charts of the reference population are therefore not appropriate for the population of the present study.

Tables for the normal ratios of FL/AC, FL/BPD, FL/HC and HC/AC for the study population have been provided. The normal range for FL/AC in the present study after 21 weeks (range: 0.21 – 0.23) was slightly different from that of Hadlock *et al.* (1983) (range: 0.20 – 0.24) and Benson *et al.* (1985) (range: 0.21 - 0.24). The HC/AC ratio was greater than 1:1 until 36 weeks, and this agreed with the study by Campbell and Thoms (1977). This is because whilst the growth rate of AC was constant across gestation, the growth rate of HC decreased from 14 mm at week 14 to 5 mm at week 40. The FL/AC was also less than 1.0 suggesting a higher growth rate of AC than FL across gestation. Consistent with the studies by Hadlock *et al.* (1983) and Snijders and Nicolaides (1994), the FL/AC and HC/AC ratios in the present study were also found to be constant and independent of gestational age. Accurate gestational age estimation is useful in diagnosing abnormal foetal growth (Salomon, 2010). Since the FL/AC and the HC/AC ratios were fairly constant after certain periods, they may be useful in assessing foetal growth even when the gestational age is unknown. The FL/BPD was less than 1.0 because the growth of BPD was slightly higher than the growth rate of FL at any week in gestation. The normal range of 0.73 ± 0.1 suggests that this ratio is also independent of gestational age. The FL/HC ratio was less than 1.0 since the growth rate of HC at each week of gestation was higher than that of FL. The FL/HC ratio increased slightly due to decreasing growth of HC. From week 25 until term the ratio appeared to be independent of gestational age with a normal range of 0.21 ± 0.01.

Studies that have constructed foetal size and growth charts either by cross-sectional approach or longitudinal approach have observed the effects of maternal age, parity, maternal height and weight, foetal sex and ethnicity on foetal growth (Gardosi *et al.*, 1995). In a longitudinal study of 533 pregnant Chinese women studied between 24-40 weeks' gestation, Pang and coworkers (Pang *et al.*, 2003) found statistically significant sex differences in FL, BPD and HC but not AC. Parity had some effect on HC and AC whereas maternal age had significant influence on HC, BPD and AC but not FL. Also, the authors observed significant effects of maternal weight on AC and FL and maternal height on BPD. In line with Pang *et al.* (2003), several authors (Bromley *et al.*, 1993; Davis *et al.*, 1993; L'ubuský *et al.*, 2006; Ramli *et al.*, 2013; Melamed *et al.*, 2013) have reported significantly larger head measurements (BPD, HC) in male foetuses than female foetuses in both the second and third trimesters of pregnancy. The present study did not assess the impacts of maternal characteristics or pregnancy characteristics on foetal biometry because the aim was not to establish customized foetal biometric charts. Moreover, a longitudinal study, rather than a cross-sectional study, is the preferred method for creating foetal growth charts (Melamed *et al.,* 2013). The present study therefore acknowledges the possible impacts of these factors on the findings. Drug or tobacco exposure, placental insufficiency, genetic syndromes, maternal diseases such as chronic hypertension or diabetes, pregnancy induced hypertension, pre-eclampsia, asthma, severe anaemia, congenital anomalies and abnormal karyotype have influence on foetal size and growth, especially in late gestation (Verburg *et al.*, 2008). Since the aim was to establish foetal size charts, depicting how foetuses grow under ideal conditions, pregnant women and foetuses known to have such conditions were excluded.

Foetal femoral lengths in the present study were statistically longer than the femur lengths of European populations (Kurmanavicius *et al.*, 1999b; Chitty *et al.*, 1994c) and an Asian population (Leung *et al*., 2008). These results are consistent with the findings of Bromley *et al.* (1993) and Shipp *et al.* (2001) who reported longer femoral length in blacks than whites. The results of the present study also agree with studies which compared the femur length of Chinese foetuses with Europeans (Lachman and Shen, 1996; Leung *et al*., 2008). The studies demonstrated that foetal femur length is mostly affected by ethnicity or race. A short femur length is one of the soft markers for Down syndrome (Benacerraf, 1996; Jung *et al.*, 2007). Failure to recognise ethnic variations in femur length may lead to wrong diagnoses of Down syndrome during genetic sonogram analysis.

