Intrauterine foetal and child growth in the context of Ethiopian Health system: Implications for Prenatal care

Intrauterine foetal growth and child linear growth in Ethiopia

Meselech Assegid Roro

Thesis for the degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
2023

UNIVERSITY OF BERGEN

Intrauterine foetal and child growth in the context of Ethiopian Health system: Implications for Prenatal care

Intrauterine foetal growth and child linear growth in Ethiopia

Meselech Assegid Roro

Thesis for the degree of Philosophiae Doctor (PhD)
at the University of Bergen

Date of defense: 09.03.2023

Year: 2023

Title: Intrauterine foetal and child growth in the context of Ethiopian Health system: Implications for Prenatal care

Name: Meselech Assegid Roro

Print: Skipnes Kommunikasjon / University of Bergen

Dedication

To mothers who have to deal with pregnancy, taking care of their offspring, and to children who live in drought-affected areas.

Scientific environment

What is this thesis about?

Understanding intrauterine foetal growth is a fundamentally important for early identification of normal and abnormal foetal growth, which can affect birth weight at birth and growth in early childhood. This thesis addresses patterns in intrauterine foetal growth, new-born weight, and child linear growth. Particular emphasis is given to patterns of intrauterine growth compared to international standards and its association with birth weight and linear child growth in the context of maternal and child health services in the study area.

The study on intrauterine growth patterns in Paper I was undertaken to evaluate the similarity and variation of foetal growth in the study area as compared to the World Health Organization (WHO) and INTERGROWTH-21st reference standards (1, 2). The results will inform subsequent use of these references. In addition, this thesis evaluated the influence of the intrauterine foetal growth pattern on birth weight, and linear child growth as measured at 11 to 24 months postnatal (Paper II). Paper III analyses the compliance of antenatal care utilization with national and WHO guidelines and its association with adverse pregnancy outcomes. Hence, this thesis presents information on how the intrauterine growth pattern relates to early child linear growth, information that may contribute important and relevant information that will improve health care given during pregnancy and its implication for child growth and development.

Research Environment

This study was conducted within the context of a large community-based cluster randomized controlled trial (MalTrials) designed to determine the impact of combined long-lasting insecticidal nets and indoor residual spraying for malaria prevention in Ethiopia (3). Within this study, a cohort of pregnant women in the community where the trial was conducted were enrolled and followed until the first three days of postpartum period. Subsequently, their children were followed up to 11 to 24 months after delivery. This prospective cohort study was conducted from July 2016 to 2018. One of the initial ideas was to investigate if malaria influenced intrauterine growth. However, we only found malaria in five of the pregnant women and thus we modified our initial objective to the one mentioned above.

The trial was conducted from 2014 to 2016 in the Adami Tullu area in the Ethiopian Rift Valley by researchers from Addis Ababa University and Hawassa University, Ethiopia, and from the University of Bergen and Norwegian University of Life Sciences in Norway.

Acknowledgements

I would like to extend my sincere gratitude to the Norwegian State Education Loan Fund and the Centre for International Health, University of Bergen and the MalTrials study funded by Research Council of Norway for funding my study. My gratitude also goes to Addis Ababa University, School of Public Health for supporting my PhD work. Oromia Regional Health Bureau, East Shewa zonal health department, Adami Tullu district health office also deserve my sincere gratitude for facilitating the fieldwork. This work was made possible by participation of pregnant mothers, field supervisors and data collectors to whom I am so grateful.

To my supervisor, Professor Bernt Lindtjørn, I would like to extend my sincere gratitude for your close supervision, professional guidance, ethics and discipline to mention a few. Your dedication, qualified support, timely and quick feedback has enormously helped me to be a much better professional capable of independently working and cultivating my career.

I would also like to express my heartfelt thanks to Professor Wakgari Deressa, my co-supervisor for your support throughout my PhD work, particularly during the time of data collection and during the write up.

I would like to express my heartfelt thanks to Professor Bente Elisabeth Moen and Dr. Mitike Molla. I am so grateful for your enormous contributions, facilitation and support to my PhD work. Finalizing this PhD work would have been unimaginable without the key roles you played to make it happen.

I wish to express my earnest appreciation to the staff of the Centre for International Health, University of Bergen for all rounded support and friendly environment. To Gunhild Koldal, Solfrid Hornell and Ingvild Hope, thank you for facilitating all logistic and practical issues.

I am grateful to Dr. Malede Birara, Dr. Balkacew Nigatu and Dr. Delayehu Bekele from St. Paul Hospital Millennium Medical College for providing support on ultrasound training and Dr. Yirgu Gebrehiwot and Dr. Nardos Temesgen from Tikur Anbessa Hospital for your support during validation of ultrasound measurements.

My appreciation goes to special families in Bergen: Geremew Huluka and wife Mette Oxnevad, Dr. Abebe Gomoro and wife Saba, and Dr. Yaliso Yaya and wife Tigist who showed me special love and care and always surprising my family with your surprise presents. I would like also to thank families of Pastor Jeto Hordofa Ala and Gemechu Adamu Ashena and all members of Bergen Oromo Covenant Evangelical church for your encouragement, support and the prayer.

A special thank goes to my family: My husband, Dr. Senbeta Guteta. I do not have words to express your love, care and immense generosity support through the long and sometimes difficult Ph.D. journey. You are source of inspiration and reason of success in my life, next to the almighty God. My children: Ebise and Jalane thank you for putting up with me when I was absent for long period of time, for your love and endurance at times demanding my full attention. Love you so much and life is beautiful with you. Love you all forever!

My parents; my mother Biritu Ameja, my sister Lebesu Belis, Mr Erketa Ejo and my brother, Reta Assegid; words cannot express my bundles of gratitude to you. Without the inspiration, drive and support you gave me, I might not be the person I am today.

I would like to thank the Almighty God for being my source of potential who make impossibilities into possibilities, without him I would not have been at this stage “I will extol you, my God, O king I will praise your name continuously; every day I will praise you! I will praise your name continually. Psalms 145: 1-2”.

Summary

Introduction

Ethiopia is a country with a low coverage of antenatal care services. In 2019, only 43% of pregnant women had the recommended four antenatal care (ANC) visits during their pregnancy while 24% of women in Ethiopia had no ANC visits at all. Different national initiatives are underway to expand and improve maternal health services utilization. These are aligned with international and national agendas and goals.

In the first 1000 days of life, starting from the time of conception, growth is viewed as a continuum between the foetal period, infancy, and early childhood. Foetal growth is dynamic. Defining normal or abnormal foetal growth requires the taking of serial measurements. If the foetal growth is abnormal, it can result in low birth weight or prematurity. Low birth weight and prematurity are major contributors of neonatal and infant mortality and morbidity.

ANC is an important care point that has a positive influence in identifying pregnancy-related complications. It can also contribute to improved pregnancy outcomes. Ethiopia implemented the World Health Organization's (WHO) focused ANC (FANC) model at all health facilities until February 2022, which was a goal orientated approach to delivering evidence-based interventions carried out at four critical times during pregnancy.

Population specific foetal growth charts that can be used to monitor foetal growth patterns are lacking, particularly in areas affected by food insecurity and drought such as are found in Ethiopia. Moreover, the influence of intrauterine uterine growth on birth weight and early childhood growth has not been examined in this country. In addition, even though ANC is taken as an opportunity for influencing the well-being of pregnant mothers and growing foetus, the evidence supporting a relationship between ANC and adverse pregnancy outcomes is unclear in Ethiopia.

Objective

The overall objective of this thesis was to examine intrauterine and child growth in a drought-affected rural area of Ethiopia in the context of the country's health system. The first objective was to assess intrauterine uterine growth patterns in comparison to the WHO and the INTERGROWTH 21st intrauterine uterine growth standards. The second objective was to examine the influence of intrauterine foetal growth on length-for-age Z-score and weight-for-length Z-score in early childhood 11–24 months of age. The third objective was to assess the compliance of ANC utilization with national and WHO guidelines and whether adverse pregnancy outcomes were associated with the use of antenatal care services.

Methods

We conducted a prospective cohort study in the rural community of Adami Tullu district in the Oromia Regional State in south central Ethiopia from July 2016 to November 2018. We included 704 pregnant women, with a gestational age of less than 24 weeks and followed them to delivery. We followed the children until they were 24 months postnatal.

At enrolment, we collected data on maternal, sociodemographic and household characteristics. We also collected data on maternal weight, blood pressure, mid upper arm circumference (MUAC), haemoglobin, and malaria test results at 26, 30, and 36 weeks of gestation. We obtained foetal biometric measurements (head circumference, biparietal diameter, abdominal circumference, and femoral length) and estimated foetal weight using ultrasound at each visit. We subsequently followed the new-borns postnatally and measured their lengths and weights once at the age of 11-24 months.

Foetal weight was estimated using the Hadlock algorithm, and the 5th, 10th, 25th, 50th, 75th, 90th, and 95th centiles were generated from this model. We compared the Z-scores and percentiles of biometric measurements and estimated foetal weight with the INTERGROWTH 21st and WHO multicentre foetal growth reference standards (Paper I).

After birth, we measured the weights and lengths of 554 children at age of 11–24 months. The birth-weight-for-gestational-age Z-score was calculated using INTERGROWTH 21st international new-born birth standards. We determined Z-scores of length-for-age, weight-for-age and weight-for-length of the children using the 2006 WHO child growth standards. We used a multilevel mixed effect linear regression model to examine the influence of foetal biometric measurements, new-born (birth weight, gestational age at delivery, sex), maternal (age, height, education, occupation, parity) and household (household wealth, family size) characteristics on birth weight, child length-for-age and weight-for-age (Paper II).

We used the WHO and national ANC guidelines to compare the service utilization patterns, and collected data on ANC utilization among 704 pregnant women at three prescheduled visits during pregnancy and at birth. Data on the extent of antenatal care content received, timing of antenatal care, location of antenatal care, and location and mode of delivery were obtained by interviewing the pregnant women. Adverse pregnancy outcomes was computed as the sum of preterm birth, intrauterine foetal deaths, and stillbirths (Paper III).

Results

The distribution of biometric measurements and estimated foetal weight in our study were similar to the WHO and INTERGROWTH-21st references. Most measurements were between -2 and +2 of the reference Z-scores. Based on the smoothed percentiles, the 5th, 50th, and 95th percentiles, our study had similar distribution patterns to the WHO chart, and the 50th percentile was similar to the INTERGROWTH-21st chart (Paper I).

We found that foetal factors, duration of pregnancy, child age, maternal height and family size were the main predictors of linear growth. Both birth weights and linear growth were influenced by early intrauterine foetal growth. Birth weight was also influenced by foetal growth during late pregnancy. Environmental factors had more influence on the child's linear growth compared to their effect on birth weight. We observed a large variation in length-for-age Z-score (30%) and weight-for-length Z-score (22%) among kebeles (local wards) than in the birth weight of new-borns (11%) indicating more heterogeneity in clusters for length-for-age Z-score and weight-for-length Z-score than for birth weight (Paper II).

We found that pregnant mothers had a poor compliance of ANC utilization compared to the national and the WHO guidelines. In addition, we found that the current FANC utilization status were not associated with the adverse pregnancy outcomes that we measured (Paper III).

Conclusions

In conclusion, this thesis demonstrated that; (i) foetal growth patterns were similar to the INTERGROWTH-21st and the WHO multicentre foetal growth reference standards, (ii) early intrauterine foetal growth affected both birth weight and linear growth while foetal growth during late pregnancy influenced birth weight only. In addition, there was more influence of environmental factors on child linear growth compared to their effects on birth weight and, (iii) ANC service utilization is low in the context of national and WHO guidelines. In addition, there was no association between the current focused antenatal health care service and adverse pregnancy outcomes.

Summary in Norwegian

Fostervekst og vekst hos små barn på den etiopiske landsbygd.

Etiopia er fortsatt et av verdens fattigste land, og bruken av helsetjenester er lav. Mødre dødeligheten er også høy. Og, mange barn har både akutt og kronisk underernæring. Det er derfor behov for studier til å bedre forståelsen av fostervekst og barns vekst. Bedre innsikt av intrauterin fostervekst er en viktig for tidlig identifisering av normal og unormal fostervekst, noe som kan påvirke fødselsvekt ved fødselen og vekst i tidlig barndom. Målsetningen med denne avhandlingen var å måle intrauterin fostervekst, og se hvorledes barns lengdevekst var i de første to leveår. Avhandlingen vurderer også hvorledes slike mål kan brukes i den eksisterende mødre- og barnehelsetjenesten på den etiopiske landsbygd.

Studien ble utført i den sentrale delen av Riftdalen i Etiopia. Omtrent 700 gravide kvinner ble undersøkt, og deres barn ble fulgt opp til de var omtrent to år. Studieområdet er et typisk landbruksområde, har gjentatte ganger vært rammet av tørke og hungersnød.

Selv om det har vært matmangel i området, viser studien at intrauterin vekst er sammenlignbart med Verdens helseorganisasjon (WHO) og INTERGROWTH-21st referansene. Imidlertid er det mange barn som får en lav lengdevekst de først to år. Dette kan forklares både med faktorer under graviditeten og årsaker som oppstår i de tidlige barneårene.

I den siste artikkelen i avhandlingen beskrives og analyseres hvorledes svangerskapsomsorgen fungerer sammenlignet med de nasjonale og WHOs retningslinjer. Det er betydelige mangler med dagens graviditetskontroller. Det er derfor viktig å styrke mor-barn helsearbeidet.

List of original papers

The thesis is based on the following original research papers that will be referred by their respective Roman numerals.

Paper I *Meselech Roro, Wakgari Deressa and Bernt Lindtjørn.* Intrauterine growth patterns in rural Ethiopia compared with WHO and INTERGROWTH-21st growth standards: A community-based longitudinal study. PLoS ONE (2019), 14 (12): Weblink: https://doi.org/10.1371/journal.pone.0226881

Paper II *Meselech Roro, Wakgari Deressa, Bernt Lindtjørn.* Influence of intrauterine factors on birth weight and on child linear growth in rural Ethiopia: a prospective cohort study. PLoS ONE (2022), 17(8): Weblink: https://doi.org/10.1371/journal.pone.0272620

Paper III *Meselech Roro, Wakgari Deressa, Bernt Lindtjørn*. Antenatal care utilization and compliance with national and WHO guidelines in rural Ethiopia: a cohort study. BMC Pregnancy and Childbirth (2022), 22:849: weblink: https://doi.org/10.1186/s12884-022-05171-3

Abbreviations

AC	Abdominal circumference
ANC	Antenatal care
BCG	Bacille Calmette-Guérin
BP	Blood pressure
BMI	Body mass index
BPD	Bipareital diameter
CI	Confidence interval
COVID-19	Coronavirus disease 2019
DPT	Diphtheria, Pertussis, Tetanus
EDHS	Ethiopian Demographic and Health survey
EFW	Estimated Foetal Weight
FANC	Focused antenatal care
FL	Femur length
GA	Gestational age
HAD	Health Development Army
HCs	Health centres
HC	Head circumference
HDT	Health Development Team
HEW	Health Extensions Workers
HepB	Hepatitis B
Hgb	Haemoglobin
Hib	*Haemophilus influenzae* type b
HP	Health post
IFAS	Iron and Folic Acid Supplementation
IRS	Indoor residual spraying
IUG	Intrauterine growth
IUGR	Intrauterine growth restriction
LAZ	Length-for-age Z-score
LLIN	Long-lasting insecticidal net
LMIC	Low-and middle-income countries
LBW	Low birth weight

MUAC	Mid-Upper-Arm Circumference
PCA	Principal Component Analysis
PCV	Pneumococcal Conjugate Vaccine
RV	Rotavirus vaccine
SD	Standard deviation
SFH	Symphysis-fundus height
SGA	Small for Gestation Age
Wt	Weight
WHO	World Health Organization
WLZ	Weight-for-length Z-score

Table of contents

Introduction

Maternal and child health in Ethiopia

Ethiopia has made progress in terms of reducing maternal mortality between 1990 and 2015. Maternal mortality ratio was reduced from 950 per 100 000 live births in 2000 to 353 per 100 000 live births in 2015. Ethiopia is considered as a country that is making progress in this area (4). Prevention of deaths from the maternal and neonatal complications requires quality maternal and new-born care being both accessible and optimally used by the mothers and caretakers.

In its strategic health sector transformation plan, the Ethiopian government has put strong emphasis on reducing maternal mortality. Its aim is to reduce the maternal mortality ratio from 401 per 100 000 live births in 2017 to 277 per 100 000 live births by the end of 2025 (5). One of the aims of the strategic plan is to strengthen antenatal, delivery, and postnatal care services (6, 7).

The Ministry of Health (MoH) of Ethiopia has implemented a set of high impact interventions, including antenatal care, skilled birth services, and postnatal care. The proportion of pregnant women who received antenatal care from a skilled provider at least once increased from 27% in 2000 to 74% in 2019. The percentage of live births delivered by a skilled provider increased from 5% in 2000 to 49.8% in 2019. Women who received a postnatal care check-up in the first 2 days after birth increased from 8% in 2000 to 34% in 2019 (8, 9). Although the ANC coverage has shown an increase over the past two decades, the coverage for the recommended four ANC visits is still only 43% (6).

Considerable progress has been made to improve the child health in Ethiopia. The infant mortality rate declined from 123/1000 live births in 1990 to 59/1000 in 2010, and the under-five mortality rate declined from 184/1000 live births in 1990 to 88/1000 in 2010 (10). For the 5-year period preceding the Ethiopian Demographic and Health Survey (EDHS) in 2019, the under-5 mortality rate was 55/1000 live births, and the infant mortality rate was 43 deaths per 1000 live births. According to EDHS 2016, 37% of children under age 5 were stunted (short for their age); 7% were wasted (thin for their height) and 21% are underweight (thin for their age) (8).

Before 2011, Ethiopia's universal immunisation of children was against six common vaccine-preventable diseases. These included tuberculosis, diphtheria, whooping cough (pertussis), tetanus, polio, and measles. The government introduced four additional immunizations of vaccine preventable diseases in addition to the previous ones from 2011 to 2012. These were hepatitis B, *Haemophilus influenzae* type b (Hib), pneumococcal conjugate vaccine (PCV 13) and monovalent human rotavirus vaccine (RV1) (8). The percentage of children aged 12-23 months who received all the basic vaccinations, one dose of BCG vaccine, three doses of DPT-HepB-Hib, three doses of polio vaccine, and one dose of measles, increased from 39% in 2016 to 43% in 2019 (8, 11).

Antenatal care

Antenatal care during pregnancy is one of the recognized health care interventions that has been shown to prevent and manage complications occurring during pregnancy, childbirth, and post-delivery. ANC provides a measure of access to the health system. It is critical in ensuring proper continuity of care to identify maternal risks and improve health outcomes for mothers and new-borns (WHO 2011a). In 2014, global estimates indicate that only 52% of all pregnant women received the recommended number of ANC visits during pregnancy in developing regions (12, 13).

Although the ANC coverage has shown an increase over the past two decades, it is still insufficient. Studies have found that ultrasound use is associated with an increase of ANC attendance (14, 15). Ultrasound assessment during ANC is done for various purposes depending on the timing during the pregnancy. Early ultrasound scans, before 24 weeks of gestation, are recommended to estimate gestational age. These early scans are also helpful for early detection of foetal anomalies and multiple pregnancies. In addition, they provide guidance for the proper preparation and management of preterm and post-term births, reduce induction of labour for post term pregnancies, and help create a positive pregnancy experience (16).

Antenatal care in Ethiopia

Ethiopia has been implementing an ANC program adapted from the WHO's focused antenatal care model (FANC)at all health facilities until 2021. FANC is a goal orientated approach to delivering evidence-based interventions carried out at four critical times during pregnancy

(17). For normal pregnancies, the ANC visits should occur at gestational ages between 8 and 12 weeks, 24 and 26 weeks, at 32 weeks, and between 36 and 38 weeks. Women with high-risk pregnancies and those who develop pregnancy complications are required to have more frequent ANC visits, or they are referred to the next level of care (18). Before the FANC, Ethiopia implemented the "risk approach" for maternal and child health care that was adapted from the 1978 World Health Organization ANC guideline (19).

The MoH published a new guideline for ANCs in February 2022. This guideline adopted the 2016 WHO ANC guideline that recommends eight ANC visits, instead of the four visits in the FANC, for all women without specific pregnancy-related complications (20).

According to the guidelines for ANC in Ethiopia, every pregnant woman is expected to receive ANC from a skilled provider. This includes a comprehensive physical examination, blood tests for essential screening investigations (Haemoglobin, HIV test, blood group, VDRL, HBsAg) a urine test, tetanus toxoid injections, iron and folate supplements, and medications for deworming. The guideline also recommends one ultrasound scan before 24 weeks of gestation (21).

Community-based Health Extension Workers (HEWs) in their respective kebeles deliver ANC service at a health post, a part of the first level of primary health care unit. The HEWs also identify pregnant women in their catchment areas and link them to health centres and hospitals. However, they do not measure blood pressure, do not screen for anaemia or infections (except for malaria), do not perform blood glucose or urine test for protein (21). Routine ANC service delivery is carried out in the health centre that is linked with the health post. Pregnant women with past history of obstetric complications, current high risk obstetric conditions or medical illnesses such as cardiac or kidney problems are referred to higher facilities for specialized antenatal care and closer follow up or hospital delivery (22).

According to the mini EDHS 2019, only 43% of pregnant women in Ethiopia received the recommended four ANC visits (8). In a Ethiopian setting, ultrasound service is being provided at secondary and tertiary level public health facilities mainly by obstetricians, and radiologists. The ultrasound service is also provided by other health professionals trained on comprehensive emergency obstetric care and emergency surgery services at primary health care level (6).

Despite the progress in maternal and child health service coverage in Ethiopia, significant inequalities still exist in the delivery of ANC, postnatal care, neonatal care, and early child development based on differences in economic status, education, and place of residence. In addition, much remains to be done towards improving the quality of the services at each level of the health system.

Growth monitoring, both intrauterine and early childhood

Historical overview of prenatal and childcare

An increasing understanding of foetal growth and development comes from better systematic measurement taking and registration of birth weights during the last century. One of the current focuses of prenatal care is foetal size and growth. During the first half of the 20th century, knowledge of foetal development and factors influencing birth weight was based on examination that occurred after abortions and birth (23-25). The majority of births during that time took place at home (26). There was an increase in the number of birth institutions from 1920 to 1960 and women increasingly chose institutional delivery (26). There was little or no organized registration of medical information relating to births for those who delivered outside institutions. Antenatal care was practically non-existent in the early 1900s (27).

For assessment of foetal size, abdominal palpation was largely replaced by measurement of the fundal height. Fundal height, introduced in Stockholm, Sweden in 1972 by Westin, is the symphysis-fundus height (SFH) measurement for foetal size (28). SFH measurement was introduced in Ethiopia by Kiserud in 1986 in his investigation to describe the SFH pattern according to gestational age (29).

Both SFH and abdominal palpation have low sensitivity in detecting gestational age of small (SGA) foetuses (30, 31). Until the introduction of ultrasound imaging, SF height and abdominal palpation were the only antenatal methods available to identify possible foetal growth problems. In 1958, Ian Donald established the potential use of ultrasound technology (32). In 1961, Donald and Brown introduced the measurement of biparietal diameter (BPD) (33), which later was shown to correlate with foetal weight (34).

The introduction of ultrasound in obstetric care provided a unique opportunity to monitor foetal development and growth. As knowledge has increased and technical developments have continued, reference charts for foetal size and growth pattern have regularly been updated with the use of ultrasound. Moreover, ultrasound imaging has various other applications during pregnancy. It has been used to diagnose foetal congenital abnormalities, single or multiple pregnancies, non-cephalic presentations, incomplete abortions, molar pregnancy, ectopic pregnancy, polyhydramnios, oligohydramnios and placenta previa. It has also been used to measure pelvic outlet and to estimate gestational age. One reasons that it is important to have a proper assessment of gestational age is to distinguish pre-term new-borns from low birth weight (LBW) new-borns (but not pre-term), as the interventions needed may differ (35).

Foetal growth

Intrauterine foetal growth is one of the factors that influence a child's health. Moreover, adequate intrauterine growth (IUG) is a basic feature of a healthy pregnancy. Abnormal foetal growth has been associated with adulthood diseases, such as cardiovascular disease, diabetes mellitus, and obesity (36, 37).

In the first trimester the development of foetus is mainly organogenesis, and the embryo obtains its nutritional supply from the yolk sac up to late in the first trimester when the placental circulation becomes established (38). The foetus' demand for nutrients and oxygen, which are provided by the placenta, increases during the second and third trimesters.

Foetal growth is influenced by genetic, environmental, sociologic, anatomic, biochemical, and physiologic factors (39). Additional influences include maternal dietary intake of macronutrients and micronutrients, exercise, ethnicity, parity, height and weight, smoking, alcohol abuse, and spacing of pregnancies, as well as paternal height (39). A multicentre study by the WHO and other studies also identified maternal age and height, maternal weight, parity, and foetal sex as factors influencing foetal growth (1). In a study based on serial ultrasounds conducted in an urban Congolese setting, maternal nutritional factors such as low weight during pregnancy were found to contribute to lower foetal weight (40).

There are increasing influences from many of these factors during pregnancy and they contribute to the wide normal variation in foetal size at birth. This variation is well demonstrated in the reference charts for foetal size and growth. The charts are helpful in identifying intrauterine growth restriction (IUGR) and SGA (41).

Foetal growth measurement

Foetal growth measurement is important for identifying abnormal foetal growth. In clinical practice, the common methods used for foetal growth measurement include abdominal palpation, symphysio-fundal height (SFH) measurements, and obstetric ultrasound.

Foetal growth in singleton low-risk pregnancies has routinely been assessed by using abdominal palpation or SFH measurements. The assumption in these techniques is that the distance (in centimetres) from symphysis pubis, which is a fixed point, to the uterine fundus, which is a variable point, corresponds to the gestational age in weeks. To monitor foetal growth during antenatal care, repeated measurements of SFH are used (42-44). Several biomarkers for predicting IUGR have also been proposed. These include biomarkers related to endothelial function/oxidative stress, placental protein/hormone, and others such as serum levels of vitamin D, urinary albumin: creatinine ratio, thyroid function tests, and metabolic profiles. However, none of the biomarkers assessed so far can accurately predict IUGR (45). Therefore, screening relies on routine measurement of uterine fundal height, complemented by ultrasound measurement of foetal size in women with pregnancy complications or with a relevant history or clinical evidence of foetal growth restriction (45). However, the sensitivity of SFH in detecting SGA foetuses is highly variable (14-76%) and is reported to be low in many studies (44, 46). Thus, the high false-negative rate of SGA identification by SFH needs to be taken into consideration during its use.

When SFHs are low or stationary, pregnant mothers are usually referred for ultrasound estimation of foetal size. Foetal growth assessment using ultrasound improves the detection of IUG restrictions and helps to identify those foetuses under risky conditions during the neonatal period (47). Obstetric ultrasound remains the most reliable and objective way for estimating gestational age and monitoring foetal growth. However, in Ethiopia, as in most low-resource areas, access to obstetric ultrasound remains poor. Strategies are needed to improve access to ultrasounds such as training of health workers, educating the public on importance of obstetric ultrasound, and improving access to basic equipment.

Foetal size in the first trimester is commonly determined by crown rump length. First trimester foetal growth is associated with birth weight (48, 49). Calculation of estimated foetal weight (EFW) by ultrasound is based on a combination of different biometry measurements including femur length (FL), abdominal circumference (AC), head circumference (HC), and bipareital diameter (BPD). For calculation of EFW, one can use a variety of formulas such as those of Hadlock, Combs, Mielke and Dudley (50, 51). The accuracy of EFW in prediction of birth weight has been reported to have a mean absolute prediction error between 7.5% and 18.8% (52).

To assess foetal size and growth, appropriate reference ranges should be used (53). Although cross-sectional reference ranges are appropriate for the assessment of foetal size at a given gestational age, they are poorly suitable to assess growth. Growth is defined as change in size over a period of time. The most appropriate tools for assessing foetal growth are longitudinal reference ranges based on serial observations (41, 54).

Two recent multicentre studies that have been used to develop IUG standards are the WHO Multicentre Growth Reference Study and the INTERGROWTH-21st project (1, 2). Other "birth weight-for-gestational-age references" have been developed with large, mostly population-based databases, and they provide birth weight percentiles by gestational week (47, 55).

The WHO and INTERGROWTH-21st studies are examples of multicentre and multi-country studies that assessed foetal growth using serial ultrasound measurements and established standards that can be used as references for interpreting routine ultrasound measurements (1, 2).

Both of these studies were conducted on presumably healthy and well-nourished pregnant women. The applicability of these foetal growth charts in a setting with different socioeconomic background is problematic. For example, their utility in assessing the IUG pattern in situations that are repeatedly affected by drought and food insecurity in areas such as Ethiopia is unclear. Poor maternal nutrition could be an important contributor to IUG restriction and subsequent LBW (39). As IUGR is reportedly high in African countries, foetal growth charts built on reliable data from the local population need to be developed.

Birth weight

A number of factors affect neonatal weight at birth. These include genetic, sex of the foetus, ethnic origin, weight and height of the parents, maternal age, parity and maternal smoking during pregnancy (56). Some of these factors, such as the sex of the foetus, can be considered as mainly 'constitutional' rather than 'environmental'. They have a physiological effect on birth weight, through effects on the intrinsic growth potential of the foetus (57).

Children born to mothers in lower socioeconomic groups have been reported to have are more often LBW (58). A previous report from Ethiopia indicated that improvement in maternal body mass index (BMI) was associated with improved birth size (59). Individual and social factors including maternal age, lower education, marital status, parity, and pregnancy complications were found to have effect on preterm birth and LBW (60).

Child growth

Childhood undernutrition is common in many countries (61, 62). Stunting (height- for- age <_2 Z-scores) affects 164.8 million (22.7%) children globally, 148 million of whom live in low- and middle-income countries (LMIC). Additionally, 8%, or 52 million children, are wasted. Childhood undernutrition is well known to increase the risk of mortality and morbidity (61, 62).

The timing and pattern of growth faltering in the first 2 years of life is well established. Length for age Z-scores in LMIC declines soon after birth to a lowest point of -1.75 to <2 Z-scores by 24 months of age, and little if any subsequent catch-up growth being evident up to 5 years of age (63). Previous studies have also found that the growth rate of children is adequate in the first few months of life and growth retardation often starts after the age of three months (64, 65).

Child linear growth is influenced by multifactorial and interrelated factors including socioeconomic conditions, maternal adult factors, child factors and caregiving practices. Numerous factors, including inappropriate breastfeeding and infant and young child feeding practices, lack of adequate quality and amount of complementary foods, infections and other environmental exposures are known to contribute to growth faltering in under-resourced settings.

Based on several conceptual frameworks, Prado EL et al (66) developed a model of potential influences on 18-month linear growth status (Figure 1). They give a theoretical framework for determinants of linear child growth in different categories:

i. Maternal height may be related to the child's genetic potential for adult height that can be attained. In populations with a high prevalence of stunting, maternal height is also partly a reflection of growth restriction experienced by the mother during early life.
ii. Socioeconomic disparities and other environmental effects on child linear growth may be mediated by maternal factors, caregiving practices, and child factors or may directly affect linear growth.
iii. Effects of maternal factors on child growth may be mediated by child factors and caregiving practices or it may directly affect child growth.
iv. Effects of infant feeding practices on child growth may be mediated by child factors or caregiving practices may directly affect child growth.
v. Effects of preterm birth or intrauterine growth restriction on later child linear growth status may be mediated by postnatal child factors (appetite, illness, haemoglobin (Hgb)/iron status, physical activity, stress) or may be direct effects.
vi. Effects of child factors (appetite, illness, Hgb/iron status, physical activity, stress) on child growth may be mediated by caregiving behaviour in response to these factors or may be direct effects.

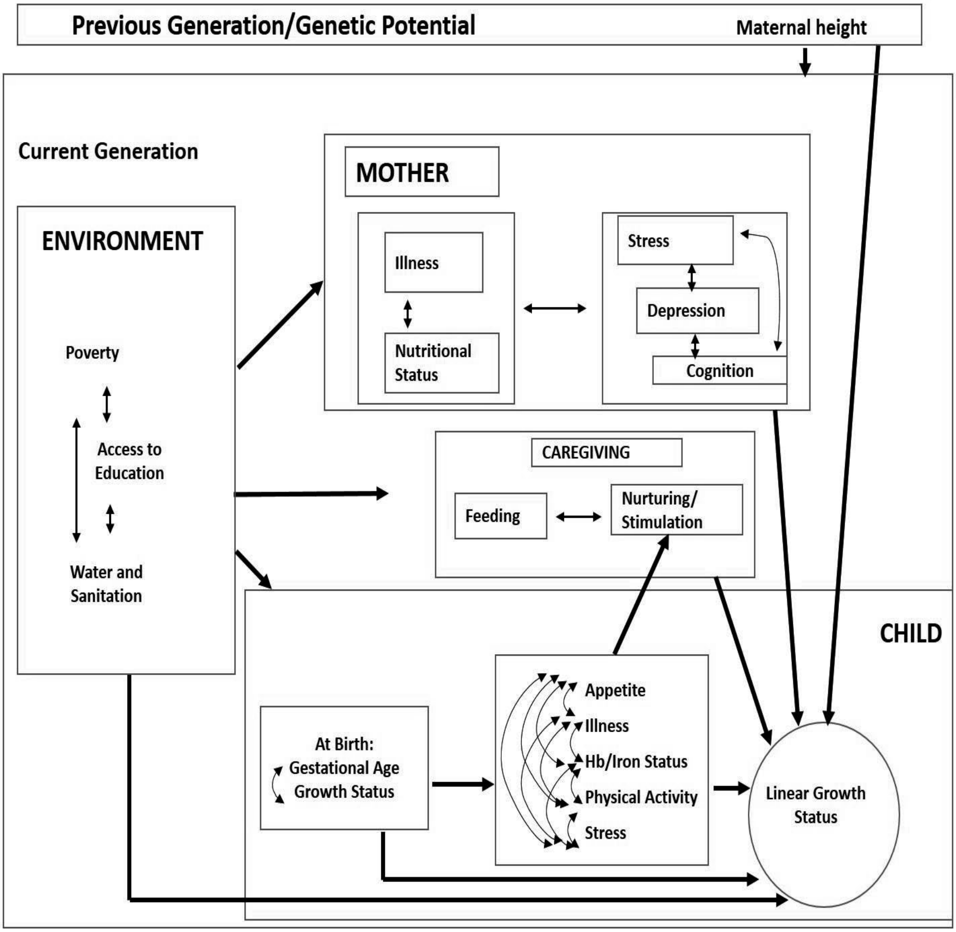


Figure 1. A conceptual model for the determinants of linear child growth (adapted from Prado EL et al framework 2019) (66)

Child growth measurement

The linear growth of a child is commonly assessed by cross sectional design using the length-for-age (LAZ) score and longitudinally through assessing growth velocity (67). Both methods use anthropometry measurements and compare the results against reference standards. Growth velocity is used to quantify attained change in body mass and size of child at particular time through measurements taken at two time points (68). The child growth rate velocity through time indicates the rate of change in height between different times points (growth velocity curve) obtained from length or height measurements. In this thesis, we used the LAZ score to determine the status of child growth (69).

Foetal growth and its relationship with birth weight and child growth

The time from conception up to 2 years of age, the first 1000 days of life span, is considered the most important development phase of a child (63, 70). Studies linking birth weight and childhood undernutrition (70-72), suggest that growth in the first 1,000 days is better viewed as a continuum between the foetal period and infancy and early childhood.

Foetal growth has implications for birth outcome and child growth and development, and might influence the long-term health of children (37). Birth weight is a result of a composite interaction among genetic, maternoplacental and environmental factors (73-75). Normally there is a wide normal biological variation in foetal weight and this variation increases during the course of pregnancy (76). New-borns that are SGA have an increased risk of poor outcomes relative to new-borns with a birth weight appropriate for their gestational age (77, 78). Notably, infants that are SGA have higher perinatal mortality (79, 80) and morbidity (81, 82).

A multitude of factors that happen during foetal period or after birth can affect the early years of child growth and development. Early healthy child growth and development includes physical, social, emotional, and cognitive domains of development. What happens to the child in these early days can affect the child's later development or growth (70, 83, 84).

Birth cohort studies from high-income countries have suggested that there is a continuity in the growth between the foetal period and infancy and early childhood period (72, 85).

However, little is known about the influence of intrauterine foetal factors on childhood growth in low-income countries. It is thus important to examine the effect of intrauterine foetal growth on early childhood growth in low-income countries.

Definitions

For monitoring of intrauterine foetal growth, its outcome and child growth, it is important to understand what is meant by normal or abnormal growth. One of the indicators of abnormality is an SGA, which is defined as EFW or birth weight below the 10^{th} percentile of certain reference at a given gestational age (47). Another indicator is LBW, which is defined by the WHO as a birth weight <2500 g (up to and including 2499 g). WHO classifies weight < 1500g as very LBW (86). Preterm birth, defined as babies born alive before 37 weeks of pregnancy, is another indicator of foetal outcome (87).

A growth trajectory is observed at each stage of development from embryo to foetus and may indicate a need to evaluate for possible growth impairments. Anthropometric measurements that might fall below 2 standard deviations (SDs) of the median include Z-score of the foetal biometry, estimated foetal weight, sex-specific weight-for-age (underweight), height-for-age (stunting), and weight-for-height (wasting) as compared to the WHO Child Growth Standards median (88, 89).

Stunting refers to a child that is short for his/her age but not necessarily thin. It is known as chronic malnutrition that carries long-term developmental risks (88). An underweight child can be either thin or short for his/her age. This may reflect a combination of chronic and acute malnutrition (89). In both cases, children are most likely to suffer from impaired development and are more vulnerable to disease and illness. However, wasting refers to low weight-for-height, where a child is thin for his/her height but not necessarily short. It is known as acute malnutrition and carries an immediate increased risk of morbidity and mortality (89).

Knowledge gap in foetal growth monitoring and child linear growth

Accurate estimations of gestational age are essential for the correct interpretation of foetal growth. They also facilitate proper scheduling of antenatal care and inform decision-making at different stages of a pregnancy. In rural settings of countries such as Ethiopia, obtaining an accurate estimation of gestational age is challenging as this is dependent on the date of the last menstrual period. Accuracy of the last menstrual period is very low, as most of the women do not remember the exact date (42).

