

Yale University

EliScholar – A Digital Platform for Scholarly Publishing at Yale

Yale Medicine Thesis Digital Library

School of Medicine

January 2020

Developing Normal Placental Growth Curves Using 2-D Ultrasound In A Zimbabwe Maternity Hospital

Belinda Juliana Nhundu

Follow this and additional works at: <https://elischolar.library.yale.edu/ymtdl>

Recommended Citation

Nhundu, Belinda Juliana, "Developing Normal Placental Growth Curves Using 2-D Ultrasound In A Zimbabwe Maternity Hospital" (2020). *Yale Medicine Thesis Digital Library*. 3939.
<https://elischolar.library.yale.edu/ymtdl/3939>

This Open Access Thesis is brought to you for free and open access by the School of Medicine at EliScholar – A Digital Platform for Scholarly Publishing at Yale. It has been accepted for inclusion in Yale Medicine Thesis Digital Library by an authorized administrator of EliScholar – A Digital Platform for Scholarly Publishing at Yale. For more information, please contact elischolar@yale.edu.

Developing Normal Placental Growth Curves using 2-D Ultrasound in a Zimbabwe Maternity Hospital

A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

by

Belinda Juliana Nhundu

2020

Abstract

Developing Normal Placental Growth Curves using 2-D Ultrasound in a Zimbabwe Maternity Hospital

Nhundu BJ, Galerneau F, Kliman HJ. Department of Obstetrics, Gynecology, and Reproductive Services, Yale University, School of Medicine, New Haven, CT.

The placenta aids in providing nutrients and oxygen from the mother to the developing fetus. Using a validated tool to measure Estimated Placenta Volume (EPV) prior studies have shown a small EPV predicts low birthweight in pregnant women in US institutions. The aim of this study was to develop Estimated Placental Volume (EPV) normative curves for a population of women in Zimbabwe across a range of gestational ages. Additionally, to determine if low EPV measurements were predictive of IUFD or stillbirth. From January to June of 2019 a total of 150 women at Mbuya Nehanda Maternity Hospital in Harare Zimbabwe underwent obstetric ultrasound scans between 11+0 to 38+ 6 weeks gestational age (GA). EPVs were calculated using the previously validated Merwins' calculator. Analysis of EPV versus gestational age revealed a parabolic curve with the following best fit equation: $EPV = (0.3923 GA - 0.000486 GA^2)^3$. Two participants had stillbirths associated with low EPV measurements. We conclude that placental volume increases throughout gestation in our cohort of Zimbabwean women and follows a predictable parabolic curve. With a larger patient cohort and more follow up EPV maybe a simple and cost-effective screen to identify women in low resource settings who are carrying fetuses at risk for intrauterine growth restriction, IUFD and stillbirth an allow for increased prenatal care in pregnancy.

Acknowledgements

This project would not have been made possible without the vision and guidance of my mentor and advisor **Dr Harvey Kliman**. Your passion for your patients and EPV is admirable and I was honored to take EPV to Zimbabwe.

I would like to thank my mentors at the University of Zimbabwe **Dr Muchabayiwa Gidiri** and **Dr Claudius Verenga** for their guidance and support throughout my time in Zimbabwe.

To my colleagues at the University of Zimbabwe – **Dr Tinovonga Murinye**, **Dr Mervyn Venge** and soon to be doctor **Loice Makomborero Dodzo** thank you for assisting with the day to day running of the project, this project is yours as much as it is mine.

To **my family** – thank you for your love and support over the years even from thousands mile away.

Table of Contents

1. Introduction.....	5
2. Statement of Purpose.....	14
3. Methods.....	16
4. Results.....	22
5. Discussion.....	29
6. References.....	31

Introduction

Prenatal care is defined as preventative care provided to ensure the health of mother and fetus throughout the duration of pregnancy. The goal is to accurately determine gestational age, provide appropriate screening and testing at each gestational milestone thus mitigating risk for morbidity and ensuring continued evaluation until time of delivery. Access to prenatal care is dependent on the socioeconomic status differs drastically from low-middle income countries and high-income countries [1]. Prenatal care typically begins in the first trimester with frequency of visits determined by risk assessment of the mother and fetus. Typically, in high income countries prenatal visits occur every 4 weeks for the first 28 weeks and then every 2 weeks until 36 weeks of gestation. Weekly visits occur thereafter until delivery [2]. The World Health Organization (WHO) recommends pregnant mothers receive at least four antenatal visits [2].

The Landscape of Prenatal Care in Zimbabwe:

The current study was conducted in Harare, Zimbabwe. Like many other sub-Saharan African countries, Zimbabwe bears a heavy burden of high maternal, neonatal and child mortality when compared to countries in other regions of the world. The Maternal Mortality Ratio has continued to increase over the years, from 283 deaths per 100,000 live births to 578 deaths per 100,000 live births in 2005. The Under-Five Mortality rate is currently 82 deaths per 1,000 live births, which shows an improvement when compared to 102 deaths per 1,000 live births in 1999 [3].

Zimbabwe is divided into 10 administrative Provinces, which are divided into 59 Districts. Harare, the biggest Province is made up of urban districts unlike all the other Provinces which are comprised of both urban and rural districts [3]. Zimbabwe faces tremendous resource limitations and thus antenatal care best practices are guided by the Who Health Organization (WHO) toolkit for developing nations. This is a minimum package that a country can use to build an appropriate program that is best suited for its circumstances. All women are encouraged to book or register at their nearest clinic by 12 weeks of pregnancy (first trimester). In sub-Saharan Africa only 69% of women book for Antenatal care (ANC), in Zimbabwe however that number is higher with over 90% of women booking. Of note this data also includes women presenting for one initial ANC visit without evidence of subsequent visits [3]. Reasons for non-registrations includes poor economic and psychological backgrounds. The Zimbabwean government has alleviated this by waiving user fees at rural and district hospitals.

