UNIVERSITY OF NAIROBI

THYROID FUNCTION AMONG PREGNANT WOMEN ATTENDING ANTENATAL CLINIC AT THE KENYATTA NATIONAL HOSPITAL

PRINCIPAL INVESTIGATOR:

DR PRISCA ANYANGO MUNGLA

H58/74616/2014

A RESEARCH FOR THE PARTIAL FULFILMENT OF A MASTER OF MEDICINE IN CLINICAL MEDICINE AND THERAPEUTICS, UNIVERSITY OF NAIROBI

2017
DECLARATION

STUDENTS DECLARATION

This study is my original work and has not been presented for any academic purpose in any other University.

Signature………………………………………….    Date……………………………………………….

DR PRISCA MUNGLA

H58/74616/2014

Department of Clinical medicine and Therapeutics, Internal Medicine

School of Medicine

University of Nairobi
UNIVERSITY OF NAIROBI
DECLARATION OF ORIGINALITY

Name of the student  Dr. Prisca Anyango Mungla
Registration Number  H58/74616/2014
College  College of Health Sciences
School  School of Medicine
Department  Clinical Medicine and Therapeutics
Course name  Masters of Medicine in Internal Medicine
Title of the work  Prevalence of thyroid function among pregnant women attending antenatal clinic at Kenyatta National Hospital

DECLARATION

I understand what plagiarism is and I am aware of the University’s policy in this regard.

I declare that this dissertation is my original work and has not been submitted elsewhere for examination, award of a degree or application. Where other people’s work or my own work has been used, this has properly been acknowledged and referenced in accordance with University of Nairobi’s requirements.

I have not sought or used the services of any professional agencies to produce this work.

I have not allowed, and shall not allow anyone to copy my work with the intention of passing it off as his/her own work.

I understand that any false claim in respect of this work shall result in disciplinary action, in accordance with University plagiarism policy.

Signature  ……………………… Date………………………………..
SUPERVISORS’ DECLARATION

This study has been presented with our full approval as supervisors

PROFESSOR ARTHUR OBEL
MD, MBChB, MRCP (U.K), PhD (LONDON), ENDOCRINOLOGIST (UON)

SIGNATURE………………………………………… DATE……………………………………

DR JOHN ONG’ECH
MBChB, M.MED, MPH, HONORARY LECTURER, UON, SCHOOL OF MEDICINE
CHIEF MEDICAL SPECIALIST OBSTETRICS & GYNEAECOLOGY AT KNH

SIGNATURE………………………………………… DATE……………………………………

PROFESSOR MARK JOSHI
MBChB, M.MED, MPH, FACC
CARDIOLOGIST (UON)

SIGNATURE………………………………………… DATE……………………………………

PROFESSOR ANGELA AMAYO
MBChB, M.MED, DEPARTMENT OF CLINICAL CHEMISTRY (UON)

SIGNATURE………………………………………… DATE……………………………………
## Table of Contents

DEDICATION

ACKNOWLEDGEMENT

LIST OF ABBREVIATIONS

LIST OF TABLES

ABSTRACT

CHAPTER 1. INTRODUCTION

CHAPTER 2. LITERATURE REVIEW

2.1 Background

2.2 Universal versus targeted screening of thyroid function in pregnancy

2.3 Thyroid hormone reference levels in pregnancy

2.4 Thyroid function in pregnancy and foetal growth

CHAPTER 3. JUSTIFICATION

CHAPTER 4. RESEARCH QUESTION AND OBJECTIVES

4.1 RESEARCH QUESTION

4.2 OBJECTIVES

4.2.1 BROAD OBJECTIVE

4.2.2 SPECIFIC OBJECTIVES

4.2.2.1 PRIMARY

4.2.2.2 SECONDARY

CHAPTER 5. METHODOLOGY

5.1 Study Design

5.2 Study Area

5.3 Study Population

5.4 Case Definitions

5.5 Inclusion Criteria

5.6 Exclusion Criteria

5.7 Sample Size Calculation

5.8 Sampling

5.9 Screening and Recruitment

5.10 DATA COLLECTION

5.10.1 Clinical methods
DEDICATION

I dedicate this work to my best friend and partner, parents, teachers, friends and fellow residents without whom it would not have been possible to complete my study.
ACKNOWLEDGEMENT

I would like to appreciate my supervisors for their immense and tireless guidance during the process of proposal development, execution of the study, data analysis and presentation and finally writing of the final book for submission. It is their supervision that has made my study a complete success. Secondly, I would also like to acknowledge the staff at Kenyatta National Hospital at the reproductive clinic and the pregnant women attending the ante-natal clinic who accepted to participate in my study.

Finally, I would like to thank my family for their continued and unwavering support in all that I do.
LIST OF ABBREVIATIONS

ANC- Ante- Natal Clinic

KNH- Kenyatta National Hospital

ELISA- Enzyme Linked Immunosorbent Assay

BMI- Body Mass Index

BHCG- Beta Human Chorionic Gonadotropin

FT4- Free Thyroxine

FT3- Free tri- iodothyronine

TSH- Thyroid Stimulating Hormone

TBG- Thyroxine Binding Globulin

SCH- Sub Clinical Hypothyroidism

IQ- Intelligent Quotient

TPOAb- Thyroid Peroxidase Antibodies

ATA- American Thyroid Association

PI- Principal Investigator

TFT- Thyroid Function Test

UON- University of Nairobi

ERC- Ethics and Research Committee

EDTA- Ethylenediaminetetraacetic acid

SPSS- Statistical Package for the Social Science

HIV- Human Immunodeficiency Virus
VDRL- Venereal Disease Research Laboratory

IUGR- Intrauterine Growth Restriction

CRL- Crown Rump Length

BPD-Bi- parietal diameter

HC- Head Circumference

AC- Abdominal circumference

EFW- Estimated Fetal Weight

GA- Gestational Age

RI- Restrictive Index

BPP- Biophysical Profile

NST- Non- Stress Test

AFV- Amniotic Fluid Volume

SCD- Sickle Cell Disease

DVT- Deep vein thrombosis

SD- Standard deviation

IQR- Inter Quartile Range
LIST OF TABLES

Table 1: Baseline characteristics.................................................................................20
Table 2: Clinical characteristics......................................................................................21
Table 3: Serum thyroid biochemical profile......................................................................22
Table 4: Obstetric ultrasound findings..............................................................................23
Table 5: Characteristics of participants who had an obstetric ultrasound performed and those who did not have an ultrasound........................................................................24
Table 6: Thyroid dysfunction and fetal well-being............................................................29

LIST OF FIGURES

Figure 1: Participants recruitment and flow during the study........................................19
Figure 2: Ultrasound normogram abdominal and head circumference ratios ...................46
Figure 3: Estimated fetal weight normogram....................................................................47
Figure 4: Ultrasound fetal measurements standard chart..................................................48
ABSTRACT

Background

Maternal thyroid hormone levels are an important determinant of pregnancy and fetal outcomes. Both hyperthyroidism and hypothyroidism have been shown to have adverse maternal and fetal outcomes. There is no data on the magnitude and profile of thyroid dysfunction among pregnant women in Kenya.

Objective of the study

To determine the prevalence of thyroid dysfunction among pregnant women attending Antenatal Clinic (ANC) at the Kenyatta National Hospital (KNH) and to determine association between thyroid dysfunction in pregnancy to fetal well-being status using a trimester specific obstetric ultrasound.

Methods

This was a cross-sectional descriptive study. The participants were consenting pregnant women attending ANC aged 18 years and above. One hundred and eight participants were recruited using consecutive sampling. Relevant history and physical examination was carried out using a standard study proforma. Analysis of TSH and FT4 was carried out in the KNH biochemistry laboratory using an automated electro-chemiluminescence immunoassay machine (cobas ® e 6000) and thereafter a trimester specific ultrasound was performed to assess fetal well-being.

Results

An analysis of the complete data of 107 participants was performed, one participant was excluded due to intrauterine fetal death based on ultrasound. The median age was 29 years. The median gestational age was 32.2 weeks with majority (61.7%) in the third trimester. Only eight (7.5%) participants had previously tested thyroid function while twelve (11.2%) had a family history of goiter. Six out of a hundred and seven participants had thyroid dysfunction giving a prevalence of 5.6% (95% CI 1.9-10.2) with majority (5/6) being diagnosed with subclinical hypothyroidism. Only one participant had overt hypothyroidism and none with either overt or subclinical hyperthyroidism. Only one participant who had reported history of previous pregnancy loss had
subclinical hypothyroidism. Ten participants who had a history of previous pregnancy loss had normal thyroid function tests. Study directed obstetric ultrasounds were carried out on eighty-four participants (77.8%) among whom eight (7.4%) had abnormal fetal well-being which was classified as being small for dates using trimester specific parameters and one had intra-uterine fetal death (IUFD). There was no significant association (p=0.646) between thyroid dysfunction and markers of fetal well-being. However, the significance of this finding needs further evaluation to determine impact on fetal and maternal outcomes.