The abdominal circumference measurements in the present were significantly higher than the Chinese chart (Leung *et al*., 2008) in the second and third trimesters. Leung *et al.*

(2008) also observed a smaller AC in the Chinese in comparison to the British (Chitty *et al.*, 1994b) and the French (Salomon *et al.*, 2006) charts. Lai and Yeo (1995) in a sample of 6374 foetuses also observed that the FL, AC, HC and BPD of the Chinese foetuses were smaller than the charts from Chitty *et al.* (1994a, b, c). The 50th centile of AC in the present study was significantly larger early in the second trimester and late third trimester but significantly smaller between 20-34 weeks in comparison with both the British chart (Chitty *et al.*, 1994b) and the American chart (Hadlock *et al.*, 1982b; Hadlock *et al.*, 1984a). Giorlandino *et al.* (2009) in a study of 4896 Italian foetuses observed a smaller HC and AC than the French (Salomon *et al.*, 2006) and the British (Snijders and Nicolaides, 1994) populations. Giorlandino *et al.* (2009) explained that the differences might be due to the way the circumferences were obtained. In the Italian chart, the circumferences were measured directly using the ellipse facility, whereas in the British and the French charts they were calculated using the formula for HC and AC. In contrast the AC calculated from the anteroposterior abdominal and transverse diameters in both Kurmanavicius *et al.* (1999b) and Chitty *et al.* (1994b) charts were significantly smaller throughout gestation in comparison with the present study where the AC was obtained directly using the ellipse facility. Whereas the calculated AC by Chitty *et al.* (1994b) was significantly smaller throughout gestation, their plotted AC was only significantly smaller in early second trimester and late third trimester. The difference in AC between the present study and the two AC charts by Chitty *et al.* (1994b) is not simply due to differences in measurements for where the plotted AC measurements were smaller than the present study, their calculated AC measurements were much smaller. The difference observed by Giorlandino *et al.* (2009) therefore cannot be due to the measurement methods since circumferences derived using the ellipse facility are greater than the calculated circumferences, and the difference increases with gestational age (Chitty *et al.*, 1994b; Kehl *et al.*, 2010). Racial differences and not differences in the measuring techniques might be the cause. Hadlock *et al.* (1982e) found no statistically significant difference between the two methods in generating the circumferences and therefore used both methods in deriving foetal size and age charts in 1984a (Hadlock *et al.* 1984a). Not knowing the differences in the measuring techniques by Hadlock *et al.* (1982b) and Hadlock *et al.* (1984a) for deriving the circumferences may lead to wrong estimation of gestational age and foetal size.

The outer-outer BPD measurements of Chitty *et al.* (1994a) and Kurmanavicius *et al.* (1999a) were significantly higher than the outer-inner BPD measurements of the present study. In a further comparison of the outer-inner BPD of the present study with both the outer-inner and outer-outer BPD measurements of Chitty *et al.* (1994a), a higher deviation was observed between the outer-outer BPD of Chitty's chart (Chitty *et al.*, 1994a) and the present chart than between the outer-inner BPD of Chitty's chart (Chitty *et al.*, 1994a) and the present study. These confirm the findings of other studies which reported larger BPD measurements using the outer-outer compared to the outer-inner measurements (Hadlock *et al.*, 1981; Leung *et al.*, 2008). Failure of the sonographer to check the measuring techniques used by the reference chart and adopt that accordingly may lead to wrong estimation of foetal size which can result in severe consequences. The BPD measurements in the present study were significantly larger in the second trimester but smaller in the third trimester in comparison with the outer-inner BPD charts by Chitty *et al.* (1994a), Hadlock *et al*. (1982d) and Leung *et al.* (2008). Bromley *et al.* (1993) also reported a larger BPD in blacks than whites between weeks 16-21 (0.327 mm, 95% CI 0.03 – 0.625). Jacquemyn *et al.* (2000) however reported no significant difference in the BPD of Belgians, Moroccans and Turkish living in Belgium from 18-40 weeks of gestation. These investigators (Jacquemyn *et al.*, 2000) however reported significant inter ethnic differences in FL, AC and HC. Foetuses of low risk Iranian pregnancies have been shown to have shorter FL and smaller BPD, HC and AC than Australian foetuses in the third trimester (Niknafs and Sibbald, 2001).

The differences observed in the HC obtained with the ellipse facility in the present study with both the plotted and the derived HC charts by Chitty *et al.* (1994a) shows the error one would encounter when the measuring techniques of the reference chart is not followed. Although it was noticed that the 50th and 95th centiles of the present study were higher in the second trimester but smaller in the third trimester, the observed differences with the plotted HC and the derived HC were not the same. Chitty *et al.* (1994a) in comparing the plotted HC and the derived HC found the plotted HC to be significantly higher than the derived HC especially in the third trimester. Surprisingly their derived HC in the third trimester was higher than the plotted HC in the present study. Though measurement techniques can affect the result of foetal biometry, racial differences may skew it to another direction. The result of their 5th centile was very striking and confirms this assertion. The 5th centile of their plotted HC was higher than the present study throughout gestation whereas their calculated HC was higher only between weeks 26-35. Several investigators have reported that the calculated or derived method is less accurate than the ellipse or plotted method (Hadlock *et al.*, 1982a; Shields *et al.*, 1987; Chitty *et al.* 1994a).