Early booking within the first trimester allows for accurate pregnancy dating and reducing the risk of post-term pregnancy. If dates are uncertain an ultrasound scan is recommended prior to 24 weeks for accurate dating. Initial visits are also an opportunity for sexually transmitted disease screening such as syphilis, anemia, HIV and UTIs [3]. Low risk women are recommended to be seen six times in every pregnancy in Zimbabwe which is higher than the 4 visits recommended by WHO. Zimbabwe instituted a six-visit minimum in order to maximize the opportunities to detect and manage intrauterine growth restriction. The two extra visits are scheduled for week 20-22 and at 40-41 weeks. Currently for low risk women intrauterine growth restriction is assessed by measurement of the symphysis-fundal height (SFH) in centimeters using a tape measure. A

measurement is done at every visit and recorded on a graph. Failure of an increase in SFH over two consecutive measurements or a single measurement below the 5th percentile for gestation is an indication for referral to a tertiary hospital [3-4].

All women getting ANC in public hospitals get routine iron and folate supplementation throughout pregnancy with a known anemia prevalence of 25%. Routine tetanus and toxoid vaccination are given to all women with doses 4 weeks apart. All women living in malaria endemic areas are given malaria prophylaxis comprising of 3 tablets of sulfadoxine, pyrimethamine at the first two ANC visits [3-4]. All women found to be HIV positive receive counselling with their partners. Currently highly active (triple) anti-retroviral therapy yields best results and is offered to expectant mothers in Zimbabwe [3-4].

Goals

	First visit 8–12 weeks	Second visit 24–26 weeks	Third visit 32 weeks	Fourth visit 36–38 weeks
Goals	Confirm pregnancy and EDD, classify women for basic ANC (four visits) or more specialized care. Screen, treat and give preventive measures. Develop a birth and emergency plan. Advise and counsel.	Assess maternal and fetal well-being. Exclude PIH and anaemia. Give preventive measures. Review and modify birth and emergency plan. Advise and counsel.	Assess maternal and fetal well-being. Exclude PIH, anaemia, multiple pregnancies. Give preventive measures. Review and modify birth and emergency plan. Advise and counsel.	Assess maternal and fetal well-being. Exclude PIH, anaemia, multiple pregnancy, malpresentation. Give preventive measures. Review and modify birth and emergency plan. Advise and counsel.
Activities				
History (ask, check records)	Assess significant symptoms. Take psychosocial, medical and obstetric history. Confirm pregnancy and calculate EDD. Classify all women (in some cases after test results)	Assess significant symptoms. Check record for previous complications and treatments during the pregnancy. Re-classification if needed	Assess significant symptoms. Check record for previous complications and treatments during the pregnancy. Re-classification if needed	Assess significant symptoms. Check record for previous complications and treatments during the pregnancy. Re-classification if needed
Examination (look, listen, feel)	Complete general, and obstetrical examination, BP	Anemia, BP, fetal growth, and movements	Anemia, BP, fetal growth, multiple pregnancy	Anemia, BP, fetal growth and movements, multiple pregnancy, malpresentation
Screening and tests	Haemoglobin; Syphilis; HIV; Proteinuria; Blood/Rh group*; Bacteriuria*	Bacteriuria*	Bacteriuria*	Bacteriuria*
Treatments	Syphilis; ARV if eligible; Treat bacteriuria if indicated*	Anthelmintic**, ARV if eligible Treat bacteriuria if indicated*	ARV if eligible Treat bacteriuria if indicated*	ARV if eligible; If breech, ECV or referral for ECV Treat bacteriuria if indicated*
Preventive measures	Tetanus toxoid; Iron and folate+	Tetanus toxoid, Iron and folate IPTp ARV	Iron and folate; IPTp ARV	Iron and folate ARV
Health education, advice, and counselling	Self-care, alcohol and tobacco use, nutrition, safe sex, rest, sleeping under ITN, birth and emergency plan	Birth and emergency plan, reinforcement of previous advice	Birth and emergency plan, infant feeding, postpartum/postnatal care, pregnancy spacing, reinforcement of previous advice	Birth and emergency plan, infant feeding, postpartum/postnatal care, pregnancy spacing, reinforcement of previous advice

[adapted from WHO ANC guidelines http://www.who.int/pmnch/media/publications/aonsectionIII_2.pdf] Acronyms: (EDD = estimated date of delivery; BP = blood pressure; PIH = pregnancy induced hypertension; ARV = antiretroviral drugs for HIV/AIDS; ECV = external cephalic version; IPTp = intermittent preventive treatment for malaria during pregnancy; ITN = insecticide treated bednet).

*Additional intervention for use in referral centres but not recommended as routine for resource-limited settings.

** Should not be given in first trimester, but if first visit occurs after 16 weeks, it can be given at first visit.

+Should also be prescribed as treatment if anaemia is diagnosed.

doi:10.1371/journal.pone.0093025.t001

Table 1: Focused antenatal care (ANC): The four-visit ANC model outlined in WHO clinical guidelines.

Intrauterine Growth Restriction and Low Birth Weight

Low birth weight (LBW) is regarded as an important predictor of public health and a measure of progress toward sustainable development goals (SDGs) in developing countries. According to the WHO about 17% of infants in the developing world were born with LBW with an average of about 13% of birth in sub-Saharan Africa [6]. WHO has set a threshold for LBW for international comparison at a birth weight of less than 2.5 kg (5.5 lb). Studies have found that LBW babies are about 20 times more likely to die in infancy compared to normal birth weight (NBW) babies, and those who survive, share a greater burden of various physical and psychological complications, such as behavioral and cognitive disorders [6]. The resulting health-care expenditures are also higher for the surviving LBW babies. LBW can have an impact on the health outcomes of the infant but more so influences family planning decisions and decreased desire for future children. Some studies have suggested mothers of LBW infants have increased levels of stress and are more prone to depression [6]. Ultimately, LBW has far reaching socioeconomic consequences for families in the developing world. As such the WHO has committed to a 30% reduction of LBW by the year 2025 [6]. A growing body of evidence has suggested utilization of antenatal care (ANC) is correlated to improved pregnancy outcomes.