Conclusion

The prevalence of thyroid dysfunction among pregnant women attending ANC was 5.6% with majority (5/6) diagnosed with subclinical hypothyroidism. There were very few study participants with thyroid dysfunction and hence this study was not able to assess any association with markers of fetal well-being.
CHAPTER 1. INTRODUCTION

The thyroid gland is an important endocrine gland that has a lot of influence on the reproductive system. Due to the normal physiological changes that happen in pregnancy, the thyroid gland is under a lot of hormonal influence. In the first trimester, the rise in beta human chorionic gonadotropin (BHCG) leads to a rise in free thyroxine (FT$_4$) and free tri-iodothyronine (FT$_3$), and by negative feed-back to a suppression of thyroid-stimulating hormone (TSH). Estrogen leads to an increase in thyroxine-binding globulin (TBG), which leads to decreased FT4 levels. There is also altered iodine clearance in the kidneys and placental metabolism of thyroid hormone (1).

The most common disorder in pregnancy has been noted to be hypothyroidism with sub-clinical hypothyroidism being more prevalent than overt hypothyroidism. Nutritional deficiency most notably iodine, is the most common factor leading to thyroid disease followed by autoimmune thyroiditis then others like thyroid nodules and malignancies which are rare (2). These conditions are difficult to diagnose in pregnancy as they have symptoms that mimic the normal physiological changes that occur in pregnancy. Risk factors associated with thyroid disease in women include: age more than 30 years, family history of thyroid disease, Body Mass index (BMI) more than 40kg/m2, history of infertility, history of any other autoimmune disorder, use of amiodarone, lithium or recent neck radiation (2). Thyroid dysfunctions are most prevalent in women between 15 – 35 years when a woman is considered most fertile and are associated with a lot of fetal and maternal complications if left untreated. The most feared complication has been neurocognitive problems in children born by mothers who suffered hypothyroidism. In Kenya there are no studies carried out to determine the magnitude of thyroid function among pregnant women and hence the need to undertake this study.
CHAPTER 2. LITERATURE REVIEW

2.1 Background

Women of reproductive age are at risk of endocrine disorders, second among them after diabetes mellitus is thyroid disorders. Thyroid dysfunction if untreated in pregnancy is associated with increased risk of complications such as: early pregnancy loss; placental disorders e.g. abruption and placental insufficiency leading to intrauterine growth retardation and gestational hypertension.

The spectrum of thyroid disorders includes: overt hypothyroidism, subclinical hypothyroidism, Graves’ disease and goiter and post-partum thyroid function.

Subclinical hypothyroidism (SCH) is more common than overt hypothyroidism with an estimated prevalence of 2-3%. The main cause of hypothyroidism worldwide and especially in developing countries still remains iodine deficiency despite iodination of most foods and table salt. Autoimmune thyroiditis is believed to be the main cause of hypothyroidism in iodine-sufficient regions, and thyroid autoantibodies are believed to be the indicators of the disease (3). The problem with hypothyroidism in pregnancy is that the symptoms are very similar to the normal physiological changes that occur in a pregnant woman’s body hence they are difficult to diagnose and high index of suspicion is needed (3).

Hyperthyroidism is less common than hypothyroidism, with an approximate incidence during pregnancy of 0.2% with Graves’ disease being the most common (3). Transient Gestational thyrotoxicosis is common especially in the first trimester. A cross-sectional study done in Kenya among 72 pregnant women in the first trimester found the prevalence of gestational thyrotoxicosis to be high at a prevalence of 8.3% (4). The elevated levels of BHCG in first trimester that predispose pregnant women to hyperemesis gravidarum has been shown to have thyroid stimulating activity as well as increase iodide intake by thyroid cells (5).

The most feared complication of thyroid disorders especially hypothyroidism has been childhood neurodevelopmental abnormalities (6). In the first trimester of pregnancy the fetal thyroid hormone demands are met exclusively by the mother. In the second and third trimesters, the fetal source of thyroid hormones is from both the maternal and the developing fetus although predominantly from the mother. Maternal thyroxine is important for fetal neurological development (7) and thyroid
dysfunction in pregnancy can lead to impaired fetal psycho-neurologic development. In a prospective study among 220 pregnant women that followed up the children till ten months of age was able to show that low maternal free T4 concentrations in during pregnancy is associated with a significantly increased risk of impaired neurodevelopment in the infant (8).

Thyroid dysfunction in pregnancy is associated with poor maternal and fetal outcomes. Allan et al, who carried out a prospective cohort study among 9,403 pregnant women, found a positive correlation between serum TSH level >10.0mIU/l and increased rate of intrauterine fetal demise (9). A study done by Casey et al. among 25,756 pregnant women was able to demonstrate that pregnant women with subclinical hypothyroidism were three times more likely to experience pregnancy related complications like placenta abruption and preterm delivery as compared to euthyroid women (10).

2.2 Universal versus targeted screening of thyroid function in pregnancy
The main conflict has been between the endocrine society and college of obstetricians on whether targeted or universal screening of thyroid function in pregnancy should be adopted. Current guidelines only recommend targeted screening of women at high risk and the following categories are included: women more than 30 years, Body Mass Index of more than 40kg/m2, history of infertility, those with a history of thyroid disease, type 1 diabetes mellitus, or other autoimmune disease, current or past use of thyroid therapy, or a family history of autoimmune thyroid disease (11).

Due to the controversy involving universal versus targeted screening some studies have shown that targeted approach may miss out on a large proportion of women with overt or sub clinical hypothyroidism. With prevalence range of 33-81% (2, 12, 13, 14), most clinicians still call for universal screening in order to prevent perinatal and fetal complication (6, 13, 15). A prospective cohort study by Negro et al in Italy among 4,562 pregnant women to assess the impact of thyroid dysfunction during pregnancy under two conditions: universal screening and case finding, was able to show that fewer obstetric complications occurred with universal screening and benefited from hypo/hyperthyroidism treatment (16).
Vaidya et al in the United Kingdom carried out a prospective study that screened 1,560 pregnant women was also able to confirm that, testing only the high-risk pregnant women would miss about one third of women with hypothyroidism (11).

Wang et al in China who did a large multicenter cohort study involving 2,899 pregnant women looked at prevalence of thyroid dysfunction in early pregnancy and use the first trimester specific TSH and FT4 reference ranges (14). This study was able to show that despite the prevalence of hypothyroidism being higher in the high-risk group than in the low-risk group, targeted screening would still miss out on 81% of pregnant women with hypothyroidism (14). Wang used two different series of reference intervals to compute the prevalence of hypothyroidism and found that 2% patients with subclinical hypothyroidism would be misclassified if general population reference intervals were used and they were able to show that the first trimester-specific reference ranges must be used to evaluate thyroid function in pregnancy(14), this is important especially in countries that do not have local trimester specific ranges, they can use those provided in guidelines instead of non-pregnant ranges.

Dhanwal et al, who looked at the prevalence of thyroid dysfunction at a tertiary Indian hospital found a higher prevalence of hypothyroidism, both overt and subclinical, at 14% (17), which was mainly attributed to dietary iodine deficiency. However, Bandela et al (18) and Gayathri et al (19) both reported lower prevalence in their studies and this is maybe due to the fact that they excluded those pregnant women classified as high risk and also the use of different upper limit cut-offs for TSH.

In Egypt, a study carried out among 168 pregnant women showed that the prevalence of hypothyroidism was 56% in low risk group versus the high-risk group at 44.6% (not statistically significant). The authors concluded that universal screening should be adopted throughout Egypt to avoid missing out on 34.5% of pregnant women with either clinical or subclinical hypothyroidism had a targeted approach been used. The TSH and FT4 reference ranges used in this study were as stated in American Thyroid Association (20).

In Tunisia, Feki et al looking at the prevalence of thyroid disorders and identifying groups at risk for thyroid disorders in Tunisian pregnant women where they sampled 1519 and found a
prevalence of 9.7%, which showed that thyroid disorders are common and are also associated with poor outcomes hence need for routine screening (21).