Foetal growth monitoring has been done using either abdominal palpation or SFH measurements as a first-line screening tool. Even though this method is simple, inexpensive, and easy to implement, it has potential to identify only extremes of foetal growth disorders and is less accurate for detecting small-for-gestational age. The accuracy of abdominal palpation remains low regardless of the risk profile of the pregnancy. Ultrasound biometric measurements have better accuracy in monitoring foetal growth. There is no study done on foetal growth monitoring using ultrasound in Ethiopian setting. There are several studies done on factors that affect child growth. However, there was no study that examined the influence of IUG on child linear growth in Ethiopia.

Evidence relating to the potential benefits of ANC on pregnancy outcomes has most often come from cross-sectional or retrospective studies. In addition, scientific arguments on the association between ANC and pregnancy outcomes remain unresolved. There is no prospective study done to demonstrate the benefit of ANC on pregnancy outcomes in Ethiopia.

Health services in Ethiopia

Ethiopia: The country

Ethiopia is located in the Horn of Africa. The country shares boarders with Eritrea, Djibouti, Somalia, Kenya, South Sudan, and Sudan. With about 115 million people (2020), Ethiopia is the second most populous nation in Africa, after Nigeria. More than 80% of Ethiopians live in rural areas while the majority (more than 70%) is still employed in the agricultural sector (90). The country is home to various ethnicities, with diverse cultural background and more than 80 different spoken languages. Ethiopia is experiencing a rapid population growth (2.6%) and has a young age structure. The fertility rate in the country is high, with an average of 4.6 births per woman (2.3 in urban areas and 5.2 in rural areas) and crude birth rate of 32 per 1000 in 2016. The average household size is 4.6 (91).

Ethiopia is administratively divided into twelve regional states and two city administrations. Each of the regions is divided into zones and each zone into lower administrative units called woredas, or districts. Each woreda is subdivided into the lowest administrative unit, called a kebele. The two city administrations are also divided into sub city administrations and woredas (92). According to a 2022 World Bank and Africa Development Bank Group report, Ethiopia has been one of the fastest growing economies in the region. However, Ethiopia's real gross domestic product growth slowed down from 6.1% growth in 2020 to 5.6% in 2021, due to the effects of civil conflict and the COVID-19 pandemic (93, 94). Despite its economic growth, Ethiopia remains considered as one of the poorest countries in the world (90).

Access to a skilled birth attendant was been improving. Two decades ago, about 94% of deliveries in the rural areas were conducted by traditional birth attendants. This was recently reduced to 50% (8).

Health service

Ethiopia's health service is currently structured into a three-tier system: primary, secondary and tertiary levels of care (Figure 2) (95). The primary level of care includes primary hospitals, health centres (HCs) and health posts (HPs) while the secondary level includes a general hospital serving 1-1.5 million people. The tertiary level health care includes a specialized hospital that provide services for 3.5 to 5 million people. The HP is the first level of Ethiopian health service delivery, and provides services at kebele level, each on average covering 5000 people. Each HP is staffed by two Health Extension Workers (HEWs). The HPs are accountable to HCs and kebele administration (7, 96, 97). The Health Extension Program (HEP) was introduced in 2003. Maternal, new-born and child health were one of the focus areas when the HEP was initially designed (98).

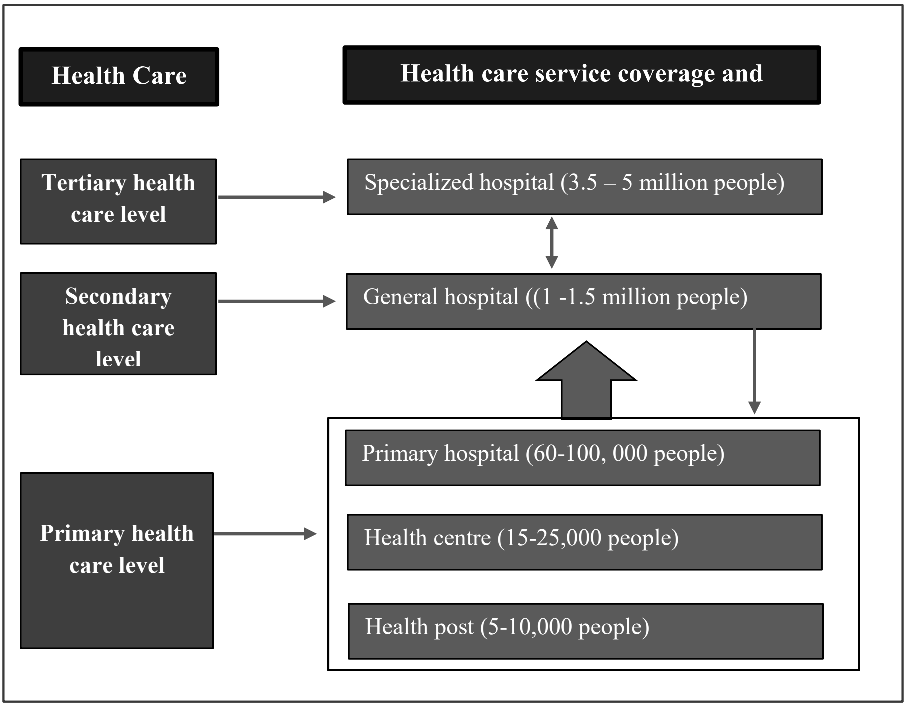


Figure 2: Ethiopia's health care delivery system (adapted from the Federal Ministry of Health Sector Transformation Plan, 2021(95)

A community is linked to the primary health care system through health development army (HDA), formed by members from the community. Organizing a functional HDA requires the establishment of health development teams (HDTs), which involve up to 30 households residing in the same neighbourhood. The HDT is further divided into smaller groups of six members (households), commonly referred as “one-to-five” networks (6, 99) .

A health management information system of the organizations at each level from health post to national level share their information, maintaining the structural linkages between these bodies to facilitate information sharing between the parties operating within this structure (6).

Access to health services has improved due to the efforts undertaken during the implementation period of HSTP-I. This included strengthening the primary health care services and encouraging strong community engagement in building capacity. However, weak linkages between HEP and primary health care units was observed, which resulted from different factors such as high leadership turnover at all levels, and lack of integration across service components along the continuum of care. Moreover, despite significant improvements, mortality and morbidity from maternal and child health conditions, disparity in service utilization and sub-optimal health care remains high (6). Currently the second Health Sector Transformation Plan is developed and being implemented. It aims to expand access to services and improve the provision of quality and equitable comprehensive health services at all levels in the country (95).

Rationale of the study

Children's well-being is highly influenced by intrauterine foetal growth and adequate IUG is a basic feature of a healthy pregnancy. Abnormal foetal growth has been associated with adulthood diseases, such as cardiovascular disease, diabetes mellitus, and obesity (36, 37). This thesis aims to asses three key issues in a rural and drought-affected population in Ethiopia. It aims 1) to assess the pattern of intrauterine foetal growth, 2) to examine the influence of intrauterine foetal growth on birth weight and child growth, 3) to assess the compliance of ANC utilization with the national and the WHO guidelines, and its association with adverse pregnancy outcomes.

Ultrasound imaging is an indispensable tool to determine foetal size and gestational age. Foetal growth assessment using ultrasound improves detection of IUG restrictions and helps identify those foetuses at risk of sickness during the neonatal period (47). Since the early 1980s, several ultrasound-based foetal weight references have been published (100). Most are based on cross-sectional or retrospective studies (47, 101, 102), with only one observation for each woman. Moreover, these references include foetal size only and thus provide limited information about foetal growth. Prospective studies, in comparison, can confirm gestational age and assess foetal growth via repeated measurements (103). Some earlier longitudinal ultrasound studies were conducted using small sample sizes, and those with larger sample sizes were performed on predominantly Caucasian populations (104). Evidence from some of these studies shows that differences in foetal growth depend on racial category, sex, parity, and maternal size (104).

Two recent multicentre studies that have been used to develop IUG standards are the WHO Multicentre Growth Reference Study and the INTERGROWTH-21st project (1, 2). Other "birth weight-for-gestational-age references" have been developed with large, mostly population-based databases, and they provide birth weight percentiles by gestational week (47, 55). The WHO study, which identifies differences in EFW between countries, finds that maternal age, parity, height, and weight only partially explain the differences (1). Both the WHO and INTERGROWTH-21st studies measure biometric growth, although INTERGROWTH-21st does not present percentile data for EFW. The INTERGROWTH-21st study estimates foetal weight during ultrasound using head circumference and abdominal circumference, whereas the WHO study uses the Hadlock 3 algorithm to generate EFW using head circumference, abdominal circumference, and femoral length. Both standards can be used as references for interpreting routine ultrasound measurements.

Because these studies were conducted on presumably healthy and well-nourished pregnant women, the risk of adverse perinatal outcomes in areas such as Ethiopia, which is repeatedly affected by drought and food insecurity, remains unclear. Poor maternal nutrition could be an important contributor to IUG restriction and subsequent LBW (105, 106). Furthermore, the WHO study recommends the establishment of population-specific foetal growth charts (1). As IUGR is reportedly high in African countries (107), a foetal growth chart that reflects reliable data from the local population needs to be developed. This thesis presents a foetal weight chart based on EFW using serial ultrasound measurements to elucidate foetal growth patterns in a drought-affected rural area of south-central Ethiopia and compares them with the INTERGROWTH-21st and the WHO multicentre foetal growth reference standards (Paper I).

The time from conception up to 2 years of age, referred to as the first 1000 days of life, includes the time of foetal growth, and is considered the most important developmental period in a child's life (63, 70). Early healthy child development includes physical, social, emotional, and cognitive domains of development. Children during early years undergo rapid growth. Child growth can be affected by a multitude of factors that happen during pregnancy or after birth, and some of these may lead to childhood undernutrition (70, 83, 84). Studies suggest that growth in the first 1000 days is better viewed as a continuum between the foetal period, infancy and early childhood while others have found a link between birth weight and childhood undernutrition (70-72). The evidence on the association between foetal growth and childhood nutritional status is not sufficient as it based on only few birth cohort studies that were done in developed countries (72, 85). We thus examined the influence of intrauterine foetal growth on LAZ and weight-for-length Z-score (WLZ) in early childhood using a prospective cohort data from 24 weeks of gestation up to 11-24 months of postnatal age in drought affected rural Ethiopia (Paper II).

Ethiopia is implementing the WHO focused ANC model at all health facilities. FANC is a goal-orientated approach to delivering ANC service four times during pregnancy. Women with normal pregnancies need to have ANC visits at gestational ages between 8 and 12 weeks, 24 and 26 weeks, 32 weeks, and between 36 and 38 weeks. Women with high-risk pregnancies and those who develop pregnancy complications are required to have more ANC visits (18, 21). Several studies have examined the usefulness of ANC on the uptake of safe delivery care and the reduction of maternal and infant mortality (108, 109). Studies from several countries have found that poor ANC attendance is an important risk factor for adverse pregnancy outcomes (110, 111). As the number of ANC visits decreases, there is an increase in the risk of preterm birth and stillbirth (112-115). Women who had no ANC follow-up and those who had fewer than 4 ANC visits during pregnancy were also found to have a low birth weight (LBW) baby (113, 116, 117).

Although the above studies report potential benefits of ANC on pregnancy outcomes, they possess several limitations. They were most often cross-sectional or retrospective studies or reports not published in peer-review journals. Covariates, such as wealth status, that may affect the outcome were not included in the analysis of these studies. In addition, scientific arguments on the association between ANC and pregnancy outcomes are continuing and are unresolved. For instance, a review article on randomized trials and meta-analysis did not find any relationship between ANC follow-up and preterm birth (118-121).

Thus, this study addresses a need to assess the compliance of ANC utilization with national and WHO guidelines in rural south-central Ethiopia setting. In addition, we assessed if adverse pregnancy outcomes, including intrauterine foetal death, stillbirth, low birth weight and preterm birth, were associated with higher use of antenatal services (Paper III).

Objectives

General objective

The overall objective of the thesis was to examine intrauterine and child growth in rural area in the context of Ethiopian health system.

Specific objectives

I. To assess intrauterine foetal growth patterns in a rural and drought-affected population in Ethiopia (Paper I);
II. To examine the influence of intrauterine foetal growth on birth weight and childhood linear growth in Ethiopia (Paper II);
III. To assess the compliance of antenatal care utilization with the national and the WHO guidelines and to examine the association of antenatal care utilization with adverse pregnancy outcomes (Paper III).

Methods

Study area and settings

Papers in this thesis used studies conducted in the Adami Tullu part of the Adami Tullu and Jiddo Kombolcha *woreda* or district (hereafter referred to as Adami Tullu district) in the East Shewa Zone of the Oromia Regional State in Ethiopia (Figure 3). *Woreda* is the third-level local administrative division in the country, and each woreda is further subdivided into several *kebeles*, or groups of neighbourhood villages. A *kebele* is the smallest unit of local government and each has a population size of approximately 3000 to 5000 people. Each *kebele* is further subdivided into *gares*, or neighbourhood villages (or clusters). There are 48 kebeles in the district, with 24 of them located in the Adami Tullu part. The district is located in the Great Rift Valley in south-central Ethiopia, with altitudes ranging from 1500 m to 2300 m. The capital of the district is Batu (or Zeway), which is located approximately 160 km south of Addis Ababa. Batu is located along the highway connecting Addis Ababa to Nairobi via Hawassa. The town has a latitude of 7°56′N and a longitude of 38°E and its average maximum temperature ranged from 27 C^0 in 2014, and 29 C^0 in 2015 (122).

Adami Tullu, our study area, is one of the areas in Ethiopia affected by repeated droughts and food shortage. In 2015 and early 2016, the population in the area encountered severe drought that was triggered by El Nino (123) and thus the communities were receiving food aid. Moreover, a non-governmental organization was screening and treating children and pregnant women with acute malnutrition (124).

According to the 2007 National Census , the projected population of Adami Tullu was approximately 177 390 people in 2015 (91). The study was undertaken as part of a large community-based cluster randomized controlled trial conducted to evaluate the effect of combined use of long lasting insecticidal nets (LLINs) and indoor residual spraying (IRS) on the incidence of malaria (3, 125). All women of reproductive age (15-49 years) permanently residing in the study area and living in the households included in the malaria trial were used as a source population for the current foetal and postnatal growth study.

The main ethnic group in this area is the Oromo, and the predominant religion is Muslim. The majority of the population lives in rural areas in houses constructed with mud or cement walls and thatched or iron roofs. Local residents primarily depend on farming, livestock rearing, and to a lesser extent on fishing in Lake Zeway for their subsistence.

Culturally, the people in Oromia region and Adami Tullu district are governed by the *Gadaa* system. This system is an indigenous democratic socio-political system of the *Oromoo.* The *Gadaa* system incorporates pivotal institutions to safeguard women's rights (126, 127). Some of these institutions are motherhood related rituals. Among these are services or ceremonies held for women in their last months of pregnancy and during postnatal period (126). The ceremonies are performed at the home of the pregnant woman or at the pregnant woman parent's home. The ceremonies made for women in their last months of pregnancy is called *Faatimaayyee* while those relating to the postnatal period are called *Shanan* and *Afurtamii Shanan*. The names may vary from one area to another.

Faatimaayyee is a ritual of praying for pregnant women to deliver her child safely. The praying is often performed during the last trimester of the pregnancy (usually after seventh months of pregnancy) up to the time baby is born safely. The praying is performed at the home of the pregnant woman or at the pregnant woman's parents' home (126).

Shanan and *Afurtamii Shanan* are ceremonies performed on the fifth and forty-fifth days after child is born. *Shanan* is also known by the names *Bulluqaa, Nafa Dhiqaa. Askutii* or *Ulumaa*. Women perform the *Shanan* ceremony on the fifth day after a child is born. The *Afurtamii Shanan* ceremony relates to the postpartum mother. *Afurtamii Shanan* symbolizes the celebration performed at the end of postpartum period on forty-fifth day after child birth. During this time, the mother gets special care, nutrition, protection and privilege. This special period usually extends to six months postpartum (126).

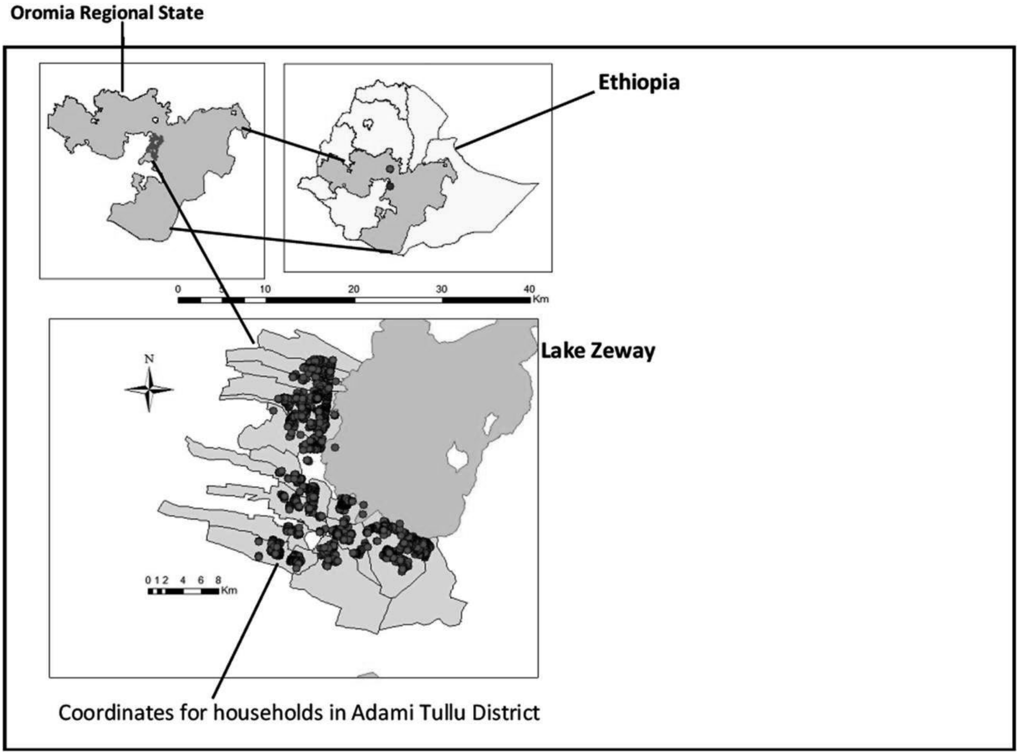


Figure 3. Map of Adami Tullu district in Oromia Regional State in south-central Ethiopia. Reprint under a CCBY license, with permission from Deressa et al Trials (2016).

Study design and data collection

We conducted a prospective cohort study in the rural community of Adami Tullu district from July 2016 to November 2018. We enrolled 727 pregnant women living in the study district's villages or in the clusters of the previously mentioned malaria trials study. Of these, 23 women left the study area and thus the thesis is based on 704 pregnant women who were followed until delivery. For assessment of intrauterine growth pattern, we included 675 women with singleton pregnancy and with a gestational age (GA) of less than 24 weeks (Paper I). We included 554 children with complete data for the evaluation of the influence of intrauterine factors on child linear growth (Paper II). A descriptive cross-sectional study design was used in Paper III. We included 704 pregnant women for the assessment of ANC compliance and its association with adverse pregnancy outcomes.

We used a predetermined approach to select the study populations. Pregnant women were identified by trained data collectors, who went house to house to identify women of reproductive age (15–49 years). The data collectors used a WHO checklist to determine with reasonable certainty that a woman was not pregnant (128). For those women who were suspected to be pregnant, an ultrasound scan was performed to verify the pregnancy and estimate gestational age. We included all pregnant women with a gestational age of less than 24 weeks in the study and followed them through delivery and until the age of 24 months (Figure 4).

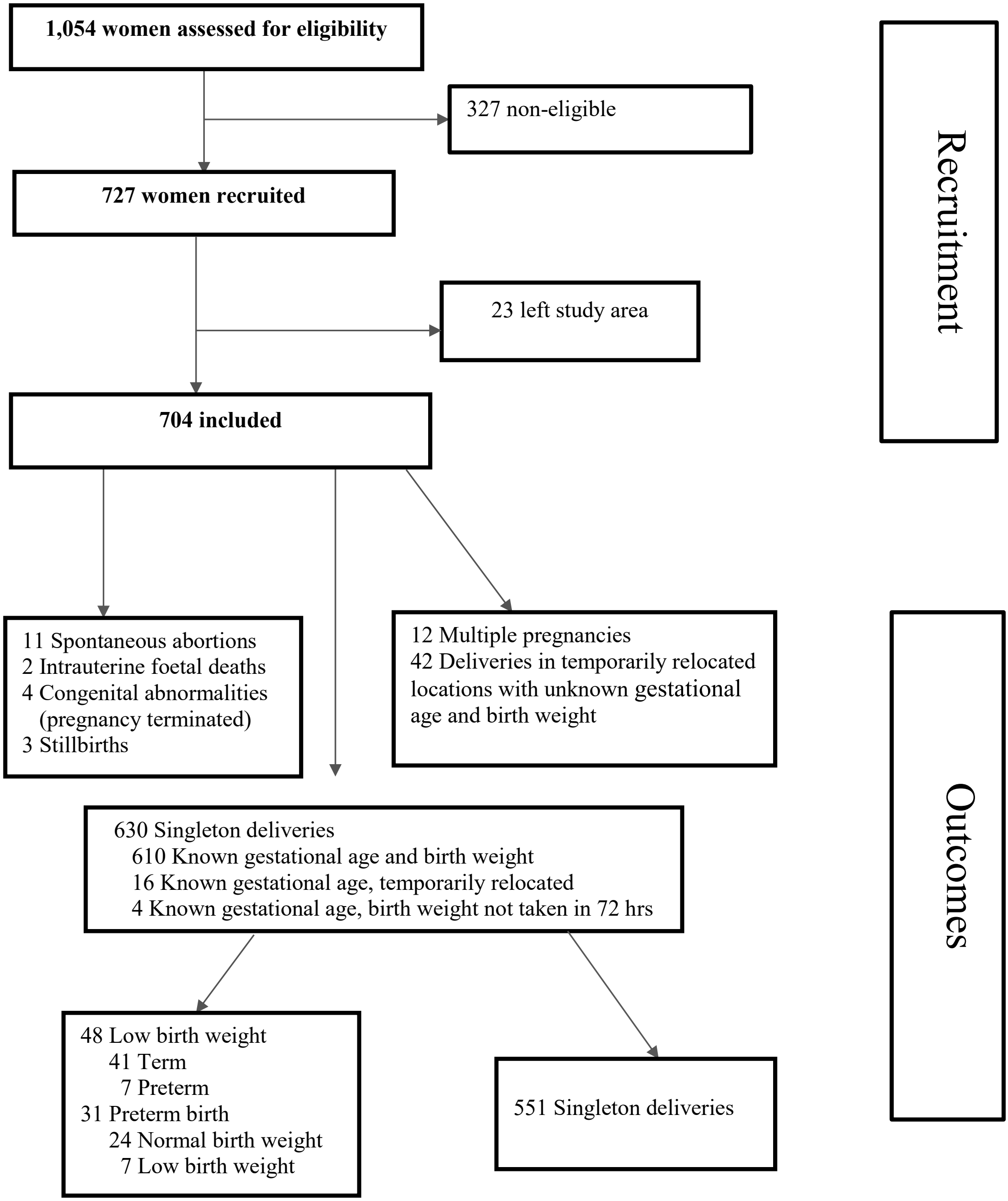


Figure 4. Flowchart of study participants included in the recruitment and outcomes of the study.

Instruments and data collection

Interviews

An interview administered pre-tested structured questionnaire was used to collect data. The questionnaire had four sections. The first section contained questions on the mother's sociodemographic and economic characteristics, ownership of fixed assets and household members. The second section covered past and present obstetric history and gestational age and expected date of delivery estimation by ultrasound. The third section covered the status of the pregnancy and ultrasound examinations including maternal anthropometry, blood pressure, and haemoglobin and malaria testing during the follow up periods. The fourth section covered child linear growth assessment. The questionnaire for sociodemographic and economic characteristics were adapted from the EDHS questions (8, 11). The second to fourth sections of the questions were developed by reviewing related literature (1, 2, 66).

The questionnaires used for data collection were developed in English and translated into the local *Afan Oromo* language. The questionnaires were pretested on 30 pregnant mothers before the actual data collection began and any necessary amendments to improve the clarity of the questions was done accordingly (questionnaire appendix).

Thirteen nurses were trained in data collection and they were provided a skill- based training on how to take maternal and new-born, and child anthropometric measurements. These nurses were assigned to each health post or to especially established stations in each kebele and were responsible for collecting the data.

Antenatal care service utilization

We interviewed each pregnant woman at each visit to determine if she had been attending antenatal care or not. In those who were having antenatal care visit we asked for the number of antenatal visits she had attended, place of the antenatal care attendance, iron and folic acid supplementation (IFAS) received there, and duration of IFAS. Information on the status of pregnancy, and birth outcome were collected during pregnancy and at delivery.

Measurement

Ultrasound measurements

At enrolment, gestational age was calculated based on ultrasound measurement of biometric parameters using multiple parameter formula of Hadlock et al. using the biparietal Diameter (BPD), head circumference (HC), abdominal circumference (AC), and femur length (FL) measurements for pregnancies more than 13 weeks and 4 days (51, 129). Pregnancy assessments were performed at each visit: 26 weeks of gestation (±2 weeks), 30 weeks of gestation (±2 weeks), and 36 weeks of gestation (±2 weeks). All ultrasound examinations and sonographic measurements were done by the primary author using standardized procedures according to Hadlock's criteria (51, 129) after being trained. The quality and accuracy of measurements were validated by a senior obstetrician at Addis Ababa University. Foetal biometric measurements taken during ultrasound assessment were BPD, HC, AC and FL. Estimated foetal weight was calculated using Hadlock's formula (51). All serial ultrasound examinations and foetal biometric measurements were performed for all pregnant woman with a portable Sonosite M-Turbo diagnostic imaging and a full colour flow mapping ultrasound machine (FUJIFILM SonoSite, Inc, USA) using standard technique (130).

Birth weight

Birth weight of new-born were taken and recorded by trained nurses within 72 hours of delivery. The nurses followed each of the pregnant women and visited her regularly until she gave birth. In addition, they notified the nurses on phone in case the woman gave birth at night. Birth weight was measured using a digital infant weighing scale (Beurer Digital Baby Scale).

Anthropometric measurements post-delivery

Weights and lengths of children were taken at 11-24 months of post-delivery. Length of children were measured in supine position (recumbent length) since they were younger than 24 months of age. A standard wooden board was used to measure length of children to the nearest 1 mm. All weight measurements of children were taken using a digital weighing scale (Coline) to the nearest 100 gram. The age of the children (in months) was calculated from the day anthropometric measurements were taken and the recorded date of delivery.

Figure 5 summarizes the data collection timeline and variables used in this study. Sociodemographic characteristics and anthropometry of women and gestational age estimation with estimated date of delivery were performed at enrolment. In subsequent visits, biometric and estimated foetal weight measurements were done using ultrasound. In addition, data on antenatal care service utilization was collected at each visit. At delivery we recorded date of delivery, birth weight and sex of child. Weight and length of children were collected during postnatal period.

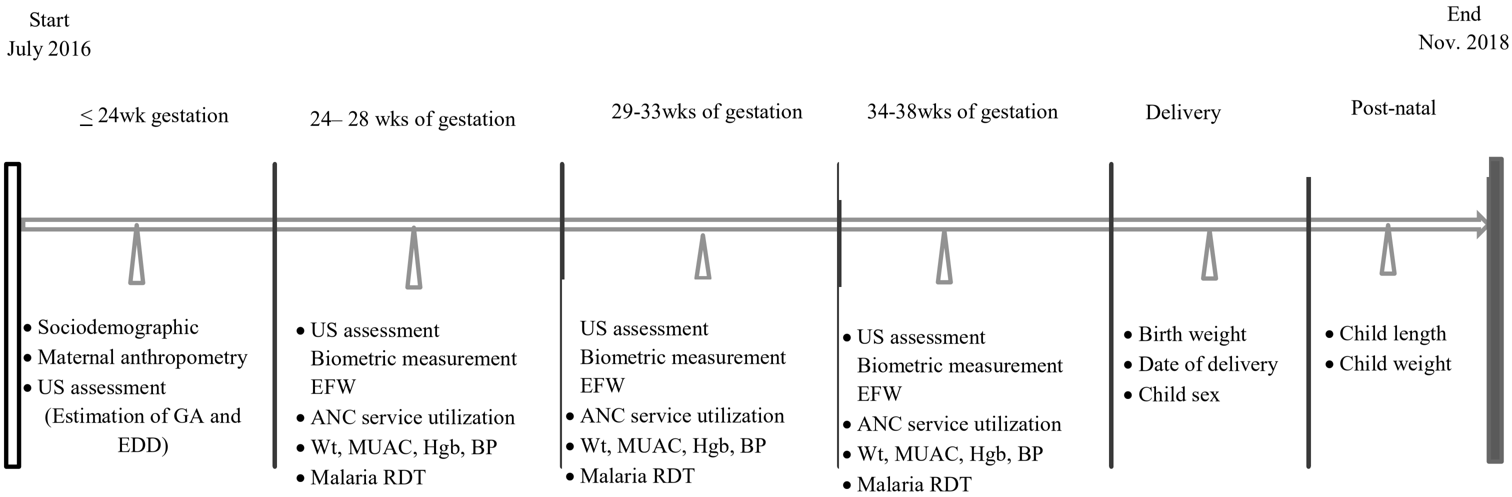


Figure 5. Data Collection timeline of the study

The overview of the main outcome and exposure variables considered in this thesis are presented in Table1 and Table 2 with their respective definitions.

Table 1. Definitions of outcome variables used in this thesis

Variable	Definition/measurement	Paper
Foetal growth	Foetal growth was developed using multiple foetal biometric parameters measured using parameter formula of Hadlock et al from 24 to 38 weeks of gestation	I and II
Preterm	Babies born alive before 37 weeks of pregnancy that was calculated (in months) from the estimated date of delivery by ultrasound and the recorded date of birth.	I and III
Low birth weight	New-borns weighing less than 2500g at birth measured using digital baby weighing scale (Coline) within 72 hours of delivery.	I and III
Birth weight	Weight of a new-born baby taken within 72 hours of delivery.	
Length-for-age Z-score (Stunting)	A child with a length-for-age Z-score of less than 2SD (Standard deviation) of the WHO 2006 median growth reference was considered as stunted	II
Weight-for-age Z-score (Wasting)	A child with a weight-for-length Z-score of less than 2SDof the WHO 2006 median growth reference was considered as wasted.	II
Compliance of Antenatal care utilization	ANC use was categorized as “yes” or “no”; “yes” if the woman attended ANC and “no” if she did not attend ANC.	III
Intrauterine foetal death	A foetus with no signs of life in utero on ultrasound examination	
Stillbirth	A baby born with no signs of life, such as beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles	
Adverse pregnancy outcome	Adverse pregnancy outcome was categorized as “yes” or “no”; “yes” if there were any of the adverse pregnancy outcomes; low birth weight, preterm birth, intrauterine foetal death or stillbirth present, and “no” if none of them were present.	III

Table 2. Definitions of exposure variables used in this thesis

Variable	Level	Definition	Paper
Foetal growth	Individual	Foetal growth was developed using multiple foetal biometric parameters measured using parameter formula of Hadlock et al from 24 to 38 weeks of gestation	II
Preterm	Individual	Babies born alive before 37 weeks of pregnancy that was calculated (in weeks) from the estimated date of delivery calculated using ultrasound and the recorded date of delivery.	III
Low birth weight	Individual	New-born weighing less than 2,500 g measured using digital baby weighing scale (Coline) within 72 hours of delivery.	III
Birth weight	Individual	Eight of a new-born baby taken within 72 hours of delivery	II
Wealth index	Household	Wealth index was constructed using principal component analysis from household assets-related variables. The households were then ranked into three categories; poor, medium and rich.	I, II, III
Educational status	Individual	Assessed from the question that asked attending education and if attended the highest education level attained by mother. Then, it was classified as not attended formal education, read and write, primary and secondary.	III
Haemoglobin	Individual	A mother was considered anaemic if the Hgb concentration was less than 11 g/dl where Hgb concentration was assessed using HemoCue HB 301.	I,II and III
Family size	Household	Number of family members living in the household	II

Data analysis and statistics

Data were entered and cleaned using SPSS version 24 (SPSS Inc., Chicago, IL, USA) and analysed using Stata software version 15 (Stata Corp., College Station, TX, USA). A descriptive analysis was performed.

Wealth index

A relative household wealth index was constructed using principal component analysis (PCA) (131). Fourteen household assets were used to calculate wealth: presence of electricity, ownership of a radio, mobile telephone, chair, table, bed, bicycle, land, separate kitchen from living area, ownership of animals or animal carts, types of roof and walls, and presence of potable drinking water. A relative socioeconomic status was then constructed by grouping household wealth into three to define poor, middle, and rich (Paper I, II, III).

Intrauterine growth pattern analysis

Reference curves were estimated based on centiles for individual BPD, HC, AC, and FL biometric parameters. EFW was derived at each gestational age from 24 to 38 weeks. The reference curve was fitted using centiles for reference models and the 5^{th}, 10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th}, and 95^{th} centiles. The proportion of foetuses in the cohort that were small for gestational age was evaluated for weights that fell below the 10^{th} percentile for specific gestational age and the overall study population (106). The three-round Z-scores and percentiles of biometric measurements and EFW were calculated and fitted to INTERGROWTH-21^{st} International Standards for Foetal Growth application software (2) (Paper I).

We categorized the measurements taken from 24 to 38 weeks of pregnancy into 3 periods. Period 1 covered 24 to 28 +6 days, period 2 from 29 to 32+ 6 days, and period 3 from 33 to 38 weeks of gestation. The association of the three-round Z-scores of estimated foetal weight and foetal biometric measurements on birth weight and child linear growth were considered separately. The Z-scores and percentiles of biometric measurements and EFW were calculated and fitted to INTERGROWTH-21^{st} International Standards for Foetal Growth (132).

Small for gestational age

We calculated 5^{th}, 10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th}, and 95^{th} centiles of estimated foetal weight for gestational age and fitted for reference models.

Adverse pregnancy outcomes

Adverse pregnancy outcome, a composite variable, was computed as the sum of low birth weight, preterm birth, intrauterine foetal death and stillbirth.

ANC service utilization

The extent of ANC content received, timing of the ANC(s), location of the ANC(s), and location and mode of delivery were computed according to the WHO and national guidelines. ANC service utilization was categorized as "yes or no". Being "yes" if the woman attended ANC and "no" if she did not attend ANC during her current pregnancy. We compared the actual use of ANC with the national and WHO guidelines.

Exposure and outcome association assessment

We measured the influence or association between intrauterine growth and birth weight and growth among children 11 to 24 months of age employing a multilevel model that accounts for clustering due to repeated measures of an individual child at multiple times (136). We checked for the presence of clustering before fitting a multilevel model in the following steps: First, a null single level (standard) regression model, and then a null multilevel model with the random individual effect were fitted. Thus, to account for the clustering, a multilevel model was fitted to estimate the unadjusted and adjusted coefficient (β) with a 95% confidence interval (CI)). Finally, bivariate and multivariate multilevel mixed effect regression analysis was carried out and beta was reported (Paper II).

Univariate logistic regression analyses was run to examine the association between antenatal care service utilization with adverse pregnancy outcome. Crude odds ratio with 95% confidence interval (CI) was calculated (Paper III).

Table 3 summarizes the main statistical methods we used in this thesis. Descriptive and principal component analysis were used in the three papers. In addition, in Paper II, a multilevel mixed effect linear regression analysis was used while a logistic regression analysis was used in Paper III.

Table 3. The main statistical analysis used in the papers of the thesis

Statistical methods	Papers
Principal component analysis (PCA)	Paper I, II and III
Descriptive analysis	Paper I, II and III
Multilevel mixed effect linear regression	Paper II
Binary logistic regression	Paper III
INTERGROWTH-21st International standards for Foetal weight and foetal biometry Z-scores	Paper I and Paper II
WHO. AnthroPlus (Z-scores)	Paper II

Ethical considerations

The study received ethical approval from the Institutional Review Board of the College of Health Sciences, Addis Ababa University, in June 2015 (ref.;005/15/SPH) and from the Regional Committee for Medical and Health Research Ethics, Western Norway (ref: 2013/986/REK Vest). Written permission to perform this study was obtained from the Oromia Regional Health Bureau and the relevant provincial and local authorities in the district. Informed written consent was obtained from each participant. Pregnant women who had indication(s) for treatment were referred to a nearby hospital. Before any anthropometric measurements were taken, we obtained informed parental assent for the children, and all procedures were conducted based on voluntary participation.

Results

Paper I: Intrauterine growth patterns in rural Ethiopia compared with WHO and INTERGROWTH-21st growth standards: A community-based longitudinal study

Introduction

Children's well-being is highly influenced by their foetal growth. Adequate intrauterine growth (IUG) is a basic feature of a healthy pregnancy. The aim of our study was to assess IUG patterns in a rural and drought-affected population in the Rift Valley area of the Adami Tullu district in Oromia, Ethiopia.

Methods

We conducted a longitudinal, community-based study of IUG patterns utilizing serial ultra-sound measurements. Data were collected for 17 months, from July 2016 to November 2017. We included 675 singleton foetuses ≤ 24 weeks old, based on ultrasound-derived estimates of gestational age, and followed them until delivery. We obtained head circumference, biparietal diameter, abdominal circumference, femur length, and estimated foetal weight at 26, 30, and 36 weeks. Foetal weight was estimated using the Hadlock algorithm, and the 5th, 10th, 25th, 50th, 75th, 90th, and 95th centiles were developed from this model. We compared the biometric measurements and foetal weight data from our study to the World Health Organization (WHO) and INTERGROWTH-21st foetal growth reference standards.

Results

Distribution of the biometric measurements and estimated foetal weights in our study were similar to those for the WHO and INTERGROWTH-21st references. Most measurements were between -2 and +2 of the reference Z-scores. Based on the smoothed percentiles, the 5th, 50th, and 95th percentiles of our study had similar distribution patterns to the WHO chart, and the 50th percentile had a similar pattern to the INTERGROWTH-21st chart.

Conclusions

Our study determined foetal growth patterns in a drought-affected rural community of Ethiopia using common ultrasound biometric measurements. We found similar IUG patterns to those indicated in the WHO and INTERGROWTH-21st foetal growth reference standards.

Paper II: Influence of intrauterine factors on birth weight and child linear growth: a prospective cohort study

Introduction

Little is known about the influence of intrauterine foetal factors on childhood growth in low-income countries. The objective of this study was to examine the influence of intrauterine foetal growth on child linear growth in rural Ethiopia.