The Role of Ultrasound in Pregnancy

Obstetric ultrasound scans have become routine in prenatal care and have been used in clinical practice for over 40 years in the high-income countries (HIC) and more recently in low to medium income countries (LMIC). The elements of the ultrasound examination vary depending on the gestational age of the fetus and the health of both the mother and the fetus. The American College of Obstetricians and Gynecologists, the

American College of Radiology, the American Institute of Ultrasound in Medicine, the Society for Maternal–Fetal Medicine, and the Society of Radiologists in Ultrasound have established standardized terminology for obstetric ultrasounds categorized into three as standard, limited and specialized [7-9].

1. Standard—Evaluation of fetal presentation, amniotic fluid volume, cardiac activity, placental position, fetal biometry, and fetal number and anatomic survey.

The maternal cervix and adnexa should be examined as clinically appropriate and when technically feasible.

2. Limited—A limited examination is performed with a specific clinical concern, such as confirming cardiac activity in the setting of vaginal bleeding or confirm placental location during labor.

3. Specialized—A detailed or targeted anatomic examination is performed when an anomaly is suspected on the basis of history, laboratory abnormalities, or the results of the limited examination or standard examination. Other forms of specialized examinations include fetal doppler ultrasonography, biophysical profile and fetal echocardiography. Other indications of a specialized examination include fetal growth restriction and multifetal gestation.

The fetal anatomy survey typically occurs after 18 weeks' gestation and includes a multitude of measurements [7-9]:

Head, Face, and Neck: lateral cerebral ventricles, choroid plexus, midline falx, cavum septum pellucidum, cerebellum, cisterna magna, and upper lip Chest: heart with four-chamber view and left and right ventricular outflow tracts

Abdomen: stomach (presence, size, and situs), kidneys, urinary bladder, umbilical cord insertion site into the fetal abdomen, umbilical cord vessel number

Spine: cervical, thoracic, lumbar, and sacral spine

Extremities: legs and arms

Fetal Sex: In multiple gestations and when medically indicated

Serial assessment of fetal size by clinical methods such as fundal height is a low-cost, relatively reliable, and easy way to screen for fetal growth disturbances in most pregnant women. When a growth disturbance is suspected clinically or there is a medical or obstetric condition that increases the risk of a growth disturbance, ultrasonography is the modality of choice to identify abnormal fetal growth [7-9].

Four standard fetal measurements generally are obtained as part of a complete obstetric ultrasound examination after the first trimester: 1) fetal abdominal circumference, 2) head circumference, 3) biparietal diameter, and 4) femur length. Fetal morphologic parameters can be converted to fetal weight estimates using published formulas and tables [7-9].

Contemporary ultrasound equipment calculates and displays an estimate of fetal weight on the basis of these formulas. Although all of the published formulas for estimating fetal weight show a good correlation with birth weight, the variability of the estimate is up to 20% with most of the formulas [7-9]

Imaging the Placenta in Pregnancy

The placenta has been shown to play a vital role in pregnancy by providing nutrients and critical oxygen to the fetus from the mother [10-14]. Much effort has been directed toward the detection and assessment of intrauterine growth restriction (IUGR). The many cases of IUGR have traditionally been subdivided into fetal, placental and maternal [12]. It is clear that a normally functioning placenta is critical for normal fetal growth and development. Adequate fetal growth depends on the efficient delivery of nutrients from the mother to the fetus and therefore requires normal uterine perfusion, normal transplacental exchange of nutrients and waste and normal umbilical perfusion. Placental thickness and volume have been used to predict chromosomal anomalies and diseases such as pre-eclampsia, thalassemia and other complications of pregnancy [13-15]. Currently sonographic assessment of placental volume is time consuming and requires expensive technology. The best approaches have been done with three-dimensional ultrasound measurements that require specialized training [16].

The relationship between small placental size and fetal complications was explored by Wolf et al. Their study of 18 pregnant patients between 16 and 20 weeks gestation, and estimated placental volume and fetal weight by ultrasound at regular intervals [17]. A plot of EPV vs GA showed a sigmoid relationship between placental volume and gestational age. Of the 19 patients 11 experienced adverse fetal outcomes in these patients, the EPV vs gestational age growth curve showed restricted placental growth. The authors concluded that placental growth restriction preceded fetal growth restriction and adverse events [17].

Wolf et al. further explored a method to measure 3D placental ultrasound. This method involved imaging parallel slices of the placenta separated by a given distance and the corresponding area of each slice [18]. The resultant equation could only be applied to placenta upto 26 weeks' gestation due to the large size of the placenta with increasing gestation [18]. Despite the mathematical strength of 3D ultrasound, the method required specialized software and enhanced imaging analysis. This made it difficult to utilize in a clinical setting and a simpler method was required for use in a clinical setting.

Azpuru et al first described a novel technique using 2-dimensional ultrasound to measure estimate placental volume they were able to show that measurements of EPV were similar to actual placental weights at birth [19]. Arleo et al further validated this method of using 2D ultrasound and developed normative EPV growth curves from a cohort of patients at Weill Cornell Medical Center [20]. They measured the EPVs of 423 patients across different gestational ages. They showed that with increasing gestational age the EPV increased in a parabolic relationship of these 423 patients 4 patients had an abnormally small EPV, they suggested such patients would be ideal candidates for demonstrating if EPV may be a useful tool for predicting adverse outcomes [21]. Further studies have been conducted by Isakov et al in a cohort of women at Yale New Haven Hospital. The study followed 366 participants to further validate EPV across a range of gestational ages. They showed that in that cohort EPV increased with gestation following a predictable parabolic curve [22]. Additionally, an analysis of birth weight outcomes showed women with EPVs of patients in the 50th percentile had 2.42 times the odds of having a newborn with a birth weight in bottom 50th percentile. Indicating a possible correlation of birth weight will low EPVs [22].