Ameel in Khartoum, Sudan during the period of May-July 2014 carried out a study to investigate the prevalence and risk of thyroid dysfunctions, to determine trimester-specific reference ranges for free Tri-Iodothyronine (FT3), Free Thyroxin (FT4) and Thyroid Stimulating Hormone (TSH) among 500 healthy pregnant Sudanese women. The prevalence of thyroid dysfunctions among the pregnant women was 9.4%. Associations found to be statistically significant was between thyroid dysfunction and previous history of miscarriage, the others like pre-term delivery, still birth, delivery of children with mental retardation did not show any significance. They were able to conclude by recommending routine investigation for thyroid function test during pregnancy and in preconception clinics (22).

2.3 Thyroid hormone reference levels in pregnancy

Diagnosis of thyroid dysfunction is mainly done by use of laboratory testing as most of the symptoms especially of SCH and hypothyroidism are non-specific (23). Elevated serum thyroid Stimulating Hormone (TSH) helps make a diagnosis of primary hypothyroidism but there needs to be trimester specific cut off due to the changed in metabolism and excretion of thyroid hormone that is mainly influenced by pregnancy hormones, especially estrogen and chorionic human gonadotropin (BHCG) (24). The use of trimester reference ranges helps to avoid misclassification of thyroid dysfunction during pregnancy (9).

Western studies have, either used the guidelines sponsored by the American Thyroid Association or by the American Endocrine Society which suggested the following TSH reference ranges for use in pregnancy: first trimester, 0.1 to 2.5 mU/l; second trimester, 0.2 to 3.0 mU/l; third trimester, 0.3 to 3.0-3.5 mU/l (11, 25, 26, 27) to be useful especially in countries with no local reference ranges to avoid over/miss diagnosis.

The big question is whether these reference ranges provided by the American Thyroid Association and the American Endocrine Society can be generalized. Two Chinese studies (28, 29) and one study from India (30), demonstrated a significantly higher TSH reference range for each trimester; in particular, the study by Li et al (29) showed that the Chinese population displays 0.12-5.08 mU/l
as first trimester reference range, this is higher than the ranges given by western countries and would suggest that a larger proportion of almost 28% of pregnant women would be hypothyroid as compared to 4% using ethnic specific range (11, 31, 32, 33). However, several studies have found variation in prevalence among national populations and ethnicities (11).

Assays used to measure thyroid hormones have also been up for debate severally since it has been noted that during pregnancy TSH, FT3, FT4 are under a lot of hormonal influence and this interferes with their serum concentrations but some authors maintain that the reliability of the standard immunoassay for FT4 is satisfactory (34) while others report that it is unreliable and emphasize the measurement of FT4 in the dialysate or ultra-filtrate using online solid phase extraction liquid chromatography tandem mass spectrometry as gold standard (35). This method is the best but is tedious, expensive, requires technical specialization, time consuming and not readily available in most clinical laboratories.

The most appropriate screening test for thyroid dysfunction in early pregnancy is still uncertain. Most would advocate using TSH as the initial screening test, because TSH is a more sensitive marker of thyroid status than FT4 and it reflects the physiologic log/linear relationship of TSH to FT4 (36). TPOAb measurement should also be considered in the presence of high TSH levels due to the relationship with adverse pregnancy events, such as post-partum thyroiditis, recurrent miscarriage, and post-partum depression.

2.4 Thyroid function in pregnancy and foetal growth
Fetal growth is dependent upon a number of endocrine, paracrine, and auto-crine events within the feto-placental unit (37). Babies born with intrauterine growth restriction (IUGR) have increased perinatal and neonatal mortality. This pathological process also causes significant morbidity, with 10% of low birth weight babies having physical handicaps and a further 5% showing neurodevelopmental delays in early childhood (38). Thyroid status is one of several factors that have been postulated to play a critical role in the pathogenesis of such morbidity, especially with respect to growth and development of the central nervous system (39,40).

Saki et al in a prospective study looking at 586 pregnant women in south of Iran showed that both hyperthyroidism and hypothyroidism are associated with IUGR and the risk is 2.18 times in SCH while overt hyperthyroidism increases the risk of IUGR by about 4.57 times (41). This is similar
to what Sahu et al found in an Indian study that looked at 633 pregnant women in the second trimester (42).

Ajmani et al looking at subclinical thyroid dysfunction among pregnant women and its effect on maternal and fetal outcome found that preeclampsia was the most common maternal complication in hypothyroid patients followed by abruption. They also showed that occurrence of fetal loss (spontaneous abortion, fetal death) was significantly increased in the pregnant women with overt hypothyroidism and the pregnant women with subclinical and overt hypothyroidism had a significant increase in the incidence of preterm delivery, fetal distress, and intrauterine growth retardation (43). These findings are similar to other studies that showed that maternal subclinical hypothyroidism increased the risk of fetal distress Goel et al (44).

A prospective study in China that looked at 8,012 pregnant women (371 women with SCH, 7,641 euthyroid women) found that the women with SCH had increased risks of gestational hypertension and premature rupture of membranes while their fetuses and infants had increased risks of intrauterine growth retardation and low birth weight. Thus, routine maternal thyroid function testing is necessary to improve maternal and perinatal outcomes (45).
CHAPTER 3. JUSTIFICATION

Normal thyroid function in pregnancy is important for both maternal and fetal well-being. Sub-clinical hypothyroidism is the most common thyroid disorder seen in pregnant women. Iodine deficiency is the commonest cause of subclinical hypothyroidism in developing countries.

Various studies around the world and some in Africa demonstrate poor maternal and fetal outcomes associated with thyroid dysfunction. There is lack of data on the burden of thyroid dysfunction among pregnant women in Kenya and hence the need to undertake this study.

This study will form a definite foundation for future studies that will inform strategy or influence screening and management of thyroid dysfunction among pregnant women in Kenya.
CHAPTER 4. RESEARCH QUESTION AND OBJECTIVES

4.1 RESEARCH QUESTION
What are the thyroid biochemical abnormalities among pregnant women attending ANC at KNH?

4.2 OBJECTIVES

4.2.1 BROAD OBJECTIVE
To determine the magnitude of thyroid dysfunction among pregnant women attending ANC at KNH.

4.2.2 SPECIFIC OBJECTIVES

4.2.2.1 PRIMARY
  1. To determine the prevalence of thyroid dysfunction among pregnant women attending ANC at KNH.

4.2.2.2 SECONDARY
  1. To determine association between thyroid dysfunction in pregnancy and fetal well-being status by use of trimester-specific ultrasonic parameters.
CHAPTER 5. METHODOLOGY

5.1 Study Design
Descriptive cross-sectional study

5.2 Study Area
Kenyatta National Hospital, a tertiary referral hospital located in the capital city of Kenya, Nairobi. It was established in 1900 and is the largest hospital in Eastern and Central Africa. It has a capacity of 2000 beds. It serves as the teaching hospital for the University of Nairobi, College of Health Sciences, both for the undergraduate and the post-graduate programs. The hospital offers specialized Ante-Natal and Post-Natal care to pregnant women and those in puerperium. This study was carried out at the Antenatal clinic which runs from Monday through to Thursday. Monday clinic is mainly for the women attending the clinic for the first time and other clinic days are for those on follow up. The Antenatal Clinic attends to an average of 11,000 patients per year and approximately 916 patients in a month. The clinic activities involve routine ante-natal check-ups and ante-natal profile carried out. The testing of the thyroid function test will be an additional test carried out.

5.3 Study Population
Pregnant women attending ante-natal clinic at Kenyatta National Hospital

5.4 Case Definitions
1. Any ambulatory pregnant woman presenting at ANC in KNH with confirmed viable pregnancy.

5.5 Inclusion Criteria
1. Written informed consent to participate in the study

5.6 Exclusion Criteria
1. Obstetric emergencies that warrant hospitalization
2. Documented multiple pregnancy

5.7 Sample Size Calculation
Fisher’s formula was used to calculate the sample size as follows:

\[ n = \frac{Z^2 \times P(1-P)}{d^2} \]
n – Sample size

Z – 1.96 (95% confidence interval)

P – Estimated prevalence of thyroid dysfunction among pregnant women 9.4% (Saeed et al, 2015 in Sudan)

d – Margin of error (precision error) = ±5.5%

Substituting into the formula,

\[ n = \frac{Z^2 \cdot P \cdot (1-P)}{d^2} \]

\[ n = \frac{1.96^2 \cdot 0.094 \cdot (1-0.094)}{0.055^2} \approx 108 \]

A minimum of 108 pregnant women will be required to estimate prevalence of thyroid dysfunction within 5.5% margin of error.

5.8 Sampling
Consecutive sampling procedure used with each pregnant woman attending the ANC who fulfilled inclusion criteria being included in the study in order to achieve the sample size of 108.