Methods

We conducted a prospective community-based cohort study from July 2016 to October 2018. All pregnant women with gestational age of 24 weeks or below living in 13 kebeles, in central Ethiopia were enrolled. The foetuses were followed from pregnancy up to 11-24 months after birth. We measured biparietal diameter, head circumference, femoral length, and abdominal circumference at 26, 30 and 36 weeks of pregnancy. At birth, we measured infant weight. At 11-24 months of age, Z-scores of length-for-age, and weight-for-length were calculated. A multilevel, mixed-effect, linear regression model was used to examine the influence of foetal, newborn, maternal, household factors, and residence area on child linear growth.

Results

We included 554 children. The prevalence rate of stunting was 54.3% and that of wasting was 10.6%. Foetal biparietal diameter, head circumference, and abdominal circumference, were significantly associated with birth weight. Femoral length Z-score in early pregnancy, gestational age at delivery, and child age were significantly associated with length-for-age Z-score. Family size was significantly associated with length-for-age Z-score. Family size and maternal height were associated with weight-for-height Z-score. There was a larger variation in the length-for-age Z-scores (Intra cluster correlation, or rho (rho) = 0.30) and weight-for-length Z-scores (rho = 0.22) than in the birth weight of the newborns (rho = 0.11) in the kebeles indicating more heterogeneity in the clusters for length-for-age Z-score and weight-for-length Z-score than for birth weight.

Conclusions

Child linear growth was influenced by foetal growth, duration of pregnancy, maternal height, and family size. Environmental factors that are associated with the area of residence play a bigger role for linear growth than for birth weight.

Paper III: Antenatal care utilization and compliance with national and WHO guidelines in rural Ethiopia: a cohort study

Background

Antenatal health care utilization has the potential to influence maternal and newborn health. In this study, we assessed compliance of antenatal health care utilization with national and World Health Organization (WHO) guidelines. We also examined the association of antenatal health care utilization with adverse pregnancy outcomes as secondary outcome.

Methods

This was a community-based cross-sectional study conducted from July 2016 to November 2017 in rural south-central Ethiopia. We described the antenatal care received by pregnant women, whom we followed at three prescheduled visits during pregnancy and collected birth data at time of delivery. The extent of the antenatal care content received, the timing of antenatal care, the location of the antenatal care, and the location and mode of delivery were obtained and computed according to national and WHO guidelines. For adverse pregnancy outcomes, computed as the sum of low birth weight, preterm birth, intrauterine foetal death, and stillbirth, the exposure variable used was antenatal care utilization.

Results

Seven hundred and four (704) women participated in the study, and 536 (76.1%) had attended at least one antenatal care visit. Among the women who attended an antenatal care visit, the majority, 421 (79.3%), had done so at health centres and hospitals, while 110 (20.7%) attended at a health post. The average number of antenatal care visits was 2.5, which is less than the number recommended in the national and WHO guidelines. Only 18 (2.6%) women had attended antenatal care in their first trimester, which is much lower than the expected 100% specified in the guidelines. Less than half (47%) of the women delivered in a health facility. This is in contrast to the 100% expected health institution deliveries. Low birth weight was a factor in 7.9% (n=48) of the births, and there were 4.9% (n=31) preterm births. There were 12 twin pregnancies, three stillbirths, 11 spontaneous abortions, and two intrauterine foetal deaths. We did not find any significant association between adverse pregnancy outcomes and antenatal care utilization (COR = 1.07, 95% CI 0.62, 1.86).

Conclusion

This study showed that antenatal care service utilization in the study area was markedly lower than that recommended in national and WHO guidelines. The level of antenatal health care utilization was not associated with the registered adverse pregnancy outcomes.

Additional analysis

To check if our sample size was adequate, we calculated the power for the variables of interest (Table 4). The power for wealth status was adequate. The power for the other variables was low. This may indicate that the lack of association for most variables might be due to low statistical power of the variables.

The table presented results of power calculated for non-significant independent variables used in the determination of the effect of intrauterine factors on child linear growth (Paper II).

Table 4. Power calculated for non-significant independent variables

Variable		**Outcome (Stunting)**		**Power**
		Yes	No	
Wealth status	Lower level	106	69	82.14%
	Upper level	193	182	
Parity	Null Para	105	99	11.8%
	Multipara	196	154	
Maternal age	<= 24yrs	142	125	11.7%
	>= 25 yrs	159	127	
Maternal education	No formal education	158	131	8.1%
	Formal education	140	119	
Maternal occupation	Housewife	285	238	7.3%
	Others	16	15	
Maternal height	<= 150cm	43	39	23.9%
	> 150cm	255	210	
Child Sex	Male	179	145	9.1%
	Female	122	180	

Discussion

This section deals with a discussion of the methodologies that we used in this study followed by discussion of main findings included in this thesis.

Methodological discussion

Study design

We used a prospective cohort study design and followed eligible pregnant women in the study area until delivery to assess the foetal growth (Paper I) and subsequently the growth of their children until the age of 11-24 months (Paper II). Cross-sectional study design was also used in Paper III. Antenatal care utilization during pregnancy was also examined for those enrolled mothers to assess compliance with national and WHO guidelines and any possible association with adverse pregnancy outcomes registered during the study period (Paper III).

A cohort study is useful in establishing temporal relationship between exposure and outcome variable and less susceptibility to bias compared to other observational studies such as case-control, cross-sectional and ecological studies (137, 138). The advantages of a prospective study design are exploited in our study.

One of the limitations of a prospective cohort study design is that it takes a long time to enrol participants and is prone to loss to follow up. For example, in this thesis (Paper I and Paper III), we had a 3.2% loss to follow up. The reason for low loss to follow up is mainly due to the fact that most pregnant women appreciated the additional ultrasound examinations during their pregnancy and that motivated them to attend the subsequent follow ups.

However, we reported 9.1% loss to follow up in Paper II. This figure is relatively higher compared to the proportion of loss to follow up in Paper I and III (139). To address this and minimize error, we performed a sensitivity analysis and we found no significant difference in the baseline characteristics of those who were lost to follow-up and those who were included in the final analysis (Paper I).

We also used a descriptive cross-sectional study design in Paper III. We recorded ANC use at each visit. We documented adverse pregnancy outcomes during follow up visits (intrauterine foetal death) and at delivery (still birth, preterm). Among the limitations of a cross-sectional study is its decreased ability to show causality. This is because direct evidence for the time sequence of events cannot be demonstrated by a cross sectional study (140).

Internal validity

The aim of epidemiologic studies is to obtain valid (precise and accurate) results and minimal errors. However, epidemiologic studies often appear to be affected by random errors (chance) that affect precision, as well as systematic errors (bias and confounding) that affect accuracy. Internal validity refers to the extent to which the results of an observation are true for the subjects being studied (140, 141), or the degree to which a study is free from bias (142). This implies a validity of inference to the source population, and is considered as a prerequisite for external validity (143).

There are three main types of systematic errors that influence internal validity. These include selection bias (biased sampling), information bias (biased measurements), and confounding (false inferences on associations).

Selection bias

Selection bias is a systematic error that could be introduced due to a problem in the study design, where participants are differentially enrolled into the study (144, 145). It may occur if the effects on the dependent variable can be modified by differences between the study population and those not included in the study, but who were theoretically eligible for the study. This is a bias that arises from the procedures used to select study subjects (143) or the absence of comparability among the studied groups, and can occur from loss to follow-up, refusal, nonresponse or an agreement to participate in the study (145).

Another form of selection bias is volunteer bias (self-selection bias) occurs when individuals who volunteer to participate in the study differ in relevant characteristics from those who do not (145). In this thesis, the possibility of volunteer participation was less likely as we used set criteria to recruit the study participants. For example, specific gestational age of pregnancy that was measured by ultrasound was used for inclusion criteria.

The response rate in our study was large as our study enrolled all eligible pregnant women residing within the selected kebeles. The presence of ultrasound examinations at the community level could have motivated the study participants involved to complete the study. Thus, the results of the papers included in this thesis were minimally affected by a non-response bias.

Selection bias could result from a loss to follow-up, and this is common in cohort studies. The study subject participants no longer wants to participate in the study or can no longer be located (138). The loss to follow-up can be differential when the loss is more or less likely to occur among exposed participants who develop the outcome than among unexposed participants who develop the outcome. It can be non-differential when the loss of a person with an outcome happens unequally among those exposed and unexposed (138, 143).

In Paper I the loss to follow-up in our study was small (3.2%). We tried to minimize loss to follow up by including all permanent residents who intended to stay in the study area throughout the study period. In addition, we undertook a sensitivity analysis and we found no significant difference ($P > 0.05$ for age, height, occupation and wealth status) in the baseline characteristics of those who were lost to follow-up and those who were included in the final analysis.

In Paper II, selection bias could have been introduced because of a sizable number (9.1%) of children lost to follow-up (4.0 % could not be located, and 4.2% left the study area). In this case we expected that loss to follow-up is by chance (missing completely at random) and its effect on the results of the study might be minimal.

Moreover, we found a higher male to female proportion in our study compared to a previous study in the same area (146). The male dominance in our study is an unexpected finding and is probably due to a selection bias which we are unable to explain adequately. However, this may not have affected our analysis on linear growth as we have adjusted for sex distribution in the multivariate analysis.

Information bias

Information bias is a systematic error in epidemiologic studies, in which differential measurements of exposures or outcomes are made between groups. It can occur when different sources or methods are used for data collection or variables are classified in a non-standardized way. It is a systematic bias that could arise during measuring the exposure or outcome variables (228).

In Papers I, II and III, the census and data on repeated visits were collected using interviewer administered structured questionnaires that were validated in earlier studies (1, 2, 11).

We tried to minimize information bias during the interviews by training the data collectors, pre-testing the questionnaires and supervising the data collectors.

In this thesis, information bias could occur during measuring height and MUAC of mothers, birth weight and length and weight of the children. We attempted to minimize this measurement error by standardizing the instruments and through close supervision. We also conducted standardization exercises and calculated intra- and inter-technical measurement errors for anthropometry, and repeated training was given until the error reached the recommended cut-off points (Paper I and II). In addition, birth weight was measured within 72 hours of delivery to minimize variations related with physiological changes that occur after72 hours (147). However, we were not able to measure birth weight for about 9.4% (n = 65) of the sample size. The reason may be because some women left the area and went to their parent's home for the ceremonies that are held in their last months of pregnancy and during postnatal period; see the description about the context of this thesis (126). This could also potentially introduce selection bias in our study as those births with no measurements could be different from those we had measurements.

Measurement error could also occur during taking biometric measurements using ultrasound. One source of error could be from the ultrasound machine. The acceptable difference in linear and circumference measurements or EFW results is 1% (148). We do not expect this to be a source of significant systematic error as the equipment was calibrated and intensive training was provided to measurers at the start of the study.

We attempted to minimize this measurement error, inter -and intra-observer variation, by validating biometric measurements (see Paper I). Measurement of serial biometry using ultrasound by one person could minimize inter observer reliability bias. Standardized methods were used in the ultrasound measurements and clearly defined cut offs are used for the outcome variables. In the study area, we measured ANC coverage and not the quality of ANC service. We also used the sum of adverse effects rather than every single adverse outcome. This might be one reason for the lack of association between use of ANC and adverse outcomes (Paper III).

Confounding and effect modification

Confounding is a variable that affects both the exposure and outcome variables, resulting in a spurious association (149). Confounding can be controlled during the design or analysis of the study. The methods of controlling confounding in the design phase include randomization, restriction and matching. (138). We included all eligible pregnant women residing in the study area in our study.

The other method of controlling confounding is restriction, as the admissibility criteria for study subjects are limited for a variable that might be a confounder (143). We restricted gestational age at inclusion to the study to less than 24 weeks of gestation to determine the expected date of deliver (Paper I, II, III). Ultrasound estimates of gestational age becomes less accurate in later pregnancy after 24 weeks of gestation because of an increasing foetal size and variability (150). We thus believe that the restriction of gestational age at enrolment does not limit the generalizability of the findings. In addition, in Paper II we only included those children who had all the measurements during foetal period, at birth and at the age of 11-24 months postnatal in the analysis.

The third control method for confounding is matching, which is the process of making a study group and a comparison group comparable with respect to extraneous variables (138). We did not use matching in our study.

In the analysis phase, confounding can be controlled using standardization, stratification, and a multivariate analysis to adjust for a variable considered to be a confounder (143, 151). In Paper I and II, we excluded the multiple pregnancies and congenital abnormalities known to confound foetal growth, birth weight and child linear growth. We used multivariate analysis to adjust for the effect of confounders. We conducted multilevel, mixed-effect, regression analyses for different times using kebele as group identity and Random-effect parameters estimation to control effect of confounders. The effect of socio-demographic variables such as maternal age, educational status and wealth status of the parent, and child sex and age were adjusted to measure the association between foetal growth and birth weight and child linear growth (Paper II). However, this does not prevent the possibility of residual confounding as we did not adjust for dietary aspects, community sanitation, or asymptomatic infections that may influence birth weight, child LAZ and WLZ. We estimated intra cluster correlation as the ratio of the between kebele variance to the total variance in LAZ and WLZ. We found a large variation in child LAZ and WLZ between villages (kebeles). This might explain some of the difference in the dietary aspects, community sanitation, or asymptomatic infections between the kebeles.

Effect modification is a factor in which the effect of exposure is stronger in some strata than other. We found gestational age to be an effect modifier in the study of child linear growth. We found that intrauterine foetal growth influences child linear growth at gestational age less than 28 weeks as compared to later gestational age (Paper II). To control this effect, we used multilevel, mixed-effect, regression analyses for three rounds of foetal biometry at 24–28 weeks, 29–33 weeks and 34–38 weeks of gestation.

Sample size and sampling

The importance of having an adequate sample size in a research study enables it to have sufficient power to detect differences considered to be important. It also improves the precision of any estimates made (152). If a study does not have adequate power, it is more likely to report non-significant associations (type II errors). A type II error is defined as statistically non-significant association between independent and outcome variables even though there is an association (153).

We calculated sample size for this thesis with a power of 80%. We determined the sample size based on birth weight, the primary outcome measure that aims to have an adequate sample to detect a birth weight difference of 110 grams among rich and poor based on wealth status and with previous estimates of standard deviation of birth weight being about 500g. The calculated sample size was 716. This sample size was used for the consecutive papers in this thesis. We also calculated post-hoc to evaluate whether we had an adequate sample size for the consecutive papers and found that the sample size was adequate.

We included 675 women having a singleton pregnancy with a gestational age (GA) of less than 24 weeks, who were living in the 13 kebeles, study district's villages (Paper I). For this paper the loss to follow up was minimal and did not show any significant difference on the sensitivity analysis done for the loss to follow up and the ones included in the study.
For evaluation of the influence of intrauterine factors on child linear growth (Paper II) we included 554 children with complete data from pregnancy, birth and the postnatal period. However, the loss to follow up rate was greater than we had anticipated, and this might have introduced a type II error. The loss of samples due to this factor might have resulted in non-significant associations between risk factors for birth outcome and child linear growth. We tested if the sample size was adequate for non-significant results by calculating the power, and found it to be low. This may indicate that the lack of significant associations for some variables might be due to low statistical power.
For the assessment of ANC compliance and its association with adverse pregnancy outcomes, we included 704 pregnant women (Paper III). The absence of statistical significance in the association of antenatal care use and adverse pregnancy outcome could be explained partly by inadequacy of power for adverse pregnancy outcome (type II error). To reduce the effect of low statistical power, we analysed continuous variables (Birth weight, LAZ, WLZ) directly and did not reduce them to a categorical variable. The sample size had adequate power (81.5%) for the initial exposure variable (wealth status) used in the sample size calculation.

Chance

The observed association between outcome and exposure could be due to chance (145). One can explain the role of chance using P-values or a 95% confidence interval. Unlike P-values that address only chance, the measure of association with confidence interval is useful to reveal the likelihood of the occurrence of chance, as well as the strength, direction and range of an effect (141). We examined the role of chance using multilevel mixed-effects regression to measure the association between intrauterine foetal growth measured at different time periods as exposure and LAZ as an outcome variable in Paper II. In paper III, we performed logistic regression to assess the association of antenatal care with adverse pregnancy outcomes. We used a $P < 0.05$ and a 95% confidence interval to evaluate statistical significance.

Causation

Bradford Hill suggests nine criteria for evaluating whether the associations in epidemiological studies are causal (155). These include the strength (effect size), consistency, specificity of the association, temporality (i.e., the causal predictor preceding the outcome), biological gradient (dose-response relationship), plausibility and coherence with current knowledge, and experimental and analogous examples. In this section, we discuss our findings according to the criteria listed above by taking examples from the papers (see below).

Papers I and III had reached sufficient power strength because they included the required number of pregnant women for monitoring foetal growth and ANC service utilization.

The Paper I study demonstrated a temporal relationship of the exposure and outcome variables. Early intrauterine foetal growth influenced the birth weight and child LAZ. In addition, foetal growth during late pregnancy influenced the birth-weight. The study has also demonstrated a dose-response relationship as an increase in femoral length was associated with increasing LAZ. Thus a strong association we found would be more likely to be causal as we used cohort design that reduces the risk of reverse causality (unmeasured variables accounting for observed associations). Moreover the study was conducted as planned and the effect of confounders and effect modifier controlled for the measured variables in the study.

The finding of similarity of intrauterine growth pattern in our study area with that of the international reference standards (Paper I) confirms the plausibility and coherence of our results with current knowledge. This was also demonstrated in the relationship between the intrauterine foetal growth and child linear growth (Paper II). However, the lack of association between ANC service utilization and adverse pregnancy outcomes (Paper III) is consistence with a review article on randomized trials and meta-analysis (118-121). Despite this, an association between ANC service use and pregnancy outcome was reported from cross-sectional and retrospective studies (110, 111). In addition, these latter studies did not summarize the adverse outcomes in the same manner as in the present study (156). We summed up adverse pregnancy outcomes because their frequency was small. This is unlike other studies that assessed the association for each adverse pregnancy outcome. The IUG patterns in our study are in line with the WHO and INTERGROWTH-21st multicentre foetal growth reference studies (Paper I) (1, 2, 157).

External validity

External validity refers to whether the findings can be generalized to a population in different settings (158). In the studies reported in Papers I and III, we included all pregnant women and households for a study that aimed to construct reference charts for foetal growth and size as well as examining the association of antenatal care with adverse pregnancy outcome. The study population was composed of rural residents within the catchment area of the community health post in their respective *kebeles* in the Rift Valley of Ethiopia. In Paper I, we found similar IUG patterns to those indicated in the WHO and INTERGROWTH-21st foetal growth reference standards. The area where we conducted the studies are similar to other Ethiopian rural communities or other areas with similar ecological settings. However, the interpretation of our findings for generalization should take the context of the study area into consideration. Our result may be applicable to areas that have similar characteristics regarding drought and food shortages.

In our studies, we included all pregnant women and households. The study population are rural residents within the catchment area of the community health post in their respective *kebeles* in the Rift Valley of Ethiopia. The study aimed to construct reference charts for foetal growth and size (Paper I). We found similar IUG patterns to those indicated in the WHO and INTERGROWTH-21st foetal growth reference standards. These IUG pattern findings may not be generalizable to a high-risk population of pregnant women because women who had multiple pregnancy, abortion, congenital abnormalities, or intrauterine foetal death were excluded from our analysis. But the findings of this study can be generalized to population of women with low-risk pregnancies. Foetal factors, duration of pregnancy, child age, maternal height and family size were found to be the main predictors of linear child growth measured by LAZ and WLZ in children aged 11–24 months (Paper II). These can be generalized to other areas in the Refit valley of Ethiopia that have similar characteristics regarding drought and food shortages but a higher loss to follow up may limit the generalizability.

During pregnancy, the compliance of ANC utilization with national and WHO guidelines was low (Paper III). The ANC utilization did not have an association with adverse pregnancy outcome. There are no reports of diabetes mellitus, HIV, or syphilis that might potentially contribute to adverse pregnancy outcomes in the study participants. This may affect the generalizability of the findings to a maternal population with different medical backgrounds.

Our findings may be applicable to populations with similar ecological settings to our study area.

Neutrality and interests

Regarding neutrality, all the papers in this thesis have strengths. We collected data from the community. Nurses employed by our research group collected all data. The primary author took the ultrasound measurement but did not tell the sex of the foetus to the mothers. Even though we cannot altogether exclude the chance that research nurses had affected the answers of study participants, the researchers presented the data collected as neutrally as possible with no interest in influencing the results.

No authors had any conflicting interests. The funders were independent of the studies and were not involved in data collecting, analysing, and publishing.

For all published papers, we attempted to ensure accuracy and completeness of reporting the studies according to the Strengthening The Reporting of Observational Studies in Epidemiology checklist (159).

Ethical considerations

The study received ethical approval from the Institutional Review Board of the College of Health Sciences, Addis Ababa University, in June 2015 (ref.;005/15/SPH) and from the Regional Committee for Medical and Health Research Ethics, Western Norway (ref: 2013/986/REK Vest). Written permission to perform this study was obtained from the Oromia Regional Health Bureau and relevant provincial and local authorities in the district. Informed written consent was obtained from each participant. Pregnant women who had indication(s) for treatment were referred to a nearby hospital. Before anthropometric measurements, informed parental consent was obtained for their children, and all procedures were conducted based on voluntary participation.

Discussion of main findings

In this section, discussion is focused on the context of the study and main findings demonstrated by the thesis.

In this thesis, the overall aim was to examine intrauterine and child growth in a rural, drought affected area in the context of Ethiopian health system. We demonstrated the similarity of intrauterine growth patterns in the study area with that of international reference standards. We found that intrauterine foetal growth influenced birth weight and child linear growth. We did not find an association between adverse pregnancy outcomes and utilization of ANC service. Even though ANC service is provided at all levels of health facility, its utilization was low compared to the national and WHO guidelines.

We found that IUG patterns in the rural part of the Rift Valley, south-central Ethiopia, are mostly within the same distribution to that of the WHO and INTERGROWTH-21st multicentre foetal growth reference studies (Paper I) (1, 2, 157). The study area is affected by repeated droughts, food shortages and maternal under-nutrition is common (160). There was a severe drought triggered by El Nino in the area in 2015 and early 2016 (123). The communities were thus receiving food aid (124). Despite the presence of maternal under-nutrition in more than 40% of the women at the start of the study, the EFWs remained within normal ranges. This might be explained by placental adaptation. Maternal under-nutrition is also associated with degenerative placental changes. However, degenerative placental changes may not impair the placenta's transport capacity sufficiently enough to alter foetal nutrition and were not thereby associated with a reduction in foetal growth or birth weight (161). The other possible explanation could be the supplementary food support given to pregnant women. Indeed, pregnant mothers with MUACs < 23 cm in the study area do receive preferential and regular food supplements (124).

We found that intrauterine foetal factors influenced the child linear growth as measured by LAZ and WLZ in children aged 11–24 months (Paper II). The other main predictors of child linear growth were duration of pregnancy, child age, maternal height and family size. Early intrauterine foetal growth influenced the birth weight and LAZ. While foetal growth during late pregnancy influenced the birth weight.

Moreover, we observed a large variation in LAZ and WLZ between villages (kebeles) demonstrating that the influence of environmental factors is more on the child linear growth than the birth weight. Some factors that were found to contribute to growth faltering in low resource settings in other studies were inappropriate breastfeeding, lack of adequate quality and quantity of complementary foods, insufficient infant and young child feeding practices, infections, and other environmental exposures (70-72).

These findings of our study are in line with the birth cohort studies that suggested that growth in the first 1000 days of life can be viewed as a continuum between the foetal period and infancy and early childhood period (72, 163). This underlines the importance of follow up and growth monitoring starting from the antenatal period. In our study we found that intrauterine growth pattern using ultrasound is similar to the international growth reference standards. Thus the use of ultrasound in monitoring of intrauterine growth is less likely to be useful in low-risk pregnancies. The International Federation of Gynecology and Obstetrics (FIGO) also does not recommend the routine use of ultrasound for the detection of foetal growth restriction in low-risk pregnancies as there is no evidence to support it (164). A meta-analysis of 13 trials found that there is no association between routine EFW determination using ultrasound and adverse pregnancy outcomes in low-risk pregnancies (165).

The benefit of antenatal health service utilization is the provision of evidence-based clinical interventions such as maternal health education and counselling, examinations, and arranging specialized care when the need arises (166). Antenatal care gives an opportunity for influencing the future health and well-being of pregnant women, foetuses and neonates. It helps to identify high-risk women to facilitate timely management during pregnancy and child birth (167).

We found that the compliance of ANC utilization in the study area with that of the national and the WHO guidelines was low (Paper III). Only about one third of the pregnant women fulfilled the WHO minimum number of four or more ANC visits. This is lower than the global LMIC proportion of 55% and report from Myanmar of 59% (168-170). Those women who initiated ANC during the first trimester were very low (2.6%) compared to other LMIC such as Myanmar (47%) (168, 170) and the WHO guideline that expects all pregnant women to start ANC follow up during the first trimester (167). The low rate of the four ANC follow-ups in our study is similar to other studies undertaken in Ethiopia. Women may not be able to attend the subsequent ANC follow-ups because of distance, low level of education and poor wealth index (171-173). These factors were also documented in studies from other low-income countries (174-177). The other reasons for the low rate of ANC utilization may be related to the low quality of the services provided and a lack of trust the women feel about the expertise of the service providers (Health Extension Workers) at the health posts (178, 179).

The information collected on ANC service utilization was what was reported by the women. We did not cross check their responses with the medical records. This could have introduced a misclassification bias. The proportion of women who had one ANC in our study (76.1%) is higher than the national ANC attendance (62%). In addition, the loss to follow-up in our study is small (3.2%). The fact that we screened women at home, invited them to enter the study, and advised them to have an ultrasound scan may introduce exposure or intervention bias. That may have contributed to the higher ANC attendance and lower loss to follow up in our study.

We did not find a significant difference between those mothers who visited health facilities for ANC and those mothers who did not have ANC follow-up relating to adverse pregnancy outcomes. This is consistence with a review article on randomized trials and meta-analysis that did not find an association between ANC and adverse pregnancy outcome (118-121). However, it is in contrast to other studies (180, 181), that found an association between ANC utilization and pregnancy outcomes. These studies did not summarize the adverse outcomes in the same manner as in our study (156). One possible explanation for the absence of association between ANC follow-up and the pregnancy outcomes could be because of the low number of ANC follow-ups in the focused or 'reduced' ANC model. Evidence shows that the "standard" ANC model (attending at least eight ANC visits) offers better pregnancy outcomes and a more likelihood of getting helpful maternal health interventions when compared to the "FANC" model (86). In addition, the lack of association could be because we measured coverage rather than the quality of ANC service. Therefore, these findings should be interpreted with caution, as they are not referring to a single adverse outcome.

Conclusion and Recommendations

Conclusion

The conclusion of this Thesis is presented in relation to the objectives of each of the Papers included in this Thesis as follows.

Objective 1: We aimed to assess intrauterine growth patterns in a rural and drought-affected population in Ethiopia (Paper I), and we recommend the following. The main conclusion related to intrauterine growth was as follows.

- The foetal growth patterns, as measured by common ultrasound biometric measurements, were similar to the intrauterine growth patterns of the INTERGROWTH-21st and the WHO multicentre foetal growth reference standards.
- Despite the presence of maternal under-nutrition in more than 40% of the women at the start of the study, the estimated foetal weights remained within normal ranges.

Objective 2: We aimed to examine the influence of intrauterine foetal growth on birth weight and childhood linear growth in Ethiopia (Paper II), and we concluded the following:

- Birthweight and child linear growth were significantly associated with early intrauterine foetal growth
- Late intrauterine foetal growth was only associated with birth weight.

The role of intrauterine growth factor on child linear growth (70%) was higher than the role of environmental factors (30%). Environmental factors associated with the area of residence were more important for linear growth than for birth weight.

Objective 3: To assess the compliance of antenatal care utilization with the national and the WHO guidelines and to examine the association of antenatal care utilization with adverse pregnancy outcomes (Paper III).

- Antenatal care service utilization was low compared to the national and WHO guidelines
- Antenatal care utilization was not associated with the adverse pregnancy outcomes that we measured.

Recommendations

Operational and Policy

- We aimed to assess intrauterine growth patterns in a rural and drought-affected population in Ethiopia (Paper I), and we recommend the following. The routine use of ultrasound in monitoring of intrauterine growth for low-risk pregnancies is not likely to be especially useful
- The growth standard reference developed by our study can be used for Ethiopian and African settings of with similar contexts

We aimed to examine the influence of intrauterine foetal growth on birth weight and childhood linear growth in Ethiopia. (Paper II), and we recommend the following:

- Monitoring foetal growth during early pregnancy is important to identify those prone to linear growth faltering during childhood and to identify factors that affect birth weight.
- Monitoring foetal growth during late pregnancy is important to identify factors that affect birth weight.
- More focus needs to be given for intrauterine growth monitoring during follow-up even though environmental factors had a substantial role on birth weight and child linear growth

We aimed to assess the compliance of antenatal care utilization with the national and the WHO guidelines and to examine the association of antenatal care utilization with adverse pregnancy outcomes (Paper III).

- The policy attention given to expanding ANC services and skilled birth delivery should be backed by an equal commitment to improve components of ANC service including nutritional counselling and other services in health facilities.
- Programme planners and implementers need to give due attention to the provision of quality and comprehensive ANC care during pregnancy
- The fact that the current provision of FANC were not found to be associated with adverse pregnancy outcomes highlight the importance of providing more frequent visit of ANC follow-up with more focused services.
- Strengthening the quality of health facilities at all levels is essential to increase the utilization rate of antenatal care services.

For further research

- A study including nutritional information, environmental, psychosocial and related factors, and which starts before conception may give a more detailed information of how growth trajectories for foetal growth are set and modified during the entire pregnancy ultimately affecting child growth.

References

1. Kiserud T, Piaggio G, Carroli G, Widmer M, Carvalho J, Neerup Jensen L, et al. The World Health Organization Fetal Growth Charts: A Multinational Longitudinal Study of Ultrasound Biometric Measurements and Estimated Fetal Weight. PLoS medicine. 2017;14(1):e1002220.
2. Papageorghiou AT, Ohuma EO, Altman DG, Todros T, Cheikh Ismail L, Lambert A, et al. International standards for fetal growth based on serial ultrasound measurements: the Fetal Growth Longitudinal Study of the INTERGROWTH-21st Project. Lancet. 2014;384(9946):869-79.
3. Loha E, Deressa W, Gari T, et al. Long-lasting insecticidal nets and indoor residual spraying may not be sufficient to eliminate malaria in a low malaria incidence area: results from a cluster randomized controlled trial in Ethiopia. Malaria Journal. 2019;18(141):1-15.
4. WHO. Trends of maternal mortality:1990 to 2015. WHO, UNICEF, UNFPA and the World Bank estimates. 2015.
5. Ministry of Health. Reproductive Health Strategic Plan 2021-2025. Addis Ababa Ethiopia2021.
6. Ministry of Health. Health Sector Transformation Plan 2015/16 - 2019/20. Addis Ababa Ethiopia 2015.
7. Ministry of Health. Health Sector Development Plan II: 2002/03–2004/05. Addis Ababa Ethiopia; 2021.
8. Ministry of Health, Ethiopian Public Health Institute, ICF. Mini Demographic and Health Survey 2019. Addis Ababa Ethiopia; 2019.
9. Central Statistical Agency Ethiopia, and ICF International. Ethiopia Demographic and Health Survey 2000. Addis Ababa, Ethiopia, and Rockville, Maryland, USA. CSA andICF 2000; 2000.
10. Ministry of Finance and Economic Development Ethiopia, United Nations Country Team Ethiopia. Assessing progress towards the Millenium Development Goals: Ethiopia MDGs report 2012.
11. CSA. Ethiopia Demographic and Health Survey. Addis Ababa, Ethiopia; 2016.
12. United Nations. The Millennium Development Goals Report. New York; 2015.
13. UNICEF. Antenatal care coverage current progress. 2015.
14. Ross AB, DeStigter KK, Rielly M, Souza S, Morey GE, et al. A low-cost ultrasound program leads to increased antenatal clinic visits and attended deliveries at a health care clinic in rural Uganda. PLoS One. 2013;8:e78450.
15. Mbuyita S, Tillya R, Godfrey R, Kinyonge I, Shaban J, et al. Effects of introducing routinely ultrasound scanning during ante Natal Care (ANC) clinics on number of visits of ANC and facility delivery: a cohort study. Arch Public Health. 2015;73(36).
16. WHO. WHO recommendations on antenatal care for a posetive pregnancy experiance. 2016.
17. Lincetto O, Mothebesoane-Anoh, Gomez P MS. Antenatal care. Opportunities for Africa’s Newborns: practical data, policy and programmatic support for newborn care in Africa Geneva: World Health Organization; 2006. p. 51–62.
18. World Health Organization. WHO recommendations on antenatal care for a positive pregnancy experience. 2016.
19. World Health O. Risk approach for maternal and child health care : a managerial strategy to improve the coverage and quality of maternal and child health/family planning services based on the measurement of individual and community risk. Geneva: World Health Organization; 1978.
20. Federal Ministry of Health-Ethiopia. National Antenatal Care Guideline. Available at https://e-library.moh.gov.et/library/wp-content/uploads/2022/03/ANC-GUIDELINE_Feb-24-2022.pdf. 2022.
21. Ministry of Health. National Antenatal Care: Ensuring Positive Pregnancy Experiance. Addis Ababa, Ethiopia. February 2021.
22. Ministry of Health. Obstetrics Management Protocol for Health Centers. 2021.
23. Backe BJTfDnl. Svangerskapsomsorgen i Norge–mange unødvendige kontroller. 2002.
24. Brandt K, Læreboki f. Antenatal care in Norway: Too frequent visits? ødselshjælp: Aschehoug & Co. 2002;122:1989–92.
25. Lovset JB. E. Lærebok i obstetrikk for jordmødre. Oslo: Aschehoug & Co; 1959.

26. Pedersen A. 100 år med redusert spedbarnsdødelighet. Statistisk sentralbyrå. 2003.
27. Roberts E, Wood P. Birth weight and adult health in historical perspective: evidence from a New Zealand cohort, 1907-1922. Social science & medicine 2014;107:154-61.
28. Westin B. Gravidogram and fetal growth comparison with biochemical supervision. Acta obstetricia et gynecologica Scandinavica 1977;56(4):273-82.
29. Kiserud T. Fundal Height Growth in Rural Africa. Acta Obstetricia et Gynecologica Scandinavica. 1986;65(7):713-5.
30. Neilson JP. Symphysis-fundal height measurement in pregnancy. The Cochrane database of systematic reviews. 2002(2);CD000944.
31. Bais JM, Eskes M, Pel M, Bonsel GJ, Bleker OP. Effectiveness of detection of intrauterine growth retardation by abdominal palpation as screening test in a low risk population: an observational study European journal of obstetrics, gynecology, and reproductive biology. 2004;116(2):164-9.
32. Donald I, Macvicar J, Brown TG. Investigation of abdominal masses by pulsed ultrasound. Lancet. 1958;1(7032):1188-95. Lancet. 1958;1(7032):1188-95.
33. Donald I, Brown TG. Demonstration of tissue interfaces within the body by ultrasonic echo sounding The British journal of radiology 1961;34:539-46.
34. Willocks J, Donald I, Campbell S, Dunsmore IR. Intrauterine growth assessed by ultrasonic foetal cephalometry The Journal of obstetrics and gynaecology of the British Commonwealth. 1967;74(5):639-47.
35. Kim ET, Kavita S, Allisyn M, Deborah A, Naoko K. Obstetric ultrasound use in low and middle income countries: a narrative review. Reproductive Health 2018;15:129.
36. Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. The New England journal of medicine. 2008;359(1):61-73.
37. Barker DJ. Adult consequences of fetal growth restriction. Clinical obstetrics and gynecology. 2006;49(2):270-83.
38. Burton GJ, Hempstock J, Jauniaux E. Nutrition of the human fetus during the first trimester--a review. Placenta 2001;22 Suppl A:S70-7.
39. David A, Sacks M. Determinants of Fetal Growth. Current Science Inc. 2004;4:281–7.
40. Landis.H.S, Ananth.V.C, Lokomba.A, et.al. Ultrasound-derived fetal size nomogram for a sub-Saharan African population: a longitudinal study. Ultrasound Obstetrics and Gynecology. 2009;34:379-86.
41. Johnsen SL, Rasmussen S, Wilsgaard T, Sollien R, Kiserud T. Longitudinal reference ranges for estimated fetal weight Acta obstetricia et gynecologica Scandinavica. 2006;85(3):286-97.
42. Wanyonyi SZ, Mutiso SK. Monitoring fetal growth in settings with limited ultrasound access. Best Practice & Research Clinical Obstetrics and Gynaecology. 2018.
43. Pay A, Froen JF, Staff AC, Jacobsson B, Gjessing HK. Prediction of small-forgestational-age status by symphysis-fundus height: a registry-based population cohort study. BJOG : an international journal of obstetrics and gynaecology. 2015.
44. Pay AS, Wiik J, Backe B, Jacobsson B, Strandell A, Klovning A. Symphysis-fundus height measurement to predict small-for-gestational-age status at birth: a systematic review. BMC pregnancy and childbirth. 2015;15(22).
45. Conde-Agudelo A, Papageorghiou AT, Kennedy SH, Villar J. Novel biomarkers for predicting intrauterine growth restriction: a systematic review and meta-analysis. BJOG 2013;120:681–94.
46. Backe B, . NJ. Effectiveness of antenatal care: a population based study British journal of obstetrics and gynaecology 1993;100(8):727-32.
47. Lubchenco LO, Hansman C, Dressler M, Boyd E. Intrauterine growth as estimated from liveborn birthweight data at 24 to 42 weeks of gestation. Pediatrics. 1963;32:793–800.
48. Dickey RP, Gasser RF. Ultrasound evidence for variability in the size and development of normal human embryos before the tenth post-insemination week after assisted reproductive technologies Human reproduction. 1993;8(2):331-7.
49. Smith GC, Smith MF, McNay MB, Fleming JE. First-trimester growth and the risk of low birth weight The New England journal of medicine The New England journal of medicine. 1998;339(25):1817-22.