Statement of Purpose

Currently placental volume is not assessed in the routine care of pregnant women, despite its importance in prenatal development, mainly due to the technical difficulties hindering placental volume measurements. Kliman Labs has developed and validated a simple method of calculating the EPV, which can be done routinely by any healthcare provider in less than one minute using only a simple ultrasound device.

The study was conducted at Mbuya Nehanda Maternity Hospital in Harare Zimbabwe. The study aimed to establish a new standard in prenatal care by allowing pregnant women to know if their fetus is well nourished or at risk for unexpected and sudden demise using low cost 2D ultrasound to measure the volume of the placenta. This knowledge would empower caregivers to identify and intervene in cases where a low EPV would be the first indication of an IUFD.

Research Aims:

1. To develop population normative curves for EPV measurement in a cohort of Zimbabwean women and compare with normative curves from a cohort of women at Yale New Haven Hospital and Cornell Such normative data will form the basis for the generation of tables, which could be incorporated into future ultrasound devices.
2. To evaluate the relationship between EPV and birthweight in women undergoing obstetrical ultrasound at Mbuya Nehanda Maternity in Zimbabwe.
3. To determine if EPV measurements are predictive of adverse outcomes such as

Intra uterine fetal demise and still birth.

Hypothesis:

1. Normative curves from a cohort of Zimbabwean women are comparable to normative curves acquired from Yale New Haven Hospital and Cornell studies.
2. Small EPV is associated with a statistically significant risk for low birthweight in Zimbabwean women
3. EPV measurement can be used as a tool for flagging patients at risk for IUFD.

Research Methods

This prospective study was approved by the Yale University School of Medicine Human Investigation Committee (protocol number 0905005157) as well as the University of Zimbabwe Medical Research Council of Zimbabwe (protocol number ZW118).

Patients with singleton pregnancies presenting for a routine prenatal visit and/or obstetric ultrasound at Mbuya Nehanda Hospital were enrolled in the study and informed written consent was obtained by researcher BN. Each patient was interviewed regarding their antepartum course and medical history sufficient to validate the inclusion and exclusion criteria.

Inclusion Criteria:

- Gestational age between 8 and 42 weeks by last menstrual period.
- Singleton gestation
- 18 years old or greater

Exclusion Criteria:

- Rupture of membranes
- Intramural fibroid
- Placenta previa
- Women in active labor who have not received an epidural/other analgesia
- A pain score of four or greater based on the Wong-Baker Faces Pain Scale.

Placental measurements were performed on 150 patients using the Philips Z

model 2D ultrasound machine by trained researcher BN. The placenta was imaged at the maximal cross section with the probe placed perpendicular to the base of the placenta. The width measurements were taken from the tip edge to the opposite tip edge. The Top apex point of the maternal surface placenta was then located. A line was then created from the apex point to the width line until it lies perpendicular to the width line. Lastly the thickness was measured by measuring from the top apex point to the fetal surface of the placenta. The thickness is always equal to (in the case of flax placenta) or less than the height line (Figure 1-3)

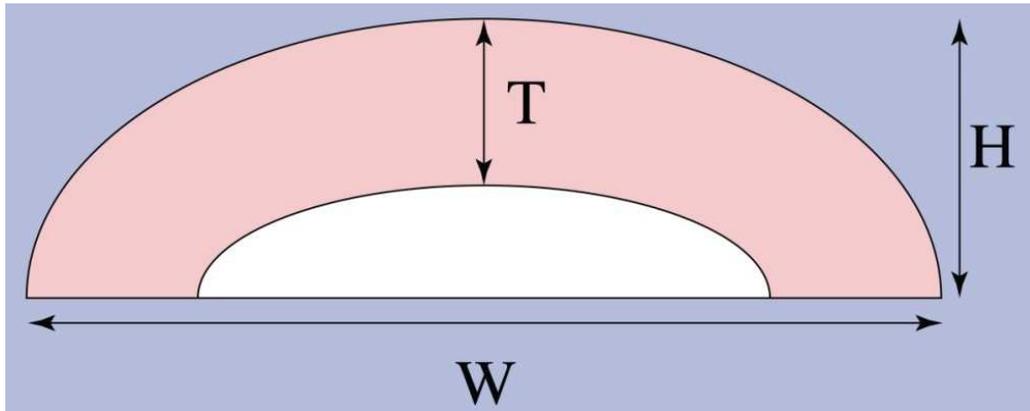


Fig. 1. Diagram showing parameters measured to calculate estimated placental volume (EPV). W = maximal width, H = height at maximal width, T = thickness at maximal width.

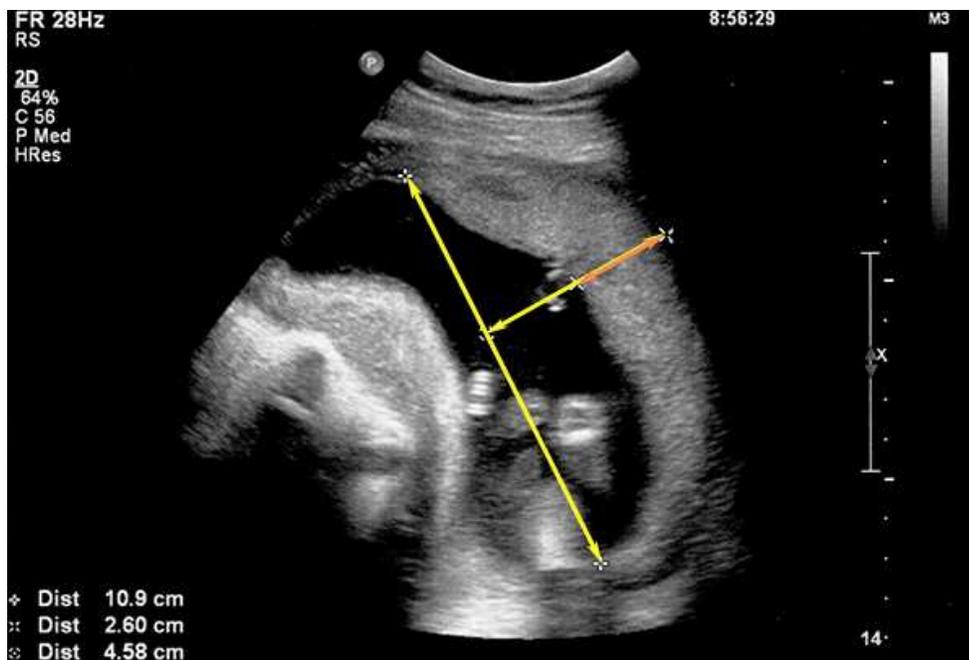


Fig. 2: Representative image of an anterior placenta. Image shows a crescent shaped placenta with baseline width, height and thickness measured.