The low values of HC with the calculated method might be due to under-measurement of the occipitofrontal diameter, especially during late gestation (Leung *et al.*, 2008).

Except differences in the sample size, the study design, statistical analysis and measurement techniques between the Chinese chart by Leung *et al*. (2008) and the British chart by Chitty *et al.* (1994a, b, c) were the same as that of the present study. The differences with the Kurmanavicius' charts (Kurmanavicius *et al.*, 1999a, b) were the sample size and also the way the BPD and circumferences were obtained. Due to the very large sample size (n = 6557) used by Kurmanavicius *et al.* (1999a, b), several sonographers were involved. Moreover the women originated from different parts of the world (indigenous Swiss, Italian, Portuguese, Spanish, German, Asian, American, African, Australian, Greek, ex-Yugoslav, Austrian, British). These may partly explain some of the differences between the charts of the present study and Kurmanavicius' charts (Kurmanavicius *et al.,* 1999a, b). Apart from the small sample size used in the present study, compared to the charts developed by Hadlock and coworkers (Hadlock *et al.*, 1982a, b, c, d) there is some difference in the methodology. The standard deviation was not modeled throughout the foetal size range; instead, Hadlock *et al*. (1982a, b, c, d) calculated the gestational age-associated standard deviation at weekly intervals and each interval was in the middle of the week.

The quality of ultrasound measurement is dependant on the competence of the sonographer (Ioannou *et al.*, 2012). In this study, certified competent and skilled sonographers performed the ultrasound examinations. Since the same statistical analysis used by the reference charts were adopted in the present study, the significant differences between the present study and the reference studies cannot be attributed solely to methodological differences in measurement techniques and sample size. Ethnicity may play a role in the observed differences, as well as foetal sex, parity, maternal age, maternal height and weight, socioeconomic and nutritional factors. In a review of the methodologies used in developing foetal size charts, Ioannou *et al.* (2012) concluded that differences in foetal size between populations can be attributed to biological variations only when the highest methodological quality are followed uniformly in the different populations.

The standard deviations obtained for femur length (FL) and biparietal diameter (BPD) in the present study were lower than the standard deviations for abdominal circumference (AC) and head circumference (HC). With small variability associated with FL and BPD measurements, each parameter may be used to predict the values of HC and AC. Although BPD and FL can each be used to predict the value of AC due to the high R^2 of 95.5% and 96.3% respectively, their standard error of the estimate (SEE) were more than 15 mm and therefore may not be clinically useful. The present study generated regression equations for estimating BPD. It was shown that HC or FL could predict BPD with R^2 of 0.983 and 96.3% respectively with SEE less than 3.7 mm between 14 - 40 weeks' gestation. This may be useful when variation in head shape and breech placentation make BPD measurements unreliable. The relatively high standard deviation observed in the present study for AC was similar to the findings of Chitty *et al.* (1994b), Lai and Yeo (1995) and Frančišković *et al.* (2011). The wide standard deviation confirms the difficulty associated in measuring the abdominal circumference and its low reproducibility in the third trimester (Butt and Lim, 2014). Therefore cautions should be taken when using AC alone in dating pregnancy.

The charts are presented with the 3rd, 5th, 50th, 95th and 97th centiles since in obstetric practice the 3rd or 5th and the corresponding 97th or 95th centiles respectively are used as cut-off points for indicating small-for-gestational-age foetuses and large-forgestational-age foetuses respectively. The use of a chart that is not appropriate to the study population may result in diagnosing a normal foetus as too small or large for gestational age. This may lead to maternal anxiety and unnecessary evaluations and interventions due to wrongfully assumed abnormal foetal growth (Brakohiapa *et al.*, 2012).