50. Mielke G, Pietsch-Breitfeld B, Salinas R, Risse T, Marzusch K. A new formula for prenatal ultrasonographic weight estimation in extremely preterm fetuses Gynecologic and obstetric investigation. 1995;40(2):84-8.
51. Hadlock FP, Harrist RB, Sharman RS, Deter RL, Park SK. Estimation of fetal weight with the use of head, body, and femur measurements - a prospective study. Am J Obstet Gynecol 1985;151:333–7.
52. Nahum GG, Stanislaw H. Ultrasonographic prediction of term birth weight: how accurate is it? American journal of obstetrics and gynecology. American journal of obstetrics and gynecology. 2003;188(2):566-74.
53. Altman DG, Chitty LS. Charts of fetal size: 1. Methodology. British journal of obstetrics and gynaecology 1994;101(1):29-34.
54. Kiserud T, Johnsen SL. Biometric assessment. Best practice & research Clinical obstetrics & gynaecology 2009;23(6):819-31.
55. Sovio U, White IR, Dacey A, Pasupathy D, Smith GCS. Screening for fetal growth restriction with universal third trimester ultrasonography in nulliparous women in the Pregnancy Outcome Prediction (POP) study: a prospective cohort study. Lancet. 2015;386(10008):2089-97.
56. Kramer MS. Determinants of low birth weight: methodological assessment and meta-analysis. Bull World Health Organ 1987;65:663–737.
57. Mamelle N, Cochet V, Claris O. Definition of fetal growth restriction according to constitutional growth potential Biol Neonate 2001;80:277–85.
58. Altenhöner T, Köhler M, Philippi M. The Relevance of Maternal Socioeconomic Characteristics for Low Birth Weight - a Case-Control Study. Geburtshilfe und Frauenheilkunde. 2016;76(3):248-54.
59. Golan J, D Heacdey, K Hirvonen, and Hoddinot. Changes in Child Undernutriton in Ethiopia, 2000 - 2016: The Oxford Handbook of Ethiopian Economy. New York: Oxford University Press2019.
60. Chiavarini M, Bartolucci F, Gili A, Pieroni L, Minelli L. Effects of individual and social factors on preterm birth and low birth weight: empirical evidence from regional data in Italy. International journal of public health. 2012;57(2):261-8.
61. Black RE, Allen LH, Bhutta ZA, et al. Maternal and child undernutrition: global and regional exposures and health consequences Lancet. 2008;371:243-60.
62. Pelletier DL. The relationship between child anthropometry and mortality in developing countries: implications for policy, programs and future research J Nutr. 1994;124:S2047-S81.
63. Victora CG, de Onis M, Hallal PC, Blossner M, Shrimpton R. Worldwide timing of growth faltering: revisiting implications for interventions. Pediatrics. 2010;125 e473–80.
64. Yarbrough C, Habicht J-P, Malina RE, Lechtig A, Klein RE. Length and weight in rural Guatemalan Ladno children: birth to seven years of age. Am J Phys Anthropol. 1975;42:439–48.
65. Rivera JA, Ruel M. Growth retardation starts in the first three months of life among rural Guatemalan children Eur J Clin Nutr 1997;51:92-6.
66. Prado E L, Yakes Jimenez E , Vosti S, & et al. Path analyses of risk factors for linear growth faltering in four prospective cohorts of young children in Ghana, Malawi and Burkina Faso. BMJ Glob Health. 2019;4.
67. Borghi E, de Onis M, Garza C, Van den Broeck J, Frongillo EA, Grummer-Strawn L, et al. Construction of the World Health Organization child growth standards: selection of methods for attained growth curves. 2006;25(2):247-65.
68. Himes JHJMihgr. Why study child growth and. 2004;39:1.
69. Hauspie R C, Cameron N, and Molinari L. Methods in human growth research United States of America: Cambridge University Press; 2004.
70. Black RE, Victora CG, Walker SP, Bhutta ZA, Christian P, de Onis M, et al. Maternal and child undernutrition and overweight in low-income and middle-income countries. The Lancet. 2013;382(9890):427–51.
71. United Nations, Subcommittee on Nutrition. Third report on the world nutrition situation: a report compiled from information available to the ACC/SCN. Geneva: United Nations; 1997.
72. Christian P. Prenatal origins of malnutrition. In: Kalhan SC, Prentice AM, Yajnik CS (eds). Emerging societies—coexistence of childhood malnutrition and obesity. Vevey, Switzerland: S Karger Ag; 2009.

73. Magnus P. Causes of variation in birth weight: a study of offspring of twins Clinical genetics. 1984;25(1):15-24.
74. Little RE, Sing CF. Genetic and environmental influences on human birth weight. American journal of human genetics. 1987;40 (6):512-26.
75. Godfrey K, Robinson S, Barker DJ, Osmond C, Cox V. Maternal nutrition in early and late pregnancy in relation to placental and fetal growth Bmj. 1996;312(7028):410-4.
76. Skjaerven R, Gjessing HK, Bakketeig LS. Birthweight by gestational age in Norway. Acta obstetricia et gynecologica Scandinavica. 2000;79(6):440-9.
77. Boulet.L.S, Alexander.R.G, Salihu. M.H, R. S. Kirby. S.R, and Carlo.A.W. “Fetal growth risk curves: defining levels of fetal growth restriction by neonatal death risk,” American Journal of Obstetrics and Gynecology. 2006;195:pp. 1571–7.
78. Mayer.C. and Joseph. K. S. “Fetal growth: a reviewof terms, concepts and issues relevant to obstetrics,” Ultrasound in Obstetrics &Gynecology. 2013;vol. 41:pp. 136–45.
79. McIntire. D.D, Bloom. S.L, Casey. B.M aLKJ. “Birth weight in relation to morbidity and mortality among newborn infants". The New England journal of medicine. 1999;vol. 340, no. 16,:pp. 1234–8.
80. PMMRC. Eleventh Annual Report of the Perinatal and Maternal Mortality Review Committee: Reporting mortality 2010 Wellington: Health Quality & Safety Commission; 2012.
81. Gilbert M.W, and B. Danielsen. B. “Pregnancy outcomes associated with intrauterine growth restriction,” American Journal of Obstetrics and Gynecology 2003;vol. 188, no. 6:pp. 1596–601.
82. Mandruzzato. G, Meir. Y.J, Natale. R, and Maso. G. “Antepartal assessment of IUGR fetuses,” Journal of Perinatal Medicine. 2001;vol. 29, no. 3:pp. 222–9.
83. World Health Organization. Childhood stunting: challenges and opportunities. Report of a colloquium on promoting healthy growth and preventing childhood stunting. Geneva: World Health Organization; 2014.
84. Williams AM, Suchdev PS. Assessing and improving childhood nutrition and growth globally Pediatr Clin North Am 2017. 2017;64:755–68.
85. Jennifer A. Hutcheon, Geir W. Jacobsen, Michael S. Kramer, Marit Martinussen, and, Robert W. Platt. Small Size at Birth or Abnormal Intrauterine Growth Trajectory: Which Matters More for Child Growth? American Journal of Epidemiology. 2016;183(12).
86. Organization WH. International statistical classification of diseases and related health problems, tenth revision. 2nd ed: World Health Organization; 2004.
87. World Health Organization. Recommendations on interventions to improve preterm birth outcomes. Geneva, Switzerland2015 26447264]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK321160/.
88. KY Ge, et al. Definition and Measurment of Child Malnutrition. Biomed Environ Sci. 2001;14(4):283-91.
89. Duggan MB. Anthropometry as a Tool for Measuring Malnutrition: Impact of the New WHO Growth Standards and Reference. Ann Trop Paediatr. 2010;30(1):1-17.
90. CIA-USA the world fact book. Africa-Ethiopia, Economy: Ethiopia. 2019.
91. Central Statistical Agency. Population Projection of Ethiopia for All Regions At Wereda Level from 2014 – 2017. Addis Ababa, Ethiopia; 2013.
92. Ethiopia Administrative Regions, Cities and Population. Accessed on February 16, 2022 at http://www.ethiovisit.com/ethiopia/ethiopia-regions-and-cities.html.
93. World Bank. Ethiopia Overview: Development news, research, data. Available at https://www.worldbank.org/en/country/ethiopia/overview 2022
94. Africa Development Bank Group. Ethiopia Economic Outlook: Recent macroeconomic and financial developments. Available at https://www.afdb.org/en/countries/east-africa/ethiopia/ethiopia-economic-outlook 2022
95. Federal Ministry of Health. Health sector transformation plan II: 2020/21- 2024/25. Available: https://e-library.moh.gov.et/library/wp-content/uploads/2021/07/HSTP-II.pdf. 2021.
96. Sebhatu A. Ethiopia good practice – the implementation of Ethiopia’s Health Extension Program: an overview. Addis Ababa; 2008.
97. Teklehaimanot HD, Teklehaimanot A. Human resource development for a community-based health extension program: a case study from Ethiopia Human Resources for Health. 2013;11(39).

98. Federal Ministry of Health. Realizing universal health coverage through Pimary Health Care. A Roadmap for Optimizing the Ethiopian Health Extension Program 2020 - 2035. 2020.
99. Federal Democratic Republic of Ethiopia MoH. Health development army guidelines. Addis Ababa2005.
100. Johnsen SL, Wilsgaard T, Rasmussen S, Sollien R, Kiserud T. Longitudinal reference charts for growth of the fetal head, abdomen and femur. Eur J Obstet Gynecol Reprod Biol. 2006;127(2):172-85.
101. Snijders RJ, Nicolaides KH. Fetal biometry at 14-40 weeks' gestation. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 1994;4(1):34-48.
102. Hadlock FP, Harrist RB, Martinez-Poyer J. In utero analysis of fetal growth: a sonographic weight standard. Radiology. 1991;181(1):129-33.
103. Owen P, Donnet ML, Ogston SA, Christie AD, Howie PW, Patel NB. Standards for ultrasound fetal growth velocity. Br J Obstet Gynaecol. 1996;103(1):60-9.
104. Zhang J, Merialdi M, Platt LD, Kramer MS. Defining normal and abnormal fetal growth: promises and challenges. Am J Obstet Gynecol. 2010;202(6):522-8.
105. Salam RA, Syed B, Syed S, Das JK, Zagre NM, Rayco-Solon P, et al. Maternal nutrition: how is Eastern and Southern Africa faring and what needs to be done? African health sciences. 2015;15(2):532-45.
106. Lausman A, Kingdom J, Maternal Fetal Medicine C. Intrauterine growth restriction: screening, diagnosis, and management. Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC. 2013;35(8):741-8.
107. Imdad A, Yakoob MY, Siddiqui S, Bhutta ZA. Screening and triage of intrauterine growth restriction (IUGR) in general population and high risk pregnancies: a systematic review with a focus on reduction of IUGR related stillbirths BMC Public Health. 2011 Apr;11 (Suppl 3:S1).
108. Carroli G, Rooney C, Villar J. How effective is antenatal care in preventing maternal mortality and serious morbidity? An overview of the evidence. Paediatr Perinat Epidemiol. 2001;15(Suppl 1):1–42.
109. Owolabi OO, Wong KLM, Dennis ML, et!al. Comparing the use and content of antenatal care in adolescent and older !rst- time mothers in 13 countries of West Africa: a cross- sectional analysis of demographic and health surveys. Lancet Child Adolesc Health. 2017;1:203–12.
110. Blondel B, Dutilh P, Delour M, S. U. Poor antenatal care and pregnancy outcome. Eur J Obstet Gynecol Reprod Biol. 1993;50(3):191-6.
111. Blondel B, Marshall B. Poor antenatal care in 20 French districts: risk factors and pregnancy outcome. J Epidemiol Community Health. 1998;52:501-6.
112. Katherine E. Debiec, Kathleen J. Paul, Caroline M. Mitchell, Jane E. Hitti. Inadequate prenatal care and risk of preterm delivery among adolescents: a retrospective study over 10 years. Am J Obstet Gynecol 2010;203(122).
113. Bater J, Lauer JM, Ghosh S, Webb P, Agaba E, Bashaasha B, et al. Predictors of low birth weight and preterm birth in rural Uganda: Findings from a birth cohort study. PloS one. 2020;15(7):e0235626-e.
114. Jesmin Pervin, Syed Moshfiqur Rahman, Monjur Rahman, Shaki Aktar, Anisur Rahman. Association between antenatal care visit and preterm birth: a cohort study in rural Bangladesh. BMJ Open. 2020;10.
115. Partridge S, Balayla J, Holcroft CA, Abenhaim HA. Inadequate prenatal care utilization and risks of infant mortality and poor birth outcome: a retrospective analysis of 28,729,765 U.S. deliveries over 8 years. Am J Perinatol. 2012;29(10):787-93.
116. Dilaram Acharya, Jitendra Kumar Singh, Rajendra Kadel , Seok-Ju Yoo, Ji-Hyuk Park , and Kwan Lee. Maternal Factors and Utilization of the Antenatal Care Services during Pregnancy Associated with Low Birth Weight in Rural Nepal: Analyses of the Antenatal Care and BirthWeight Records of the MATRI-SUMAN Trial. Int J Environ Res Public Health. 2018;15:1-4.
117. Zhou H, Wang A, Huang X, Guo S, Yang Y, Martin K, et al. Quality antenatal care protects against low birth weight in 42 poor counties of Western China. PLoS One. 2019;14(1):e0210393.
118. Fiscella K. Does prenatal care improve birth outcomes? A critical review. Obstetrics & Gynecology. 1995;85:468-79.

119. Goldenberg RL, and Rouse DJ. Prevention of premature birth. New England Journal of Medicine. 1998;339:313-20.
120. Kramer MS. Determinants of low birth weight: methodological assessment and meta-analysis. Bull World Health Organ. 1987;65(5):663-737.
121. McDuffie RS, Jr, Beck A, Bischoff K, Cross J, Orleans M. Effect of Frequency of Prenatal Care Visits on Perinatal Outcome Among Low-Risk Women: A Randomized Controlled Trial. JAMA. 1996;275(11):847-51.
122. National Meteorology Agency. Adami Tullu and Zeway town annual meteorology data. 2016.
123. International Federation of Red Cross and Red Crescent Societes Ethiopia. Drought-Emergency plan of action operations update number 3 (MDRET0016): Availablefrom: https://reliefweb.int/report/ethiopia/ethiopia-drought-emergency-plan-action-12-month-update-mdret0016.
124. Ministry of Agriculture and Rural Development. Guidelines for the Management of Moderate Acute Malnutrition, in Ethiopia. Addis Ababa: Ministry of Agriculture and Rural Development; September 2012.
125. Deressa W, Loha E, Balkew M, et al. Combining long-lasting insecticidal nets and indoor residual spraying for malaria prevention in Ethiopia: study protocol for a cluster randomized controlled trial. Trials. 2016;17(20).
126. Muluken Kassahun Amid. GADAA SYSTEM AND WOMEN’S RIGHTS. The Role of Oromoo Women’s Customary Institutions in Ensuring The Protection of Rights of Women. Center for the Advancement of Rights and Democracy. 2021.
127. Tesema Ta’a. The Gadaa System and Some of Its Institutions among the Booranaa: A Historical Perspective. EJOSSAH 2016;XII(2).
128. WHO. Medical Eligibility Criteria for contraceptive use. 4ed ed2010.
129. Hadlock FP, Deter RL, Harrist RB, Park SK. Estimating fetal age: computer-assisted analysis of multiple fetal growth parameters. Radiology. 1984;152:497–501.
130. Trish Chudleigh T, Thilaganathan B. Obstetric Ultrasound:How, Why and When. Third Edition ed2004.
131. Vyas S, Kumaranayake L. Constructing socio-economic status indices: how to use principal components analysis. Health policy and planning. 2006;21(6):459-68.
132. University of Oxford. International Fetal Growth Standards: Application. 2017.
133. Org/en/d/Jhe/ WECJhhd. Physical status: the use and interpretation of anthropometry. 1995.
134. WHO. Recommendations on interventions to improve preterm birth outcomes. Geneva, Switzerland2015.
135. WHO. AnthroPlus: Software for assessing growth of the world's children and adolescents Geneva, Switzerland; 2009.
136. Twisk JWR. Applied Multilevel analysis: A practical guide. Fourth printing. United States of America: Cambridge University press; 2010.
137. Broeck JVd, Brestoff JR. Epidemiology: Principles and practical guidelines2013.
138. Aschengrau A, III GRS. Essential of epidemiology in Public Health. Toronto, Canada: Jones and Bartlett; 2008.
139. Kristman V, Manno M, Côté PJEjoe. Loss to follow-up in cohort studies: how much is too much? 2004;19(8):751-60.
140. Bonita R, Beaglehole R, Kjellström T. Basic Epidemiology: World Health Organization; 2006.
141. Grimes DA, Schulz KF. An overview of clinical research: The lay of the land. Lancet. 2002;359:57-61.
142. Porta M. A dictionary of Epidemiology. New York, USA: International Epidemiological Association; 2006.
143. Rothman KJ, Greenland S, Lash TL. Modern Epidemiology2008.
144. Sedgwick PJB. Bias in observational study designs: cross sectional studies. 2015;350.
145. Grimes DA, Schulz KF. Bias and causal associations in observational research. Lancet. 2002;359:248-52.
146. Gari T, Loha E, Deressa W, Solomon T, Atsbeha H, Assegid M, et al. Anaemia among children in a drought affected community in south-central Ethiopia. PLoS ONE. 2017;12(3).

147. Diane DiT, Mary C. Systematic review of expected weight changes after birth for full-term, breastfed newborns. AWHONN, the Association of Women's Health, Obstetric and Neonatal Nurses. 2019;48(6).
148. Dudley NJ. The management of error in ultrasound fetal growth monitoring. Ultrasound (Leeds, England). 2021;29(1):4-9.
149. Timothy L. Lash, Tyler J. VanderWeele, Sebastien Haneuse, Kenneth J. Rothman. Modern Epidemiology. Chapter 12. Confounding and Confounders: Lippincott Williams & Wilkins; 2020.
150. Verburg BO, Steegers E, De Ridder M, Snijders R, Smith E, Hofman A, et al. New charts for ultrasound dating of pregnancy and assessment of fetal growth: longitudinal data from a population-based cohort study. 2008;31(4):388-96.
151. Pourhoseingholi MA, Baghestani AR, Vahedi M. How to control confounding effects by statistical analysis. Gastroenterol Hepatol Bed Bench. 2012;5(2):79-83.
152. Bonita R, Beaglehole R, Kjellström T, 2006 nee. Basic Epidemiology: World Health Organization; 2006.
153. Bryan Kestenbaum. Epidemiology and Biostatistics. An Introduction to Clinical Research: Springer; 2009.
154. Royston P, Altman DG, Sauerbrei WJSim. Dichotomizing continuous predictors in multiple regression: a bad idea. 2006;25(1):127-41.
155. Hill AB. The environment and disease: association or causation? Proc R Soc Med. 1965;58(5):295-300.
156. Andemel N, Gaoussou S, Barry A, et al. Adverse pregnancy outcomes among women presenting at antenatal clinics in Ouélessébougou, Mali. BMC Reproductive Health. 2020 17:39.
157. Kiserud T, Benachi A, Hecher K, Perez RG, Carvalho J, Piaggio G, et al. The World Health Organization fetal growth charts: concept, findings, interpretation, and application. Am J Obstet Gynecol. 2018;218(2S):S619-S29.
158. Bobby JC, Phillips LW, Tybout AM. The Concept of External Validity. Journal of Consumer Research 9. 1982;9(3).
159. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370(9596):1453-7.
160. IFRC. Ethiopia: Drought- Emergency plan of action operations update number 2(MDRET016) : International Federation of Red Cross and Red Crescent Societes 31 August 2016:Accessed 2016 September 15; 5.
161. Jones AP, L.S. Crnic. Maternal mediation of the effects of malnutrition. Handbook of Behavioral Teratology. New York: Plenum Press; 1986. Pp. 409–26 p.
162. Gari T, Loha E, Deressa W, Solomon T, Atsbeha H, Assegid M, et al. Anaemia among children in a drought affected community in south-central Ethiopia. PLoS One. 2017;12(3):e0170898.
163. Jennifer AH, Geir WJ, Michael SK, Marit M, and Robert WP. Small size at birth or abnormal intrauterine growth trajectory: which matters more for child growth? American Journal of Epidemiology. 2016;183(12).
164. Nir Melamed, Ahmet Baschat, Yoav Yinon, et al. FIGO (International Federation of Gynecology and Obstetrics) initiative on fetal growth: Best practice advice for screening, diagnosis, and management of fetal growth restriction. Int J Gynecol Obstet. 2021;152:3–57.
165. Bricker L, Medley N, Pratt JJ. Routine ultrasound in late pregnancy (after 24 weeks' gestation). Cochrane Database Syst Rev. 2015;(6) CD001451.
166. World Health Organization (WHO). Pregnancy, childbirth, postpartum and newborn care: A guide for essential practice. Geneva: World Health Organization; 2009.
167. Tunçalp Ö, Pena-Rosas J, Lawrie T, Bucagu M, Oladapo O, Portela A, et al. WHO recommendations on antenatal care for a positive pregnancy experience—going beyond survival. 2017;124(6):860-2.
168. WHO. World health statistics 2016: monitoring health for the SDGs, sustainable development goals. Switzerland; 2016.
169. WHO, and International Center for Equity in Health/Pelotas. State of inequality: reproductive, maternal, newborn and child health. Geneva2015.

170. Mugo NS, Mya KS, Raynes-Greenow C. Country compliance with WHOrecommended antenatal care guidelines: equity analysis of the 2015–2016 Demography and Health Survey in Myanmar. BMJ Global Health. 2020;5.
171. Tiruneh GT, Demissie M, Worku A, Berhane Y. Predictors of maternal and newborn health service utilization across the continuum of care in Ethiopia: A multilevel analysis. PLoS ONE. 2022;17(2).
172. Tekelab T, Chojenta C, Smith R, Loxton D. Factors affecting utilization of antenatal care in Ethiopia: A systematic review and meta-analysis. PLoS ONE. 2019;14(4).
173. Muluneh AG, Kassa GM, Alemayehu GA, Merid MW. High dropout rate from maternity continuum of care after antenatal care booking and its associated factors among reproductive age women in Ethiopia, Evidence from Demographic and Health Survey 2016. PLOS ONE. 2020;15(6).
174. Kuhnt J, Vollmer S. Antenatal care services and its implications for vital and health outcomes of children: evidence from 193 surveys in 69 low-income and middle-income countries. 2017;7(11):e017122.
175. Campbell OMR, Calvert C, Testa A, Strehlow M, Benova L, Keyes E, et al. The scale, scope, coverage, and capability of childbirth care. The Lancet. 2016;388(10056):2193-208.
176. Wang W, Alva S, Wang S, and Alfredo Fort. Levels and Trends in the Use of Maternal Health Services in Developing Countries. Maryland, USA: ICF Macro; 2011.
177. Rosário EVN, Gomes MC, Brito M, Costa D. Determinants of maternal health care and birth outcome in the Dande Health and Demographic Surveillance System area, Angola. PLOS ONE. 2019;14(8):e0221280.
178. Birhanu Z, Godesso A, Kebede Y, Gerbaba M. Mothers' experiences and satisfactions with health extension program in Jimma zone, Ethiopia: a cross sectional study. BMC Health Serv Res. 2013;13(74).
179. Mergia M, Shegaze M, Ayele G, Andarge E, Yeshitila YG, Wassihun B, et al. Mothers' satisfaction with health extension services and the associated factors in Gamo Goffa zone, Southern Ethiopia. PLoS ONE. 2020;15(5).
180. Tadesse Z.T, Sisay KT., Birhanu AT., Antehunegn GT. Prevalence of low birth weight and its associated factor at birth in Sub-Saharan Africa: A generalized linear mixed model. PLOS ONE. 2021;16(3).
181. Tshotetsi L., Dzikiti L., Hajison P, Feresu S. Maternal factors contributing to low birth weight deliveries in Tshwane District, South Africa. PLoS ONE 2019;14(3).

Original articles I-III and Appendices

Paper I

PLOS ONE

RESEARCH ARTICLE

Intrauterine growth patterns in rural Ethiopia compared with WHO and INTERGROWTH-21st growth standards: A community-based longitudinal study

Meselech Roro[1,2]*, Wakgari Deressa[3], Bernt Lindtjørn[1]

1 Centre for International Health, University of Bergen, Bergen, Norway, **2** Department of Reproductive Health and Health Service Management, School of Public Health, College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia, **3** Department of Preventive Medicine, School of Public Health, College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia

* meselua@yahoo.com

Citation: Roro M, Deressa W, Lindtjørn B (2019) Intrauterine growth patterns in rural Ethiopia compared with WHO and INTERGROWTH-21st growth standards: A community-based longitudinal study. PLoS ONE 14(12): e0226881. https://doi.org/10.1371/journal.pone.0226881

Editor: R. Matthew Chico, London School of Hygiene and Tropical Medicine, UNITED KINGDOM

Received: February 25, 2019

Accepted: December 7, 2019

Published: December 31, 2019

Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: This study was funded by University of Bergen in Norway and the Research Council of Norway (project number: 220554). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The author(s) received no specific funding for this work.

Abstract

Introduction

Children's well-being is highly influenced by their fetal growth. Adequate intrauterine growth (IUG) is a basic feature of a healthy pregnancy. The aim of our study was to assess IUG patterns in a rural and drought-affected population in the Rift Valley area of the Adami Tullu district in Oromia, Ethiopia.

Methods

We conducted a longitudinal, community-based study of IUG patterns utilizing serial ultrasound measurements. Data were collected for 17 months, from July 2016 to November 2017. We included 675 singleton foetuses $\leq$ 24 weeks old, based on ultrasound-derived estimates of gestational age, and followed them until delivery. We obtained head circumference, biparietal diameter, abdominal circumference, femur length, and estimated fetal weight at 26, 30, and 36 weeks. Fetal weight was estimated using the Hadlock algorithm, and the 5th, 10th, 25th, 50th, 75th, 90th, and 95th centiles were developed from this model. We compared the biometric measurements and fetal weight data from our study to the World Health Organization (WHO) and INTERGROWTH-21st fetal growth reference standards.

Results

Distribution of the biometric measurements and estimated fetal weights in our study were similar to those for the WHO and INTERGROWTH-21st references. Most measurements were between -2 and +2 of the reference z-scores. Based on the smoothed percentiles, the 5th, 50th, and 95th percentiles of our study had similar distribution patterns to the WHO chart, and the 50th percentile had a similar pattern to the INTERGROWTH-21st chart.

Competing interests: The authors have declared that no competing interests exist.

Conclusions

Our study determined fetal growth patterns in a drought-affected rural community of Ethiopia using common ultrasound biometric measurements. We found similar IUG patterns to those indicated in the WHO and INTERGROWTH-21st fetal growth reference standards.

Introduction

Children's well-being is highly influenced by fetal growth. Adequate intrauterine growth (IUG) is a basic feature of a healthy pregnancy. Abnormal fetal growth has been associated with adulthood diseases, such as stunting, cardiovascular disease, diabetes mellitus, and obesity [1, 2]. Ultrasound imaging constitutes an indispensable tool for estimating gestational age and fetal size. Fetal growth assessment using ultrasound improves detection of IUG restrictions and helps identify those foetuses at risk of sickness during the neonatal period [3]. Since the early 1980s, several ultrasound-based fetal weight references have been published [4]. Most are based on cross-sectional or retrospective studies [3, 5, 6], with only one observation from each woman. Moreover, these references include fetal size only and thus provide limited information about fetal growth. Prospective studies, in comparison, can confirm gestational age and assess fetal growth via repeated measurements [7]. Some earlier longitudinal ultrasound studies were conducted using small sample sizes, and those with larger sample sizes were performed on predominantly Caucasian populations [8]. Evidence from some of these studies shows that differences in fetal growth depend on racial category, sex, parity, and maternal size [8].

Two recent multicentre studies that have been used to develop IUG standards are the World Health Organization (WHO) Multicentre Growth Reference Study and the INTERGROWTH-21st project [9, 10]. Other "birth weight-for-gestational-age references" have been developed with large, mostly population-based databases, and they provide birth weight percentiles by gestational week [3, 11]. The WHO study, which identifies differences in estimated fetal weight (EFW) between countries, finds that maternal age, parity, height, and weight only partially explain the differences [9]. Both the WHO and INTERGROWTH-21st studies measure biometric growth, although INTERGROWTH-21st does not present percentile data for EFW. The INTERGROWTH-21st study estimates fetal weight during ultrasound using head circumference and abdominal circumference, whereas the WHO study uses the Hadlock 3 algorithm to generate EFW using head circumference, abdominal circumference, and femoral length. Both standards can be used as references for interpreting routine ultrasound measurements.

Because these studies were conducted on presumably healthy and well-nourished pregnant women, the risk of adverse perinatal outcomes in areas such as Ethiopia, which is repeatedly affected by drought and food insecurity, remains unclear. Poor maternal nutrition could be an important contributor to IUG restriction and subsequent low birth weight [12, 13]. Furthermore, the WHO study recommends the establishment of population-specific fetal growth charts [9]. As Intrauterine growth restriction (IUGR) is reportedly high in African countries [14], a fetal growth chart that reflects reliable data from the local population needs to be developed. This chart will serve as a basis to verify if the current growth charts can be used to assess populations in Africa. We hypothesised that the IUG pattern in our study site would differ from those of the WHO and INTERGROWTH-21st Project. The aim of our study thus was to assess IUG patterns in a rural and drought-affected population in Ethiopia.

Materials and methods

Study design and settings

This longitudinal, ultrasound-based study was conducted in the rural Adami Tullu district in the East Shewa Zone of the Oromia Regional State in Ethiopia. The district is in the Rift Valley area of south-central Ethiopia. According to the 2007 National Census, the projected population of Adami Tullu was approximately 177,390 people in 2015 [15]. We followed women residing in the district within the context of a recently conducted large, community-based, cluster-randomized, controlled trial to determine how the combined use of long-lasting insecticidal nets and indoor residual spraying affected malaria incidence compared with nets alone or spraying alone in the rural part of the district [16].

Study population

We included pregnant women living in the study district's villages or in the clusters of the previously mentioned malaria trials and followed them until delivery. Pregnant women were identified by data collectors, who went house to house interviewing every woman of reproductive age (15–49 years) to ask if she was pregnant. If a woman responded that she was not pregnant or did not know her pregnancy status, the data collectors used a WHO checklist to determine with reasonable certainty that a woman was not pregnant [17]. For those women who were suspected to be pregnant based on their interview responses or the WHO checklist, an ultrasound scan was performed to verify the pregnancy and estimate gestational age. We then included all pregnant women with a gestational age of less than 24 weeks who agreed to participate in the study.

The sample size was determined based on birth weight, the primary outcome measure. The size should be adequate to detect a birth weight difference of 110 g, based on WHO and INTERGROWTH-21st findings and on previous estimates of standard deviations of birth weight of approximately 500 g [9, 18]. Thus, the estimated sample size was 325 in each group (power of 80%). Allowing for a 5% non-response rate and 5% loss to follow-up, the total sample size was 716.

Enrolment was conducted from July 2016 to June 2017, and follow-up was completed in November 2017 when the last woman gave birth. All consenting pregnant women with a gestational age $\leq$ 24 weeks and who lived in the study area were included in the study. Those pregnant women who left the study area or who had histories of multiple pregnancy, abortion, congenital abnormalities, or intrauterine fetal death were excluded from the analysis.

Data collection

After enrolment, we collected data on baseline socioeconomic status, maternal age, obstetric history, occurrence of chronic diseases, anthropometric measurements (e.g. maternal weight, height, and mid-upper-arm circumference), blood pressure, haemoglobin, and rapid diagnostic test results for malaria. Conditions that could affect fetal growth and birth weight, such as twin pregnancy, congenital malformation, hypertensive disorders, malnutrition, anaemia, and malaria were assessed. Testing for maternal diabetes, HIV, and syphilis was not performed, but these data were collected from the history reported by those women who received antenatal care at health facilities. All assessments were conducted at nearby health posts. The women were then given a follow-up card to visit the health posts to attend three prescheduled visits at 26, 30, and 36 weeks of gestation. Data collectors visited the women's homes one day prior to their appointments to remind them.

During each scheduled visit, we recorded the ultrasound results, anthropometric measurements, blood pressure, haemoglobin measurements, and malaria test results. Haemoglobin was measured using a portable spectrophotometer (HemoCue, Ängelholm, Sweden). Anaemia was defined as a haemoglobin concentration of less than 11 g/dl [19]. Malaria infection was tested using a rapid diagnostic test (Parascreen TM Zephyr Biomedicals, Goa, India; Paracheck Orchid Biomedical Systems, Goa, India; or ParaHIT Span Diagnostics Ltd., Surat, India). Blood pressure was measured using a digital measuring machine (BOSCH+ SOSH, Germany). A mother was considered to be hypertensive when systolic blood pressure exceeded 140 mmHg or diastolic pressure exceeded 90 mmHg [20]. Maternal weight was determined using a digital weighing scale (Coline) to the nearest 100 gm. We measured the height of each pregnant woman at baseline using a standard wooden board. The mid-upper-arm circumference (MUAC) was determined using a standard MUAC tape. Circumferences of less than 23 cm indicated maternal malnutrition [21]. According to the Ethiopian Targeted Supplementary Feeding Programme guideline, pregnant mothers with an MUAC below 23 cm should receive food supplements to treat moderate malnourishment [22].

Ultrasound examination was performed using portable SonoSite M-Turbo diagnostic imaging and a full-colour, flow-mapping ultrasound system (FUJIFILM SonoSite Inc.,Bothell, WA 98021 USA) at enrolment and each subsequent visit. We used ultrasound to estimate gestational age for all pregnancies at enrolment and at each scheduled visit [23]. At enrolment, gestational age and estimated date of delivery were calculated utilizing the formula from Hadlock et al., which uses biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), and femur length (FL) [24]. Crown rump length was used to estimate gestational age until 13 weeks and 4 days of pregnancy (fetal length $\leq$ 75 mm). The average of two measurements was calculated for each biometric parameter and recorded at enrolment and at the three scheduled visits. Fetal weight was estimated using the Hadlock algorithm for BPD, HC, AC, and FL [25]. Biometric measurements were assessed based on the standards [26]. Birth weights were measured using a digital infant weighing scale (Beurer Digital Baby Scale). Newborn birth weight, sex, head and chest circumference, and length were recorded by trained nurses within 72 hours of delivery, whether at home or at a facility. The nurses visited the pregnant mothers regularly until they gave birth.

Data quality assurance

Thirteen trained nurses conducted the anthropometric measurements and blood tests for anaemia and malaria. We provided these nurses with two days of training on anthropometry measurement techniques prior to the start of the study. Intra- and inter-technical measurement errors were checked, and repeated training was given until the measurements reached the recommended cut-off points (largest acceptable differences between repeated measurements of 1.0 cm for height and 0.5 cm for MUAC) [27]. The intra-technical error was 0.38 cm for height and 0.32 cm for MUAC, and the inter-technical error was 0.37 cm for height and 0.33 cm for MUAC. Ultrasound assessment was done by the first author, who was trained by a senior obstetrician and gynaecologist at St. Paul Hospital Millennium Medical College. The author's training was validated at Tikur Anbessa Specialized Teaching Hospital of Addis Ababa University. Based on biometric measurements of 27 foetuses, the calculated Pearson's correlations (r) between the two independent measurements on the same foetus were r = 0.98 for BPD and HC, 0.96 for AC, and 0.89 for FL.

Statistical analysis

Data were entered and cleaned using SPSS version 24 (SPSS Inc., Chicago, IL, USA) and analysed using Stata software version 15 (Stata Corp., College Station, TX, USA). A descriptive analysis was performed. Reference curves were estimated based on centiles for individual BPD, HC, AC, FL biometric parameters. EFW was derived at each gestational age from 24 to 38 weeks. The reference curve was fitted using centiles for reference models and the 5^{th}, 10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th}, and 95^{th} centiles. The proportion of foetuses in the cohort that were small for gestational age was evaluated for weights that fell below the 10^{th} percentile for specific gestational age and the overall study population [13]. Fractions of estimated biometric measurements were computed to the nearest whole number for all constructed tables of EFW, BPD, HC, AC, and FL. The z-scores and percentiles of biometric measurements and EFW were calculated and fitted to INTERGROWTH-21^{st} International Standards for Fetal Growth [10]. Newborns weighing less than 2,500 g were categorized low birth weight [28]. Babies born alive before 37 weeks of pregnancy were considered preterm [29]. A mother was defined as malnourished if her MUAC fell below 23 cm. A household wealth index also was constructed using principal component analysis [30]. Fourteen household assets were used to calculate wealth: presence of electricity; ownership of a radio, mobile telephone, chair, table, bed, bicycle, or land; separate kitchen from living area; ownership of animals or animal carts; types of roof and walls; and presence of potable drinking water.

Ethical considerations

The study received ethical approval from the institutional review board of the College of Health Sciences, Addis Ababa University, in June 2015 (ref.;005/15/SPH) and from the Regional Committee for Medical and Health Research Ethics, Western Norway (ref: 2013/986/REK Vest). Written permission to perform this study was obtained from the Oromia Regional Health Bureau and relevant provincial and local authorities in the district. Informed written consent was obtained from each participant, and all procedures were conducted based on voluntary participation. Pregnant women who had indication(s) for treatment were referred to a nearby hospital.

Role of funding source

The funding sources for this study had no role in the design, data collection, analysis, interpretation of the results, or writing of the report.

Results

Out of 1,054 self-reported pregnant women, 727 met the inclusion criteria, as shown in Fig 1. Among those who did not meet inclusion criteria, 11 (3.0%) were not pregnant on ultrasound examination, and 316 (30%) exceeded 24 weeks of gestation. Among those who met the inclusion criteria, 23 (3.2%) left the study district; 15 (2.1%) had terminations, either spontaneously or due to medical indications related to congenital abnormalities and pregnancy complications; 12 (1.7%) were twins; and two experienced intrauterine fetal deaths. As shown in the S1 Table, we found no significant difference in the baseline characteristics of those who were lost to follow-up and those who were included in the final analysis. The final analysis comprised 1,808 ultrasound scans from 675 singleton foetuses. Growth patterns were analysed, and a growth chart was developed based on the EFW of these 675 singleton foetuses.

Baseline characteristics

Table 1 shows the socio-demographic and economic characteristics of the study participants. The mean ± standard deviation (SD) of maternal age at enrolment was 24.9 ± 5.4 (15–45) years, the highest proportion of pregnancies occurring in the 15–24 age group. Family size of

Fig 1. Flowchart of pregnant women included in the study and final analysis.

https://doi.org/10.1371/journal.pone.0226881.g001

the study participants ranged from 2 to 14 (mean: 5.6) persons. All study participants were married, and 52% (351/675) did not have formal education. At baseline, the mean maternal height was 157.1 cm (133 cm to 178 cm) and mean body mass index (BMI) was 21.5 (range 14.8 to 31.5), with 10.9% (73/668) having a BMI under 18.5 kg/m^2. At baseline, 40.6% (281) of the women had an MUAC under 23 cm, and 17.7% (114) of the women were anaemic (Table 1).