5.9 Screening and Recruitment
The principal investigator (PI) and two research assistants (qualified clinical officers) perused the files of the pregnant women attending the ante-natal clinic on every clinic day for eligibility based on the inclusion and exclusion criteria. Those who met the inclusion criteria were invited to participate in the study. The participants were then given all the relevant information about the study and those who gave written informed consent (Appendix I) were recruited.

5.10 DATA COLLECTION

5.10.1 Clinical methods
Once written informed consent (Appendix 1) was obtained from the participants, a study proforma (Appendix 2) was administered to capture demographic data, relevant history and a focused physical examination of the thyroid gland and the fundal height assessment was carried out by the principal investigator and the findings recorded. The thyroid examination was aimed at identifying features suggestive of thyroid gland disease e.g. goiter, nodules or tenderness (10). The fundal height measurement was done using a tape measure to get the distance from the upper edge of the
pubic symphysis and top of uterine fundus, the measurement in centimeters corresponds to the gestational age in weeks (46).

### 5.10.2 Laboratory Methods

All blood samples were collected by the principle investigator and the 2 trained research assistants. Each participant had four milliliters of blood sample collected. The blood samples were then transferred to a plain partial draw vacutainer (red top) that was clearly labelled with participant’s unique study identification number and transported to the KNH biochemistry laboratory at the end of the day’s collection for analysis. The TSH and FT4 estimation was by use of an automated electro-chemiluminescence immunoassay machine (cobas ® e 6000).

### 5.10.3 Obstetric ultrasound

The ultrasound was performed at a study designated center (Plaza imaging) using General Electronics scan that uses a curvilinear probe with a frequency of 3-5 MHz. The ultrasounds were done by a study dedicated ultrasound technician and checked by a study dedicated consultant radiologist. The scans were trimester-specific as this allowed assessment of the fetal well-being at different gestational ages.

1. First trimester scan- was performed between 10+0 and 13+6 weeks to establish accurate gestational age. CRL (Crown Rump Length) and BPD (bi-parietal diameter) was used to estimate gestational age.

2. Second trimester scan- was performed between 18 and 22 weeks of gestation to determine gestational age and fetal weight as shown by the Shepherd’s formula below. The following parameters were measured: bi-parietal diameter (BPD), head circumference (HC) and abdominal circumference (AC).

3. Third trimester scan- was performed after 29 weeks. It included parameters used in second trimester together with doppler studies and biophysical profile.

Fetal well-being was assessed using all the following parameters

1. Estimated fetal weight (EFW) using Shepherd’s formula (47)

\[
\text{EFW} = \frac{2.646 \times (\text{AC} \times \text{BPD})}{1000}
\]

The weight was compared against the expected weight and if less than 10<sup>th</sup> percentile was noted as small for gestational age.
2. Head to Abdominal circumference ratio: was calculated and a ratio greater than 2 standard deviations (SD) above the mean for GA was considered abnormal (48).

3. Doppler studies- were done at a gestation age of 28 weeks and above. The umbilical artery was evaluated and recorded as a ratio/ index. A systolic/ Diastolic (S/D) ratio >3.0 or RI (Resistive Index) >0.6 was considered abnormal (49).

4. Biophysical profile (BPP) - is a noninvasive test that predicts the presence or absence of fetal asphyxia and, ultimately, the risk of fetal death in the ante-natal period (50). The BPP integrates 5 parameters to yield a biophysical profile score. The parameters are: the non-stress test (NST), ultrasound guided measurement of the AFV (Amniotic fluid Volume), observation of the presence or absence of fetal breathing movements, gross body movements, and tone (51, 52). The BPP allows 2 points for each parameter that is present, yielding a maximum score of 10. Each of the components is given a score of 2 (normal) or 0 (abnormal or absent). A composite score of 8 or 10 is normal, a score of 6 is equivocal and a score of 4 or less is abnormal.

Fetal well-being was summarized as small for gestational age or normal-growth for gestational age based on parameters above, numbers 1-4. Any abnormal report of the numbers 1-4 above downgrades the fetal well-being and was classified as small for gestational age.

All the results were communicated to the participants and those found with ultrasound features indicative of abnormal fetal well-being (small for gestational age) were advised to consult the obstetrician. A copy of all the results were filed.

5.11 QUALITY CONTROL

5.11.1 Clinical
The research assistants were trained by the PI and they ensured that data was collected efficiently, on time and that it was recorded accurately. All recorded data was verified by the PI, who also ensured that the study proforma was completely and accurately filled.

5.11.2 Laboratory
Standard operating procedures for specimen collection, preparation and storage were followed to minimize pre-analytical errors. The laboratory tests were carried out in the biochemistry laboratory
at KNH by a study dedicated technician. Controls for the various concentration ranges were run individually at least once every 24 hours when the test was in use, once per reagent kit, and following each calibration.

5.11.3 Obstetric ultrasound
The obstetric ultrasounds were performed at Plaza imaging Centre. The obstetric ultrasounds were carried out by a qualified study dedicated sonographer and the results counter checked by the consultant radiologist to ensure accuracy. Ten random study participants who had prior scans done in the course of the study period were identified and requested to come on a different day for a second scan and compared with previous scans for consistency. The radiologist was blinded to thyroid status of the participants and to the ones who came for repeat ultrasound.

5.12 STUDY VARIABLES

5.12.1 Definition of outcome variables
The American Thyroid Association (ATA) guidelines provide the following Thyroid Stimulating Hormone (TSH) and FT4 ranges for use in pregnancy:

1. 1st trimester TSH levels 0.1 to 2.5 mU/l
2. 2nd trimester TSH levels 0.2 to 3mU/l
3. 3rd trimester TSH levels 0.3 to 3.0-3.5mU/l

The Free Thyroxine (FT4) reference ranges were determined based on ATA guidelines which recommend calculation of FT4 levels as 1.5-times the non-pregnant level (75nmol/l to 195nmol/l).

Based on the above hormone levels thyroid function was defined as follows (10):

1. Euthyroid state defined as normal TSH and FT4 levels
2. Overt hypothyroidism defined as elevated TSH and decreased FT4
3. Sub- clinical hypothyroidism (SCH) defined as elevated TSH levels and normal FT4
4. Overt hyperthyroidism defined as decreased TSH and elevated FT4
5. Sub-clinical hyperthyroidism defined as decreased TSH and normal FT4

Thyroid function was defined as normal or dysfunctional based on serum levels of TSH and FT4 and was classified based on American Thyroid Association guidelines (11). Normal thyroid function was defined by euthyroid state and thyroid dysfunction was defined as presence of either:
overt hypothyroidism, sub-clinical hypothyroidism, overt hyperthyroidism or sub-clinical hyperthyroidism.

The foetus was termed as having normal intrauterine growth if the trimester specific parameters were within normal range and small for gestational age if any one of the ultrasound fetal parameters was abnormal.

5.13 DATA MANAGEMENT AND ANALYSIS
5.13.1 Data Collection

Data was collected by use of study proforma specifically designed for this study (appendix 2). The participants’ files were reviewed and study specific information were identified and entered appropriately. Participants were also interviewed to verify the information on the files and give any additional information required.

5.13.2 Data Privacy

Standards to protect personal data were followed. Data collection instruments had minimum possible subject identifiers; only the study number was entered in the study questionnaire and specimen labels.

5.13.3 Data Storage

The completely filled study proforma, laboratory results forms, and copy of obstetric ultrasound results were verified for completeness by the principal investigator. The data forms were stored in a secure lockable cabinet only accessible by the PI and the statistician.

5.13.4 Data entry and analysis

Data was recorded in the study proforma and entered into secure password-protected data entry sheets after verification and cleaning. Data entry and analysis was done using SPSS version 23.0. Upon completion of entry, the hard copy forms were used to clean and verify correctness of the entered data and then stored safely in the lockable cabinet. The electronic file was backed up in three compact discs and stored offsite.
The study population was described using socio-demographic characteristics and clinical history. Categorical variables were presented as percentages and continuous data summarized into means (standard deviations) or medians (interquartile ranges). The prevalence of thyroid dysfunction defined by low or high sensitive TSH and FT4 levels, was analyzed and presented as a proportion with 95% confidence interval. Uni-variate analysis of fetal well-being (summarized as normal intrauterine growth and small for gestational age) was done. Any association of thyroid dysfunction with fetal growth was assessed using Chi square test. All statistical tests were performed at 5% level of significance. Data summary was presented in tables.

ETHICAL CONSIDERATION

This study was carried out upon approval from the Department of Clinical Medicine and Therapeutics (UON), Kenyatta Hospital Administration and the Kenyatta National Hospital/University of Nairobi – Ethics & Research committee (KNH/UON-ERC).