5.3 GESTATIONAL AGE ESTIMATION

5.3.1 GESTATIONAL AGE ESTIMATION USING CROWN-RUMP LENGTH

In the present study an attempt was made to develop reference charts for foetal age assessment based on ultrasonographic measurements of crown-rump length (CRL) from 6-14 weeks of gestation. Although the growth pattern of foetuses in the first trimester has been shown to be uniform, racial and foetal sex, maternal age and smoking may have significant effect beyond 10 weeks' gestation (Parker *et al.,* 1982; Grisolia *et al.*, 1993; Mongelli *et al.*, 2003; Salomon, 2010). Bottomley *et al.* (2009) also reported significant effects of race and maternal age in crown-rump length measurements. They found a significant increase in the growth rate of CRL in foetuses of black women than white (0.019 mm per day gestation) and Asian women (0.030 mm per day gestation). A difference of 4.18 mm in CRL at 12 weeks' gestation was also found between women of 20 years and women of 40 years. The CRL of the present study (black) was also longer than all the reference charts after 8 weeks. This racial difference may explain the 1-3 days overestimation of gestational age by Robinson and Fleming (1975), Hadlock *et al.* (1992) and Sahota *et al.* (2009) in comparison with the present study for CRL greater than 22 mm (at least 8 weeks). Pexsters *et al.* (2010) also reported a 1-day overestimation by Hadlock *et al.* (1992), and a 2-day overestimation by Robinson and Fleming (1975) for CRL dating between 11-14 weeks. Pexsters *et al.* (2010) used a large sample size of 3710 foetuses and measured the CRL between 5.5 - 14 weeks using both transabdominal and transvaginal sonography. Although the difference in gestational age (GA) is small, accurate dating of pregnancy using CRL in the first trimester is critical to the quality of prenatal screening assessment since the distribution of nuchal translucency and serum markers vary according to the gestational age. A difference of 1 to 2 days GA can alter the risk assessment of Down syndrome based on mid-trimester serum quadruple (alphafetoprotein, human chorionic gonadotropin, estriol and inhibin-A) screening from high chance to low chance, or vice versa (Loughna *et al.*, 2009). The average 3.5 - 6 days underestimation of GA by Hadlock *et al.* (1992), Robinson and Fleming (1975) and Sahota *et al.* (2009) for CRL below 10 mm in comparison with the present study may be due to measurement errors, ultrasound equipment used and the different ranges used in establishing the reference charts. The range for dating CRL for Hadlock *et al.* (1992), Robinson and Fleming (1975) and Sahota *et al.* (2009) were 5-18 weeks, 6-14 weeks and 6-15 weeks respectively. The trends established within a range of data may not hold outside that range (Schluter *et al.*, 2007). Robinson and Fleming (1975) used static-image ultrasound equipment for CRL less than 10 mm which might result in underestimation due to poor resolution. Other investigators (Sahota *et al.*, 2009; Verburg *et al.*, 2008; Papaioannou *et al.*, 2009; Pexsters *et al.*, 2010) have also reported 1-5 days underestimation of Robinson and Fleming (1975) for CRL less than 10 mm. The difference between the present study and that of Hadlock's curve (Hadlock *et al.*, 1992) agrees with the findings of Pexsters *et al.* (2010) who also reported a 3-day underestimation of GA by Hadlock's curve (Hadlock *et al.*, 1992) at 6 weeks. Pexsters *et al.* (2010) explained that this might be due to the improved image resolution of the ultrasound equipment since 1992. Transabdominal sonography (TAS) also underestimates CRL measurements by an average of 2.8 mm (95% CI 4.2–0.9 mm) for embryos 57 – 62 days' gestation compared to transvaginal sonography (Lohr *et al.*, 2010). This is because transvaginal sonography (TVS) has a higher frequency, enabling it to visualize early embryonic structures better than transabdominal sonography (TAS) (Grisolia *et al.*, 1993; Lohr *et al.*, 2010). Kaur and Kaur (2011) reported that TVS was able to detect CRL of 3 mm whereas TAS could not detect CRL below 7 mm. Since the use of TAS in estimating gestational age has only been reported to be similar to TVS after 6 weeks (Kaur and Kaur, 2011; Butt and Lim, 2014), the use of the transabdominal approach in the present study for measuring CRL less than 10 mm (at most 7 weeks) might also account for the smaller CRL measurements of the present study. Hadlock *et al.* (1992) used both the transvaginal and transabdominal approach whilst Robinson and Fleming (1975) and Sahota *et al.* (2009) used only the transabdominal approach in constructing the CRL dating charts.

The embryo is hyperflexed around 6 – 9 weeks, so measurements within those periods may lead to underestimation of GA (Loughna *et al.*, 2009; Salomon *et al.*, 2013). Also inclusion of the yolk sac in the measurement of CRL can overestimate the gestational age (Loughna *et al.*, 2009). Due to the high discrepancies in GA estimation that may result in dating very small foetuses at early gestations (Hearn-Stebbins, 1995; Salomon *et al.*, 2013), the National Institute for Health and Clinical Excellence (NICE) has recommended the assessment of gestational age using crown-rump length between 10 to 13 completed weeks. The Society of Obstetricians and Gynaecologists of Canada however recommends crown-rump lengths above 10 mm, that is, at least 7 weeks of gestation (Butt and Lim, 2014).