Most (84.9%; 573/675) study participants were multigravida, and 19.9% (134/675) had a history of abortion. At the start of the study, 87% (587/675) had a gestational age of 12 weeks or more. The majority (54%; 329/607) had their first antenatal care visit after 26 weeks of gestation: 29.8% (315) had two visits, and 33.5% (354) had three visits. A small number (0.7%; 5/675) of the mothers had malaria infection (3 had *plasmodium vivax*, 1 had *plasmodium falciparum*, and 1 was mixed species). Only one mother was diagnosed with hypertension. None reported to have diabetes, HIV, or syphilis (Table 2).

Birth outcome

More than half (53.1%; 333/627) delivered at home (Table 2). Most (98.1%; 607/627) were spontaneous vaginal deliveries, and Caesarean sections were performed on 1.3% (8/627). Information on the date of delivery for 6.7% (45/627) and place of delivery for 7.1% (48/627) was not obtained, as the mothers left the study area when their delivery date approached. Among newborns with available birth information on the date of delivery, 85.1% (536/630) delivered between the 37th and 42nd weeks, and 4.9% (31/630) were preterm. The mean birth weight was 3212.5 g (1292–5000 g), and 7.9% (48/610) were born with a low birth weight (Table 2).

Intrauterine growth

Overall, 1,808 ultrasound measurements were taken. Most (90.8%; 613/675) had three ultrasound-derived weight measurements, and the remaining had one (n = 51) or two (n = 11) measurements only. The mean number of scans per foetus was 2.5, ranging from 1–4. Most

Table 1. Socio-demographic and economic characteristics of mothers who participated in the study (Adami Tullu district, Oromia, south-central Ethiopia, 2016–2017).

Variable		n (%)
Age in years (n = 673)	15–24	324 (48.0)
	25–34	306 (45.3)
	35–45	45 (6.7)
Education status (n = 671)	No formal education	351 (52.2)
	Primary school	264 (39.3)
	Secondary school	57 (8.5)
Ethnicity (n = 675)	Oromo	634 (94.4)
	Gurage	9 (1.3)
	Amhara	3 (0.5)
	Other	26 (3.9)
Religion (n = 675)	Muslim	582 (86.6)
	Orthodox	78 (11.6)
	Protestant	11 (1.6)
	Catholic	1 (0.2)
Occupation (n = 673)	Housewife	515 (76.3)
	Farmer	119 (17.6)
	House maid	15 (2.2)
	Other*	24 (3.9)
Wealth status (n = 675)	Poor	220 (32.8)
	Middle	228 (34.0)
	Rich	222 (33.1)
Family size (n = 675)	2–5	333 (49.3)
	>5	342 (50.7)
Haemoglobin (n = 665)	<110 g/dl	114 (17.7)
	<110 g/dl	551 (81.3)
Mean maternal height (cm) ± SD		157.1± 6.5
Mean maternal weight (kg) at baseline ± SD		53.1 ±6.9
Body mass index (n = 668)	Underweight	73 (10.9)
	Normal weight	533 (79.8)
	Overweight	62 (9.3)
Mean maternal MUAC (cm) at baseline ± SD		23.6 ±2.3

* Day labourer, tradesperson, fisher, student, government employee, and non-governmental organization employee

https://doi.org/10.1371/journal.pone.0226881.t001

92% (621/675) of the fetal biometric measurements were taken at the second visit (25–27 weeks). Table 3 shows the distribution of ultrasound examinations and descriptive statistics of EFW by gestational age. It is worth noting that the coefficient of variation decreased as the number of ultrasound observations or measurements increased.

Fig 2 presents a chart for the EFWs of 1,808 ultrasound measurements compared to WHO and INTERGROWTH-21st standards. This reference chart was plotted for the 5th, 50th, and 95th percentiles for our study and WHO, and the 50th percentile for INTERGROWTH-21st. We used the smoothed percentile to present the plot. As shown in the S1 Fig, the percentiles we calculated for EFW had similar distribution patterns as those for the WHO and INTER-GROWTH-21st charts. The S2 Table shows comparisons of the 10th and 90th percentiles for the other biometric measurements and EFW.

Table 2. Past and present obstetric and clinical characteristics of participating women and their newborns (Adami Tullu district, south-central Ethiopia, 2016–2017).

Variable*		n (%)
Gravida (n = 675)	Primigravida	102 (15.1)
	Multigravida	573 (84.9)
Parity (n = 675)	Nulliparous	121 (17.9)
	Multiparous	449 (66.5)
	Grand multiparous	105 (15.6)
Previous abortion history (n = 673)	Yes	134 (19.9)
	No	539 (80.1)
Gestational age at inclusion (n = 675)	< = 12 weeks	88 (13.0)
	>12–24 weeks	587 (87.0)
Place of delivery (n = 626)	Home	333 (53.1)
	Health post	2 (0.3)
	Health centre	148 (23.6)
	Hospital	143 (22.8)
Mode of delivery (n = 618)	Spontaneous vaginal delivery	607 (98.1)
	Assisted (forceps/vacuum) delivery	4 (0.6)
	Emergency Caesarean section	8 (1.3)
Sex of newborn (n = 623)	Male	363 (58.3)
	Female	260 (41.7)
Mean birth weight (g) (n = 610)		3214 (1292–5000)
Time of birth weight measurement (n = 610)	Within 24 hours after delivery	538 (88.2)
	Within 48 hours after delivery	68 (11.1)
	Within 72 hours after delivery	4 (0.7)
Birth status	Low birth weight (<2500 g) (%)	48/610 (7.9)
	Preterm birth (<37 weeks)	31/630 (4.9)
Malaria (n = 5)	*Plasmodium vivax*	3 (0.4)
	Plasmodium falciparum	1 (0.1
	Mixed species	1 (0.1
Hypertension		1(0.1

* Numbers enclosed in parentheses in the first column indicate the number of women examined

https://doi.org/10.1371/journal.pone.0226881.t002

Table 4 shows the corresponding reference values of our study percentiles of EFW, with respect to gestational age.

The S3–S6 Tables show growth of the fetal outer-inner diameter of BPD, HC, AC, and FL percentiles with the corresponding gestational age. Overall, the EFW fell below the 10th centile (small for gestation) was 9.8% (177/1808) of the measurements in our study. The incidence of foetuses that were small for gestational age was the same for both sexes: 10% (95/951) for male and 10% (72/682) for female newborns. The S7 and S8 Tables show the corresponding reference value of percentiles of EFW for both sexes.

Comparison with the INTERGROWTH-21st International fetal growth standard

The z-score of the estimated fetal weight ranged from -2.36 to 1.89, with a mean of 0.13 and standard deviation of 0·44. Fig 3 and the S2 Fig show biometric measurements and EFW standardized z-scores that were calculated and compared with the INTERGROWTH-21st fetal growth standard. Distribution of our biometric measurements for HC, FL, AC, and EFW were

Table 3. Descriptive characteristics of estimated fetal weight and distribution of ultrasound examinations in relation to gestational age (Adami Tullu district, south-central Ethiopia, 2016–2017).

Gestational age (weeks)	Number of observations	Estimated fetal weight (g)			
		Mean ± SD	Minimum	Maximum	CV%
24	25	644 ± 36	575	718	5·6
25	36	769 ± 58	658	915	7·5
26	238	861±49	723	996	5·7
27	226	961+55	808	1130	5·7
28	80	1097 ± 67	952	1280	6·1
29	74	1263 ± 90	985	1471	7·1
30	208	1447 ±82	1236	1661	5·7
31	189	1589 ± 88	1362	1994	5·5
32	107	1765 ± 114	1465	2274	6·5
33	43	2024 ±175	1777	2902	8·6
34	61	2261 ± 116	2012	2528	5·1
35	133	2517 ± 131	2165	2808	5·2
36	249	2716 ± 131	2355	3058	4·8
37	100	2913 ± 156	2497	3395	5·3
38	27	3093 ± 260	2044	3555	8·4

CV, coefficient of variation (SD/mean), expressed as a percentage

https://doi.org/10.1371/journal.pone.0226881.t003

similar to those for the INTERGROWTH-21st reference, and most measurements fell between -2 and +2 of the reference z-score. However, the z-score distribution of BPD was between -3 and +1 of the reference z-score.

Discussion

We presented a fetal weight chart based on EFW using serial ultrasound measurements to elucidate fetal growth patterns in a drought-affected area of south-central Ethiopia. We generated

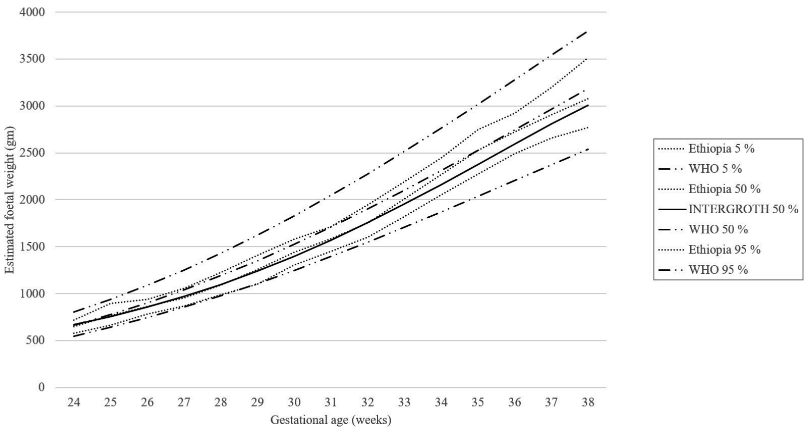


Fig 2. Distribution of estimated 5th, 50th, and 95th percentiles for fetal weight by study, WHO, and INTERGROWTH-21st for gestational ages 24 to 38 weeks.

https://doi.org/10.1371/journal.pone.0226881.g002

Table 4. Growth chart for estimated fetal weight percentiles for both sexes (Adami Tullu district, south-central Ethiopia, 2016–2017).

Gestational age (weeks)	Number of observations	Estimated fetal weight (g) by percentile						
		5th	10th	25th	50th	75th	90th	95th
24	25	580	599	614	645	663	710	717
25	36	663	697	735	765	802	848	893
26	238	781	795	828	865	897	921	936
27	226	871	892	924	957	994	1029	1058
28	80	985	1016	1053	1087	1141	1194	1226
29	74	1100	1148	1212	1257	1319	1371	1406
30	208	1304	1347	1395	1441	1502	1555	1582
31	189	1450	1479	1528	1585	1649	1695	1713
32	107	1600	1614	1696	1753	1838	1892	1946
33	43	1820	1843	1921	2011	2074	2165	2194
34	61	2051	2108	2181	2267	2341	2429	2449
35	133	2273	2350	2434	2527	2599	2689	2748
36	249	2492	2550	2627	2721	2811	2869	2923
37	100	2657	2730	2825	2905	3009	3081	3197
38	27	2367	2891	3033	3078	3232	3331	3515

https://doi.org/10.1371/journal.pone.0226881.t004

a fetal growth chart using repeated growth assessments on the same foetus from a representative community sample of 675 singleton pregnancies without congenital malformations. Our main conclusion is that IUG patterns in the rural part of the Rift Valley are mostly within the same distributions as those from the WHO and INTERGROWTH-21st multicentre fetal growth reference studies [9, 10, 31].

These findings indicate that, despite the presence of maternal under-nutrition in more than 40% of the women at the start of the study, the EFWs remained within normal ranges. A

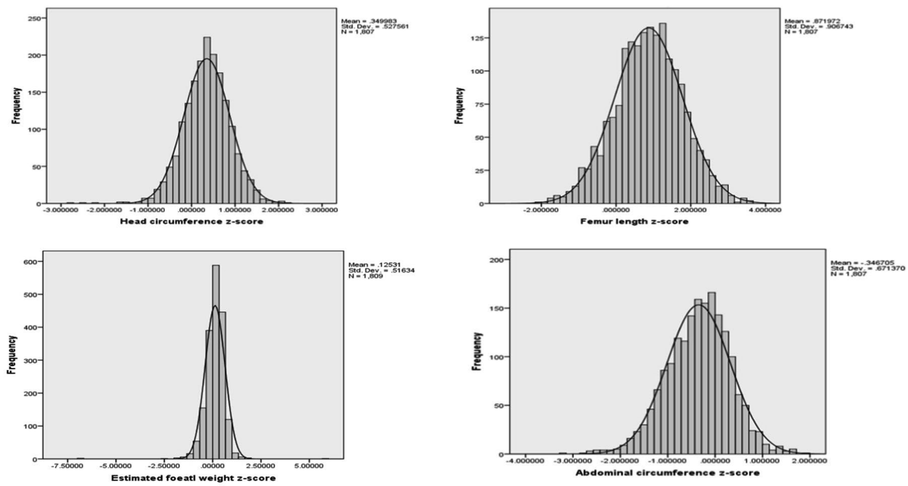


Fig 3. Z-score of biometric measurements and estimated fetal weight compared with the INTERGROWTH-21st fetal growth standard, 2016–2017.

https://doi.org/10.1371/journal.pone.0226881.g003

possible explanation for this could be that, although the area was affected by drought [32] and there was a food shortage resulting in under-nutrition, pregnant women in these areas received supplementary food. Indeed, pregnant mothers with MUACs < 23 cm do receive preferential and regular food supplements [22].

We also found that 9.8% of foetuses were small for gestational age, with a z-score for EFW below the 10^{th} percentile. This finding is suggestive of IUG restriction [13]. A study in Tanzania found similar results [33]. Compared to a previous study done in south western Ethiopia [18], we found a lower proportion of low birth weights (7.9%). This difference could be ascribed to the time that the birth weight was taken. In our study, 88.2% of birth weights were recorded within 24 hours of delivery.

Unlike previous reference studies done on presumably healthy and well-nourished pregnant women, our study was based on longitudinal ultrasound examinations in a population affected by drought. The availability of nutrients for the foetus depends on maternal nutrition. In drought-affected areas, low maternal food intake results in a reduced nutrient stream from the mother to the foetus, with consequent IUG restriction [13]. The presence of maternal undernutrition and consequent fetal growth restriction also might influence malnutrition rates among children younger than 5 years old, as previously reported in our study area by Taye et al. [34].

The z-scores of HC, FL, and AC in this study were similar to the standards, when fitted to INTERGROWTH-21^{st} application software [10, 35]. However, the z-score distribution of BPD was between -3 and +1 of the reference z-score. This difference is probably related to the difference in the method of BPD measurement in our study. Specifically, we measured BPD from outer to inner diameter of the parietal bone, whereas INTERGROWTH-21^{st} measures from outer to outer diameter. The difference in measurement between our study and INTERGROWTH-21^{st} is the thickness of the parietal bone, which is estimated to be less than 3 mm. This 3-mm difference is expected to shift the z-score to the right by at least one SD, as the SD in the INTERGROWTH-21^{st} study is approximately 1.74 mm. When accounting for the thickness of the parietal bone, the difference in BPD between our study and INTERGROWTH-21^{st} may not be significant [36].

Our study also differed from the INTERGROWTH-21^{st} study in determining EFW. Most studies, including WHO, use the Hadlock formula. For EFW, Hadlock 4 uses BPD (outer to inner diameter of the parietal bone), HC, AC, and FL. INTERGROWTH-21^{st} uses HC and AC only. In their study, Lufee Wong et al. concluded that EFW using Hadlock 3, Hadlock 4, and INTERGROWTH-21^{st} produces similar results, except for slight differences at gestations less than 27–28 weeks [37]. Previous studies have validated the use of Hadlock 3 and 4 formulae. The INTERGROWTH-21^{st} regression formula has yet to be prospectively validated against birth weights outside of the INTERGROWTH-21^{st} study [37].

Our study has many strengths. The study instruments were standardized and validated, and the women were representative of the community in this part of the Ethiopian Rift Valley. This population sample avoided possible selection bias, which can occur when data are collected at health facilities. The women were more likely to have an indication for follow-up or supervision. Moreover, longitudinal data produced reference intervals for both fetal size and growth, unlike cross-sectional studies that provide information on fetal size only. Migration of the study participants out of the study area as an effect of drought constitutes a possible limitation that could affect the results of this study. However, the proportion of those who migrated out of the study area was small (3.2%). Also, as our study evaluated EFWs at up to 36 weeks of gestation, the results might not determine whether growth faltering occurs in later gestational ages.

In conclusion, we measured IUG patterns using serial ultrasound measurements in a drought-affected rural community of Ethiopia and compared them with the INTERGROWTH-21st and the WHO multicentre fetal growth reference standards. The fetal growth patterns, as measured by common ultrasound biometric measurements, were similar to the IUG patterns of the reference standards. The findings of our study also detected preterm births (4.9%) and low birth weights (7.9%) among participants. Subsequent studies on risk factors or underlying causes of preterm birth and low birth weight must be conducted to guide appropriate interventions.

Supporting information

S1 Fig. Growth chart of the 5th, 50th, and 95th percentiles for our study and WHO reference standards and 50th percentile for INTERGROWTH-21st reference standards.
(TIF)

S2 Fig. Z-score of biparietal diameter compared with the INTERGROWTH-21st fetal growth standard 2016–2017.
(TIF)

S1 Table. Comparison of baseline characteristics of those lost to follow up with those included in the final analysis.
(DOCX)

S2 Table. Growth chart of fetal outer-inner biparietal diameter at gestational ages 24–38 weeks (Adami Tullu district, south-central Ethiopia, 2016–2017).
(DOCX)

S3 Table. Growth chart of fetal head circumference (Adami Tullu district, south-central Ethiopia, 2016–2017).
(DOCX)

S4 Table. Growth chart of fetal abdominal circumference at gestational ages 24–38 weeks (Adami Tullu district, south-central Ethiopia, 2016–2017).
(DOCX)

S5 Table. Growth chart of fetal femur length at gestational ages 24–38 weeks (Adami Tullu district, south-central Ethiopia, 2016–2017).
(DOCX)

S6 Table. Growth chart of the 10th and 90th percentiles for our study and WHO reference standards.
(DOCX)

S7 Table. Estimated fetal weight for male newborns (Adami Tullu district, south-central Ethiopia, 2016–2017).
(DOCX)

S8 Table. Estimated fetal weight for female newborns (Adami Tullu district, south-central Ethiopia, 2016–2017).
(DOCX)

Acknowledgments

This research was made possible with great support from several individuals and institutions. We are grateful to all mothers who participated in the study; data collectors and supervisors for their support in data collection support; and the East Shewa Zonal Health Department, Adami Tullu district health office, and Oromia Regional Health Bureau for facilitating the fieldwork. We are indebted to Dr. Malede Birara, Dr. Balkacew Nigatu, and Dr. Delayehu Bekele from St. Paul Hospital Millennium Medical College for providing support on ultrasound training and Dr. Yirgu Gebrehiwot and Dr. Nardos Temesgen from Tikur Anbessa specialized Teaching Hospital for validating ultrasound measurements. We also extend our gratitude to Bergen university and Addis Ababa university for the support they provided.

Author Contributions

Conceptualization: Meselech Roro, Wakgari Deressa, Bernt Lindtjørn.

Data curation: Meselech Roro, Bernt Lindtjørn.

Formal analysis: Meselech Roro, Wakgari Deressa, Bernt Lindtjørn.

Funding acquisition: Bernt Lindtjørn.

Investigation: Meselech Roro, Wakgari Deressa, Bernt Lindtjørn.

Methodology: Meselech Roro, Wakgari Deressa, Bernt Lindtjørn.

Project administration: Meselech Roro, Wakgari Deressa, Bernt Lindtjørn.

Resources: Wakgari Deressa, Bernt Lindtjørn.

Supervision: Meselech Roro, Wakgari Deressa, Bernt Lindtjørn.

Validation: Meselech Roro, Wakgari Deressa, Bernt Lindtjørn.

Visualization: Meselech Roro.

Writing – original draft: Meselech Roro, Bernt Lindtjørn.

Writing – review & editing: Meselech Roro, Wakgari Deressa, Bernt Lindtjørn.

References

1. Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. The New England journal of medicine. 2008; 359(1):61–73. https://doi.org/10.1056/NEJMra0708473 PMID: 18596274
2. Barker DJ. Adult consequences of fetal growth restriction. Clinical obstetrics and gynecology. 2006; 49 (2):270–83. https://doi.org/10.1097/00003081-200606000-00009 PMID: 16721106
3. Lubchenco LO, Hansman C, Dressler M, Boyd E. Intrauterine growth as estimated from liveborn birthweight data at 24 to 42 weeks of gestation. Pediatrics. 1963; 32:793–800. PMID: 14075621
4. Johnsen SL, Wilsgaard T, Rasmussen S, Sollien R, Kiserud T. Longitudinal reference charts for growth of the fetal head, abdomen and femur. European journal of obstetrics, gynecology, and reproductive biology. 2006; 127(2):172–85. https://doi.org/10.1016/j.ejogrb.2005.10.004 PMID: 16289532
5. Snijders RJ, Nicolaides KH. Fetal biometry at 14–40 weeks' gestation. Ultrasound in obstetrics & gynecology: the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 1994; 4(1):34–48.
6. Hadlock FP, Harrist RB, Martinez-Poyer J. In utero analysis of fetal growth: a sonographic weight standard. Radiology. 1991; 181(1):129–33. https://doi.org/10.1148/radiology.181.1.1887021 PMID: 1887021
7. Owen P, Donnet ML, Ogston SA, Christie AD, Howie PW, Patel NB. Standards for ultrasound fetal growth velocity. British journal of obstetrics and gynaecology. 1996; 103(1):60–9. https://doi.org/10.1111/j.1471-0528.1996.tb09516.x PMID: 8608100
8. Zhang J, Merialdi M, Platt LD, Kramer MS. Defining normal and abnormal fetal growth: promises and challenges. American journal of obstetrics and gynecology. 2010; 202(6):522–8. https://doi.org/10.1016/j.ajog.2009.10.889 PMID: 20074690

9. Kiserud T, Piaggio G, Carroli G, Widmer M, Carvalho J, Neerup Jensen L, et al. The World Health Organization Fetal Growth Charts: A Multinational Longitudinal Study of Ultrasound Biometric Measurements and Estimated Fetal Weight. PLoS medicine. 2017; 14(1):e1002220. https://doi.org/10.1371/journal.pmed.1002220 PMID: 28118360

10. Papageorghiou AT, Ohuma EO, Altman DG, Todros T, Cheikh Ismail L, Lambert A, et al. International standards for fetal growth based on serial ultrasound measurements: the Fetal Growth Longitudinal Study of the INTERGROWTH-21st Project. Lancet. 2014; 384(9946):869–79. https://doi.org/10.1016/S0140-6736(14)61490-2 PMID: 25209488

11. Sovio U, White IR, Dacey A, Pasupathy D, Smith GCS. Screening for fetal growth restriction with universal third trimester ultrasonography in nulliparous women in the Pregnancy Outcome Prediction (POP) study: a prospective cohort study. Lancet. 2015; 386(10008):2089–97. https://doi.org/10.1016/S0140-6736(15)00131-2 PMID: 26360240

12. Salam RA, Syed B, Syed S, Das JK, Zagre NM, Rayco-Solon P, et al. Maternal nutrition: how is Eastern and Southern Africa faring and what needs to be done? African health sciences. 2015; 15(2):532–45. https://doi.org/10.4314/ahs.v15i2.28 PMID: 26124800

13. Lausman A, Kingdom J, Maternal Fetal Medicine C. Intrauterine growth restriction: screening, diagnosis, and management. Journal of obstetrics and gynaecology Canada: JOGC = Journal d'obstetrique et gynecologie du Canada: JOGC. 2013; 35(8):741–8. https://doi.org/10.1016/S1701-2163(15)30865-3 PMID: 24007710

14. Imdad A, Yakoob MY, Siddiqui S, Bhutta ZA. Screening and triage of intrauterine growth restriction (IUGR) in general population and high risk pregnancies: a systematic review with a focus on reduction of IUGR related stillbirths BMC Public Health. 2011 Apr; 11 (Suppl 3:S1).

15. Central Statistical Agency. Population Projection of Ethiopia for All Regions At Wereda Level from 2014–2017. Addis Ababa, Ethiopia; 2013.

16. Deressa W, Loha E, Balkew M, Hailu A, Gari T, Kenea O, et al. Combining long-lasting insecticidal nets and indoor residual spraying for malaria prevention in Ethiopia: study protocol for a cluster randomized controlled trial. Trials. 2016; 17:20. https://doi.org/10.1186/s13063-016-1154-2 PMID: 26758744

17. WHO. Medical Eligibility Criteria for contraceptive use. 4ed ed2010.

18. Wado YD, Afework MF, Hindin MJ. Effects of maternal pregnancy intention, depressive symptoms and social support on risk of low birth weight: a prospective study from southwestern Ethiopia. PloS one. 2014; 9(5):e96304. https://doi.org/10.1371/journal.pone.0096304 PMID: 24848269

19. World Health Organization. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. 2011.

20. The American Academy of Cardiology. High Blood Pressure (Hypertension) Signs, Causes, Diet, and Treatment. 2017.

21. Ververs MT, Antierens A, Sackl A, Staderini N, Captier V. Which anthropometric indicators identify a pregnant woman as acutely malnourished and predict adverse birth outcomes in the humanitarian context? PLoS currents. 2013; 5.

22. Guidelines for the Management of Moderate Acute Malnutrition, in Ethiopia. Addis Ababa: Ministry of Agriculture and Rural Development; September 2012.

23. Lynch CD, Zhang J. The research implications of the selection of a gestational age estimation method. Paediatric and perinatal epidemiology. 2007; 21 Suppl 2(Suppl. 2):86–96.

24. Hadlock FP, Deter RL, Harrist RB, Park SK. Estimating fetal age: computer-assisted analysis of multiple fetal growth parameters. Radiology. 1984; 152(2):497–501. https://doi.org/10.1148/radiology.152.2.6739822 PMID: 6739822

25. Hadlock FP, Harrist RB, Sharman RS, Deter RL, Park SK. Estimation of fetal weight with the use of head, body, and femur measurements—a prospective study. Am J Obstet Gynecol 1985; 151(3):333–7. https://doi.org/10.1016/0002-9378(85)90298-4 PMID: 3881966

26. Trish C, Basky T. Obstetric Ultrasound: How, Why and When Third ed: Elsevier; 2004.

27. Onyango AW, Martorell R, Chumlea WC, Van den Broeck J, Araujo CL, Baerug A, et al. Reliability of anthropometric measurements in the WHO Multicentre Growth Reference Study. Acta Paediatr. 2006; 95:38–46. https://doi.org/10.1080/08035250500404085

28. Organization WH. International statistical classification of diseases and related health problems, tenth revision. 2nd ed: World Health Organization; 2004.

29. World Health Organization. Recommendations on interventions to improve preterm birth outcomes. Geneva, Switzerland2015 26447264]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK321160/.

30. Vyas S, Kumaranayake L. Constructing socio-economic status indices: how to use principal components analysis. Health policy and planning. 2006; 21(6):459–68. https://doi.org/10.1093/heapol/czl029 PMID: 17030551

31. Kiserud T, Benachi A, Hecher K, Perez RG, Carvalho J, Piaggio G, et al. The World Health Organization fetal growth charts: concept, findings, interpretation, and application. American journal of obstetrics and gynecology. 2018; 218(2S):S619–S29. https://doi.org/10.1016/j.ajog.2017.12.010 PMID: 29422204

32. IFRC. Ethiopia: Drought- Emergency plan of action operations update number 2(MDRET016): International Federation of Red Cross and Red Crescent Societes 31 August 2016:Accessed 2016 September 15; 5.

33. Schmiegelow C, Scheike T, Oesterholt M, Minja D, Pehrson C, Magistrado P, et al. Development of a fetal weight chart using serial trans-abdominal ultrasound in an East African population: a longitudinal observational study. PloS one. 2012; 7(9):e44773. https://doi.org/10.1371/journal.pone.0044773 PMID: 23028617

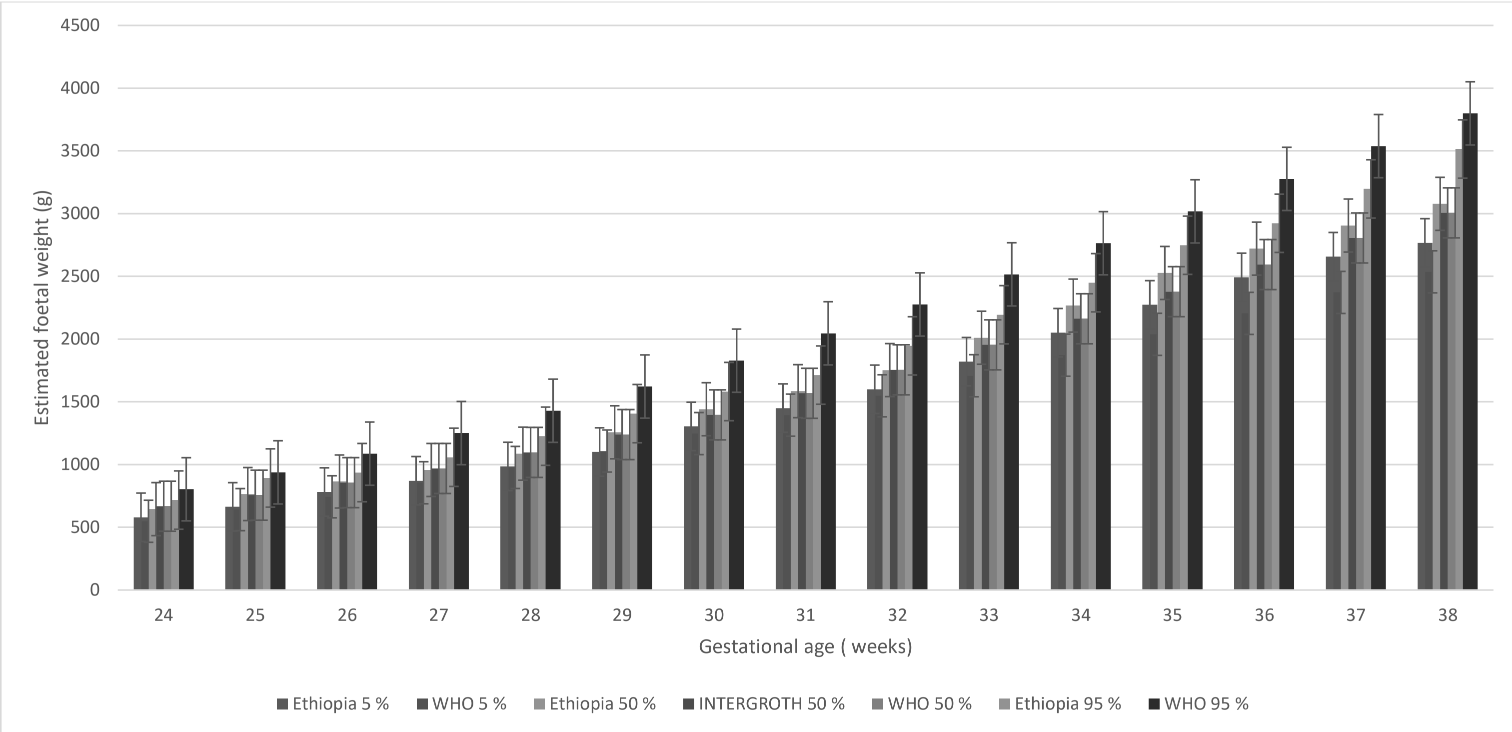
34. Gari T, Loha E, Deressa W, Solomon T, Atsbeha H, Assegid M, et al. Anaemia among children in a drought affected community in south-central Ethiopia. PloS one. 2017; 12(3):e0170898. https://doi.org/10.1371/journal.pone.0170898 PMID: 28291790

35. University of Oxford. International Fetal Growth Standards: Application. 2017.

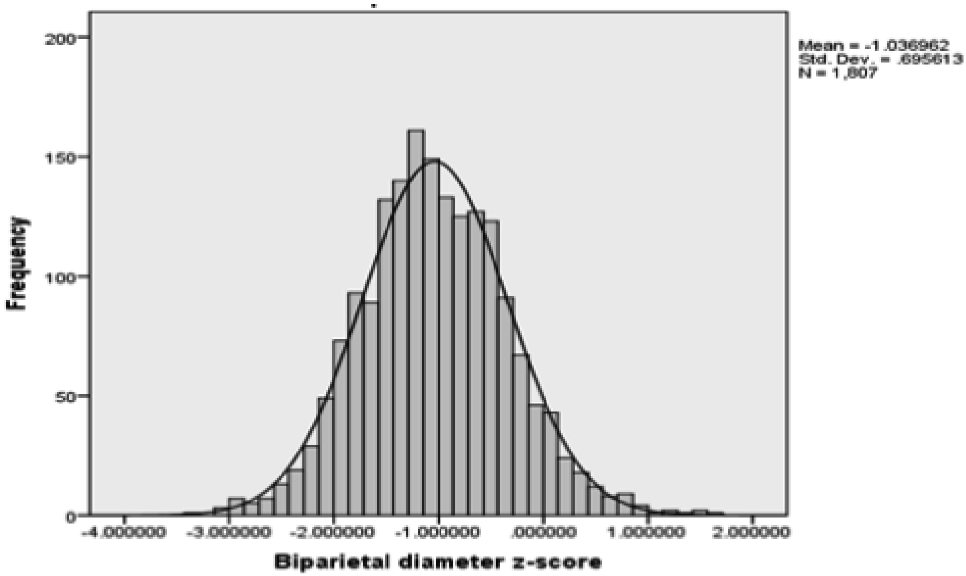
36. Nyberg David A., McGahan John P., Pretorius Dolores H., Gianluigi Pilu. Diagnostic Imaging of Fetal Anomalies 530 Walnut Street, Philadelphia, PA 19106 USA: Lippincott Williams & Wilkins. 2003

37. Wong L, Paul E, KM Murday H, et al. Biparietal diameter measurements using the outer-to-outer versus outer-to-inner measurement: A question of pedantry? AJUM 2018; 21 (3):161–8.

S1 Fig. Growth chart of the 5th, 50th, and 95th percentiles for our study and WHO reference standards and 50th percentile for INTERGROWTH-21st reference standards.



S2 Fig. Z-score of biparietal diameter compared with the INTERGROWTH-21st fetal growth standard 2016–2017.



S1 Table. Comparison of baseline characteristics of those lost to follow up with those included in the final analysis.

Variable	**Loss to follow up**		**P-value**
	Yes (23, 3.3%)	No (666, 96.7%)	
Mean age (SD)	23.4 (5.3)	24.9 (5.4)	P = .16 [t (687) = -1.4, two-tailed]
Mean height	156.5 (5.9)	157.3 (6.5)	P = .57 [t (687) = -.57, two-tailed]
Occupation			
Others (%)	5(3)	159 (97)	P=0.90 (COR 1.07 (0.39- 2.94)
House wife	17(3.2)	507(96.8)	1
Wealth status			
Poor (%)	8 (3.6)	216 (96.4)	1
Middle (%)	8 (3.4)	226 (96.6)	P=0.93 (COR 1.05 (0.39- 2.84)
Rich (%)	5 (2.2)	221 (97.8)	P=0.39 (COR 1.64 (0.53- 5.08)

S2 Table. Growth chart of fetal outer-inner biparietal diameter at gestational ages 24–38 weeks (Adami Tullu district, south-central Ethiopia, 2016–2017)

Reference Chart	**Measurement**	**Gestational Week**			
		24	**28**	**32**	**36**
10th percentile	**Biparietal diameter mm)**				
	Ethiopia	57	68	78	86
	WHO	56	67	76	84
	Head circumference (mm)				
	Ethiopia	217	253	289	320
	WHO	211	251	282	306
	Abdominal circumference (mm)				
	Ethiopia	177	218	257	299
	WHO	184	225	260	294
	Femural length (mm)				
	Ethiopia	40	49	58	68
	WHO	41	49	57	65
	Estimated foetal weight (g)				
	Ethiopia	599	1016	1614	2550
	WHO	576	1026	1635	2352
90th percentile	**Biparietal diameter mm)**				
	Ethiopia	63	72	83	92
	WHO	64	76	86	93
	Head circumferance (mm)				
	Ethiopia	233	272	304	330
	WHO	233	277	311	336
	Abdominal circumference (mm)				
	Ethiopia	197	218	257	299
	WHO	210	256	298	340
	Femural length (mm)				
	Ethiopia	46	55	64	73
	WHO	46	55	64	72
	Estimated foetal weight (g)				
	Ethiopia	710	1194	1892	2869
	WHO	765	1368	2187	3153

S3 Table. Growth chart of fetal head circumference (Adami Tullu district, south-central Ethiopia, 2016–2017)

Gestational age (weeks)	Number of observations	Mean ± SD	Biparietal diameter (mm) by percentile						
			5th	10th	25th	50th	75th	90th	95th
24	25	59.5± 1.7	57	57	58	59	60	63	63
25	36	61.03±2.3	56	58	60	61	63	64	65
26	238	64.6± 1.7	61	62	64	65	66	67	67
27	226	67.1±1.9	64	64	66	67	69	69	70
28	80	69.9± 1.9	66	68	68	70	71	72	73
29	74	72.2 ± 2.2	69	70	71	72	74	75	75
30	208	75.0 ± 1.9	72	73	74	75	76	77	78
31	189	77.6 ± 2.2	74	75	76	78	79	81	81
32	107	80.2 ± 2.1	76	78	79	80	82	83	84
33	43	83.3 ± 2.5	79	80	82	83	85	86	87
34	61	84.0 ± 2.2	81	81	83	84	86	88	88
35	133	86.2 ± 2.4	82	83	84	86	88	89	90
36	249	89.0 ± 2.2	86	86	87	89	90	92	92
37	100	91.1 ± 2.7	86	88	90	91	93	94	95
38	27	94.4 ± 2.8	87	91	93	95	96	98	99

S4 Table. Growth chart of fetal abdominal circumference at gestational ages 24–38 weeks (Adami Tullu district, south-central Ethiopia, 2016–2017).