Informed consent and assent was obtained from all the study participants. Cases found to have thyroid abnormality that required treatment, were referred to the obstetrician clinic for urgent review and intervention.

Confidentiality was maintained at all times. An anonymous study-number was assigned to each study subject and was the only identification that appeared on the study proforma, specimen bottles and laboratory request forms. Patients were free to withdraw from the study during the study period without discrimination.

The principal investigator met the cost of the obstetric ultrasounds while the cost of thyroid function tests was funded by the Kenyatta Research and Programs fund.
CHAPTER 6. RESULTS

6.1 Recruitment
The study participants were recruited between 1\textsuperscript{st} and 30\textsuperscript{th} September 2016. Approximately 400 pregnant women attended the ante-natal clinic during the study period. 132 consecutive pregnant women were approached and 24 who did not give informed consent were excluded. The final analysis included 107 participants, one was excluded due to intrauterine fetal demise based on obstetric ultrasound (Figure 1).

![Participants' recruitment flow chart in the study](image)

Figure 1: Participants’ recruitment flow chart in the study
6.2 Demographics characteristics
The demographic and clinical characteristics of the 107 participants is depicted in Table 1. The median age was 29 years, 100 (92.6%) were married, 86 (80.4%) had attained post primary education and 76 (71.0%) were employed.

Table 1: Baseline demographic characteristics of subjects enrolled in the study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Frequency (%) n=107</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>29.3</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>median</td>
<td>29</td>
</tr>
<tr>
<td>Range</td>
<td>18-39</td>
</tr>
<tr>
<td>Education level</td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>21 (19.6)</td>
</tr>
<tr>
<td>Secondary</td>
<td>29 (27.1)</td>
</tr>
<tr>
<td>Tertiary</td>
<td>57 (53.3)</td>
</tr>
<tr>
<td>Employment status</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>76 (71.0)</td>
</tr>
<tr>
<td>No</td>
<td>31 (29.0)</td>
</tr>
</tbody>
</table>

6.3 Clinical information
The median gestational age was 32.2 weeks (IQR 25-36.3) as depicted in Table 2. The mean fundal height was recorded at 32.9 with a median of 32 centimeters (IQR 26.0-36.0). 66 (61.7%) were in the third trimester. The median weight was 74 kilograms. The mean blood pressure recorded was 114.1/69.9 mmHg (Table 2). Nine had abnormal blood pressure, among whom seven had a high blood pressure reading while two had a low blood pressure reading.

Ten (9.3%) reported having had difficulty getting pregnant. 37 (34.6%) reported a history of preterm delivery and 71 (66.4%) had a history of at least one pregnancy loss. 16 (15.0%) reported a history of current follow up for medical illness, which include hypertension in six, diabetes mellitus in four, anemia in two and one each with Human Immunodeficiency Virus (HIV), deep vein thrombosis, uterine fibroids and sickle cell disease. Eight (7.4%) had previously been tested for thyroid function. 12 had a family history of goiter. Only one participant was on follow up for goiter prior to pregnancy. Only one participant had history of previous neck radiation.
Table 2: Clinical characteristics of subjects enrolled in the study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD)</th>
<th>Median (IQR)</th>
<th>Min-Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestation age (in weeks)</td>
<td>30.3 (7.9)</td>
<td>32.2 (25-36.3)</td>
<td>7-40</td>
</tr>
<tr>
<td>Fundal height (in centimeters)</td>
<td>32.9 (17.7)</td>
<td>32.0 (26.0-36.0)</td>
<td>14-40</td>
</tr>
<tr>
<td>Weight in kilograms</td>
<td>74.6 (12.5)</td>
<td>74 (67-81)</td>
<td>49-115</td>
</tr>
<tr>
<td>Blood pressure recording in mmHg</td>
<td>114.1 (15.5)</td>
<td>69.9 (11.8)</td>
<td></td>
</tr>
<tr>
<td>Variable</td>
<td>Frequency (%) n=107</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trimester</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First</td>
<td>4 (3.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second</td>
<td>37 (34.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Third</td>
<td>66 (61.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primigravida</td>
<td>20 (18.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiparous</td>
<td>87 (81.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of difficulty getting pregnant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10 (9.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>97 (90.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of any medical illness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>16 (15.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>91 (85.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

6.4 Thyroid function test

6.4.1 Serum thyroid hormone profile

The median TSH and FT4 levels were at 1.85 mU/l (IQR 1.41-2.73) and 139.20 nmol/l (IQR 124-153.2) respectively and were within normal reference range as shown in table 3. The reference levels used for TSH and FT4 were trimester specific as recommended by the ATA guidelines. The prevalence of thyroid dysfunction in this study was 5.6% (95% CI 1.9-10.2) as shown in Table 3. Six participants had elevated TSH levels. Five had isolated elevated TSH levels with normal FT4
levels (sub-clinical hypothyroidism) while one had both elevated TSH levels and low FT4 levels (overt hypothyroidism). Among the six study participants with thyroid dysfunction two were in first trimester, one in second trimester and three in third trimester. The only study participant with overt hypothyroidism was in the third trimester. The participant with previous neck radiation exposure had subclinical hypothyroidism.

Table 3: Serum thyroid biochemical profile of the study participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median (IQR)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH (mU/l)</td>
<td>1.85 (1.41-2.73)</td>
<td>0.31-5.21</td>
</tr>
<tr>
<td>FT4 (nmol/l)</td>
<td>139.20 (124-153.2)</td>
<td>60.25-193.20</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>n=107 (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid function status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysfunction/ abnormal</td>
<td>6 (5.6)</td>
<td>1.9-10.2</td>
</tr>
<tr>
<td>Normal</td>
<td>101 (94.4)</td>
<td>89.8-98.1</td>
</tr>
</tbody>
</table>

6.5 Obstetric ultrasound results

84/108 (77.8%) had fetal well-being assessment using study directed obstetric ultrasounds. The median gestational age (ultrasound derived) was 33 weeks. Only 9/84 (8.3%) had an obstetric ultrasound that did not correspond to clinical assessment; eight had small for gestational age fetus and one had intra-uterine fetal death (IUFD).

The participant with IUFD was excluded in the analysis of the results (Table 4) based on the absence of a viable pregnancy on ultrasound although the thyroid function test result was noted to be normal. The exclusion of this participant from the final data analysis did not affect the power of the study in calculating the prevalence of thyroid dysfunction.
Table 4: Obstetric ultrasound findings of the study participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gestation age</strong> (in weeks)</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>30.0 (8.3)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>33 (25.5-36.5)</td>
</tr>
<tr>
<td>Range</td>
<td>9 – 41</td>
</tr>
<tr>
<td><strong>The overall fetal growth (n=84)</strong></td>
<td></td>
</tr>
<tr>
<td>Normal for gestational age</td>
<td>75 (69.4)</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>8 (7.4)</td>
</tr>
<tr>
<td>IUFD</td>
<td>1 (0.9)</td>
</tr>
</tbody>
</table>

6.51 Characteristics of study participants without obstetric ultrasound assessment

Out of 107 study participants 24 (22.4%) were unable to undertake obstetric ultrasounds to assess fetal well-being due to inconvenience. The mean age in this group was 30 years. Majority 18/24 were in the third trimester. The only participant on follow up for goiter was among those without fetal well-being assessment. Only one patient was on follow up for medical illness notably hypertension and was on appropriate medication. Nine reported history of previous pregnancy loss, three had a family history of goiter while two had previously been tested for thyroid function. These findings are comparable to the whole study population as shown in Table 5.

The median TSH level was 1.78mU/l with a range of 0.66- 3.35mU/l and the median FT4 level was 143.60nmol/l with a range of 104- 188.00nmol/l. The median levels were comparable to that of the whole study population.