The sample size for developing the crown-rump length dating chart for the present study was 63 compared to the 334 - 416 singleton foetuses used in the 3 published equations (Robinson and Fleming, 1975; Hadlock *et al.*, 1992; Sahota *et al.*, 2009). The small sample size and uneven distributions of the number of observations at each week of gestation may account for the relatively wide scatter.

5.3.2 VARIATIONS IN THE ESTIMATION OF GESTATIONAL AGE

The study observed increasing uncertainty in the prediction of gestational age with increasing foetal size. The same observation has been reported by earlier studies (Hadlock *et al.*, 1982a, b, c, d; Hadlock *et al.*, 1984a; Benson and Doubilet, 1991; Altman and Chitty, 1997; Leung *et al.*, 2008). This is expected since biological variation increases with increasing gestational age. The prediction error in dating using crown-rump length (CRL) in the present study was constant (± 5 days) throughout the range of measurements, probably due to the linear relationship between the crown-rump length and gestational age. This was in agreement with the ± 4.7 days reported by Robinson and Fleming (1975) for any given CRL value. Hadlock *et al.* (1992) reported variability of ± 8% (2 SD) for GA estimation between 5-18 weeks.

Among the parameters (BPD, HC, AC and FL), head circumference had the lowest prediction error throughout the ranges of gestation: ± 6.8 days (14-18 weeks), ± 9.7 days (18-24 weeks), ± 12.6 days (24-30 weeks), ± 15.1 days (30-36 weeks) and ± 17.1 days (36 - 41 weeks). This is similar to the findings of several investigators (Hadlock *et al.*, 1984a; Benson and Doubilet, 1991; Altman and Chitty, 1997; Leung *et al.*, 2008). In contrast, Hadlock *et al.* (1982a, b, c, d) observed that BPD had the lowest 95% uncertainty of GA prediction up to 36 weeks, followed by HC. Hadlock and co-workers (Hadlock *et al.*, 1982d) explained that the high prediction error of BPD compared to HC in the late third trimester might be due to variations in head shape. They suggested that in such a situation GA estimation should be based on HC which appears to be independent of head shape. The accuracy of BPD in predicting gestational age between 14 and 24 weeks was ± 10.3 days. This is similar to the ± 10.2 days reported by Hadlock *et al.* (1984a), ± 10.5 days by Altman and Chitty (1997) but slightly higher than the ± 9.2 days reported by Leung *et al.* (2008). The small range confirms that BPD is indeed an accurate predictor of gestational age. From 30 - 36 weeks, the error in predicting GA using BPD in the present study (± 15.6 days) was significantly lower and a better estimator of GA than Hadlock *et al.* (1984a) (± 21 days), Altman and Chitty (1997) (± 24.0 days) and Leung *et al.* (2008) (± 18.2 days). The high prediction errors reported in the reference equations may be attributed to variations in foetal head shape (dolichocephaly, brachycephaly) or breech position (Hadlock *et al.*, 1981; Salomon *et al.*, 2011). Due to this, the British

Medical Ultrasound Society Foetal Measurements Working Party was of the opinion that BPD should not be used in routine clinical practice for the estimation of gestational age or foetal size in the third trimester (Loughna *et al.*, 2009). A difference of 16.2 days (95% CI 14.3 - 18.1 days) was observed in a study comparing GA estimation between BPD and HC in 111 foetuses with breech presentation from 31- 38 weeks' gestation (Lubusky *et al.*, 2007). Altman and Chitty (1997) and Johnsen *et al.* (2004) also reported that foetuses in breech presentation were respectively 2 days or 1 day older than cephalic foetuses with the same BPD. These two studies confirmed that head shape may have significant effect on gestational age estimation in both the second and third trimesters of pregnancy. In constrast, the present study observed low prediction errors in GA estimation using BPD even in the third trimester suggesting that BPD might still be useful in late gestation.

The uncertainty in predicting gestational age from femur length was ± 11.6 days (12 - 24 weeks) and ± 15.1 days (24 - 36 weeks) in the present study. Hadlock *et al.* (1984a) reported a variability (± 2 SD) of ± 11.1 days between 12 to 23 weeks and ± 17.7 days between 24 to 36 weeks of pregnancy whilst Altman and Chitty (1997) reported ± 10.0 days uncertainty between 12 - 24 weeks and ± 19.6 days between 24 to 36 weeks. Although these results were almost similar up to 24 weeks, the uncertainty of predicting GA using the present study was slightly lower than the reference equations.