Gestational age (weeks)	**Number of observations**	**Mean + SD**	**Head circumference (mm) by percentile**						
			5th	**10th**	**25th**	**50th**	**75th**	**90th**	**95th**
24	25	223 +5.4	215	217	219	223	228	233	244
25	36	235 + 6.9	224	225	229	235	240	242	247
26	238	244.1+ 4.3	237	239	241	244	247	250	251
27	226	252 +4.7	244	246	249	252	255	258	260
28	80	262.1+ 6.5	252	253	258	262	265	272	274
29	74	272..3+ 8.0	260	263	268	273	277	281	284
30	208	281 + 5.0	273	275	277	281	284	287	289
31	189	288.8 + 5.8	280	281	285	288	293	296	300
32	107	296.6 + 6.2	285	289	292	297	301	304	308
33	43	305 + 7.0	292	297	301	303	309	313	315
34	61	313.9 + 5.6	305	307	310	313	318	322	324
35	133	319.1+ 4.7	312	313	316	319	322	324	326
36	249	325.3+ 4.3	318	320	323	325	328	330	332
37	100	329.7+ 6.1	320	324	326	330	333	338	339
38	27	334.9 + 6.9	317	329	331	335	338	344	345

S5 Table. Growth chart of fetal femur length at gestational ages 24–38 weeks (Adami Tullu district, south-central Ethiopia, 2016–2017).

Gestational age (weeks)	Number of observations	Mean + SD	Abdominal circumference (mm) by percentile						
			5th	10th	25th	50th	75th	90th	95th
24	25	187.8 + 7.8	170	177	184	189	195	197	199
25	36	200.3 + 9.2	185	191	194	199	207	216	218
26	238	208.6 +7.9	196	199	203	209	215	218	222
27	226	217+ 7.6	205	208	212	216	222	227	231
28	80	227.4 + 9.3	210	218	222	227	232	237	244
29	74	238.5 + 10.6	215	224	231	238	245	253	256
30	208	249.4 + 8.6	235	238	243	249	256	260	264
31	189	257.6 + 8.5	245	246	252	258	263	269	272
32	107	268.1 + 10.4	252	257	261	268	276	280	285
33	43	280.1 + 11.0	263	269	273	279	286	290	294
34	61	290.3 + 9.8	276	279	284	289	296	307	311
35	133	302.7 + 9.4	285	289	297	303	309	314	317
36	249	311.1 + 8.8	295	299	306	312	317	322	325
37	100	317.9 + 10.7	298	305	312	319	323	330	334
38	27	325.2 + 13.9	285	314	322	326	334	338	342

S6 Table. Growth chart of the 10th and 90th percentiles for our study and WHO reference standards.

Gestational age (weeks)	Number of observations	Mean ± SD	Femur length (mm) by percentile						
			5th	10th	25th	50th	75th	90th	95th
24	25	43.3 ± 2.2	39	40	42	43	45	46	47
25	36	46.6 ± 2.2	43	44	46	47	48	49	50
26	238	48.1 ± 1.8	45	46	47	48	49	50	51
27	226	50 ± 1.7	47	48	49	50	51	52	52
28	80	52.1 ± 2.1	48	49	51	52	53	55	56
29	74	54.8 ± 2.2	51	52	53	55	56	57	58
30	208	57.4 ± 1.8	54	55	56	57	59	60	61
31	189	59 ± 2.0	55	57	58	59	60	61	62
32	107	60.7 ± 2.2	57	58	59	61	62	64	65
33	43	63.8 ± 2.7	60	61	62	63	65	67	68
34	61	66.3 ± 2.6	62	63	64	66	68	69	71
35	133	68.5 ± 2.3	64	65	67	69	70	71	72
36	249	70.2 ± 2.0	67	68	69	70	71	73	74
37	100	72 ± 2.1	69	70	70	72	73	75	76
38	27	72.9 ± 2.8	68	69	71	73	75	77	78

S7 Table. Estimated fetal weight for male newborns (Adami Tullu district, south-central Ethiopia, 2016–2017).

Gestational age (weeks)	**Number of observations**	**Male estimated foetal weight (g) by percentile**						
		5th	10th	25th	50th	75th	90th	95th
24	25	575	580	610	633	666	693	732
25	36	664	677	728	753	809	877	926
26	238	776	792	818	857	904	914	947
27	226	860	884	917	958	1008	1025	1060
28	80	989	1025	1053	1085	1131	1191	1231
29	74	997	1119	1204	1243	1328	1332	1377
30	208	1309	1349	1393	1437	1509	1554	1570
31	189	1442	1478	1519	1578	1658	1696	1735
32	107	1601	1612	1686	1741	1818	1895	1934
33	43	1777	1809	1872	1944	2115	2097	2213
34	61	2027	2076	2152	2267	2327	2429	2435
35	133	2274	2319	2435	2515	2648	2658	2790
36	249	2502	2540	2605	2698	2817	2858	2887
37	100	2656	2745	2817	2915	3017	3084	3202
38	27	2680	2610	2975	3075	3283	3346	3532

S8 Table. Estimated fetal weight for female newborns (Adami Tullu district, south-central Ethiopia, 2016–2017).

Gestational age (weeks)	Number of observations	Female estimated foetal weight (g) by percentile						
		5th	10th	25th	50th	75th	90th	95th
24	25	604	604	621	653	650	678	744
25	36	658	676	743	766	799	880	919
26	238	789	809	838	869	888	921	930
27	226	885	907	932	957	997	1044	1073
28	80	989	1011	1060	1104	1144	1194	1238
29	74	1125	1210	1250	1303	1313	1420	1466
30	208	1305	1333	1400	1455	1494	1564	1587
31	189	1458	1499	1552	1602	1645	1693	1704
32	107	1596	1609	1701	1753	1837	1876	1886
33	43	1859	1907	1967	2012	2059	2202197	2324
34	61	2139	2177	2186	2251	2371	2435	2453
35	133	2246	2329	2437	2531	2576	2691	2747
36	249	2470	2554	2647	2750	2782	2879	2926
37	100	2506	2728	2826	2876	3005	3104	3302
38	27	3016	3016	3038	3119	3226	3385	3630

Paper II

PLOS ONE

RESEARCH ARTICLE

Influence of intrauterine factors on birth weight and on child linear growth in rural Ethiopia: A prospective cohort study

Meselech Roro[1,2]*, Wakgari Deressa[2], Bernt Lindtjørn[1]

1 Centre for International Health, University of Bergen, Bergen, Norway, **2** School of Public Health, College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia

* meselua@yahoo.com

Abstract

Introduction

Little is known about the influence of intrauterine fetal factors on childhood growth in low-income countries. The objective of this study was to examine the influence of intrauterine fetal growth on child linear growth in rural Ethiopia.

Methods

We conducted a prospective community-based cohort study from July 2016 to October 2018. All pregnant women with gestational age of 24 weeks or below living in 13 kebeles, in central Ethiopia were enrolled. The fetuses were followed from pregnancy up to 11–24 months after birth. We measured biparietal diameter, head circumference, femoral length, and abdominal circumference at 26, 30 and 36 weeks of pregnancy. At birth, we measured infant weight. At 11–24 months of age, z-scores of length- for- age, and weight-for-length were calculated. A multilevel, mixed-effect, linear regression model was used to examine the influence of fetal, newborn, maternal, household factors and residence area on child linear growth.

Results

We included 554 children. The prevalence rate of stunting was 54.3% and that of wasting was 10.6%. Fetal biparietal diameter, head circumference, and abdominal circumference, were significantly associated with birth weight. Femoral length z-score in early pregnancy, gestational age at delivery and child age were significantly associated with length-for-age z-score. Family size was significantly associated with length-for-age z-score. Family size and maternal height were associated with weight-for-height z-score. There was a large variation in length-for-age z-score (Intra cluster correlation, or ρ (rho) = 0.30) and weight-for-length z-score (ρ = 0.22) than of birth weight of new-born (ρ = 0.11) in kebeles indicating heterogeneity in clusters for length-for-age z-score and weight-for-length z-score than birth weight.

Check for updates

OPEN ACCESS

Citation: Roro M, Deressa W, Lindtjørn B (2022) Influence of intrauterine factors on birth weight and on child linear growth in rural Ethiopia: A prospective cohort study. PLoS ONE 17(8): e0272620. https://doi.org/10.1371/journal.pone.0272620

Editor: Felix C.C. Wekere, Rivers State University Teaching Hospital, NIGERIA

Received: September 21, 2021

Accepted: July 22, 2022

Published: August 5, 2022

Peer Review History: PLOS recognizes the benefits of transparency in the peer review process; therefore, we enable the publication of all of the content of peer review and author responses alongside final, published articles. The editorial history of this article is available here: https://doi.org/10.1371/journal.pone.0272620

Data Availability Statement: All data files are available from the Open Science Framework (OSF). Here is the link to the data: osf.io/t9n8q.

Funding: This study was funded by University of Bergen in Norway and the Research Council of Norway (project number: 220554). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The author(s) received no specific funding for this work.

Competing interests: The authors have declared that no competing interests exist.

Conclusions

Child linear growth was influenced by fetal growth, duration of pregnancy, maternal height, and family size. Environmental factors that are associated with the area of residence play a bigger role for linear growth than for birth weight.

Introduction

One of the most important development phases of a child is the first 1,000 days of life, which is the time from conception up to two years of age [1, 2]. Early childhood developments happen in physical, social, emotional, and cognitive domains. If there is any incident that happens during pregnancy or in the child's first years of life, it can affect growth and lead to childhood undernutrition [2–4]. Childhood undernutrition is a major, common public health problem that increases the risk of mortality among children in developing countries [5]. Stunting affects 164.8 million (22.7%) children globally. Most of the stunted children, 148 million, live in low- and middle-income countries (LMICs). Additionally, 52 million (8%) of children worldwide exhibit signs of wasting [5, 6].

Studies of the timing and pattern of growth faltering in the first two years of life suggest that the growth rate of children is adequate in the first few months of life and growth faltering often starts after three months of life [7, 8]. In LMICs, the length/height for age z-scores (LAZ) declines soon after birth to a lowest point of -1.75 to < 2 z-scores by 24 months of age. This often results in lack of subsequent catch-up growth up to the age of five years [9].

Birth cohort studies suggest that growth in the first 1,000 days of life can be viewed as a continuum between the fetal period and infancy and early childhood period [9, 10]. Some factors that contribute to growth faltering in low resource settings include inappropriate breastfeeding, lack of adequate quality and amount of complementary foods, insufficient infant and young child feeding practices, infections, and other environmental exposures [2, 9, 11]. However, little is known about the influence of intrauterine fetal factors on childhood growth in low-income countries. It is thus important to examine the effect of intrauterine fetal growth on early childhood growth. The aim of this study was to examine the influence of intrauterine fetal growth on LAZ and weight-for-length z-score (WLZ) in early childhood using a prospective cohort study conducted starting from 24 weeks of gestation up to 11–24 months of age in rural Ethiopia.

Methods

Study design

We conducted a prospective community-based cohort study from July 2016 to October 2018. All pregnant women with gestational age of 24 weeks or below living in 13 kebeles of Adami Tullu, Oromia, Ethiopia were enrolled. We followed the fetus, using portable obstetric ultrasound, starting from the date of enrolment throughout the period of pregnancy and then until 11–24 months of age, when weight and length were measured.

The influence of fetal biometry on child linear growth was examined in this study. The fetal biometry in millimeters measured by ultrasound included were biparietal diameter (BPD), head circumference (HC), femoral length (FL), and abdominal circumference (AC). The other independent variables we included were child sex, gestational age at birth, maternal age, maternal education, maternal occupation, parity, maternal height, wealth status, and family size. The outcome measurements for child linear growth were length–for–age z-scores (LAZ) and weight-for-length z-scores (WLZ). The other intermediate outcome measurement that was evaluated for its effect on linear child growth was birth weight.

We identified and adapted independent variables that influence linear growth in children aged 11–24 months of age from previous studies [2, 3, 12, 13]. In the current study, the socio-economic conditions were family size and household wealth status. The maternal conditions were age, height, parity, education and occupation. The fetal and child factors include fetal factors (HC, BPD, AC and FL) and birth characteristics (gestational age at birth and child sex).

Study setting

This study recruited pregnant women living in 13 kebeles (lowest administrative level) of the Adami Tullu district, Oromia Regional State, Ethiopia, as previously reported [14]. At baseline, trained data collectors interviewed all women of reproductive age regarding socio-demography, household conditions and pregnancy status.

The projected population size of the district for 2015 was 177,390 people [15]. Local residents primarily depend on farming, livestock rearing, and to a lesser extent, fishing in Lake Zeway for their subsistence.

Participants

The study population and recruitment of study participants have been described in detail in previous publication [14]. Briefly, recruitment of the study participants was conducted from July 2016 to June 2017. All women of reproductive age (15–49 years) permanently residing in the study area were used as a source population for the current fetal and postnatal growth study.

Trained data collectors conducted house-to-house visits and informed eligible women about the study objectives and procedures. Eligible participants self-reported their pregnancy status or answered a modified checklist based on 2010 criteria endorsed by the World Health Organization (WHO) [16]. Pregnancy was confirmed by ultrasound, and those with a gestational age at or before 24 weeks of gestation who gave written informed consent (thumbprint or signature) were enrolled. We followed the BPD, HC, AC and FL parameters of the fetus using ultrasound through the pregnancy. At delivery, we measured birth weight within in 72 hours after delivery. Subsequently their weight and length were measured after birth by the time they were 11–24 months of age.

We instructed the participants to attend three prenatal visits that were prescheduled from 26 weeks to 36 weeks of gestation at the closest health post or established stations in each kebele for this study. The data collectors reminded the study participants a day prior to their scheduled visits.

Variables

Only singleton fetuses under 24 weeks of gestation estimated by ultrasound at enrolment were included in the analyses. Twins and fetuses with congenital anomalies were excluded. The outcome measurements for child linear growth were length-for-age z-score (LAZ) and weight-for-length z-score (WLZ), measured at 11–24 months of the child age and birth weight. Fetal biometry measured by ultrasound, sex of child, gestational age at birth (measured in weeks), maternal age, maternal education, maternal occupation, parity, maternal height, household wealth status, family size and child age were the predictor variables in this study. A household wealth status was constructed by using principal component analysis as described previously [14]. The number of household family members were used for family size.

All variables included in the model were considered as continuous except for occupation of the mother and sex of the child.

Data collection procedures

To collect data we used interview questionnaires, anthropometric measurements, and ultrasound examinations. We used questionnaires that were structured and pre-tested to collect data on maternal age, socioeconomic status, education, occupation, and parity at enrolment. We developed the questionnaires in English and then translated into the local language, *Afan Oromo*. We trained thirteen nurses for data collection. They were trained on how to take maternal, new-born, and child anthropometric measurements. We assigned them to each health post or kebele station established for the study. Fig 1 summarizes the data collection timeline and variables.

Ultrasound measurements

We calculated gestational age at enrolment based on the ultrasound measurement of biometric parameters using the Hadlock et al multiple parameter formula. The measurements were BPD, HC, AC, and FL [17, 18]. These were taken for pregnancies more than 13 weeks and 4 days. Assessments were performed at 24–28 weeks, 29–33 weeks, and 34–38 weeks of gestation. Even though sex of the fetus was identified during ultrasound assessment, the mothers were not informed about the sex of the fetus either by the researcher or by research assistant. For all ultrasound examinations and measurements, we used Sonosite M-Turbo diagnostic full-colored ultrasound machine (FUJIFILM SonoSite, Inc., USA). The primary author was trained on obstetric ultrasound. During training, the quality and accuracy of measurements were validated by a senior obstetrician at Addis Ababa University. After training, the primary author conducted the ultrasounds using standard techniques [19] and Hadlock's criteria [17, 18].

Anthropometric measurements

Trained nurses recorded the anthropometric measurements. They measured height of each pregnant woman at enrolment using a standard wooden board. Trained nurses recorded the anthropometric measurements. They measured height of each pregnant woman at enrolment

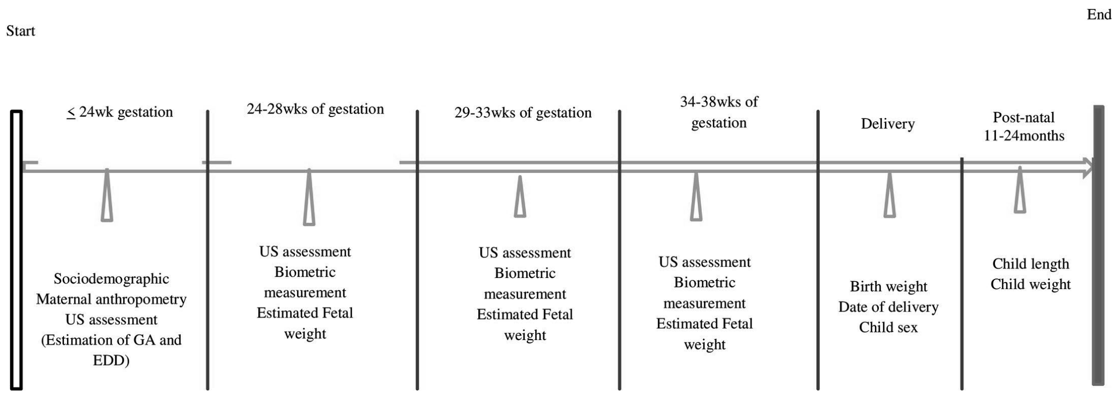


Fig 1. Data collection timeline of the study.

https://doi.org/10.1371/journal.pone.0272620.g001

using a standard wooden board. Before starting the study, they were given two days of training on anthropometry measurement techniques. We checked inter-and intra-technical measurement errors, and gave repeated training until the measurements reached the recommended cut-off points [20]. Within 72 hours of birth, the nurses measured birthweight, and recorded sex of the new-born. The weights and lengths of the children were recorded once at their age between 11–24 months. Length was measured in supine position (recumbent length) using a standard wooden board. Weight was measured to the nearest 100 gram using a digital scale [21]. The data collectors for the child anthropometry in this study were the nurses who were trained and their measurement techniques standardized in a study that was being carried out at the same time in under five children in the same area [22]. The intra and inter technical errors of measurements (TEM) were within the acceptable cut-off points [23]. They were given additional one-day refreshment training before initiation of data collection. Before taking weight measurements, the scales were checked and calibrated. Birth weight was measured within 72 hours of delivery to minimize variations related with physiological changes that occur after 72 hours.

Age of the children was calculated in months from the day on which anthropometric measurements were taken and the recorded date of birth.

Sample size

The sample size was determined based on birth weight. The aim was to have an adequate sample to detect a birth weight difference of 110 grams among rich and poor based on wealth status and with previous estimates of standard deviation of birth weight being about 500g [24, 25]. The calculated sample size in each group was 325 (power of 80%). The overall sample size became 716 considering a non-response rate of 5% and a loss to follow-up of 5%.

Statistical analysis

Trained clerks entered the data from the paper-based standardized questionnaires and forms using SPSS version 24 (SPSS Inc., Chicago, IL, USA). Data were cleaned using SPSS statistical software. We used Stata software version 15 (Stata Corp. College Station, TX, USA) for analysis. Descriptive statistics were calculated using the mean and standard deviation for continuous variables and percentages for categorical variables. In addition, scatter plot, boxplot and Inter Quartile Ranges were used for descriptive analysis. Principal component analysis was used to construct a relative wealth index [26]. It was computed using fourteen household assets. The detail was presented elsewhere [14].

The three rounds of fetal biometry at 24–28 weeks, 29–33 weeks and 34–38 weeks of gestation and birthweight were considered separately. Nutritional indices (standard deviations) and z-scores for length-for-age, weight-for-age, and weight-for-length were calculated using child growth standards [27]. Outcomes of less than -2 z-scores for length/height-for-age, weight-for-age, and weight-for-length/height were defined as stunting, wasting and underweight, respectively.

To measure the association of intrauterine growth on birth outcomes and growth among children 11 to 24 months of age, we used a multilevel, linear regression analysis model. This was to account for clustering due to repeated measures of HC,BPD,AC, and FL of the individual child at different times [28]. The other reason we used multilevel model was to account for determining factors of child linear growth (LAZ, WLZ) at household and community level that are nested in households and kebeles [29].

We first checked for distributions of the independent and outcome variables before fitting the model. We had planned to include the birth length in the model. Unfortunately, the length measurements at birth was not correctly taken, and were excluded from the final analysis. Fitting of the multilevel model was done after checking for the presence of clustering. Initially, we fitted a null, single-level (standard) regression model. Then we ran a null, multilevel model with the random individual effect. The multilevel, linear regression analysis model was fitted for each exposure variables separately with the outcome variable and the final model was fitted for all exposure variables together.

The calculated test statistics for model fit of outcome measures was strong ($P<0.001$). To estimate the unadjusted and adjusted coefficient (β) with a 95% confidence interval (CI), we fitted a multilevel model to account for clustering.

The potential predictor variables considered for birth weight, LAZ and WLZ in the model included household, maternal, and child characteristics. The household characteristics were household wealth and family size. The maternal characteristics included age, height, education, occupation, and parity. While the child characteristics were HC, BPD, AC, FL, gestational age at delivery and sex. We also included all predictive variables as potential risk factors for birth-weight outcome. Finally, we conducted multilevel, mixed-effect, regression analyses for different times and reported the adjusted beta. Kebele was used as group identity and Random-effect parameters were estimated for it. In the statistical analyses, sex and gestational age at birth were factor considered as potential effect modifiers while other factors were considered as potential confounders.

Intra cluster correlation (ICC (ρ (rho)) was estimated as the ratio of the between kebele variance to the total variance in birth weight, length-for-age z-score and for weight-for-length z-score. ICC was calculated after a mixed-effects linear model was fitted. An ICC close to one for a variable shows homogeneity in a kebele. An ICC close to zero for a variable reflects that the variable is randomly distributed among kebeles [30].

Ethical approval

We obtained ethical approval for this study in June 2015 from Addis Ababa University College of Health Sciences Institutional Review Board (ref.; 005/15/SPH) and from the Regional Committee for Medical and Health Research Ethics, Western Norway (ref: 2013/986/REK Vest). We also obtained written permission from the Oromia Regional Health Bureau and respective local authorities. All women who volunteered to participate in the study gave informed written consent and we obtained parental consent for their children.

Results

Characteristics of study participants

We screened 1,054 women of reproductive age of whom seven hundred twenty-seven pregnant women fulfilled the inclusion criteria while 327 did not meet the inclusion criteria. From the 727 pregnant women we enrolled, 23 of the pregnant mothers out-migrated before the date of delivery. From the 704 remaining study participants, 29 were excluded because of fetal or maternal causes. From those excluded, 12 of them were multiple pregnancies and 11 of the pregnancies terminated without any interference. Four pregnancies, which were referred to hospital after identifying congenital abnormalities, were terminated while two were intrauterine fetal death. Subsequently, we followed 675 fetuses throughout the pregnancy up to birth (Fig 2).

At birth, we took birth weight for 610 new-borns within 72 hours of delivery. However, birth weight for 65 new-borns were not taken. Three of them were stillbirths. Four of the new-borns weight measurements were not taken in 72 hours of birth and were thus excluded. In addition, 58 of the pregnant mothers left the study area at the time of delivery.

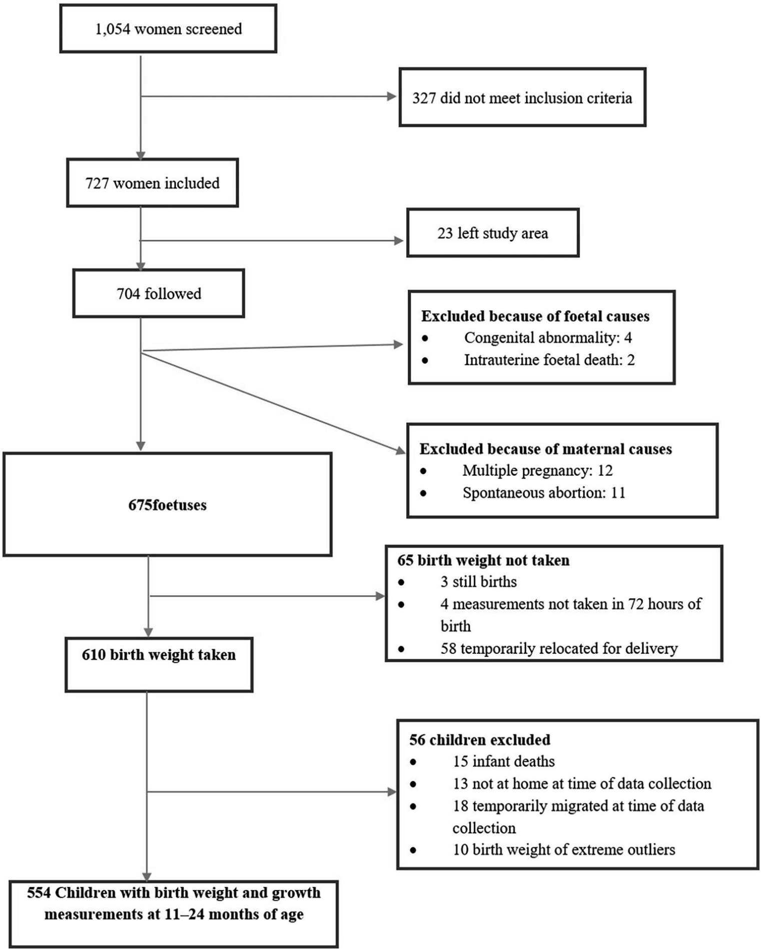


Fig 2. Flow chart of study participants from fetal to postnatal period at age of 11–24 months, Adami Tullu district (2018).

https://doi.org/10.1371/journal.pone.0272620.g002

After birth, we took weights and lengths of 554 children at age of 11–24 months. Forty-six children did not have weight and length measurements. There were 15 infant deaths reported. Thirteen children were not at home at the time of data collection. Eighteen children migrated out of the study area at time of data collection. Furthermore, 10 children were excluded from the analysis because their recorded birth weight fell in the extreme outlier range (Fig 2).

The households and maternal characteristics of the study participants are shown in Table 1. The mean family size of the study participants was 5.6 individuals per household. Two hundred eight nine (52.7%) of the mothers did not have formal education. Among the mothers, 267 (48.3%) were 15–24 years old and 248 (44.8%) were 25–34 years old. The mean parity was 2.8, and 350 (63.2%) had a history of two or more births. Most of them (523, 94.4%) were housewives.

Table 1. Household and maternal characteristics of the pregnant mothers at first measurement Adami Tullu district, 2018.

Variables	n	%	Median	Inter quartile range (IQR)
Household Characteristics				
Family size	554		5.6	2.3
Household wealth	550			333.5
Poor	175	31.8		
Middle	185	33.6		
Rich	190	34.6		
Maternal Characteristics			Mean	Standard Deviation
Height	547		157.3	6.4
Age in years (n = 553)			25.0	5.4
15–24	267	48.3		
25–34	248	44.8		
≥ 35	38	6.9		
			Median	Interquartile range (IQR)
Gravida (n = 554)			4.0	4
1	82	14.8		
2–5	307	55.4		
≥6	165	29.8		
Parity (n = 554)			2.	4
0	95	17.1		
1	109	19.7		
2–5	266	48.0		
≥6	84	15.2		
Occupation (n = 554)				
Housewife	523	94.4		
Others	31	5.6		
Education (n = 548)				
No formal education	289	52.7		
Primary	145	26.5		
Junior Secondary	67	12.2		
Secondary	47	8.6		

https://doi.org/10.1371/journal.pone.0272620.t001

We observed a larger family size for mothers who had no formal education (179 (61.9%)) and a lower family size for mothers who had secondary education (12 (25.5%)). Family size was higher for mothers who are housewives (268 (51.2%)) than those who had other occupations (9 (29.0%)). Among the mothers who had no formal education, 95.5% were housewives and 4.5% had other occupations. While among mothers who had secondary education, 85.1% were housewives and 14.9% had other occupation.

Characteristics of children during pregnancy, birth, and postnatal follow-ups

Table 2 shows characteristics of the cohort of 554 children during fetal, neonatal, and 11–24 months of follow-ups after birth. Overall, we obtained 1,479 ultrasound prenatal biometric measurements. We took 515 ultrasound measurements during 24–28 weeks, 501 ultrasound measurements during 29–33 weeks and 463 ultrasound measurements during 34–38 weeks of pregnancy.

Table 3 shows the characteristics of the cohort of children during neonatal and postnatal follow-ups. The mean birth weight of the new-born was 3,240.7gm (SD 481.0), and 324

Table 2. Fetal characteristics during pregnancy, Adami Tullu district, 2018.

Variable	n	Mean	Standard Deviation
Biparietal Diameter (mm) (n = 1,479*)		77.2	9.7
24–28 weeks	515	66.5	3.4
29–33 weeks	501	77.6	3.9
34–38 weeks	463	88.6	3.7
Head Circumference (mm) (n = 1,479*)		286.5	31.8
24–28 weeks	515	250.3	10.7
29–33 weeks	501	288.8	11.5
34–38 weeks	463	324.2	8.1
Abdominal Circumference (mm) (n = 1,479*)		259.4	40.7
24–28 weeks	515	215.0	12.2
29–33 weeks	501	258.6	15.6
34–38 weeks	463	309.4	13.1
Femoral Length (mm) (n = 1,479*)		59.2	8.8
24–28 weeks	515	49.6	2.7
29–33 weeks	501	59.1	3.1
34–38 weeks	463	69.9	2.8

n: number, mm: millimeter

*: number of biometric measurements.

https://doi.org/10.1371/journal.pone.0272620.t002

(58.5%) of them were male. Among neonates, 35 (6%) had low birthweight, and 29 (5.2%) were born before 37 weeks of gestation.

Growth measurements of height and weight were taken for 554 children at 11–24 months of age. The mean age of the children was 17.2 (SD 3.3) months. Among the 554 children, 301

Table 3. Child characteristics at birth and 11–24 months after birth, Adami Tullu district, 2018.

Variable	n	%	Mean	Standard Deviation
Birthweight (n = 554)			3,240.7	481.01
< 2,500 gm	35	6.3		
≥ 2,500 gm	519	93.7		
Gestational age at birth (n = 553)				
< 37 weeks	29	5.2		
≥ 37 weeks	524	94.8		
Sex (n = 554)				
Male	324	58.5		
Female	230	41.5		
Post-natal age in months (n = 554)			17.2	3.3
11–16	231	41.7		
>16–20	196	35.4		
>20–24	127	22.9		
Length-for-age (n = 554)			-2.092	1.521
≤ -2 z-score	301	54.3		
> -2 z-score	253	45.7		
Weight-for-length (n = 554)			0.342	1.742
≤ -2 z-score	59	10.6		
> -2 z-score	495	89.4		

n: number, gm: gram

https://doi.org/10.1371/journal.pone.0272620.t003

(54.3%) were stunted, and 59 (10.6%) had wasting. The prevalence of wasting was lower in the age group greater than 20 months (8.7%) as compared to children 11–24 months of age (11.3%). The difference was not statistically significant (95% CI, -0.37, 0.32, P-value = 0.885).

However, stunting was higher (64.6%) among children 20 and above months of age than among children 11–20 months (%). The difference was statistically significant (95%CI, 0.20, 0.79 P-value = 0.001).

Factors associated with birthweight

Associations between birth weight and measures of fetal ultrasound growth (HC, BPD, AC and FL) during the different times throughout pregnancy are shown in Table 4. The BPD ultrasound measurement at 24–28 weeks [β = 23.41 95% CI: (0.60, 46.22) P-value = 0.444], HC ultrasound measurement [β = 9.72 95% CI: (0.82, 18.63) P-value = 0.032], and abdominal circumference [β = 7.82 95% CI: (3.72, 11.91) P-value = 0.001] at the 34–38 weeks were significantly associated with birth weight. Similarly, an increase in parity [β = 34.31 95% CI: (9.99, 58.63) P-value = 0.006], educational status [β = 17.34 95% CI: (4.28, 30.40) P-value = 0.009] and gestational age at birth [β = 65.58 95% CI: (41.45, 89.72) P-value = 0.001] were associated with increased birth weight.

For birth weight, a mixed-effects linear model was fitted and the Intra cluster correlation (ICC) was estimated as the ratio of the between-kebele variance to the total variance that

Table 4. Multilevel, mixed-effects regression coefficients for associations of household, maternal, and fetal characteristics with birthweight of children in Adami Tullu district, 2018.

Variables	24–28 weeks		29–33 weeks		34–38 weeks	
	β (95% CI)	P-Value	β (95% CI)	P-Value	β (95% CI)	P-Value
Fixed effects						
Family size (number)	-3.81 (-22.73, 15.11)	0.693	7.33 (-13.18, 27.84)	0.483	-0.09 (-21.09, 20.91)	0.993
Household wealth status (index)	-0. 05 (-0.26, 0.12)	0.620	-0.06 (-0.28, 0.15)	0.564	0.0007 (-0.22, 0.24)	0.951
Maternal age (year)	-263 (-12.31, 7.052)	0.595	-1.77 (-11.73, 8.18)	0.727	2.66 (-7.55, 12.87)	0.610
Maternal education (grade)	17.34 (4.28, 30.40)	0.009	13.39 (-0.64,27.42)	0.061	15.30 (0.91,29.68)	0.037
Maternal height (cm)	2.93 (-2.22, 11.53)	0.350	2.96 (-3.72, 9.64)	0.385	0.17 (-6.53, 6.89)	0.959
Parity (number)	34.31 (9.99, 58.63)	0.006	17.43(-8.38,43.24)	0.186	21.77 (-5.18, 48.71)	0.113
Maternal occupation other than housewife (type)	-20.23 (-198.10 157.63)	0.824	-134.29 (-330.89, 2.31)	0.181	-10.54–47.68 (-232.99, 137.63)	0.614
Head circumference (mm)	-6.95 (-14.99, 1.10)	0.091	-315 (-10.60, 4.31)	0.408	9.72 (0.82,18.63)	0.032
Biparietal diameter (mm)	23.41(0.60, 46.22)	0.044	9.69 (-10.54, 29.93)	0.348	16.99 (-35.20, 1.21)	0.067
Abdominal circumference (mm)	2.89 (-1.28,7.07)	0.175	5.79(2.05, 9.54)	0.002	7.82 (3.72, 11.91)	0.001
Femoral Length (mm)	6.67 (-12.15, 25.49)	0.488	-12.36 (-30.62, 5.90)	0.185	-0.73 (-18.38, 16.92)	0.935
Gestational age at birth (week)	65.58 (41.45, 89.72)	0.001	61.48 (36.003, 86.951)	0.001	32.93 (4.36, 61.50)	0.024
Sex	-46.90 (-129.06, 35.26	0.263	-33.69 (-118.92, 51.54)	0.439	-36.49 (-125.95, 52.98)	0.424
Random-effects parameters		SE		SE		SE
Kebele (constant)*	18117.5 (5988.5, 54811.7)	10233.11	21914.57 (6726.98, 71391.37)	6726.98	22694.5 (7471.88, 68930.47)	12864.03

* Variation in birth weight among kebeles (Intra-cluster correlation coefficient: ICC (ρ) = 0.11)

ρ: rho

SE: Standard error

CI: Confidence Interval

β: coefficient

cm: centimeter

mm: millimeter

https://doi.org/10.1371/journal.pone.0272620.t004

accounts for the relatedness of birthweight data by comparing the variance within kebeles with the variance between kebeles. The estimated ICC (ρ) for birth weight was estimated to be 0.11.

Factors associated with linear child growth

Table 5 shows the associations between intrauterine growth as measured by ultrasound (HC, BPD, AC and FL) during the different times throughout pregnancy and linear child growth as measured by length-for-age z-score at 11–24 months of the child age. The linear child growth was significantly associated with femoral length measured by ultrasound during 24–28 weeks [β = 0.06 95% CI: (0.01, 0.12) P-value = 0.016], gestational age at delivery [β = 0.07 95% CI: (0.004, 0.142) P-value = 0.038] and 11–24 months child age after birth [β = -0.09 95% CI: (-0.13, -0.05) P-value = 0.001]. An increase in one millimeter of femoral length for 24–28 weeks was associated with a 0.06 increase in length-for-age z-score. An increase in one week of gestational age was associated with a.07 increase in LAZ. Length-for-age was also significantly associated with child age. An increase of child age by one month was associated with 0.11cm decrease of child LAZ. We also found a significant association between family size and length-for-age z-score [β = 0.09 95% CI: (0.04, 0.15) P-value = 0.001]. Child LAZ increased with increasing family size.

Table 5. Multilevel, mixed-effects regression coefficients for associations of household, maternal, fetal, and child characteristics with length-for-age z-score among children aged 11–24 months in Adami Tullu district, 2018.

Variables	24–28 weeks		29–33 weeks		34–38 weeks	
	β (95% CI)	P-Value	β (95% CI)	P-Value	β (95% CI)	P-Value
Fixed effects						
Family size (number)	0.09 (0.04, 0.15)	0.001	0.09 (0.04, 0.15)	0.001	0.07 (0.01, 0.13)	0.016
Household wealth status (index)	-0.0002 (-0.0008, 0.0003)	0.422	-0.0002 (-0.0008, 0.0004)	0.517	-0.0004 (-0.0010, 0.0003)	0.251
Maternal age (year)	-0.002 (-0.028, 0.025)	0.908	-0.01 (-0.04, 0.02)	0.503	-0.01 (-0.04, 0.02)	0.605
Maternal education (grade)	-0.01 (-0.05, 0.03)	0.612	0.001 (-0.04, 0.04)	0.949	-0.01 (-0.04, 0 .03)	0.810
Maternal height (cm)	0.001 (-0.02, 0.02)	0.945	0.001 (-0.02, 0.02)	0.945	0.01 (-0.01, 0.03)	0.303
Parity (number)	-0.03 (-0.10, 0.04)	0.396	-0.01 (-0.08, 0.06)	0.761	-0.01 (-0.08, 0.07)	0.843
Maternal occupation other than housewife (type)	0.13 (-0.35, 0.62)	0.594	-0.25 (-0.78, 0.28)	0.351	0.03 (-0.47, 0.53)	0.906
Head circumference (cm)	-0.02 (-0.041, 0.003)	0.100	-0.002 (-0.02, 0.02)	0.840	-0.01 (-0.03, 0.02)	0.472
Biparietal Diameter (cm)	-0.01 (-0.07, 0.06)	0.868	-0.001 (-0.06, 0.05)	0.969	0.02 (-0.03, 0.07)	0.482
Abdominal circumference (cm)	0.002 (-0.009, 0.014)	0.681	0.003 (-0.007, 0.013)	0.531	0.01 (-0.01, 0.02)	0.407
Femoral length (cm)	0.06 (0.01, 0.12)	0.016	-0.01 (-0.05, 0.04)	0.842	0.02 (-0.02, 0 .07)	0.339
Gestational age at birth (week)	0.07 (0.004, 0.142)	0.038	0.04 (-0.03, 0.11	0.236	0.04 (-0.04, 0.12)	0.349
Birth weight (gm)	-0.0002 (-0.0004, 0.0001)	0.179	-0.0001(-0.0004, 0.0001)	0.370	-0. 0001 (-0.0004, 0.0001)	0.393
Sex	-0.19 (-0.42, 0.03)	0.096	-0.013 (-0.36, 0.10)	0.270	-0.07 (-0.32, 0.17)	0.565
Child age (month)	-0.09 (-0.13, -0.05)	0.001	-0.10 (-0.14, -0.06)	0.001	-0.11 (-0.15, -0.08)	001
Random-effect parameters		SE		SE		SE
Kebele*	0.634 (0.28, 1.44)	0.264	0. .664 (0.292, 1.508)	0.278	0.612 (0 .268, 1.399)	0.258

* Variation in length-for-age among kebeles (Intra-cluster correlation coefficient: ICC (ρ) = 0.30)

ρ: rho

SE: Standard error

CI: Confidence Interval

β: coefficient

cm: centimeter

mm: millimeter

https://doi.org/10.1371/journal.pone.0272620.t005

Table 6. Multilevel, mixed-effects regression coefficients for association of household, maternal, fetal, and child characteristics with weight-for-length z-score among children aged 11–24 months in Adami Tullu district, 2018.