One participant with thyroid dysfunction (sub-clinical hypothyroidism) was among those who did not get an obstetric ultrasound carried out and was notably in the first trimester.
Table 5: Characteristics of participants who had an obstetric ultrasound performed and those who did not have an ultrasound

<table>
<thead>
<tr>
<th>Variable</th>
<th>All n= 107</th>
<th>obstetric ultrasound n= 83</th>
<th>No obstetric ultrasound n=24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (IQR)</td>
<td>29</td>
<td>29.5 (25.5-33)</td>
<td>30 (28-34)</td>
</tr>
<tr>
<td>Median gestational age(IQR)</td>
<td>32.2 (25-36.3)</td>
<td>32 (26-37)</td>
<td>32 (24-36.5)</td>
</tr>
<tr>
<td>History of difficulty getting pregnant</td>
<td>10</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>History of preterm delivery</td>
<td>37</td>
<td>22</td>
<td>15</td>
</tr>
<tr>
<td>History of medical illness</td>
<td>16</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>Family history of goiter</td>
<td>12</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Median TSH levels (IQR)</td>
<td>1.85 (1.41-2.73)</td>
<td>1.85 (1.44-2.73)</td>
<td>1.78 (1.4-2.33)</td>
</tr>
<tr>
<td>Median FT4 levels (IQR)</td>
<td>139.2 (60-193.20)</td>
<td>138.9 (121.6-152.9)</td>
<td>143.60 (128-168)</td>
</tr>
</tbody>
</table>

6.6 Thyroid dysfunction and fetal well-being

There were very few study participants with thyroid dysfunction hence this study was unable to assess effect on fetal well-being (Table 6).

Table 6: Thyroid functional status and fetal well-being among study participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Abnormal Thyroid function n=6/107 (%)</th>
<th>Normal Thyroid function n= 101/107 (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal growth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>4 (3.7)</td>
<td>71 (66.3)</td>
<td>0.646</td>
</tr>
<tr>
<td>Small for gestation age</td>
<td>1 (0.9)</td>
<td>7 (6.5)</td>
<td></td>
</tr>
</tbody>
</table>
CHAPTER 7. DISCUSSION

This is the first study carried out in Kenya that set out to evaluate thyroid function among pregnant women. Our study was able to demonstrate the prevalence of thyroid dysfunction at (5.6%); with subclinical hypothyroidism being the most common among pregnant women in third trimester attending ante-natal clinic at Kenyatta National Hospital, an urban tertiary public referral facility. This study was unable to demonstrate any association between thyroid dysfunction and fetal well-being due to the small sample size.

There are few studies carried out globally assessing thyroid dysfunction among pregnant women. Most of the studies have been carried out in Europe, Asia and few in Africa. A cross-sectional study in a referral hospital in Spain among 2509 pregnant women in the first trimester (median gestation 8 weeks, range 4–13 weeks) reported a prevalence of thyroid dysfunction at 16% (53). The high prevalence could be attributed to the use of national reference ranges used for TSH and FT4 which are higher than the reference ranges recommended by the American Thyroid Association (11).

A cross-sectional study among 1311 pregnant women within the first and third trimesters in Belgium documented a prevalence of thyroid dysfunction at 15.3%. The prevalence was higher in the first than third trimester. The study used the ATA trimester-specific reference ranges. The high prevalence of thyroid dysfunction in this study was attributed to iodine deficiency (54).

In China, a multicenter cohort study among 2899 pregnant women enrolled during their first trimester of gestation demonstrated a high prevalence of thyroid dysfunction at 10.2%. This study did not use the trimester specific reference ranges recommended by American Thyroid Association (14).

A prospective observational study in India among 1000 pregnant women attending a tertiary public hospital in the first trimester reported a prevalence of thyroid dysfunction at 14.3%, with subclinical hypothyroidism being the most common (17) and was associated with adverse fetal and maternal outcomes. The possible reasons for the high prevalence was presence of goitrogens in diet such as selenium or iron deficiency that may cause hypothyroidism and goiter (17). Similarly, another prospective study among 400 pregnant Indian women between 13 and 26 weeks
of gestation reported a high prevalence of thyroid dysfunction at 13.5% with the majority being subclinical hypothyroidism. This study used the ATA trimester-specific reference ranges (55).

There have been only three African studies carried out on the prevalence of thyroid dysfunction among pregnant women. In Sudan, cross-sectional hospital-based study among 500 pregnant Sudanese women aged 15-45 years in all trimesters, found a prevalence of 9.4% which is higher than our study and this could be attributed to the use of national reference ranges instead of the American Thyroid Association trimester specific reference ranges (22).

A cross-sectional study carried out in Tunisia among 1519 pregnant women in all trimesters demonstrated a high prevalence of thyroid dysfunction at 9.7% which was attributed to iodine deficiency. This study used the ATA trimester specific reference ranges (21).

In Nigeria, a prospective case control study among of 300 pregnant women and 100 age-matched non-pregnant controls reported a prevalence of thyroid disorders at 5.3% and 5%, respectively (56). This study used trimester specific population reference values. Majority of the participants were in the second and third trimester. The high prevalence of thyroid disorders could be attributed to the fact that the TSH upper reference value used in that study was high at 4.0 μIU/L irrespective of trimester.

Our study found a prevalence of thyroid dysfunction at 5.6% among pregnant women in the third trimester, using the ATA reference ranges. Other studies (22,55,56) have reported a prevalence of between 9.4-15.3%. This prevalence is lower than that found by two African studies; in Sudan (64) and in Tunisia (21). The difference between our study and the Sudanese one was the fact that Saeed et al used their population-specific reference ranges as opposed to the ATA trimester- specific reference ranges (22). Unfortunately, here in Kenya national trimester-specific reference ranges are not yet available. The study carried out among Tunisian pregnant women (21) was similar to our study as it was a cross-sectional study and it also recruited participants from all trimesters but it recorded a higher prevalence at 9.7%. The high prevalence in the Tunisian study was attributed to iodine deficiency unfortunately our study did not set out to establish the cause of thyroid dysfunction. According to American Thyroid Association, targeted screening of thyroid dysfunction is the preferred method due to cost-effectiveness, but a cohort study done in the United Kingdom reported that targeted screening would miss about one third of pregnant women with
overt/subclinical hypothyroidism (57) and advocated for universal screening. Other studies that have also documented a high prevalence of thyroid dysfunction among pregnant women have recommended universal versus targeted screening (21,22,56). Despite the high prevalence of thyroid dysfunction among pregnant women in this study we cannot recommend policy change to universal screening due to the small sample size.

Our study was not able to demonstrate association between thyroid dysfunction and fetal well-being. The low rate of small for gestational age fetus and thyroid dysfunction in this study can be attributed to the small sample size. However other studies in Europe and Asia have been able to show associations between thyroid dysfunction and poor fetal and maternal outcomes. A prospective population based cohort study among 2170 pregnant women in Spain demonstrated increased risk of small for age newborns and intrauterine growth retardation with thyroid dysfunction attributed them to placental insufficiency (58).

In Greece, a prospective cohort study among 1170 women in first trimester showed that pregnant women with high TSH levels carry a two-fold increased risk of having a low-birth-weight neonate (59). The potential mechanism cited between hypothyroidism and abnormal fetal growth is alteration in pituitary-thyroid axis of the newborn. The findings of this Greek study are consistent with other birth cohort studies that assessed the effect of hypothyroidism on preterm birth and intrauterine growth restriction (9, 60).

A prospective Chinese study of 8012 pregnant women that showed higher rates of intrauterine growth retardation and low birth weight among those with thyroid dysfunction compared to euthyroid women (45). Another prospective study in China among 1017 first trimester women also showed that clinical hypothyroidism was associated with a higher risk of low birth weight, while isolated hypothyroixinemia with small for gestational age infants and fetal distress (61).

A prospective Indian study among 400 women between 13 and 26 weeks of gestation demonstrated increased adverse fetal outcomes including low birth weight and intrauterine growth retardation with either both overt and subclinical hypothyroidism compared to euthyroid women. The possible explanation was due to increased placental insufficiency among pregnant women with thyroid dysfunction leading to abnormal fetal growth (55).
This study found five participants with subclinical hypothyroidism and one with overt hypothyroidism. Thyroid dysfunction especially Subclinical hypothyroidism has been associated with an increased risk of adverse maternal and fetal outcomes (6,10,41,61). On the other hand, overt hypothyroidism which is not as common as subclinical hypothyroidism has invariably been associated with an increased risk of poor pregnancy outcomes such as premature birth, low birth weight, pregnancy loss and impaired fetal neurocognitive development (8,9,10). This risk of poor fetal and maternal outcomes necessitates the need for close follow up and initiation of appropriate treatment in pregnant women with thyroid dysfunction.
CHAPTER 8. CONCLUSION

The prevalence of thyroid dysfunction among pregnant women attending ANC was 5.6%, majority (5/6) with subclinical hypothyroidism. Association between thyroid dysfunction and fetal well-being could not be established. This study establishes a useful platform for conducting further research in thyroid function among pregnant women in Kenya, because thyroid dysfunction is treatable thus potential fetal events are preventable.