Gestational age is rarely estimated using abdominal circumference (AC) alone due to its wide variability compared to other foetal parameters (Hadlock *et al.*, 1982b; Benson and Doubilet, 1991). Abdominal circumference is difficult to measure (Butt and Lim, 2014) and its measurements are associated with abnormal foetal growth (MacGregor and Sabbagha, 2008). As a result few dating charts have been constructed using AC. Benson and Doubilet (1991) found the precision of dating using AC to be ± 14.7 days (14-20 weeks) and ± 25.9 days (20-26 weeks). Hadlock *et al.* (1982b) reported a variability of ± 13.3 days between 12 to 18 weeks, ± 14.0 days between 18 to 24 weeks, ± 15.4 days between 24-30 weeks and ± 21.0 days between 30-36 weeks. The low prediction errors reported in the present study shows that AC might accurately estimate gestational age in the second trimester than previously thought.

Due to the increasing uncertainty associated with ultrasonographic estimation of GA, it is prudent that GA is estimated in the first or early second trimesters of pregnancy. It must be noted that the 95% prediction intervals used by Benson and Doubilet (1991) and all of Hadlock's charts (Hadlock *et al.*, 1982a, b, c, d) are 20% wider than the 90% uncertainity adopted in the present study and all the other reference charts in the literature (Altman and Chitty, 1997, Leung *et al.*, 2008).

5.3.3 GESTATIONAL AGE ESTIMATION IN THE SECOND AND THIRD TRIMESTERS

Accurate estimation of gestational age is essential in predicting the date of delivery and assessing foetal growth. Dating charts were therefore developed for biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC) and femur length (FL) between 14-40 weeks' gestation. These foetal parameters and their combinations are useful in estimating gestational age for the second and third trimesters of pregnancy. The crown-rump length is not recommended owing to foetal flexion and extension after week

14 (Papaioannou *et al.*, 2009) which tend to underestimate and overestimate gestational age respectively (Loughna *et al.*, 2009).

The reasons for the observed differences in gestational age between the present study and the reference equations are the same reasons stated for the differences between the present study and the reference foetal size charts. In foetal size charts, the foetal biometric measurement is plotted as a function of gestational age whereas in foetal age charts, the gestational age is plotted as a function of foetal biometric parameter. These two charts are not the same, however the 50th centile of a foetal size chart can be used to predict gestational age by simply exchanging the dependent variable (gestational age) and the independent variable (foetal parameter). Using the foetal femur length size chart of the present study as an example, at any gestational age, the femur length of the present study was found to be longer than the corresponding Chinese foetus (Leung *et al.*, 2008). If the size of a foetus with a short femur length (Chinese foetus) is used to estimate the gestational age in the present study, the gestational age would be underestimated in comparison with the Chinese reference chart (Leung *et al.*, 2008). The shorter the femur length relative to the present study, the higher the underestimation in GA. On the other hand if a foetus with a long femur length (the present study) is used to estimate the GA using the Chinese reference chart (Leung *et al.*, 2008), the gestational age would be overestimated in comparison with the present study.

It will therefore be erroneous to assume that the present dating chart using the outer-inner BPD measurements agreed better with the outer-outer BPD than with the outer-inner BPD of Altman and Chitty (1997) for BPD less than 42 mm. This was observed because the BPD measurements of the present study were closer to the outer-outer BPD measurements than the outer-inner BPD measurements within that period. In late gestation where the BPD measurements of the present study were slightly smaller than the outer-inner BPD compared to the outer-outer of Altman and Chitty (1997), a wider deviation (overestimation in GA) was observed between the present study and their outer-outer BPD chart than with their outer-inner BPD chart. This illustrates the effects of both inappropriate measuring techniques and population differences in foetal biometry.

Caliper placement should therefore conform to the reference nomogram.

5.3.4 BEST PARAMETER (S) IN ESTIMATING GESTATIONAL AGE

The head circumference was found to be the best predictor of gestational age in the second trimester. This is consistent with earlier studies (Hadlock *et al.*, 1984a; Benson and Doubilet, 1991; Ott, 1994; Chervenak *et al.*, 1998) which compared the performance of biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC) and femur length (FL) in age estimation. The use of FL (R^2 = 95.8%) in estimating gestational age in the second trimester was better than AC (R^2 = 94.9%) and the least parameter being BPD (R^2 = 93.8%). The study did not find any improvement in GA estimation in the second trimester using multiple parameters. This is in accordance with the study by Chervenak *et al.* (1998) who also found less than a day improvement using multiple parameters. However if there is a problem with head measurements, the combinations of FL and AC may provide a better estimate of gestational age (GA) than using FL or AC alone in the second trimester.