Variables	24–28 weeks		29–33 weeks		34–38 weeks	
	β (95% CI)	P-Value	β (95% CI)	P-Value	β (95% CI)	P-Value
Fixed effects						
Family size (number)	-0.10 (-0.16, -0.03)	0.006	-0.10(-0.17, -0.03)	0.005	-0.07 (-0.145, 0.002)	0.055
Household wealth status (index)	0.0005 (-0.0002,0.0013)	0.171	0.0007 (-0.00002,0.00150)	0.055	0.0006 (-0.0002, 0.0014)	0.113
Maternal age (year)	0.01 (-0.03,0.04)	0.773	0.004 (-0.03,0.04)	0.831	-0.002 (-0.04,0.03)	0.930
Maternal education (grade)	-0.01 (-0.06, 0.03)	0.587	-0.02 (-0.07,0.03)	0.465	-0.01 (-0.06,0.04)	0.657
Maternal height (cm)	0.03 (0.01, 0.05)	0.011	0.03 (0.003, 0.049)	0.025	0.02 (0.001,0.047)	0.042
Parity (number)	-0.03 (-0.12, 0.05)	0.461	-0.03 (-0.12, 0.06)	0.547	-0.02 (-0.12,0.07)	0.625
Maternal occupation other than housewife (types)	-0.43 (-1.06, 0.21)	0.189	-0.37 (-1.05, 0.31)	0.287	-0.38(-1.02, 0.26)	0.246
Gestational age at birth (week)	0.02 (-0.07, 0.11)	0.722	0.04 (-0.05, 0.13)	0.427	0.02 (-0.08, 0.12)	0.736
Birth weight (gm)	0.0003 (-0.0001, 0.0006)	0.113	0.0002 (-0.0001, 0.0005)	0.297	0.0002 (-0.0001, 0.0005)	0.208
Sex	-0.07 (-0.36, 0.23)	0.651	-0.07 (-0.37, 0.22)	0.628	-0.12 (-0.43, 0.19)	0.464
Child age (month)	-0.01 (-0.05,0.04)	0.821	0.03 (-0.02, 0.08)	0.254	0.03 (-0.02,0.08)	0.294
Random-effects parameters		SE				
Kebele*	0.697 (0.29, 1.66)	0.309	0 .793 (0 .337, 1.870)	0.347	0 .649 (0 .270, 1.558)	0 .290

* Variation in weight-for-height among kebeles (Intra-cluster correlation coefficient: ICC (ρ = 0.22)

ρ: rho

SE: Standard error

CI: Confidence Interval

β: coefficient

cm: centimeter

gm: gram

https://doi.org/10.1371/journal.pone.0272620.t006

For length-for-age z-score, a mixed-effects linear model was fitted and the Intra cluster correlation (ICC) was estimated as the ratio of the between-kebele variance to the total variance. The estimated ICC (ρ) for length-for-age z-score was 0.30.

Factors associated with weight-for-length Z-score

Weight-for-Length Z-score was associated with family size and maternal height in multivariate multilevel, mixed-effect linear regression analyses. Children from smaller family size had better WLZ [β = -0.01 95% CI: (-0.16, -0.03) P-value = 0.006] (Table 6). Similarly, an increase in maternal height had significant association with WLZ [β = 0.03 95% CI: (0.01, 0.05) P-value = 0.011]. Nonetheless, in our study WLZ was not associated with intrauterine fetal growth factors.

Discussion

In this prospective cohort study, we found that fetal factors, duration of pregnancy, child age, maternal height and family size were the main predictors of linear child growth measured by LAZ and WLZ in children aged 11–24 months. Both birth weight and LAZ were influenced by early intrauterine fetal growth. Fetal growth during late pregnancy influenced birth-weight only. However, in our study intrauterine fetal growth did not show any influence on WLZ. Moreover, we observed a large variation in LAZ and WLZ between villages (kebeles).The influence of environmental factors is more on the child linear growth than the birth weight. Our study also found that fetal, pregnancy, and maternal factors were significantly associated with birthweight z-score.

Some of the predictor factors (the fetal factor, gestational age at birth and child age) for LAZ that we identified in our study were non-modifiable factors. However, the association with family size, maternal education and area of residence emphasize the importance of modifiable household factor and long-lasting consequences for children's growth. The risk factors we found to have associations with linear growth faltering in our study were also identified in previous studies. The finding of an association between an increase in femoral length with increasing LAZ in our study is similar to the finding from a prospective cohort study that showed a highly significant correlation of femoral length with child growth (LAZ) [31]. An increase in LAZ with increasing gestational age at birth in our study is also similar to a study from prospective cohorts of young children in Ghana, Malawi and Burkina Faso that found gestational age at birth to be strongly associated with child linear growth [13].

The other predictor variable that we found to affect LAZ was child age. LAZ decreased with an increase in child age, which is similar to the finding of a study from 125 demographic health survey conducted in 57 countries that reported a decline of LAZ with increasing child age from birth until 21 months [32]. This can be explained by the fact that growth in early life is rapid and it decreases as the child ages [33, 34]. The other finding in our study is the association of family size with the linear growth of the children. In children from larger family size, the LAZ was better while the WLZ was lower. The finding of lower WLZ in larger family size was also reported in a previous study from Bangladesh [35]. A possible explanation may be that inadequate dietary intake among children, because of larger family size, increases the risk of wasting that tends to peak in early childhood, at the age of about 12 months [36, 37]. However, the evidences from previous studies on the association between family size and LAZ were not conclusive. Some have reported that child growth faltering in LAZ is less likely in those from smaller family size [36, 38, 39]. While another study, that is consistent with the finding of our study, reported that child growth faltering in LAZ is less likely in those from larger family size [40]. Wasting was also associated with maternal height in the current study where those children of taller mothers were less likely to have wasting. This is in line with evidence reported from the previous studies that showed maternal height as one of the risk factors identified for impaired growth in children [35, 41].

Some of the factors associated with birth weight in our study were similar to findings of other studies. Studies conducted in Indonesia showed that maternal education, gestational age at birth, and sex were found to be determinants of birthweight [42, 43]. Similarly studies from India [44] and Nepal [45] found significant associations between gestational age at birth and birthweight. Our study also found that biparietal diameter at early pregnancy and head and abdominal circumference at late pregnancy were significantly associated with birthweight.

The strength of our study was that we enrolled our cohort of women during pregnancy and followed their fetuses and children prospectively for 11–24 months postpartum. This allowed us to examine risk factors throughout pregnancy and early childhood. The study has demonstrated a temporal relationship of the exposure and outcome. The prospective design allowed to draw associations between exposure variables that we measured at earlier time during pregnancy or at birth and those measured later during early childhood, the outcome. It has shown the influence of intrauterine growth during pregnancy or at birth on the child linear growth. The study has also demonstrated a dose-response relationship. For instance, an increase in femoral length was associated with increasing LAZ. Measurement of serial biometry using ultrasound by the primary author that was done to characterize fetal growth could minimize inter observer reliability bias.

This study has some limitations. Firstly, we did not measure factors such as dietary, infections, access to healthcare, or environmental factors that may affect LAZ. Secondly, we did not collect data on some of the risk factors of wasting including infection, micronutrient deficiencies, and child feeding practices, community sanitation, and access to healthcare. Thirdly, we found a higher male to female proportion in our study compared to a previous study in the same area [22]. The male dominance in our study is an unexpected finding and this introduces selection bias. However, this may not have affected our analysis on linear growth as we have adjusted for sex distribution in the multivariate analysis. Fourthly, the final sample size used in this study was less than the calculated minimum sample size at the beginning of the study because of exclusion at different stages that may have resulted in non-significance association with the confounding variables. We calculated statistical power for the variables and all of them except wealth status had low power. This may indicate that the lack of association might be due to low statistical power of the variables.

In conclusion, our study shows that fetal growth, duration of pregnancy, child age, maternal height, and family size influence linear growth of children. Environmental factors that are associated with the area of residence play a bigger role for linear growth than for birth weight.

Acknowledgments

Our gratitude goes to all the women and their children who participated in this study. We would also like to thank the data collectors and supervisors involved in this study. We are grateful to the Obstetricians who provided training of ultrasound and validated the ultrasound measurements. Our appreciation also goes to Addis Ababa University and the University of Bergen for their support.

Author Contributions

Conceptualization: Meselech Roro, Wakgari Deressa, Bernt Lindtjørn.

Data curation: Meselech Roro, Wakgari Deressa, Bernt Lindtjørn.

Formal analysis: Meselech Roro, Wakgari Deressa, Bernt Lindtjørn.

Funding acquisition: Wakgari Deressa, Bernt Lindtjørn.

Investigation: Meselech Roro.

Methodology: Meselech Roro, Wakgari Deressa, Bernt Lindtjørn.

Project administration: Meselech Roro, Wakgari Deressa, Bernt Lindtjørn.

Resources: Wakgari Deressa, Bernt Lindtjørn.

Software: Meselech Roro, Wakgari Deressa, Bernt Lindtjørn.

Supervision: Meselech Roro, Wakgari Deressa, Bernt Lindtjørn.

Validation: Meselech Roro, Wakgari Deressa, Bernt Lindtjørn.

Visualization: Meselech Roro.

Writing – original draft: Meselech Roro, Wakgari Deressa, Bernt Lindtjørn.

Writing – review & editing: Meselech Roro, Wakgari Deressa, Bernt Lindtjørn.

References

1. Victora CG, de Onis M, Hallal PC, Blossner M, Shrimpton R. Worldwide timing of growth faltering: revisiting implications for interventions. Pediatrics. 2010; 125 e473–80. https://doi.org/10.1542/peds.2009-1519 PMID: 20156903
2. Black RE, Victora CG, Walker SP, Bhutta ZA, Christian P, de Onis M, et al. Maternal and child undernutrition and overweight in low-income and middle-income countries. The Lancet. 2013; 382(9890):427–51. https://doi.org/10.1016/S0140-6736(13)60937-X PMID: 23746772

3. World Health Organization. Childhood stunting: challenges and opportunities. Report of a colloquium on promoting healthy growth and preventing childhood stunting. Geneva: World Health Organization; 2014.
4. Williams AM, Suchdev PS. Assessing and improving childhood nutrition and growth globally Pediatr Clin North Am 2017. 2017; 64:755–68.
5. Black RE, Allen LH, Bhutta ZA, et al. Maternal and child undernutrition: global and regional exposures and health consequences Lancet 2008; 371:243–60.
6. Pelletier DL. The relationship between child anthropometry and mortality in developing countries: implications for policy, programs and future research J Nutr. 1994; 124:S2047–S81. https://doi.org/10.1093/jn/124.suppl_10.2047S PMID: 7931716
7. Yarbrough C, Habicht J-P, Malina RE, Lechtig A, Klein RE. Length and weight in rural Guatemalan Ladno children: birth to seven years of age. Am J Phys Anthropol. 1975; 42:439–48. https://doi.org/10.1002/ajpa.1330420311 PMID: 1146988
8. Rivera JA, Ruel M. Growth retardation starts in the first three months of life among rural Guatemalan children Eur J Clin Nutr 1997; 51:92–6.
9. Christian P. Prenatal origins of malnutrition. In: Kalhan SC, Prentice AM, Yajnik CS (eds). Emerging societies—coexistence of childhood malnutrition and obesity. Vevey, Switzerland: S Karger Ag; 2009.
10. Jennifer AH, Geir WJ, Michael SK, Marit M, and Robert WP. Small size at birth or abnormal intrauterine growth trajectory: which matters more for child growth? American Journal of Epidemiology. 2016; 183 (12).
11. Nations United, Subcommittee on Nutrition. Third report on the world nutrition situation: a report compiled from information available to the ACC/SCN. Geneva: United Nations; 1997.
12. Suchdev PS. What pediatricians can do to address malnutrition globally and at home Pediatrics 2017; 139(e20161666).
13. Prado E L, Yakes Jimenez E, Vosti S, et al. Path analyses of risk factors for linear growth faltering in four prospective cohorts of young children in Ghana, Malawi and Burkina Faso. BMJ Glob Health. 2019; 4:e001155. https://doi.org/10.1136/bmjgh-2018-001155 PMID: 30775005
14. Roro M, Deressa W, Lindtjørn B. Intrauterine growth patterns in rural Ethiopia compared with WHO and INTERGROWTH-21st growth standards: A community-based longitudinal study. PLoS One. 2019; 14 (12):e0226881. https://doi.org/10.1371/journal.pone.0226881 PMID: 31891599
15. CSA. Ethiopian population and housing census. Addis Ababa, Ethiopia: Central Statistical Agency. 2007.
16. World Health Organization. Medical eligibility criteria for contraceptive use. 4 ed2010.
17. Hadlock FP, Harrist RB, Sharman RS, Deter RL, Park SK. Estimation of fetal weight with the use of head, body, and femur measurements—a prospective study. Am J Obstet Gynecol 1985; 151:333–7. https://doi.org/10.1016/0002-9378(85)90298-4 PMID: 3881966
18. Hadlock FP, Deter RL, Harrist RB, Park SK. Estimating fetal age: computer-assisted analysis of multiple fetal growth parameters. Radiology. 1984; 152:497–501. https://doi.org/10.1148/radiology.152.2.6739822 PMID: 6739822
19. Trish CT, Thilaganathan B. Obstetric Ultrasound: How, Why and When. Third Edition ed2004.
20. Onyango AW, Martorell R, Chumlea WC, Van den Broeck J, Araujo CL, Baerug A, et al. Reliability of anthropometric measurements in the WHO Multicentre Growth Reference Study. Acta Paediatr. 2006; 95:38–46.
21. UNICEF. Electronic scale for weighing babies up to 10kg. Accessed on 18 June 2022 https://supply.unicef.org/s0145558.html.
22. Gari T, Loha E, Deressa W, Solomon T, Atsbeha H, Assegid M, et al. Anaemia among children in a drought affected community in south-central Ethiopia. PLoS ONE. 2017; 12(3).
23. World Health Organization. Reliability of anthropometric in the WHO multicentre growth reference study. Acta Paediatrica. 2006. https://doi.org/10.1111/j.1651-2227.2006.tb02374.x PMID: 16817677
24. Newman D R, Hailemariam A, Jimma D, et al. Burden of malaria during pregnancy in areas of stable and unstable transmission in Ethiopia during a nonepidemic Year. Journal of Infectious Diseases. 2003; 187:1767–72.
25. Wado YD, Afework MF, Hindin MJ. Effects of maternal pregnancy intention, depressive symptoms and social support on risk of low birth weight: a prospective study from southwestern Ethiopia. PLoS One. 2014; 9(5):e96304. https://doi.org/10.1371/journal.pone.0096304 PMID: 24848269
26. Vyas S, Kumaranayake L. Constructing socio-economic status indices: How to use principal components analysis. Health Policy Plan 2006; 21:459–68. https://doi.org/10.1093/heapol/czl029 PMID: 17030551

27. World Health Organization. AnthroPlus: Software for assessing growth of the world's children and adolescents Geneva, Switzerland; 2009.
28. Twisk JWR. Applied Multilevel analysis: A practical guide. Fourth printing. United States of America: Cambridge University press; 2010.
29. Gelman A, Hill J. Data analysis using regression and multilevel/hierarchical models. ed. n, editor: New York: Cambridge University Press; 2009.
30. Hayes R, Moulton LH. Cluster Randomised Controlled Trials. New York: Chapman &Hall/CRC Press; 2009.
31. Falkner F, Roche A F.Relarionship of femoral length to recumbent length and stature in fetal, neonatal, and early childhood growth Human Biology. 1987; 59(5):769–73.
32. Alderman H, Headey D. The timing of growth faltering has important implications for observational analyses of the underlying determinants of nutrition outcomes PLoS ONE 2018; 13(4).
33. Reed R, Stuart H. Patterns of growth in height and weight from birth to eighteen years of age Pediatrics. 1959; 24(904).
34. De Onis M, Onyango AW, Borghi E, Siyam A, Siekmann J. Development of a WHO growth reference for school-aged children and adolescents. Bull World Health Organ. 2007; 043497:660–7. https://doi.org/10.2471/blt.07.043497 PMID: 18026621
35. Svefors P, Sysoev O, Ekstrom E-C, et al. Relative importance of prenatal and postnatal determinants of stunting: data mining approaches to the MINIMat cohort, Bangladesh. BMJ Open. 2019.
36. Hong R, Banta JE, & Betancourt JA. Relationship between household wealth inequality and chronic childhood under-nutrition in Bangladesh Int J Equity Health 5. 2006; 15.
37. Schoenbuchner SM, Dolan C, Mwangome M, Hall A, Richard SA, Wells JC, et al. The relationship between wasting and stunting: a retrospective cohort analysis of longitudinal data in Gambian children from 1976 to 2016. The American Journal of Clinical Nutrition. 2019; 110(2):498–507. https://doi.org/10.1093/ajcn/nqy326 PMID: 30753251
38. Vahabzadeh D., Karandish M., Eftekhari J., Haghighizadeh M.H., Al-Taieb H. Risk factors of growth faltering among 3–36 months old children in Ahwaz, Iran Kerman University of Medical Sciences. 2013; 20(5):481–91.
39. Deborah B, Adam S, Marc L, Joanne G, Manohar S, Rafael F. Child hunger in the developing world: an analysis of environmental and social correlates. Food Policy 2005; 30(5–6):584–611.
40. Zhang Y, Zhou J, Niu F, Donowitz R J, Haque R, W A., et al. Characterizing early child growth patterns of height-for-age in an urban slum cohort of Bangladesh with functional principal component analysis BMC Pediatrics 2017; 17(84).
41. Espo M, Kulmala T, Maleta K, et al. Determinants of linear growth and predictors of severe stunting during infancy in rural Malawi. Acta Paediatr. 2002; 91:1364–70. https://doi.org/10.1111/j.1651-2227.2002.tb02835.x PMID: 12578296
42. Sebayang K S, Dibley J M, Kelly J P, Shankar VA, and Shankar HA, on behalf of the SUMMIT Study Group. Determinants of low birthweight, small-for-gestational-age and preterm birth in Lombok, Indonesia: analyses of the birthweight cohort of the SUMMIT trial Tropical Medicine and International Health august 2012; 17(8):938–50.
43. Muslimatun S, Schmidt MK, West CE, Schultink W, Gross R & Hautvast J. Determinants of weight and length of Indonesian neonates European Journal of Clinical Nutrition 2002; 56:947–51.
44. Singh S, Shrestha S, Marahatta S. Incidence and risk factors of low birth weight babies born in Dhulikhel Hospita. 2011.
45. Sharma SR, Giri S, Timalsina U, Bhandari SS, Basyal B, Wagle K, et al. Low birth weight at term and its determinants in a tertiary hospital of Nepal: A Case-Control Study PLoS ONE 2015; 10 (4):e0123962. https://doi.org/10.1371/journal.pone.0123962 PMID: 25853813

Paper III

Roro *et al. BMC Pregnancy and Childbirth* (2022) 22:849
https://doi.org/10.1186/s12884-022-05171-3

BMC Pregnancy and Childbirth

RESEARCH

Open Access

Antenatal care utilization and compliance with national and WHO guidelines in rural Ethiopia: a cohort study

Meselech Roro[1,2*], Wakgari Deressa[3] and Bernt Lindtjørn[1]

Abstract

Background: Antenatal health care utilization has the potential to influence maternal and new-born health. In this study, we assessed compliance of antenatal care utilization with national and World Health Organization (WHO) guidelines. We also examined association of antenatal care utilization with adverse pregnancy outcomes as secondary outcome.

Methods: This was a community-based cross sectional study conducted from July 2016 to November 2017 in rural south-central Ethiopia. We described antenatal care received by pregnant women, whom we followed at three prescheduled visits during pregnancy and collected birth data at time of delivery. Extent of antenatal care content received, timing of antenatal care, place of antenatal care and place and mode of delivery were obtained and computed in accordance with national and WHO guidelines. For adverse pregnancy outcomes, computed as sum of low birth weight, preterm birth, intrauterine foetal death, and stillbirth, the exposure variable used was antenatal care utilization.

Results: Seven hundred and four (704) women participated in the study, and 536 (76.1%) had attended at least one antenatal care visit. Among women who attended antenatal care visit, majority, 421 (79.3%), had done so at health centres and hospitals, while 110 (20.7%) attended at health post. Average number of antenatal care visits was 2.5, which is less than that recommended in national and WHO guidelines. Only 18 (2.6%) women had attended antenatal care in their first trimester, which is low in contrast to the expected 100% specified in the guidelines. Less than half (47%) of the women delivered in a health facility. This is in contrast to the 100% expected health institution deliveries. Low birth weight was 7.9% ($n = 48$), and preterm birth was 4.9% ($n = 31$). There were 12 twin pregnancies, three stillbirths, 11 spontaneous abortions, and two intrauterine foetal deaths. We did not find significant association between adverse pregnancy outcomes and antenatal care utilization (COR = 1.07, 95% CI 0.62, 1.86).

Conclusion: This study showed that antenatal care service utilization in the study area was markedly low compared to that recommended in national and WHO guidelines. The obtained antenatal health care utilization was not associated with the registered adverse pregnancy outcomes.

Keywords: Antenatal care, Pregnancy outcome, Adverse pregnancy outcome, Compliance, Ethiopia

*Correspondence: meselua@yahoo.com

[2] Department of Reproductive Health and Health Service Management, School of Public Health, College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia
Full list of author information is available at the end of the article

Background

The benefit of antenatal health service utilization is the provision of evidence-based clinical interventions. These include maternal health education and counselling, examinations, and arranging specialized care when the need arises [1]. Antenatal care (ANC) provides an opportunity for influencing the future health and well-being of pregnant women, foetuses, and neonates. It assists to identify high-risk women to facilitate timely management during pregnancy and child birth [2].

According to the 2016 Ethiopian Demographic and Health Survey, maternal mortality ratio for Ethiopia was 412 maternal deaths per 100,000 live births. The proportion of women who received ANC from a skilled provider was 62% in 2016. Thirty-two percent of women had at least four ANC visits during their last pregnancy. Institutional deliveries was 26% in 2016. Thirteen percent of the new-borns had low birth weight [3].

Ethiopia has emphasised strengthening the provision of ANC services at all levels in the health system to facilitate the improvement of positive pregnancy outcomes [4]. The country's health service is currently structured into a three-tier system: primary, secondary, and tertiary levels of care. Primary hospitals, health centres, and health posts are included under the primary level of care, while the secondary level comprises general hospitals serving 1 to 1.5 million people. Tertiary level health care is composed of specialized hospitals that provide services for 3.5 to 5 million people [5].

Ethiopia is implementing the World Health Organization (WHO) focused ANC (FANC) model at all health facilities. FANC is a goal-orientated approach to delivering ANC service four times during pregnancy. Women with low risk pregnancies need to have ANC visits at gestational ages between 8 and 12 weeks, between 24 and 26 weeks, at 32 weeks, and between 36 and 38 weeks. Women with high-risk pregnancies and those who develop pregnancy complications are required to have a greater number of ANC visits [4, 6].

According to the guidelines for ANC in Ethiopia, every pregnant woman is expected to receive ANC from a skilled provider. This includes a comprehensive physical examination, blood tests for screening of anaemia and infection, a urine test, tetanus toxoid injections, iron and folate supplements, and medications for deworming [4]. Community-based HEWs in their respective kebeles deliver the ANC service at health posts, which is part of the first level of primary health care unit. However, HEWs do not provide the services of blood pressure measurement, blood tests for screening of anaemia or infection (except for malaria), blood glucose level tests, and urine tests at the health posts. The HEWs do, however, also identify pregnant women in their catchment areas and link them to health centres and hospitals.

Several studies have examined the usefulness of ANC on the uptake of safe delivery care, and the reduction of maternal and infant mortality [7, 8]. An intervention study from southern Ethiopia showed that ANC is important to reduce maternal complications, maternal death, and neonatal deaths [9]. In Ethiopia, a national key indicator survey from 2016 reports that the ANC service utilization was 62% [8]. Moreover, only 20% of women had their first ANC during the first trimester. The proportion of women who had four ANC visits during their pregnancy was only 32% [10].

Studies from several countries have found that poor ANC attendance is an important risk factor for adverse pregnancy outcomes [11, 12]. As the number of ANC visits decreases, there was an increase in the risk of preterm birth and stillbirth [13–16]. Women who had no ANC follow-up and those who had an ANC visit less than four times during pregnancy were also found to have a low birth weight (LBW) baby [14, 17, 18].

Although the above studies report potential benefits of ANC on pregnancy outcomes, they possess several limitations. They were most often cross-sectional or retrospective studies or reports not published in peer-review journals. Covariates, such as wealth status, that may affect the outcome were not included in the analysis of these studies. In addition, scientific arguments on the association between ANC and pregnancy outcomes have continued and are unresolved. For instance, a review article on randomized trials and meta-analysis did not find any relationship between ANC follow-up and preterm birth [19–22].

The objective of this study was to assess the compliance of ANC utilization with national and WHO guidelines in rural south-central Ethiopia. In addition, we assessed if adverse pregnancy outcomes, including intrauterine foetal death, stillbirth, low birth weight and preterm birth, were associated with higher use of antenatal services.

Methods

Study design and settings

This cross sectional study was conducted in a rural community of south-central Ethiopia from July 2016 to November 2017. The data were gathered as part of a cohort study to monitor intrauterine growth and the association between intrauterine growth and linear growth of children [23, 24]. We assessed the compliance of ANC utilization with national [4] and WHO [6] guidelines, and examined the association between the utilization of antenatal health care services and adverse pregnancy outcomes. The present study is a part of a larger project on intrauterine growth and child growth in Ethiopia. Details of the methods of this study have been described elsewhere [23, 24].

This study was carried out in the Adami Tullu district in the East Shewa Zone of the Oromia Regional State in Ethiopia. In 2015, the projected population of the district was 177,390 people [25]. The livelihood of the majority of the population depends on subsistence agriculture or cattle-rearing, while some depend on fishing at a nearby lake, Lake Zeway [25].

There were 104 health extension workers (HEWs) in 43 health posts in the district in 2016. Based on the national Health Extension Program (HEP) that was launched in 2007, each of the 48 *kebeles* (lowest administrative level) in the district is intended to have at least one health post staffed by two female HEWs reporting to the health centre. The HEWs deliver key promotion and preventive health services through static and outreach programs. One of the services is family health care, which includes the promotion and provision of family health services, ANC, delivery services, postnatal care, family planning, and immunizations [26]. There was one public hospital, one non-governmental organization hospital, and 12 public health centres in the district in 2016. The health centre is primarily staffed by public health officers, nurses, midwives, pharmacists, and laboratory technicians.

Study population

We recruited pregnant women at less than 24 weeks of gestation from July 2016 to June 2017 from all pregnant women living in the study area. The study participants were followed during pregnancy until the time of delivery. The pregnant women were having routine ANC at the health facilities. During the scheduled visits, we measured blood pressure, height and weight of the pregnant women, performed haemoglobin tests, and followed intrauterine foetal growth using ultrasound at the study sites. This was a part of a project and was performed in addition to any examinations at the routine ANC.

Sample size estimation

We used the sample size calculated for another study on intrauterine foetal growth. The details of the sampling assumptions are described in detail elsewhere. In brief, a total sample size of 716 was calculated to estimate birth weight as an outcome measure [23].

In addition, we also tried to check the adequacy of the sample size for this specific paper. We estimated about 587 cases were required to detect difference in proportion of low birth weight among women who were attending ANC (13.2%) and those were not attending ANC (23.5%) [27].

Variables

Outcome variables

Antenatal care utilization was collected by interviewing each pregnant woman at each visit. For those who had attended antenatal care, they were asked to state the number of antenatal visits that they had attended. The pregnancy outcomes measured were low birth weight, preterm birth, intrauterine foetal death, and stillbirth.

Low birth weight was categorized as “yes” or “no”. “Yes” was defined as a birth weight < 2500 g, and “no” was defined as a birth weight > =2500 g, as they are defined by the WHO. Preterm birth was defined as delivery at a gestational age of less than 37 weeks [28]. Intrauterine foetal death was defined as a foetus with no signs of life in utero on ultrasound examination. Stillbirth was defined as a baby born with no signs of life, such as beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles [29]. Adverse pregnancy outcomes in the statistical analysis are a composite variable that summarizes low birth weight, preterm birth, intrauterine foetal death, and stillbirth. Adverse pregnancy outcome was categorized as “yes” or “no”; “yes” if there were any of the adverse pregnancy outcomes, and “no” if none of them were present.

Exposure variables

Antenatal care utilization was one of the exposure variables. ANC use was categorized as “yes” or “no”; “yes” if the woman attended ANC, and “no” if she did not attend ANC.

Maternal characteristics (i.e., age, occupation, wealth status, height, education, gravida, parity, haemoglobin, and systolic and diastolic blood pressure) were also obtained.

Data collection

Women in the reproductive age group were invited to participate in the study in selected kebeles by data collectors going house-to-house. Potential pregnancy was identified by using a pregnancy checklist [30] or as reported by the woman. Once pregnancy was suspected, the women were sent to a nearby health post or established study centre, where an ultrasound was performed to confirm the presence of pregnancy. All pregnant women with a gestational age of less than 24 weeks were invited to participate in the study. After the women had given written informed consent and were enrolled in the study, the pregnant women were given a card with an identification number and dates for three prescheduled consecutive visits at 26, 30, and 36 weeks of gestation at the data collection sites. More details are described in a previous publication [23].

Data at these three visits were mostly collected at health posts where routine ANC is provided. For those women who lived more than one kilometre away from the health post, a temporary station was established for the purpose of the study, in communication with the respective kebele managers. *Trained data collectors (nurses)* who were overseen by trained supervisors collected data on sociodemographic variables, past and present obstetric history, and health care service utilization. The supervisors, in addition, were communicating with respective authorities: woreda (district) health offices, kebele administrative offices, and HEWs at health posts. The HEWs were involved in facilitation of the data collection, as well. The pregnant women were advised to follow the routine ANC service provided during pregnancy at nearby health facilities. When any abnormal finding of the pregnant woman or the foetus was detected during data collection, they were referred to a nearby hospital.

A structured and pre-tested tool was used to collect data. The data were collected at enrolment and at each visit by 13 nurses whom we trained on data collection for the study. They conducted interviews, and took maternal and new-born anthropometric measurements. The nurses were given skill-based training on how to take anthropometric measurements prior to the data collection. The first author, who is a midwife and public health professional, was trained and performed the ultrasound examinations.

At enrolment, maternal anthropometric, obstetric, and sociodemographic data were collected. At the subsequent scheduled visits, we collected data on ANC utilization, pregnancy status, anthropometric measurements, blood pressure, ultrasound examinations, and haemoglobin measurements. At birth, we collected data on date of delivery, birth weight, and pregnancy outcome. We followed all of the study participants, except those loss to follow-up (3.2%), until delivery.

Antenatal care service utilization

We interviewed each pregnant woman at each visit, irrespective of whether or not she had been attending antenatal care. Information on antenatal care (ANC) service utilization was collected at the three periods of follow up during pregnancy. The three periods were during 24 to 28 weeks of gestation, 29 to 33 weeks of gestation, and 34 to 38 weeks of gestation. At each visit, we asked if she had attended ANC, the place of the ANC attendance, the iron and folic acid supplementation (IFAS) received there, and duration of IFAS. Information on the status of pregnancy and birth outcome were collected during pregnancy and at delivery. The nurse data collectors visited those pregnant women who were expected to deliver at home after 36 weeks of gestation regularly until they gave birth. We then compared these ANC utilizations with the national and WHO guidelines.

Measurement of pregnancy outcomes

Data on each outcome of pregnancy were collected by maternal interview, ultrasound assessment, and at delivery. The study was completed when the last enrolled pregnant woman delivered in November 2017. At birth, date of delivery and new-born birth weight were recorded by trained nurses within 72 hours after delivery, either at home or at a health care facility. Birth weights were measured using a digital infant weighing scale (Beurer Digital Baby Scale). Those pregnancies not ending in live birth and with no sign of life at birth were also recorded. Intrauterine deaths that occurred before birth were recorded during follow-up of the pregnancies.

We trained the data collectors (nurses) for 2 days, and the measurement techniques were standardized. To standardize the measurement techniques for maternal height, we checked the intra- and inter-tester technical errors of measurements (TEMs). We gave re-trainings until the measurement was within the recommended cut-off points [31]. For height, the intra-tester TEM was 0.38 cm, and the inter-tester TEM was 0.37 cm. We used a standard wooden board for the measurement of the height of each woman at enrolment.

Ultrasound measurements

At enrolment, we calculated gestational age and estimated date of delivery based on ultrasound measurement of biometric parameters, using the Hadlock et al. formula [32]. To estimate gestational age and expected date of delivery, we used early sonographic estimation of dating, as it is reliable when the estimation is done before 24 weeks of pregnancy [33]. The ultrasound machine that we used throughout the study was the same. The first author, who was trained by a senior obstetrician, performed all of the ultrasound examinations. Quality and accuracy of the measurements were validated. The details are presented in a previous study [23].

Statistical analysis

Data were entered and cleaned using SPSS version 24 (SPSS, Chicago, IL, U.S.A.). Then, they were exported to Stata software version 15 (Stata Corp., College Station, TX, U.S.A.) for further analysis. Descriptive statistics, frequency, percentage, mean, and standard deviation were computed.

In this study, the statistical methods used were for a cross-sectional study as we summarised the outcomes for the whole duration of the pregnancy. The outcome variables of low birth weight, gestational age at delivery, spontaneous abortion, intrauterine foetal deaths and stillbirth were assessed, and their proportion was calculated. The extent of ANC content received, timing of ANC, place of ANC, and place and mode of delivery were computed in accordance with the national and WHO guidelines. The frequency of ANC service utilization was the total visits each women had during the follow up.

Adverse pregnancy outcome, a composite variable, was computed as the sum of low birth weight, preterm birth, intrauterine foetal death, and stillbirth. Binary logistic regression analyses was used to identify the association of antenatal care service utilization on adverse pregnancy outcome. Crude odds ratio with 95% confidence interval (CI) was calculated. *P*-value < 0.05 was considered statistically significant.

Results

Description of the study population

There were 1054 self-reported pregnant women during the initial screening. From these, 727 met the criteria for inclusion in the study (Fig. 1). Eleven [11] of them were found to be not pregnant, and 316 of them were pregnant with more than 24 weeks of gestation, on ultrasound examination. Those women who left the study area, i.e., 23 (3.2%), before the follow-up period were excluded from the final analysis. We included 704 pregnant women who were enrolled prior to the 24th week of gestation in the final analysis (Fig. 1).

From the 704 pregnant women that we followed, 12 had a twin pregnancy, 11 had an abortion, two had an intrauterine foetal death, and four had congenital abnormalities. At delivery, three of the pregnancies ended in stillbirth. Birthweight was measured within 72 hours of delivery for 610 new-borns, and date of delivery was recorded for 630 new-borns. Four new-borns had a known date of delivery, but their birth weight was not measured within 72 hours of delivery. Sixteen [16] of the

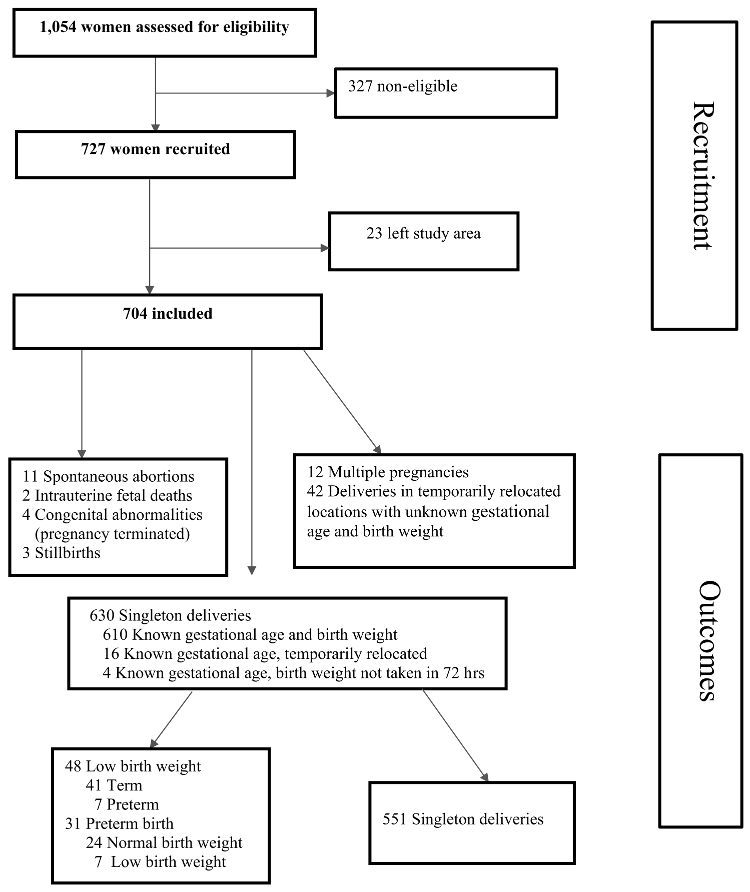


Fig. 1 Flowchart of study participants included in the recruitment and outcomes of the study

new-borns of pregnant women who were temporarily relocated for delivery to another place had a known date of delivery. Both date of delivery and birth weight were not known for 42 new-borns of the pregnant women who were temporarily relocated to another place for delivery. There were 48 low birth weight new-borns, among whom seven were preterm births. There were 31 preterm births, of whom 24 had a normal birth weight (Fig. 1).