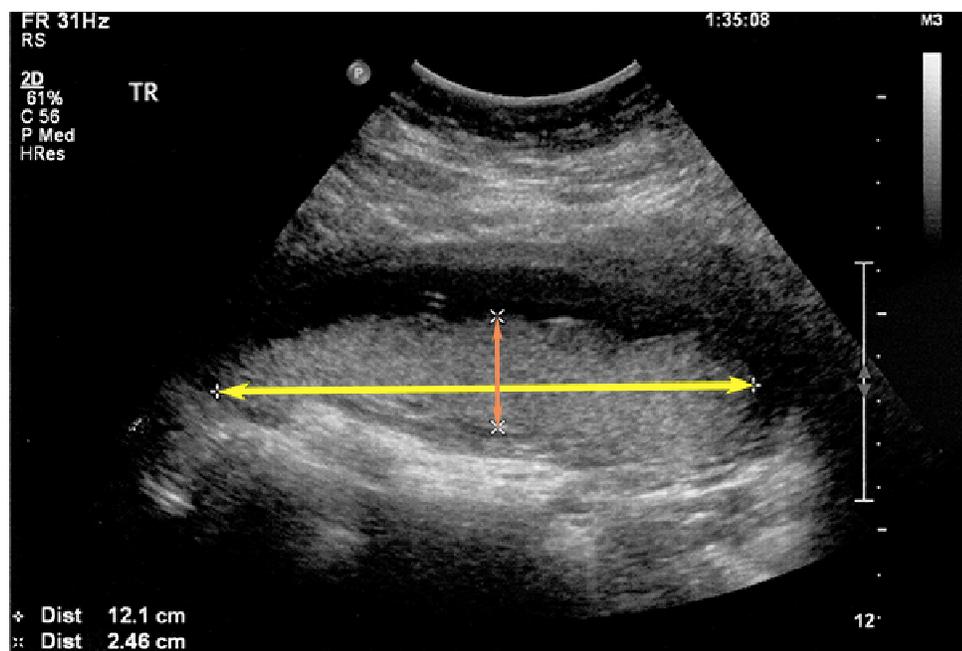


Fig. 3: A representative image of a flat placenta. The thickness and the height are the

same values for purposes of measuring the EPV.

The ultrasound measurements themselves took an additional 1 to 2 minutes beyond the routine ultrasound performed for clinical. For each patient the following data was collected and recorded. Deidentifying study number, gestational age based on last menstrual period (LMP) or estimated date of delivery (EDD) as determined by first trimester ultrasound, date of birth as well as relevant serology (HIV, syphilis and GBS.). Neonatal outcomes collected were as follows (APGAR scores, birth weight, ICU stay and other complications).

Each patient received at least one EPV measurement and a maximum of three EPV measurement at one visit. The EPV calculation was done using the Merwin's calculator at a specific gestational age (Figure 4). The EPV measurements were averaged for each patient resulting in 150 data points.



Fig. 4: Mobile Screenshot of Merwin's Calculator utilized for quickly calculating EPV and varying gestational ages. Data for width, height and thickness are inputted to generate an EPV in cc at a specific gestational age.

For the participants who delivered at Mbuya Maternity Hospital the infant's birthweight (BW), Apgar scores, mode of delivery were recorded were possible.

Data Analysis

Using R version 3.3.2 statistical software, an Estimated Placenta Volume vs Gestational Age best fit curve was generated for the patient cohort from Zimbabwe. Additionally, an EPV vs GA curves was generated and compared to data previously obtained from the patient cohort from Yale New Haven Hospital. Subgroup analysis was performed on a subgroup of participants who delivered at Mbuya Nehanda Maternity and subsequently has birth weight data available. Statistical analysis and interpretation performed by BN and HK.

Results

The first research aim was to develop population normative curves between EPV and GA in a cohort of Zimbabwean women, and then to compare this to previously published set of EPV vs GA data from Yale New Haven Hospital and Weill Cornell Medicine.

Aim 1: To develop population normative curves for EPV measurement in Zimbabwean women and compare with normative curves from the United States (Yale New Haven Hospital and Cornell).

The normative curve showing the relationship between EPV and GA in Zimbabwean participants showed a parabolic relationship with the best following best fit equation (Figure 5):

$$EPV = (0.3923 GA - 0.000486 GA^2)^3$$

The 10th and 90th percentile were within +/- 1.01 standard error. The p-value was less than 2.2×10^{-16} with an adjusted r^2 of 0.983.