In the third trimester, HC again was the best predictor of GA in the present study. The BPD, FL and AC were all significant predictors since their differences with HC were less than a day. The use of multiple parameters in the third trimester had significant improvement in gestational age estimation. This also is in agreement with earlier studies (Hadlock *et al.*, 1984a; Benson and Doubilet, 1991; Ott, 1994; Chervenak *et al.*, 1998). The addition of one (FL) parameter or two (AC and FL) parameters significantly improved the accuracy of gestational age prediction than that based on HC alone. The standard error of the estimate (SEE) was between ± 1.08 - 1.13 weeks using multiple parameters whereas it was ± 1.36 weeks using HC alone. The best regression equation for predicting GA in the third trimester involved the combinations of AC, FL and BPD since this accounted for 90.5% of the variance in gestational age estimation with SEE of ± 1.05 weeks. Combinations of AC, FL and HC accounted for 90.0% of the variance in gestational age estimation with SEE of ± 1.08 weeks. The present study also found out that once HC was in the equation, only AC or FL, but not BPD added new information. This is due to the very strong correlation between BPD and HC.

Abdominal circumference was the best univariate predictor of gestational age when both the second and third trimesters were considered because of its slightly stronger correlation with gestational age compared to the other parameters. Femur length was found to be superior to BPD in age estimation. Hadlock *et al.* (1984a) and Hill *et al.* (1992) came to a similar conclusion. The best regression equation involved the combination of AC, BPD or HC and FL. This is in contrast to the study of Hadlock *et al.* (1984a) who generated a regression equation involving all the four parameters. Since BPD has a very strong correlation with HC ($r = 0.992$), where one exist in the regression equation, the other was eliminated. Pearson's correlation coefficient between gestational age and BPD was 0.981928 whereas it was 0.981640 between GA and HC. This explains why in the best regression equation, BPD and not HC was used. Hadlock *et al.* (1984a) failed to state the significant level of each parameter in their regression equation so it is difficult to know whether the contributions of both HC and BPD in their regression equation were statistically significant. Foetuses in the present study therefore appear to have normal BPD measurements or cephalic indices (no extreme variations in head shape). This may explain the low prediction errors observed even in the third trimester. Addition of BPD or HC and FL to AC reduced the error in the prediction of GA by approximately 2 days. For women who undergo ultrasound dating scan in the third trimester, the gestational age should be estimated using the equations developed for both the second and third trimesters due to their high coefficient of determinations instead of the third trimester equations.

Multiple parameters were used to develop reference equations in the second trimester, third trimester and the entire range of gestation because combinations of parameters have been shown to provide slightly better estimate of GA than using a single parameter (Hadlock *et al.*, 1984a; Hadlock *et al.*, 1987; Hill *et al.*, 1992; Chervenak *et al.*, 1998). Moreover the four standard biometric parameters (BPD, HC, AC and FL) are routinely measured in the second and third trimesters due to their role in foetal weight estimation. Abnormal foetal growth (dwarfism, IUGR, macrosomia), variations in foetal head shape, foetal position and technical error associated with measuring a single parameter necessitate the measurements of all four parameters (Hadlock *et al.*, 1984a; MacGregor and Sabbagha, 2008; Butt and Lim, 2014). This can act as a guide for the sonographer in the use of a single parameter or combination of parameters in dating pregnancies. The sonographer should be cautious of using multiple parameters if there is a significant discrepancy in gestational age between parameters. The reason for the difference must be evaluated instead of simply using the mean gestational age. The normal range established for foetal proportions may assist the sonographer in reevaluating measurements in order to identify the parameter that is disproportionate in growth (as a result of anomaly) or measurements error and discard it accordingly in gestational age (GA) estimation. If the cephalic index is abnormal, the biparietal diameter (BPD) must be discarded. For femur length to biparietal diameter (FL/BPD) ratio abnormally less than 0.71, the FL should be discarded due to the possibility of dwarfism in the absence of brachycephaly. A FL/BPD ratio significantly greater than 0.87 may suggest microcephaly or dolichocephaly, for which the BPD must not be used in estimating GA. A femur length to abdominal circumference (FL/AC) ratio greater than 0.24 and less than 0.20 may be a sign of asymmetrical growth restriction and macrosomia respectively. In both cases the AC cannot be used in GA estimation. For these reasons, the ultrasound report should include the gestational ages of all the foetal parameters used as well as the propotionality ratios. In most ultrasound centres in Ghana, these rarely accompany the report form since the mean gestational age is often used. In the first objective of the present study it was pointed out that using the mean gestational age may not always be the best. There was a higher proportion of women whose LMP dates were in agreement with ultrasound FL dates and ultrasound AC dates than were with the average ultrasound dates.