RECOMMENDATIONS

1. The findings of this study are able to highlight the prevalence of thyroid dysfunction but was unable to demonstrate association with fetal well-being and hence a larger cross-sectional/ longitudinal follow up study would be required to be able to demonstrate this association.
2. Further studies to assess thyroid dysfunction among pregnant women in the first and second trimesters as these two groups were under represented in this study

STRENGTHS

1. This is the first study to evaluate thyroid profile among pregnant Kenyan women and is able to highlight the magnitude of thyroid dysfunction among this population.

LIMITATIONS

The limitations of this study were the study directed obstetric ultrasound were done once at point in time as opposed to serial to assess fetal well-being due to financial constraints. Secondly the study was carried out among a high-risk population of pregnant women who attend antenatal clinic at Kenyatta National Hospital, a tertiary referral hospital and cannot be generalized to all the pregnant women in Kenya. Thirdly, ultrasound was performed on 84 participants only and so markers of fetal well-being were not documented in all participants. Finally, due to the cross-sectional study design it was not possible to establish association between thyroid dysfunction and fetal well-being because the fetal changes associated thyroid dysfunction may be more functional than structural ultrasound detectable changes.
CHAPTER 9. REFERENCES


28


60. Pu-Yu Su et al; Maternal Thyroid Function in the First Twenty Weeks of Pregnancy and Subsequent Fetal and Infant Development: A Prospective Population-Based Cohort Study in China. J Clin Endocrinol Metab 2011; 96 (10): 3234-3241

CHAPTER 10. APPENDICES

10.1 APPENDIX I: CONSENT FORM
THYROID FUNCTION AMONG PREGNANT WOMEN ATTENDING ANTE-NATAL CLINIC AT THE KENYATTA NATIONAL HOSPITAL

RESEARCHER: DR PRISCA MUNGLA, REGISTRAR INTERNAL MEDICINE

You have been chosen to participate in a research study looking at the thyroid function among pregnant women attending ante natal clinic at the Kenyatta National Hospital. We are asking you to take part because you attend the ante natal clinic at the Kenyatta National Hospital. Make sure you thoroughly read this form and feel free to ask any questions/clarifications at any point, before going ahead and taking part in the study.

What the study is about: The aim of this study is to look at the thyroid function levels among women attending antenatal clinic and to relate thyroid dysfunction to fetal growth.

What we will ask you to do: should you accept to participate in the study we will ask you a few questions based on the study proforma to help us know more about you and then upon filing it completely, we will perform a full physical exam that includes examination of the thyroid gland. We will then request to draw blood from one of the veins in your arms with a sterile needle and put the sample in a well labeled red top laboratory bottle for analysis in the laboratory and also request for an obstetric ultrasound to assess fetal growth.

Risks- the only risk involved is pain and bruising at the needle prick site but there will be no endangerment to the un-born baby.

Benefits – the benefit involved is that the laboratory test to evaluate the thyroid function/obstetric ultrasound will be done at no cost to you and the results will be made available to your obstetrician who will use it to institute appropriate management.

Compensation: there will be no compensation for participating in this study.
**Confidentiality** – information obtained from this study will be kept private. In the event that we publish the results obtained we will not include any information that will make it possible to identify you. The records will be kept in a secure lock cabinet/ password protected computer only the researchers will have access to the records.

**Participation is voluntary:** Taking part in this study is completely voluntary. If you decide not to participate, it will not affect the quality of ante natal care you receive at the clinic and there will be no victimization. If you decide to participate, you are allowed to withdraw at any time.

If you have any question during the course of the study, you may contact the following:

1. DR. PRISCA MUNGLA, UNIVERSITY OF NAIROBI, DEPARTMENT OF CLINICAL MEDICINE AND THERAPEUTICS
   Mobile: 0722-809172. email: pmungla@yahoo.co.uk OR

2. DR JOHN ONG’ECH, OBSTETRICIAN GYNAECOLOGIST, KENYATTA NATIONAL HOSPITAL, TEL: 0722-282449 OR

3. CHAIRPERSON, KNH/UON ETHICAL REVIEW COMMITTEE,
   TEL: 020-2726300/0722829500/0733606400/EXT 44102. P.O. Box 20723, Nairobi.

**CONSENT /ASSENT FORM-PATIENTS**

STUDY NO………………………….. DATE………………..TIME………………

I hereby give my written and informed consent to allow myself or my…………………… participate in this study on Thyroid Function Among Pregnant women attending Ante-Natal Clinic at Kenyatta national hospital.

I have been adequately explained to about the study by Dr. Prisca Mungla. I do this with the full understanding of the purpose of the study and procedures which include a blood sample and an obstetric ultrasound and answering to a proforma which have been explained to me.

I understand that my rights will be respected, and confidentiality maintained at all times.

I also understand that the consent is voluntary, and I am at liberty to withdraw from the study without my care being affected.

Patient’s signature………………………Patient’s Name……………………………………
INVESTIGATOR’S STATEMENT:

I, the Principal Investigator, have fully educated the research participant on the purpose and implication of this study.

Signed……………………………        Date…………………………….

For any further clarification, you may contact

Dr. Prisca Mungla, at Tel No: 0722-809172.

Or:  KNH/ERC (Kenyatta National Hospital/Ethics & Review Committee)

TEL: 020-2726300/0722829500/0733606400/EXT 44102. P.O. Box 20723, Nairobi
10.1 FOMU INAYOELEZA IDHINI

UTANGULIZI


Lengo kuu yautafiti- Lengo la utafiti huu ni kuuacha ukubwaa wa kazi tezi miongoni mwa wanawake wajawazito wanaohudhuria kliniki ya wajawazito na correlate tezi dysfunction kwa ukuaji na kijusi na matumizi ya uzazi ultrasound.

Taratibu zitakazohusishwa - Lazima kukubali kushiriki katika utafiti sisi kuuliza maswali machahe kulingana na utafiti profoma. Ndipo tutakuwa kufanya mtihani wa kimwili ambayo inahusisha uchunguzi wa tezi na uchunguzi wa tumbu, basi sisi kuteka milimita tano ya damu na kutuma kwa maabara kupima ngazi kazi tezi homoni. Baada ya hapa sisombi wewe kwenye ajili ya ultrasound uzazi katika Plaza Kitu cha picha katika Hurlingham


Hasara za ushiriki - Hakuna hasara yoyote utakayopitia au kupata.

Manufaa ya kushiriki- Mwishoni mwa utafiti huu, nitawasilisha matokeo ya utafiti katika idara ya Tiba ya Ndani katika Chuo Kikuu cha Nairobi. Habari zozote muhimu zitakazotokana na utafiti na ambazo zitafanya malezi kuwa bora, walezi watafahamishwa ili hatua mwa wafaka ichukuliwe.


Ikiwa una swali lolote wakati wa utafiti, unaweza kuwasiliana na wafuatao:
1. DKT. Prisca Mungla, chuo kikuu cha nairobi, idara ya mafundisho ya udaktari na matibabu ya magonjwa Simu ya mkono 0722-809172 AU
2. Dkt John Ong’e ch nambari ya simu 0722-282449 AU
3. mwenyekiti, knh/uon kamati inayoshughulikia maadili, Nambari ya simu: 020-2726300/0722829500/0733606400/EXT 44102. P.O. Box 20723, Nairobi.

Kabla sijakuhusisha katika utafiti wangu, Naomba utie sahihi katika fomu ya idhini iliyopo hapo chini. Fomu hii ya idhini haitahusishwa na majibu yako.

Kauli ya ridhaa: Nimesoma habari hapo juu na nimepata majibu ya maswali yoyote

**FOMU YA IDHINI /KUBALI- WAGONJWA**

NAMBARI YA UCHUNGUZI………………..TAREHE………………..WAKATI…………


Ninaelewa kuwa haki zangu zitaheshimiwa, na suala la kuhifadhi utambuzi wangu utadumishwa wakati wote.

Pia ninaelewa kuwa idhini ya kushiriki ni ya kujitolea, na nina uhuru wa kujiondoa katika utafiti huu bila malezi yangu kuathiriwa.

Sahihi ya Mgonjwa……………………………………

Jina la Mgonjwa……………………………………
KAULI YA MCHUNGUZI:

Mimi, Mchunguzi Mkuu, nimemuelimisha mshiriki wa utafiti kuhusu lengo kuu la utafiti na kinachodokezwa na utafiti huu.

Sihuhi…………………………… Tarehe……………………………

Kwa maelezo zaidi, unaweza kuwasiliana na

Dkt. Prisca Mungla, katika nambari ya simu: 0722-809172.