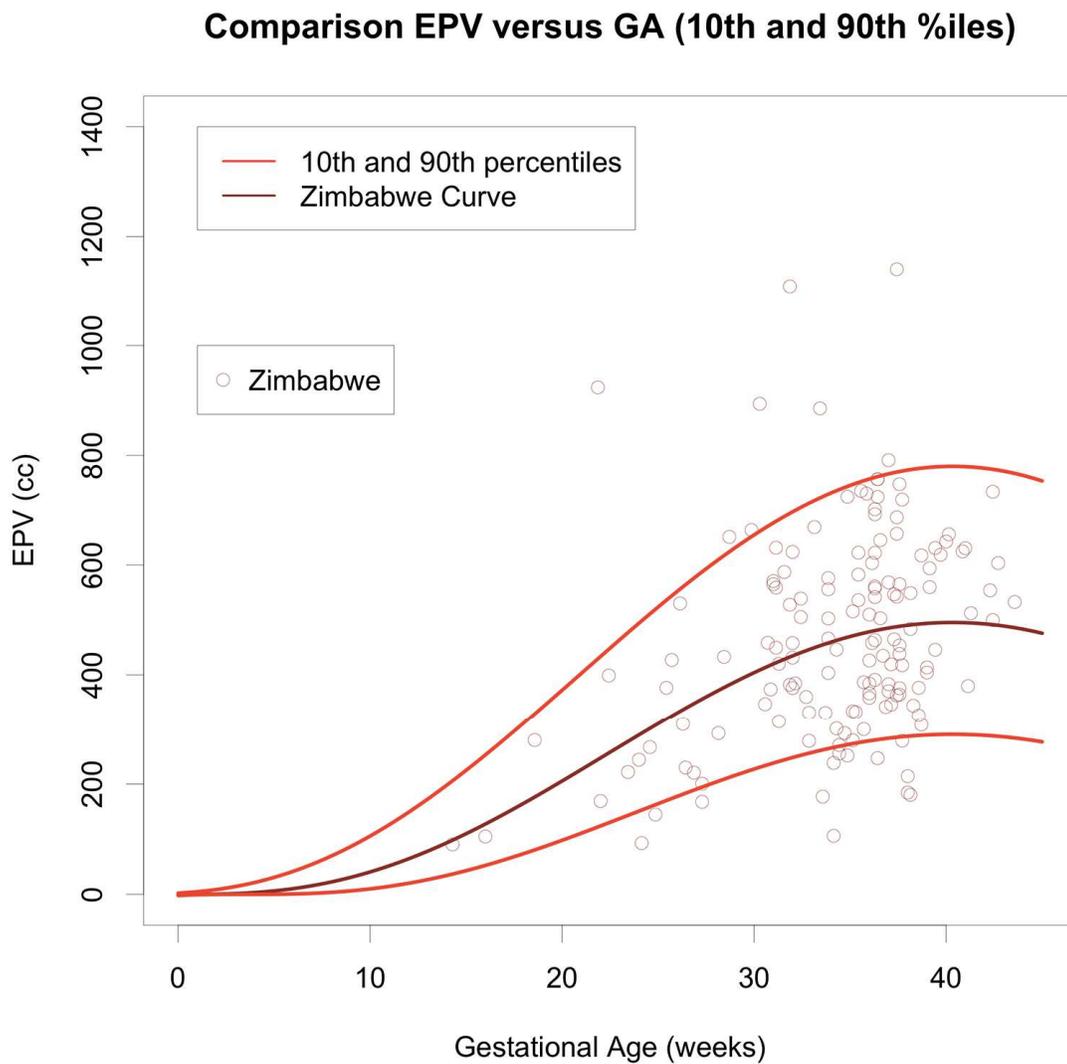


Fig. 5: Estimated Placenta Volume (cc) vs Gestational Age (weeks) showing a parabolic relationship in a cohort of Zimbabwean women.

The comparative data from Yale participants following the same inclusion and exclusion criteria showed a parabolic relationship with the following best fit equation :

$$EPV = (0.3724 GA - 0.000366 GA^2)^3$$

A composite graph showing data from both the Zimbabwe and Yale cohort showed a similar trend in the data with increasing EPV with increasing GA (Figure 6). The Yale data has more 1st and 2nd trimester EPV as compared to more 3rd trimester reading in the Zimbabwean cohort. The difference is due to late presentation for imaging among Zimbabwean women as compared to participants at Yale New Haven Hospital. Both data sets had similar coefficients in the EPV equation indicating that the placenta volumes in both groups increased at the same rate.