The charts and tables established in the present study are accurate within the given ranges. Predictions at the extremes of the data range may lead to inaccuracies (Schluter *et al.*, 2007). In comparing the present chart with published data, visual comparison showing differences at each week of gestation was deemed appropriate. This would help in identifying the week in which the difference is clinically significant. The deviation was not uniform throughout the entire range of gestation so averaging using paired Student's t-test was not a good option. It must be emphasized that a statistically significant difference may not be clinically significant. A small statistically significant difference may be within the range of intra and inter-observer errors (Chang *et al.*, 1993).

To enable comparison of the present study with other reference equations, the mean and standard deviation used to generate the centiles for both the foetal size and age charts have been provided to enable the calculation of Z-scores. The *Z*-scores are the World Health Organization's (WHO) recommended system for evaluating the performance of reference curves for a given population (Salomon *et al.*, 2006; Sananes *et al.*, 2009). Validation of the performance of the reference equations of the present study would have required a new data set. This could not be done due to time constraints.

In the present study, the sample size for generating the centiles was very small. The larger the sample size the greater the precision of the resulting centiles (Altman and Chitty, 1994). Altman and Chitty (1994) showed that several hundred observations are required to get reasonable estimates of extreme centiles and gave the minimum sample size to be 500. This might explain the significant discrepancies between the 5th and 95th centiles of the present study with the published reference charts. The number of observations was also not evenly distributed across the gestational range. No single measurement was obtained for week 19 of gestation. No intra and inter-observer analyses were done, but previous studies have confirmed a high degree of reproducibility in foetal biometric measurements throughout gestation (Perni *et al.*, 2004; Verburg *et al.*, 2008). The intention was to provide values for foetal parameters as measured in the clinical setting. For charts developed in the second and third trimesters, although the gestational age estimated by the last menstrual period was confirmed by the mean ultrasound date (±14 days agreement), the ultrasound date was not determined in the first trimester which is known to be very reliable. Participants were not followed up to delivery so foetuses that might have developed complications after scanning could not be excluded. Participants would have had to be recruited very early in the first trimester and followed up to delivery for this to be possible. Due to the limited time period, this could not be done in the present study. Notwithstanding, since no comparable data exist for the present population, the results are still valuable.

Strengths of the study were that, it was a prospective cross-sectional study where participants were recruited for the purpose of chart creation and each foetus was therefore measured only once. The statistical methods by Altman and Chitty (1994) were adhered to, such as the inclusion and exclusion criteria, modeling the standard deviation with increasing gestation and presenting scatter plots to assess the goodness of fit of the model. The study also reported the 90% confidence limits on the prediction of gestational age since this could have legal implications in case of use in management decisions.

CHAPTER SIX

CONCLUSION, RECOMMENDATIONS FOR FUTURE WORK

6.1 CONCLUSION

Results of the present study provide for the first time detailed baseline data on foetal biometry in Ghana. The study confirmed that there is significant disparity between gestational age estimated by the last menstrual period and ultrasound. Statistically significant differences in foetal biometry exist between the Ghanaian population and the American, British and Chinese populations in the literature. Therefore using standards developed for the present population may improve estimation of the expected date of delivery and prenatal diagnosis of abnormal foetal growth in Ghana than using reference charts that are not representative of the study population.

The observed differences in dating using crown-rump length suggest that foetal growth in the first trimester may not be uniform. In both the second and third trimesters of pregnancy, foetal head circumference was found to be the best single parameter in estimating gestational age in the present population. The use of multiple foetal parameters in age estimation resulted in an increase in the coefficient of determination and reduction in the standard error of the estimate. Biparietal diameter was found to be a good predictor of gestational age in the third trimester than previously reported in the literature suggesting normal cephalic indices and proper foetal presentation in the present population.

The present study observed significant correlations between foetal parameters and derived formulae for estimating the value of biparietal diameter using femur length or head circumference, in cases of abnormal head shape or breech presentation.

There were significant differences in foetal biometry when measuring techniques used in the present study were compared with reference equations which followed different anthropometric techniques.

6.2 RECOMMENDATIONS FOR FUTURE WORK

Future studies using larger sample sizes should be conducted to provide additional information for the development of reference charts for foetal size and age using a crosssectional study and a foetal growth chart using a longitudinal study. Pregnant women should be followed up to delivery.

Reference charts should be customized based on maternal characteristics (age, height, parity, weight and ethnicity), foetal sex and possibly paternal characteristics.

Further study on the menstrual history and the significant differences in gestational age between ultrasound and the last menstrual period would be more helpful in confirming the importance of the last menstrual period in gestational age estimation.

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