Characteristics of study participants

Maternal characteristics

The mean age of the women studied was 25 years. Out of the 704 study participants, 317 (45.0%) could not read or write, and only 60 (8.5%) of them attended secondary education. Their wealth status in the three categories was almost the same: poor (230 (33.0%)), middle (237 (34.0%)), and rich (231 (33.0%)).

The mean (Standard Deviation (SD)) maternal height was 157.3 (6.4) cm. We found anaemia in 135 (19.4%) of the women during pregnancy. One (0.4%) of them had severe anaemia, 31 (4.4%) had moderate anaemia, and 103 (14.6%) had mild anaemia. The majority of the women (540 (76.7%)) were housewives in occupation. One hundred and forty-one (141 women; 20.0%) of them were prim-para, and 431 (61.2%) were multipara (Table 1).

Antenatal care utilization characteristics

Most of the women (536, 76.1%) had attended at least one ANC follow-up. From those who had been attending ANC, most (408, 77.1%) had two or more ANC follow-ups. Among the pregnant women who attended ANC, only 110 (20.7%) of them reported to have attended at a health post. From the study participants, 247 (35.1%) got IFAS during their pregnancy. The majority (143 57.9%)) of them took IFAS for 1 month. Twenty-four (24 (3.4%)) of the pregnant women reported having had a test for syphilis, and 202 (28.7%) of them reported having had a test for Human Immunodeficiency Virus (HIV). Three hundred and fifteen (315 (44.7%)) of the pregnant women reported having received a tetanus toxoid vaccination during the current pregnancy.

The proportion of women who attended antenatal care in all kebeles was similar, and there was no significant difference in attendance of antenatal care ($X^2 = 17.03$, P-value $= 0.149$) among the kebeles (Supplementary Table 1). Moreover, antenatal care utilization showed no significant difference among sociodemographic and obstetric characteristics of women (Supplementary Table 2). When asked about the intended place of delivery, 480 (76.2%) of the women's intention was a health care facility. However, only 293 (46.9%) of the women gave birth at a health care

Table 1 Maternal characteristics of study participants ($n = 704$) in the Adami Tullu district, 2018

Variable	Frequency (%)	Mean (SD)
Maternal characteristics		
Maternal age (yr)		25 (5)
< 20	107 (15.2)	
20–24	238 (33.8)	
25–34	312 (44.3)	
35 and above	47 (6.7)	
Educational level		
Illiterate	317 (45.0)	
Read and write	43 (6.1)	
Primary	284 (40.3)	
Secondary	60 (8.5)	
Occupation (type)		
Housewife	540 (76.7)	
Farmer	120(17.0)	
House maid	17 (2.4)	
Others	27 (3.9)	
Wealth status (index)		
Poor	230 (33.0)	
Middle	237 (34.0)	
Rich	231 (33.0)	
Maternal height (cm)		157 (6)
< 150	73 (10.5)	
150–159	371(53.2)	
160 and above	253 (36.3)	
Gravidae (number)		
1	113 (16.1)	
2	142 (20.2)	
3	103(16.1)	
4	78 (11.1)	
5 and above	268 (38.0)	
Parity (number)		
0	132 (18.8)	
1	141 (20.0)	
2	101 (14.3)	
3	76 (10.8)	
4	79 (11.2)	
5 and above	175 (24.9)	
Systolic blood pressure (mmHg)		101.7 (10.1)
>= 140	1(0.4)	
120–139	28 (4.0)	
< 120	675 (95.6)	
Diastolic blood pressure (mmHg)		66.7 (8.1)
>= 90	0 (0)	
80–89	41 (5.8)	
< 80	663 (94.2)	
Anaemia (haemoglobin in g/dl)		11.9 (1.1)
Severe (< 7 g/dl)	1 (0.4)	
Moderate (7–9.9 g/dl)	31 (4.4)	
Mild (10–10.9 g/dl)	103 (14.6)	
None (> 11 g/dl)	569 (80.8)	

facility. A significant discrepancy was found between their intention and actual place of delivery ($X^2 = 22.58$, $p = 0.001$). From those women who had an intention to deliver at a health facility, approximately 40% of them delivered at home. Only eight (1.3%) of the women delivered by caesarean section, while four (0.6%) had vacuum delivery. The mode of delivery in all of the rest (98.1%) was spontaneous vaginal delivery. During delivery, 235 (44.3%) of the women were assisted by traditional birth attendants (Table 2).

Pregnancy outcome characteristics

Six hundred and ten (610) new-borns were included for the birth weight estimation. The mean birth weight (SD) was 3214 (525) gm. Four hundred and thirteen (413 (67.7%)) had a birth weight of more than 3000 g. During the study period, we observed 48 (7.9%) low birth weight (LBW) (< 2500 g) infants and 31 (4.9%) preterm (< 37 weeks of gestation) births (Table 3). Seven (14.6%) of the LBW infants were preterm. Twenty-four [24] of the preterm births had a normal birth weight. Twelve (12 (1.7%)) of the pregnancies resulted in live born twins. From the pregnancies not ending in live birth, 11 (1.6%) terminated without any intervention before 28 weeks of pregnancy. There were three stillbirths, four congenital abnormalities, and two intrauterine foetal deaths.

From 48 low birth weight (LBW) new-borns, 12 of them had no ANC. Moreover, out of 31 pregnancies with preterm births, five of them did not have ANC. One of the three pregnancies that resulted in stillbirths had no ANC. Among women who had spontaneous terminations of pregnancy, nine of them had no ANC. Two of the pregnancies who had no sign of life during ultrasound assessment occurred among pregnant women who did not have ANC. In addition, two of the four pregnancies with congenital abnormalities had no ANC (Table 4). The pregnancies with congenital abnormalities were terminated after they were referred to a hospital.

Table 5 below shows the compliance of antenatal and delivery service utilization with national and WHO guidelines. In our study, we found that the average number of ANC visits was 2.5, which is less than that recommended by the national and WHO guidelines. Only 18 (2.6%) women attended ANC in their first trimester (<=12 weeks), while it is expected to be 100% according to the guidelines. As part of our study, we measured the

Table 2 Characteristics of antenatal care utilization (n = 704 pregnant women), Adami Tullu district, 2018

Variable	Frequency (%)
Antenatal care follow-up (at least one)	
Yes	536 (76.1)
No	168 (23.9)
Frequency of ANC (number)	
1	123 (22.9)
2	180 (33.6)
3	204 (38.1)
4	24 (4.5)
Place of ANC visit (type)	
Health post	110 (20.5)
Health centre and hospital	426 (79.5)
Iron and folic acid supplementation	
Yes	247 (35.1)
No	457(64.9)
Duration of iron and folic acid supplementation	
One month	143 (57.9)
Two or more months	104 (42.1)
Intended place of delivery	
Home	150 (23.8)
Health institution	480 (76.2)
Place of delivery (type)	
Home	333 (53.1)
Health institution	293 (46.9)
Mode of delivery (type)	
Spontaneous vaginal delivery	609 (98.1)
Assisted delivery	4 (0.6)
Caesarean Section	8 (1.3)
Assistant at birth (type)	
Traditional birth attendant	235 (44.3)
Health professional	269 (50.8)
Friends and/or relatives	19 (1.6)
The woman herself	7 (1.3)

Table 3 Pregnancy outcome characteristics among 704 women in the Adami Tullu district, 2018

Variable	Frequency	Mean (SD)
Birth weight (gm) (*n* = 610)		3214 (525.1)
< 2500	48 (7.9)	
2500–3000	149 (24.4)	
Above 3000	413 (67.7)	
Low birth weight		
Preterm	7 (14.6)	
Term	41 (85.4)	
Gestational age at birth (*n* = 630)		
< 37 weeks	31 (4.9)	
>= 37 weeks	599 (95.1)	
Preterm birth		
Low birth weight	7 (22.6)	
Normal birth weight	24 (77.4)	
Twin pregnancy (*n* = 704)	12 (1.7%)	
Stillbirth (*n* = 658)	3 (0.4%)	

Table 4 Adverse pregnancy outcomes and antenatal care utilization in the Adami Tullu district, 2018

Adverse pregnancy outcomes	Antenatal care use	
	Yes	No
Low birth weight		
No	436	126
Yes	36	12
Preterm birth		
No	462	137
Yes	26	5
Intrauterine foetal death	0	2
No	536	166
Yes	0	2
Stillbirth	2	1
No	534	167
Yes	2	1

blood pressure of all pregnant women at each visit and tested them for malaria infection. The guidelines recommend routine measurement of blood pressure for pregnant women at each visit. We did not have information on the actual practices at the health facilities during the study period. Similarly, we did not collect malaria test practices at the health facility level.

According to the study participants' report, a tetanus toxoid vaccine was given to approximately 45%, an HIV test was done for 29%, and a syphilis test was done for only 3.4% of the women. Iron folate was supplemented for 35% of the women. Even though gestational age is routinely estimated by measuring fundal height using a tape measure, as an ultrasound is not available at the health centres, it was not assessed either in the current study or at the health facilities where routine ANC service is provided. Less than half (47%) of the women delivered in a health facility, in contrast to the 100% expected health institution delivery based on the guidelines. In this study, the number of stillbirths that we found was three (0.4%). It was also shown that assisted delivery (0.6%) and caesarean section delivery (1.3%) were lower than the expected proportion in the national and WHO guidelines [4, 6].

The association between adverse pregnancy outcome and antenatal care service utilization with other explanatory variables is shown in Supplementary Table 3 In this study, adverse pregnancy outcome had no significant association with antenatal care utilization (COR = 1.07, 95% CI 0.62, 1.86, $P = 0.806$).

Discussion

In this study, the compliance of ANC utilization with national and WHO guidelines was low. It was also found that the current focused ANC utilization did not have an association with adverse pregnancy outcome.

Our results show that the average number of ANC visits in our study was very low (2.5). Only 32% of the pregnant women fulfilled the WHO minimum number of four or more ANC visits. This is lower than the global low and middle income countries (LMIC) proportion of 55% and a report from Myanmar of 59%

Table 5 Compliance of ANC and delivery services utilization in comparison with guidelines, Adami Tullu district, 2018

Health service/outcome		Current study (%)	2021 national Ethiopian guidelines (%)	WHO guidelines 2016 (%)
Antenatal care services	No ANC	23.9		
	Number of visits (mean)	2.5	8	8
	BP measurement	100	100	100
	Iron folate supplementation	35	100	100
	TT vaccination[a]	44.7	100	100
	Syphilis test[a]	3.4	100	100
	HIV test[a]	28.7	100	100
Antenatal care done	First trimester	2.60	100	100
	Second trimester	30.90	100	100
	Third trimester	64.10	100	100
Place of antenatal care	Health centre and hospital	79.50	100	100
	Health post	20.50	0	0
Place of delivery	Institutional delivery	47	100	100
	Home delivery	53	0	0

[a] Reported by mothers, *BP* Blood Pressure, *TT* Tetanus Toxoid

[34–36]. Those women who initiated ANC during the first trimester were also very low (2.6%) compared to other LMIC, such as Myanmar (47%) [34, 36], and the WHO guideline that expects all pregnant women to start ANC follow-up during the first trimester [2]. More than half (53%) of the women gave birth at home, and 44% of all births were attended by traditional birth attendants.

Most of the pregnant women (76.1%) in our study had attended at least one ANC follow-up, while the number of women with a third and fourth ANC follow-up, which are very important in detecting early signs of complications, was alarmingly low. This is consistent with Ethiopian Demographic and Health Survey 2016, which reported that ANC service utilization was 62%, and the proportion of women who had four ANC visits during their pregnancy was only 32% [10]. However, it is lower than reports from Sub-Saharan Africa, where approximately 80% of pregnant women attended at least one ANC visit, and 52% of pregnant women received the recommended number of four antenatal care visits [37]. The low rate of the fourth ANC follow-up is usually common in studies undertaken in Ethiopia. Women may not be able to attend subsequent follow-ups because of distance, low level of education, and/or poor wealth index [38–40]. This was also documented in studies from other low-income countries [41–44].

The Ethiopian health system delivers primary health care through health centres and their satellite health posts at the community level, and the services are provided free-of-charge. However, in this study, we found that only 21% of the women used ANC services from health posts which were in their vicinity. A previous study from Ethiopia also supports this fact, in which health-care-seeking from health posts was very low, and health centres were preferred over health posts for ANC service by pregnant women [45]. This may be related to the low quality of the services provided and the low trust of women regarding the expertise of the service providers (Health Extension Workers (HEWs)) at the health posts. According to data from a service availability and readiness assessment in 2016, the availability of items for basic facilities, infection prevention, malaria diagnosis, and essential medicines at health posts was low. The general services readiness index at the health post level was 46% [46]. Studies on women's experiences and satisfaction found that pregnant women's trust in the skill and competency of HEWs to handle maternal health services was low [47, 48].

In this study, all adverse outcomes were merged, including preterm, intrauterine foetal death and stillbirth, as each of the numbers was small. As a consequence, these findings should be interpreted with caution, as they are not referring to a single adverse outcome. We did not find a significant difference between those mothers who visited health facilities for ANC and those mothers who did not have an ANC follow-up with regard to adverse pregnancy outcome. This is in contrast to other studies [49, 50], which found an association between ANC utilization and pregnancy outcomes. However, other studies have not summarized the adverse outcomes in the same manner as in the present study, and the previous studies have higher numbers of adverse outcomes [51]. One possible explanation for the absence of association between ANC follow-up and pregnancy outcomes could be the low number of ANC follow-ups in the focused or "reduced" ANC model. Only 4.5% of the pregnant women in our study had four ANC visits, while the rest either did not have an ANC follow-up or had less than four ANC follow-ups. Evidence shows that the "standard" ANC model (attending at least eight ANC visits) offers better pregnancy outcomes and a higher likelihood of receiving helpful maternal health interventions when compared to the "focused (reduced) visit" model [52].

Another explanation could be inadequacy in the content and quality of ANC service provided to the pregnant women. A study done on the relationship between ANC and preterm birth reported a significant association between preterm birth and the content and timing of care [53]. Previous literature on the quality of ANC service in public health facilities of Ethiopia showed that the proportion of pregnant women who received adequate ANC content was low [54–56]. They found that a large proportion of the pregnant women missed opportunities to receive blood pressure or weight measurement, and iron/folic acid supplementation. One of the studies also reported poor adherence of the health professionals to the FANC protocol [54].

The proportion of stillbirths in our study (0.4%) was very low compared to previous studies in Ethiopia that reported the proportion of stillbirths to be approximately 4% [55, 57]. The low proportion in our study could be due to under reporting, as there were pregnant women who left the study area for whom the outcome of the pregnancy was not known.

Strengths and limitations of the study

This study is the first community-based study that followed pregnant women from 24 weeks of gestation up to delivery that was conducted to examine the compliance of antenatal care utilization with national and WHO guidelines, and the association of antenatal health care utilization with adverse pregnancy outcomes in Ethiopia. This contributes to increased knowledge about the implications of antenatal health service utilisation. The second major contribution is the availability of population-based information on prenatal, social, and demographic characteristics collected using maternal interviews and foetal ultrasound during pregnancy.

Our study also has certain limitations. The information collected on ANC service utilization was what was reported by the women. We did not cross check their responses with the medical records. This may introduce misclassification bias. The proportion of women who had one ANC in our study (76.1%) is higher than the national ANC attendance (62%). In addition, the loss to follow up in our study is small (3.2%). The fact that we screened women at home, invited them to enter the study, and advised them to have an ultrasound scan may introduce exposure or intervention bias. That may have contributed to the higher ANC attendance and lower loss to follow up in our study. There are also no reports of diabetes mellitus, HIV, and syphilis that might be potentially contribute for adverse pregnancy outcomes in the study participants. This may affect the generalizability of the findings to a maternal population with a different medical background. Moreover, we did not assess some of the basic indicators of ANC service content and quality, such as nutrition counselling, deworming, and screening for infections that may have an influence on the adverse pregnancy outcomes.

Conclusions

In conclusion, we found that ANC service utilization is low in the context of national and WHO guidelines. In addition, we did not find any association between the current focused antenatal health care service and adverse pregnancy outcomes.

Abbreviations

ANC: Antenatal care; BP: Blood Pressure; CI: Confidence interval; COR: Crude Odds Ratio; FANC: Focused Antenatal care; gm: Gram; HEP: Health Extension Program; HEW: Health Extension Workers; HIV: Human Immunodeficiency Virus; IFAS: Iron and folic acid supplementation; LBW: Low birth weight; LMIC: Low and Middle Income Countries; SD: Standard Deviation; TEM: Technical errors of measurement; TT: Tetanus Toxoid; WHO: World Health Organization; X^2 : Chi square.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12884-022-05171-3.

Additional file 1: Supplementary Table 1. Antenatal care utilization by study villages (kebele) in Adami Tullu district, 2018. **Supplementary Table 2.** Antenatal care utilization by sociodemographic characteristics in Adami Tullu district, 2018. **Supplementary Table 3.** Binary logistic regression for ANC utilization with adverse pregnancy outcome ($n = 704$), Adami Tullu district, 2018.

Acknowledgements

Our gratitude goes to all the women who participated in this study. We would also like to thank the data collectors and supervisors involved in this study. We are grateful to the Obstetricians who provided training of ultrasound and validated the ultrasound measurements. Our appreciation also goes to Addis Ababa University and the University of Bergen for their support.

Authors' contributions

MR conceived the study, participated in the design, data collection, and coordination of the study, performed the statistical analyses, wrote the original draft manuscript, reviewed and edited the manuscript. WD participated in the design and coordination of the study, contributed to the statistical analyses, and reviewed and edited the manuscript. BL participated in conceiving the study, participated in the design, and coordination of the study, contributed to the statistical analyses, reviewed and edited the manuscript. All authors gave full approval of the version to be published.

Funding

This study was funded by the University of Bergen in Norway and the Research Council of Norway (project number: 220554). The funding sources for this study had no role in the design, data collection and analysis, interpretation of the results, writing of the report or decision to publish.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of the College of Health Sciences at Addis Ababa University (Ref: 005/15/SPH). The Regional Committee for Medical and Health Research Ethics in Western Norway also approved the study protocol (Ref: 2013/986/REK Vest). We also obtained written permission to perform this study from the Oromia Regional Health Bureau and respective offices in the East Shewa Zone. We explained the purpose of the study to the study participants using a standard information sheet in their own language. We explained that participation was voluntary, and that the study participants could withdraw at any time during the study. We also guaranteed them that their refusal to participate in the study would not affect their access or utilization of the health service. This information was read to them, and the written informed consent of the study participants was obtained at entry. When we identified pregnant women who had indication(s) for treatment, we informed them of any abnormality or deviation, and referred them to a nearby hospital. We kept the collected information confidential. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable.

Competing interests

The authors declare that there are no competing interests.

Author details

[1]Centre for International Health, University of Bergen, Bergen, Norway. [2]Department of Reproductive Health and Health Service Management, School of Public Health, College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia. [3]Department of Preventive Medicine, School of Public Health, College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia.

Received: 23 August 2022 Accepted: 31 October 2022
Published online: 17 November 2022

References

1. World Health Organization. Pregnancy, childbirth, postpartum and newborn care: a guide for essential practice. Geneva: World Health Organization; 2009.
2. Tunçalp Ö, Pena-Rosas J, Lawrie T, Bucagu M, Oladapo O, Portela A, et al. WHO recommendations on antenatal care for a positive pregnancy experience—going beyond survival. BJOG. 2017;124(6):860–2.

3. CSA. *Ethiopia* demographic and health survey: Addis Ababa; 2016.
4. Ministry of Health. National Antenatal Care: ensuring positive pregnancy Experiance: Addis Ababa; 2021.
5. Federal Ministry of Health. Health sector transformation plan II: 2020/21–2024/25. Available: https://e-library.moh.gov.et/library/wp-content/uploads/2021/07/HSTP-II.pdf. 2021.
6. World Health Organization. WHO recommendations on antenatal care for a positive pregnancy experience. 2016.
7. Carroli G, Rooney C, Villar J. How effective is antenatal care in preventing maternal mortality and serious morbidity? An overview of the evidence. Paediatr Perinat Epidemiol. 2001;15(Suppl 1):1–42.
8. Owolabi OO, Wong KLM, Dennis ML, et!al. Comparing the use and content of antenatal care in adolescent and older !Rst- time mothers in 13 countries of West Africa: a cross- sectional analysis of demographic and health surveys. Lancet child Adolesc. Health. 2017;1:203–12.
9. Lindtjørn B, Mitiku D, Zidda Z, Yaya Y. Reducing maternal deaths in Ethiopia: results of an intervention Programme in south West Ethiopia. PLoS One. 2017;12(1):e0169304.
10. Central Statistical Agency (CSA) [Ethiopia], and ICF International. Ethiopia Demographic and Health Survey. Key indicators report: Addis Ababa, Ethiopia, and Rockville, Maryland. USA: CSA andICF; 2016. p. 2016.
11. Blondel B, Dutilh P, Delour M, S. U. Poor antenatal care and pregnancy outcome. Eur J Obstet Gynecol Reprod Biol. 1993;50(3):191–6.
12. Blondel B, Marshall B. Poor antenatal care in 20 French districts: risk factors and pregnancy outcome. J Epidemiol Community Health. 1998;52:501–6.
13. Debiec KE, Paul KJ, Mitchell CM, Hitti JE. Inadequate prenatal care and risk of preterm delivery among adolescents: a retrospective study over 10 years. Am J Obstet Gynecol. 2010;203:122.
14. Bater J, Lauer JM, Ghosh S, Webb P, Agaba E, Bashaasha B, et al. Predictors of low birth weight and preterm birth in rural Uganda: findings from a birth cohort study. PLoS One. 2020;15(7):e0235626-e.
15. Pervin J, Rahman SM, Rahman M, Aktar S, Rahman A. Association between antenatal care visit and preterm birth: a cohort study in rural Bangladesh. BMJ Open. 2020;10:e036699.
16. Partridge S, Balayla J, Holcroft CA, Abenhaim HA. Inadequate prenatal care utilization and risks of infant mortality and poor birth outcome: a retrospective analysis of 28,729,765 U.S. deliveries over 8 years. Am J Perinatol. 2012;29(10):787–93.
17. Acharya D, Singh JK, Kadel R, Yoo S-J, Park J-H, Lee K. Maternal factors and utilization of the Antenatal care services during pregnancy associated with low birth weight in rural Nepal: analyses of the Antenatal care and BirthWeight records of the MATRI-SUMAN trial. Int J Environ Res Public Health. 2018;15:1–4.
18. Zhou H, Wang A, Huang X, Guo S, Yang Y, Martin K, et al. Quality antenatal care protects against low birth weight in 42 poor counties of Western China. PLoS One. 2019;14(1):e0210393.
19. Fiscella K. Does prenatal care improve birth outcomes? A critical review. Obstet Gynecol. 1995;85:468–79.
20. Goldenberg RL, Rouse DJ. Prevention of premature birth. N Engl J Med. 1998;339:313–20.
21. Kramer MS. Determinants of low birth weight: methodological assessment and meta-analysis. Bull World Health Organ. 1987;65(5):663–737.
22. McDuffie RS Jr, Beck A, Bischoff K, Cross J, Orleans M. Effect of frequency of prenatal care visits on perinatal outcome among low-risk women: a randomized controlled trial. JAMA. 1996;275(11):847–51.
23. Roro M, Deressa W, Lindtjørn B. Intrauterine growth patterns in rural Ethiopia compared with WHO and INTERGROWTH-21st growth standards: a community-based longitudinal study. PLoS One. 2019;14(12):1–15.
24. Roro M, Deressa W, Lindtjørn B. Influence of intrauterine factors on birth weight and on child linear growth in rural Ethiopia: a prospective cohort study. PLoS One. 2022;17(8):1–16.
25. CSA. *Ethiopia*n population and housing census. Addis Ababa: Central Statistical gency; 2007.
26. Sebhatu A. Ethiopia good practice – the implementation of Ethiopia's health extension program: an overview: Addis Ababa; 2008.
27. Endalamaw A, Engeda E, Ekubagewargies D, Belay G, Tefera M. Low birth weight and its associated factors in Ethiopia: a systematic review and meta-analysis. Ital J Pediatr. 2018;44:141.
28. World Health Organization. Recommended definitions, terminology and format for statistical tables related to the perinatal period and use of a new certificate for cause of perinatal deaths, modifications recommended by FIGO as amended October 14, 1976. Acta Obstet Gynecol Scand. 1977;56:247–53.
29. Confidential enquiry into maternal and child health (CEMACH). Perinatal mortality 2007. London: United Kingdom,CEMACH; 2009.
30. World Health Organization. Medical eligibility criteria for contraceptive use. 4 ed, 2010.
31. World Health Organization. Reliability of anthropometric in the WHO multicentre growth reference study. Acta Paediatr. 2006;450:38–46.
32. Hadlock FP, Deter RL, Harrist RB, Park SK. Estimating fetal age: computer-assisted analysis of multiple fetal growth parameters. Radiology. 1984;152(2):497–501.
33. Verburg BO, Steegers EA, De Ridder M, Snijders RJ, Smith E, Hofman A, et al. New charts for ultrasound dating of pregnancy and assessment of fetal growth: longitudinal data from a population-based cohort study. Ultrasound Obstet Gynecol. 2008;31(4):388–96.
34. World Health Organization. World health statistics 2016: monitoring health for the SDGs, sustainable development goals. Switzerland; 2016.
35. World health Organization, and International Center for Equity in health/Pelotas. State of inequality: reproductive, maternal, newborn and child health. Geneva; 2015.
36. Mugo NS, Mya KS, Raynes-Greenow C. Country compliance with WHOrecommended antenatal care guidelines: equity analysis of the 2015–2016 demography and health survey in Myanmar. BMJ Glob Health. 2020;5:e002169.
37. UNICEF. Global databases based on multiple indicator cluster surveys and demographic and health survey. 2017.
38. Tiruneh GT, Demissie M, Worku A, Berhane Y. Predictors of maternal and newborn health service utilization across the continuum of care in Ethiopia: a multilevel analysis. PLoS One. 2022;17(2):e0264612.
39. Tekelab T, Chojenta C, Smith R, Loxton D. Factors affecting utilization of antenatal care in Ethiopia: a systematic review and meta-analysis. PLoS One. 2019;14(4):e0214848.
40. Muluneh AG, Kassa GM, Alemayehu GA, Merid MW. High dropout rate from maternity continuum of care after antenatal care booking and its associated factors among reproductive age women in Ethiopia, Evidence from Demographic and Health Survey 2016. PLoS One. 2020;15(6):e0234741.
41. Kuhnt J, Vollmer S. Antenatal care services and its implications for vital and health outcomes of children: evidence from 193 surveys in 69 low-income and middle-income countries. BMJ Open. 2017;7(11):e017122.
42. Campbell OMR, Calvert C, Testa A, Strehlow M, Benova L, Keyes E, et al. The scale, scope, coverage, and capability of childbirth care. Lancet. 2016;388(10056):2193–208.
43. Wang W, Alva S, Wang S, Fort A. Levels and trends in the use of maternal health Services in Developing Countries. Maryland: ICF Macro; 2011.
44. Rosário EVN, Gomes MC, Brito M, Costa D. Determinants of maternal health care and birth outcome in the Dande health and demographic surveillance system area, Angola. PLoS One. 2019;14(8):e0221280.
45. Medhanyie A, Spigt M, Kifle Y, Schaay N, Sanders D, Blanco R, et al. The role of health extension workers in improving utilization of maternal health services in rural areas in Ethiopia: a cross sectional study. BMC Health Serv Res. 2012;12:352.
46. Ethiopian Public Health Institute (EPHI). Ethiopian Service Availability and Readiness Assessment 2016 Summary Report. Available from https://www.washinhcf.org/ Addis Ababa, Ethiopia: EPHI; 2017.
47. Birhanu Z, Godesso A, Kebede Y, Gerbaba M. Mothers' experiences and satisfactions with health extension program in Jimma zone, Ethiopia: a cross sectional study. BMC Health Serv Res. 2013;13:74.
48. Mergia M, Shegaze M, Ayele G, Andarge E, Yeshitila YG, Wassihun B, et al. Mothers' satisfaction with health extension services and the associated factors in Gamo Goffa zone, southern Ethiopia. PLoS One. 2020;15(5):74.
49. Tadesse ZT, Sisay KT, Birhanu AT, Antehunegn GT. Prevalence of low birth weight and its associated factor at birth in sub-Saharan Africa: a generalized linear mixed model. PLoS One. 2021;16(3):e0248417.
50. Tshotetsi L, Dzikiti L, Hajison P, Feresu S. Maternal factors contributing to low birth weight deliveries in Tshwane District, South Africa. PLoS One. 2019;14(3):e0213058.
51. Andemel N, Gaoussou S, Barry A, et al. Adverse pregnancy outcomes among women presenting at antenatal clinics in Ouélességougou, Mali. BMC Reprod Health. 2020;17:39.

52. Organization WH. International statistical classification of diseases and related health problems, tenth revision. 2nd ed: World Health Organization; 2004.
53. Beeckman K, Louckx F, Downe S, Putman K. The relationship between antenatal care and preterm birth: the importance of content of care. Eur J Public Health. 2012;23(3):366–71.
54. Tafere ET, Afework MF, Yalew AW. Antenatal care service quality increases the odds of utilizing institutional delivery in Bahir Dar city administration, North Western Ethiopia: a prospective follow up study. PLoS One. 2018;13(2):e0192428.
55. Shiferaw K, Mengistie B, Gobena T, Dheresa M, Assefa SA. Extent of received Antenatal care components in Ethiopia: a community-based panel study international journal of Women's. Health. 2021;13:803–13.
56. Ejigu T, Woldie M, Kifle Y. Quality of antenatal care services at public health facilities of Bahir-Dar special zone, Northwest Ethiopia. BMC Health Serv Res. 2013;13:443.
57. Girma M, Yaya Y, Gebrehanna E, Berhane Y, Lindtjørn B. Lifesaving emergency obstetric services are inadequate in south-West Ethiopia: a formidable challenge to reducing maternal mortality in Ethiopia. BMC Health Serv Res. 2013;13:459.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Supplementary Table 1. Antenatal care utilization by study villages (kebele) in Adami Tullu district, 2018.

Kebele	ANC followup		Total
	No (%)	Yes (%)	
Wolin Bula	5 (19.2)	21(80.8)	26
Negalegn	3 (12.5)	21(87.5)	24
Ilka Chelemo	13 (7.8)	60 (82.2)	73
Edo Gojola	14 (28.0)	36 (72.0)	50
Abine Geremama	15 (23.8)	48 (76.2)	63
Qamo Garbi	2 (12.5)	14 (87.5)	16
Garbi Widena Boramo	4 (28.6)	10 (71.4)	14
Halaku	3 (14.3)	18 (85.7)	21
Anano Shisho	15 (18.5)	66 (81.5)	81
Golba Aluto	11 (17.7)	51 (82.3)	62
Dodicha	13 (24.1)	41 (75.9)	54
Boccessa	24 (34.8)	45 (65.2)	69
Abayi Deneba	46 (30.5)	105 69.5)	151
Total	168 (23.9)	536 (76.1)	704

Supplementary Table 2. Antenatal care utilization by sociodemographic characteristics in Adami Tullu district, 2018.

Variable	Yes (n (%))	No (n (%))	X^2 (P-value)
Age			3.150 (0.369)
<20	76 (71.0)	31 (29.0)	
20-24	184 (77.3)	54 (22.7)	
25-34	243 (77.9)	69 (22.1)	
35 and above	33 (70.2)	14 (29.8)	
Parity			1.429 (0.489)
Nullpara	101 (76.5)	31 (23.5)	
Primipara	102 (72.3)	39 (27.7)	
Mutipara	333 (77.3)	98 (22.7)	
Educational status			1.814 (0.612)
Illiterate	238 (75.1)	79 (24.9)	
Read and write	32 (74.4)	11 (25.6)	
Primary	223 (78.5)	61 (21.5)	
Secondary	43 (71.7)	17 (28.3)	
Occupation			3.474 (0.324)
Housewife	411 (76.1)	129 (23.9)	
Farmer	95 (79.2)	25 (20.8)	
Housemaid	10 (58.8)	7 (41.2)	
Others	125 (76.2)	39 (23.8)	
Wealth status			1.969 (0.374)
Poor	170(32.0)	60 (35.9)	
Middle	178 (33.5)	59 (35.3)	
Rich	183 (34.5)	48 (28.7)	
Intended place of delivery			2.578 (0.108)
Home	110 (72.8)	41 (27.2)	
Health institution	382 (79.1)	101 (20.9	
Place of delivery			0.010 (0.921)
Home	261 (77.4)	76 (22.6)	
Health institution	231 (77.8)	66 (22.2)	

Supplementary Table 3. Binary logistic regression for ANC utilization with adverse pregnancy outcome (n=704), Adami Tullu district, 2018.

		Adverse pregnancy outcome			
Characteristics		**Yes**	**No**	**Crude OR**	***P*-value**
Age					
	< 24 yrs	30	272	1	
	>= 24 yrs	46	356	1.17 (0.72, 1.91)	0.523
Educational status					
	No formal	33	327	0.71 (0.44, 1.14)	0.156
	Formal	43	301	1	
Occupation					
	Housewife	60	480	1.16 (0.65, 2.07)	0.625
	Others	16	148	1	
Gravida					
	Primi gravida	15	98	1	
	Multigravida	61	530	0.75 (0.41, 1.38)	0.335
Parity					
	Null para	18	114	1	
	Multipara	58	514	1.39 (0.79, 2.46)	0.245
DBP					
	80-89	6	35	0.69 (0.28, 1.69)	0.417
	<80	70	593	1	
Maternal haemoglobin					
	<=10.99	16	119	1	
	>=11	60	509	1.14 (0.64, 2.05)	0.660
Maternal height					
	<150	12	61	0.57 (0.29, 1.12)	0.102
	>=150	63	561	1	
Wealth status					
	Poor	23	207	0.84 (0.47,1 .51)	0.560
	Middle	25	212	0.89 (0.50, 1.59)	0.690
	Rich	27	204	1	
ANC utilization					
	Yes	57	479	1	
	No	19	149	1.07 (0.62,1.86)	0.806

Appendix II: Ethical Approvals

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK vest	Anne Berit Kolmannskog	55978497	11.08.2016	2013/986/REK vest
			Deres dato:	**Deres referanse:**
			04.08.2016	

Vår referanse må oppgis ved alle henvendelser

Bernt Lindtjørn
Universitetet i Bergen

2013/986 Vil en kombinasjon av myggnett og innendørs sprøyting med insektmidler bedre forebyggelsen av malaria i Etiopia?

Body responsible for the research: Universitetet i Bergen
Project Manager: Bernt Lindtjørn

With reference to your application dated 04.08.2016 about the above mentioned project. The application has been processed by Committee leader of REC Western Norway in accordance to the Health Research Act § 11. Committee leader of REC Western Norway reviewed the application.

Change to the project
A new amendment is added to the main project. The main objective of this Phd study is to determine the burden of malaria and its effect on pregnancy and foetal outcome among pregnant women in AdamiTullu district. The PhD candidate is Meselech Roro.

The new project
A cohort of pregnant women will be enrolled and followed until the first three days of postpartum period. Pregnancy will be confirmed by ultrasound assessment. Data will be collected using standardized data forms and questionnaires, ultrasound and specimens. As part of the MalTrials project the women will be visited every week and assess if they have malaria. Three ultrasound examinations will be conducted if possible, one during each trimester, to estimate gestational age and intrauterine growth of the foetus.

Risk and benefits
According to the protocol there are minimal risk when participating in the study. "Women with symptoms or sign of malaria will be treated immediately; those pregnant women requiring hospital admission will be referred to hospital for treatment. Any abnormalities identified during pregnancy (maternal or fetal) will be referred to the nearest health facilities for further investigation and management. All participants will receive information on care and services provided for pregnant women. Women with underweight and preterm baby will be given an advices and will be referred to the nearest health facility for treatment."

Review
REC Western Norway has no objections to the new amendment presented. We find the proposed study sound and well prepared.

Decision
REC Western Norway approves the project change in accordance with the submitted application.

Appeal

The Project Manager may appeal the committee's decision, see the Administration Act § 28. The appeal must be sent to the REC Western Norway within three weeks of receiving this letter. If the decision is upheld by REC Western Norway, the appeal will be forwarded to the National Research Ethics Committee for Medical and Health Research for a final assessment.

Yours Sincerely

Ansgar Berg
Prof. Dr.med
Head of Committee

Anne Berit Kolmannskog
executive officer

Kopi til: *postmottak@uib.no*

ANNEX 3

Form AAUMF 03-008

IRB's Decision

Meeting No: 003/2015 Date: May, 2015

Protocol number: 005/15/SpH Assigned No..................

Protocol Title: Malaria in pregnancy : a cohort study in Ethiopia	
Principal Investigators:	Meselech Assegid
Institute:	SPH-CHS-AAU
Elements Reviewed (AAUMF 01-008)	☑ Attached ☐ Not attached
Review of Revised Application ☐ Yes ☐ No	Date of Previous review:
Decision of the meeting:	☑ **Approved** ☐ Approved with Recommendation ☐ Resubmission ☐ Disapproved

I. Elements approved-
1. Protocol Version No. ...2..................................
2. Protocol Version Date....................................
3. Informed consent Version No. ...2........................
4. Informed Consent Version Date ....

II. Obligations of the PI-
1. Should comply with the standard international & national scientific and ethical guidelines
2. All amendments and changes made in protocol and consent form needs IRB approval
3. The PI should report SAE within 10 days of the event
4. End of the study, including manuscripts and thesis works should be reported to the IRB

III. TO NERC ☐

Institution Review Board (IRB) Approval: Period from June 2, 2015 to June 1, 2016

Follow up report expected in

3 Months ___ 6 months ___ 9 months_______one year_√___

Chairperson, IRB ዲ.ስ አበባ ዩኒቨርሲቲ

Dr. Yimtubezinash Woldeamanuel

Signature ____

Date: 26/0_/_

Institutional Review Board Office (IRB) Faculty of Medicine ADDIS ABABA UNIVE...

Graphic design: Communication Division, UIB / Print: Skipnes Kommunikasjon AS

UNIVERSITAS BERGENSIS

uib.no

ISBN: 9788230866313 (print)
9788230852675 (PDF)