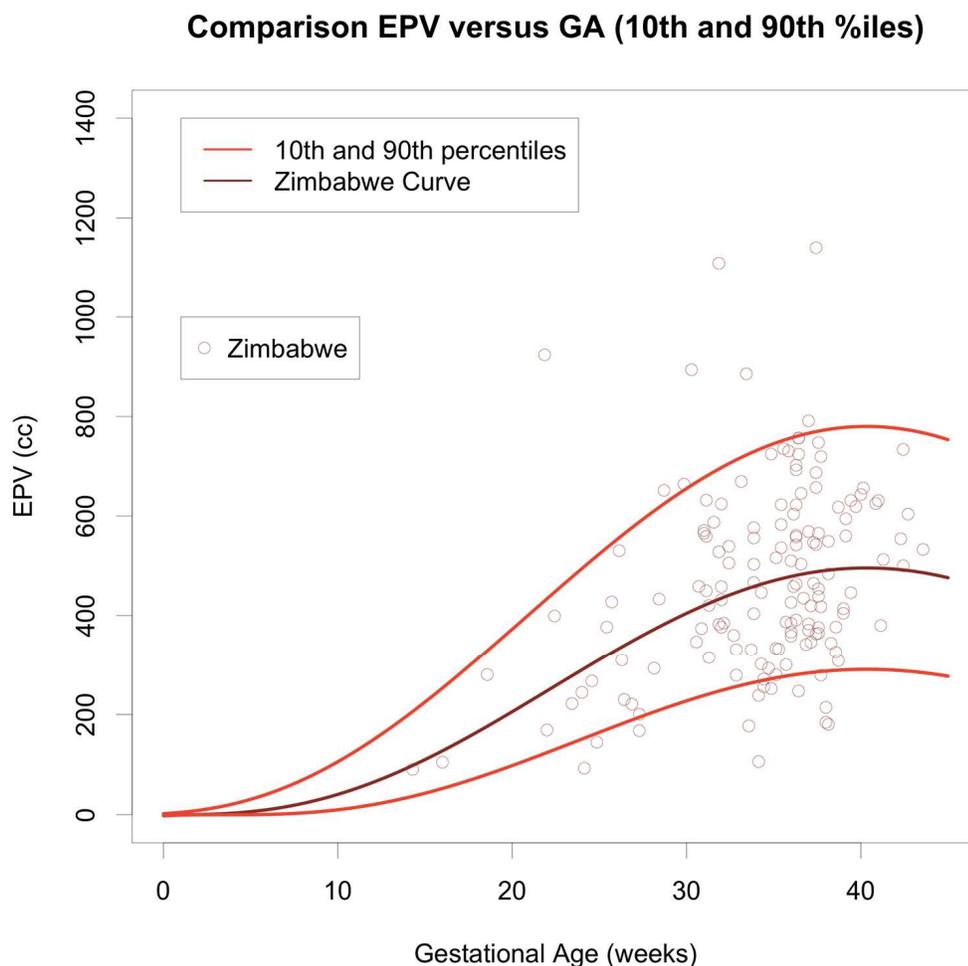


Fig. 6: Estimated Placenta Volume versus (cc) Gestational Age (weeks) curves for Yale data set (blue) and Zimbabwean cohort (red).

Aim 2: To evaluate the relationship between EPV and birthweight in a women undergoing obstetrical ultrasound at Mbuya Nehanda Maternity in Zimbabwe.

We next looked at the women who delivered at Mbuya Nehanda Maternity hospital and had their birth records available to document birth outcomes. Of the 150 women imaged for EPV measurements 19 women had complete birth records available for evaluation. Data collected included: date of delivery, birthweight and any adverse outcomes (included stillbirth and intrauterine fetal demise). EPV percentiles were

generated as per gestational age using the Merwin's' calculator. The birth weight percentile was determined using the already available normative curves for birth weight and gestational age at delivery. In general, among the participants with available birth weight data women with small EPV percentile measurements for their gestational age had babies with small birth weights. Most women with babies weighing under 2500g (considered small for gestational age) had a low EPV measurements. Additional data is required for more statistical analysis.

Table 2: EPV data from 19 participants with available birth outcomes.

	GA (weeks)	Mean EPV (cc)	EPV %	Birth Weight (g)	Birth Weight %	Birth outcome
1	27.3	201	2.00	1650	10	live
2	34.1	238	0.20	2700	10	live
3	35.1	280	0.60	3700	60	live
4	36.0	510	28.00	2720	10	Stillbirth
5	36.0	535	34.00	3500	50	live
6	36.1	458	16.00	2950	50	live
7	36.4	247	0.10	2500	10	Stillbirth
8	36.6	503	24.00	4320	97	live
9	37.3	547	32.00	2400	3	live
10	37.4	687	65.00	2510	10	live
11	37.4	658	60.00	3300	20	live
12	37.6	364	3.00	2870	20	live
13	37.6	566	36.00	2600	10	live
14	37.7	719	53.00	2996	20	live
15	38.1	549	30.00	2950	20	live
16	39.1	594	38.00	2510	3	live
17	39.1	529	23.00	3200	20	live
18	39.4	631	58.00	2940	3	live
19	41.3	513	16.00	3610	50	live

Aim 3: To determine if EPV measurements are predictive of adverse outcomes such as Intra uterine fetal demise and still birth.

We next looked at the patients who reported adverse birth outcomes in our cohort of patients. Of the 20 patients with available birth outcomes two participants reported a stillbirth.

The first a 38 year old G4P3 BMI 23.1 imaged at 36+4 weeks had a mean EPV measurement of 247cc (0.10%) follow up then showed the patient had a stillbirth at 38 weeks with a baby weighing 2500g (10%) . The ratio of estimated fetal weight (EFW) and EPV was 10.81 indicating a critically low placental volume and placental size. The patient had no prior history of pregnancy losses with no known past medical history.

The second participant a 30year old G3P2 BMI 28.6 imaged at 36 weeks had a mean EPV of 510cc (28%) follow up showed the patient had a stillbirth at 39 weeks with a baby weighing 2720g (10%). The EFW/EPV was 4.94 indicating a low placental volume and corresponding low placenta size. The patient had no past medical history.

Our data set showed 2 stillbirths in a cohort of 150 which is consistent with the rate of stillbirth of 1 in 100 pregnancies per year in the United States. There is no available data for the rate of stillbirths among Zimbabwean women. In both cases the placenta was not available for examination.

Discussion

The current study explored the utilization of Estimated Placenta Volume as a screening tool for IUFD and still birth in an antenatal clinic in Zimbabwe. The initial aim was to develop normative curves for a cohort of pregnant women presenting to an antenatal clinic in Zimbabwe. The normative curves for EPV vs GA plotted showed a parabolic curve further validating the mathematical model presented by previous authors from data sets at Yale New Haven Hospital and Weill Cornell College [12]. This study is the first to show such a model for women in Zimbabwe measurements. In both cases the EPV measurements were low enough to red flag a patient for follow up. Of note both patients were initially imaged for EPV at 36 weeks and it has no available prior imaging to determine when the placenta volume had become low. Both cases illustrate the need for the potential of incorporating the EPV into clinical practice as a tool for screening for potential adverse outcomes.

The current study shows that EPV measurements continue to be quick and easy to perform during routine prenatal ultrasound visits. A trained provider can effectively measure placenta volume within 2 minutes. This study was performed in a low resource setting clinic with a standard package 2D ultrasound machine. Unlike previous methods for determining placental volume obtaining 2D ultrasound images of the placenta and calculating EPV is fast requires minimum cost and training. A small EPV measurement could serve as an indicator to a health care provider of a fetus at risk. This information can then be utilized in further visits for serial EPV and fetal weight measurements. At present there is low clinical utility to a small EPV measurement in early pregnancy. Our study parameters initiated EPV measurements at 11 weeks gestation. A low percentile

EPV measurement in early pregnancy is best managed by serial EPV measurements. A consistently low EPV with increasing gestational age further warrants close follow up.

The present study has several limitations. While we were able to recruit a large cohort of patients from the antenatal clinic most women did not deliver at the maternity hospital and hence their birth weight data was not available to follow up for outcomes. Having more birthweight data would have increased the number of patients analyzed and increased the level of generalizability of the study in our population. Secondly most of our participants presented in their third trimester of pregnancy for ultrasound imaging making it difficult to measure large sized placentas and also for those placentas that were found to be small in size and opportunity to determine the chronicity of the placental volume defect.

This study is the first to generate normative data on a population of pregnant women in Zimbabwe, with a larger patient cohort the data can be utilized to automatically flag abnormal placental size. Such normative data will form the basis for the generation of tables, which could be incorporated into future ultrasound devices. This will empower future caregivers to identify and intervene in cases where an IUFD or preterm delivery would have been the first indication of any problems. This method will create, just as a car has a gas gauge, a “placenta tank” gauge where none has existed.

References

1. Majoko K, Munjanja SP, Magwali T, Kasule J. Best Practices For Antenatal care in Zimbabwe. *The Central African Journal of Medicine*. 2006; 52:1-2.
2. Guzha BT, Magwali TL, Mateveke B, Chirehwa M, Nyandoro G, Munjanja SP. Assessment of quality of obstetric care in Zimbabwe using the standard primipara. *BMC Pregnancy and Childbirth*. 2018;18:205
3. Munjanja SP, Masona D, Gwaze I, Chipato T. Audit of ultrasound scanning diagnosis. *The East African Medical Journal* 1987; 64:600-605.
4. Harkness UF, Mari G. Diagnosis and management of intrauterine growth restriction. *Clinics in Perinatology* 2004;31:743-64.
5. Baschat AA, Harman CR. Antenatal assessment of the growth restricted fetus. *Curr Opin Obstet Gynecol* 2001;13:161-8.
6. American College of Obstetricians and Gynecologists (ACOG). Practice Bulletin No.102 :Management of Stillbirth. ACOG. Washington, DC 2016.
7. AAP Committee on Fetus and Newborn and ACOG Committee on Obstetric Practice. Guidelines for perinatal care. 8th edition. American Academy of Pediatrics, Elk Grove Village (IL); 2017
8. American College of Obstetricians and Gynecologists (ACOG). Practice

Bulletin No. 175: Ultrasound in Pregnancy. ACOG, Washington, DC, 2016.

9. American College of Obstetricians and Gynecologists (ACOG). Practice

Bulletin No. 12: Intrauterine growth restriction. ACOG, Washington, DC, 2008.

10. Baschat AA. Doppler application in the delivery timing of the preterm growth-restricted fetus: another step in the right direction. *Ultrasound in Obstetrics & Gynecology* 2004;23:111-8.

11. Rotmensch S, Liberati M, Luo JS, et al. Color Doppler flow patterns and flow velocity waveforms of the intraplacental fetal circulation in growth-retarded fetuses. *Am J Obstet Gynecol* 1994;171:1257-64.

12. Kliman HJ. Uteroplacental blood flow. The story of decidualization, menstruation, and trophoblast invasion. *Am J Pathol* 2000;157:1759-68.

13. Elchalal U, Ezra Y, Levi Y, et al. Sonographically thick placenta: a marker for increased perinatal risk--a prospective cross-sectional study. *Placenta* 2000;21:268-72.

14. Metzenbauer M, Hafner E, Schuchter K, Philipp K. First-trimester placental volume as a marker for chromosomal anomalies: preliminary results from an unselected population. *Ultrasound in Obstetrics & Gynecology* 2002;19:240-2.

15. Hafner E, Metzenbauer M, Hofinger D, et al. Comparison between three-dimensional placental volume at 12 weeks and uterine artery impedance/notching at 22 weeks in screening for pregnancy-induced hypertension, pre-eclampsia and fetal growth restriction in a low-risk population. *Ultrasound Obstet Gynecol* 2006;27:652-7.

16. Chen CP, Wang KG, Chen CY, Yu C, Chuang HC, Chen H. Altered placental syncytin and its receptor ASCT2 expression in placental development and pre-eclampsia. *BJOG: An International Journal of Obstetrics & Gynaecology* 2006;113:152-8.
17. Hafner E, Metzenbauer M, Hofinger D, et al. Placental growth from the first to the second trimester of pregnancy in SGA-foetuses and pre-eclamptic pregnancies compared to normal foetuses. *Placenta* 2003;24:336-42.
18. Kinare AS, Natekar AS, Chinchwadkar MC, et al. Low midpregnancy placental volume in rural Indian women: A cause for low birth weight? *American Journal of Obstetrics & Gynecology* 2000;182:443-8.
19. Schuchter K, Metzenbauer M, Hafner E, Philipp K. Uterine artery Doppler and placental volume in the first trimester in the prediction of pregnancy complications. *Ultrasound in Obstetrics & Gynecology* 2001;18:590-2.
20. Merce LT, Barco MJ, Bau S. Reproducibility of the study of placental vascularization by three-dimensional power Doppler. *Journal of Perinatal Medicine* 2004;32:228-33.
21. Azpurua HJ, Funai EF, Coraluzzi L, et al. Determination of placental weight using two-dimensional sonography and volumetric mathematic modeling. 18th World Congress on Ultrasound in Obstetrics and Gynecology. Chicago, IL, 2008.
22. Schwartz N, Wang E, Parry S. 2012. Two-dimensional sonographic placental measurements in the prediction of small-for-gestational-age infants. *Ultrasound Obstet Gynecol* 40:674–679

23. Arleo EK, Troiano RN, da Silva R, Greenbaum D, Kliman HJ. Utilizing twodimensional ultrasound to develop normative curves for estimated placental volume. *Am J Perinatol.* 2014;31(8):683–8.
24. Isakov KMM, Emerson JW, Campbell KH, Galerneau F, Anders AM, Kliman HJ. Estimated Placental Volume and Gestational Age. *American Journal of Perinatology* 2018; 35:748-758.