Au: KNH/ERC (Kenyatta National Hospital/Ethics & Review Committee)

Nambari ya simu: 020-2726300/0722829500/0733606400/EXT 4
10.2 APPENDIX 2: STUDY PROFOMA

THYROID FUNCTION AMONG PREGNANT WOMEN ATTENDING ANTE-NATAL CLINIC AT KENYATTA NATIONAL HOSPITAL

BASIC INFORMATION

Study code number ..............................................................

1. Hospital Number ..........................................................
2. Telephone Contact .........................................................
3. Address .................................................................
4. Age .................................................................
5. Marital Status Single □ Married □ Separated/ Divorced □ Widowed □
6. Residence Rural □ Urban □ Peri-Urban □ (exact location .............)
7. Education Level None □ Primary □ Secondary □ Tertiary □
8. Occupation Employed □ Self-employed □ Unemployed □ Retired □
    Training/Student □

HISTORY

What is the LMP (last menstrual period) ....................... EDD ........ GBD ............

What is the Parity .....................

Have you lost any pregnancies / had a miscarriage/ preterm delivery? YES □ NO □

IF YES how many .............

<table>
<thead>
<tr>
<th>Year</th>
<th>Duration of pregnancy</th>
<th>Cause for miscarriage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Have you been tested for thyroid function before? YES □ NO □

IF YES why .............

Do you have any of the following?

1. Family history of goiter / thyroid dysfunction YES □ NO □
2. Difficulty getting pregnant YES □ NO □
3. Recent neck radiation / surgery YES □ NO □
4. Any other medical illness YES □ NO □
5. If yes which one: diabetes □ hypertension □ other □
6. Are you currently taking any medications YES □ NO? □

If YES which ones

1. ........................................
2. ........................................
3. ........................................

Do the drugs affect thyroid function? YES □ NO □

**Ante–natal profile**

1. Blood group ..........................
2. Hemoglobin levels ..................
3. HIV status ..........................
4. VDRL ..........................
5. Urinalysis ..........................
PHYSICAL EXAM

Height .......... (Meters)

Weight .......... (kgs)

Blood pressure .......... (mm Hg)

Is the blood pressure: normal?  □ high? □ Low? □

Abdominal exam:

Fundal Height in cm...........

Fetal heart rate.............Neck exam .................

THYROID FUNCTION SERUM HORMONE LEVELS

TSH.........................

FT4..........................

OBSTETRIC ULTRASOUND RESULTS

Gestational age .....................

Does it correspond to clinical assessment? YES □ NO □

what is the Estimated fetal weight .....................

Is the weight corresponding with expected weight? YES □ NO □

If no, is it small for dates? □ Or is it large for dates? □
**Measurements:**

Bi-parietal diameter (BPD)………………………………

Head circumference (HC)………………………………

Abdominal circumference (AC) or diameter………… Is it normal YES? ☐ NO ☐

Crown- rump length ………………………………………

Head to abdominal circumference ratio …………… Is it normal YES? ☐ NO ☐

Doppler results (Resistive index), normal is less than 0.6

Is the RI > 0.6? YES ☐ NO ☐

Biophysical profile results ……………………………

**Interpretation of biophysical score:**

Normal (8-10) ☐

Abnormal / Absent (less than 8) ☐

what is the overall fetal growth?

Normal for gestational age ☐

Restricted growth ☐
10.3 APPENDIX 3: STANDARD NORMOGRAMS

Figure 2: figure showing ultrasound measurement normogram of head to abdominal circumference ratio

<table>
<thead>
<tr>
<th>GA (wks)</th>
<th>5th Percentile</th>
<th>Mean</th>
<th>95th Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>13-14</td>
<td>1.14</td>
<td>1.23</td>
<td>1.31</td>
</tr>
<tr>
<td>15-16</td>
<td>1.05</td>
<td>1.22</td>
<td>1.39</td>
</tr>
<tr>
<td>17-18</td>
<td>1.07</td>
<td>1.18</td>
<td>1.29</td>
</tr>
<tr>
<td>19-20</td>
<td>1.09</td>
<td>1.18</td>
<td>1.39</td>
</tr>
<tr>
<td>21-22</td>
<td>1.06</td>
<td>1.15</td>
<td>1.25</td>
</tr>
<tr>
<td>23-24</td>
<td>1.05</td>
<td>1.13</td>
<td>1.21</td>
</tr>
<tr>
<td>25-26</td>
<td>1.04</td>
<td>1.13</td>
<td>1.22</td>
</tr>
<tr>
<td>27-28</td>
<td>1.05</td>
<td>1.13</td>
<td>1.21</td>
</tr>
<tr>
<td>29-30</td>
<td>0.99</td>
<td>1.1</td>
<td>1.21</td>
</tr>
<tr>
<td>31-32</td>
<td>0.96</td>
<td>1.07</td>
<td>1.17</td>
</tr>
<tr>
<td>33-34</td>
<td>0.96</td>
<td>1.04</td>
<td>1.11</td>
</tr>
<tr>
<td>35-36</td>
<td>0.93</td>
<td>1.02</td>
<td>1.11</td>
</tr>
<tr>
<td>37-38</td>
<td>0.92</td>
<td>0.98</td>
<td>1.05</td>
</tr>
<tr>
<td>39-40</td>
<td>0.87</td>
<td>0.97</td>
<td>1.06</td>
</tr>
<tr>
<td>41-42</td>
<td>0.93</td>
<td>0.96</td>
<td>1</td>
</tr>
</tbody>
</table>

Head Circumference / Abdominal Circumference Ratio
Campbell S and Thomas A.
Ultrasound measurement of the fetal head to abdominal circumference in the assessment of growth retardation
Br J Obstet Gynaecol 1977;84:165-174
Figure 3: figure showing estimated fetal weight normogram
Figure 4: ultrasound fetal measurements standards chart

**NOTE:** +/- Standard deviations shown in (brackets). Measurements are for completed weeks.

<table>
<thead>
<tr>
<th>Gestation (weeks)</th>
<th>BPD (mm)</th>
<th>OFD (mm)</th>
<th>Head circumference (mm)</th>
<th>Abdominal circumference (mm)</th>
<th>Femur (mm)</th>
<th>Humerus (mm)</th>
<th>Gestation (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>16 (2.0)</td>
<td>21 (2.0)</td>
<td>59 (15)</td>
<td>52 (10)</td>
<td>8 (2.0)</td>
<td>8 (3.0)</td>
<td>11</td>
</tr>
<tr>
<td>12</td>
<td>20 (4.0)</td>
<td>24 (2.0)</td>
<td>70 (15)</td>
<td>63 (10)</td>
<td>10 (2.5)</td>
<td>9 (2.0)</td>
<td>12</td>
</tr>
<tr>
<td>13</td>
<td>24 (4.0)</td>
<td>29 (3.0)</td>
<td>84 (15)</td>
<td>74 (10)</td>
<td>11 (2.5)</td>
<td>11 (3.0)</td>
<td>13</td>
</tr>
<tr>
<td>14</td>
<td>28 (4.0)</td>
<td>34 (3.0)</td>
<td>96 (15)</td>
<td>84 (10)</td>
<td>15 (3.0)</td>
<td>14 (4.0)</td>
<td>14</td>
</tr>
<tr>
<td>15</td>
<td>31 (4.0)</td>
<td>38 (3.0)</td>
<td>108 (15)</td>
<td>96 (10)</td>
<td>17 (3.5)</td>
<td>17 (5.5)</td>
<td>15</td>
</tr>
<tr>
<td>16</td>
<td>36 (5.0)</td>
<td>46 (3.0)</td>
<td>128 (15)</td>
<td>106 (10)</td>
<td>22 (4.0)</td>
<td>21 (4.0)</td>
<td>16</td>
</tr>
<tr>
<td>17</td>
<td>39 (5.0)</td>
<td>50 (3.0)</td>
<td>141 (15)</td>
<td>120 (15)</td>
<td>25 (4.0)</td>
<td>25 (5.0)</td>
<td>17</td>
</tr>
<tr>
<td>18</td>
<td>42 (4.0)</td>
<td>54 (3.5)</td>
<td>151 (20)</td>
<td>131 (15)</td>
<td>28 (5.0)</td>
<td>27 (5.5)</td>
<td>18</td>
</tr>
<tr>
<td>19</td>
<td>45 (5.0)</td>
<td>57 (3.5)</td>
<td>160 (20)</td>
<td>140 (15)</td>
<td>30 (5.0)</td>
<td>29 (5.0)</td>
<td>19</td>
</tr>
<tr>
<td>Gestation (weeks)</td>
<td>BPD (mm)</td>
<td>OFD (mm)</td>
<td>Head circumference (mm)</td>
<td>Abdominal circumference (mm)</td>
<td>Femur (mm)</td>
<td>Humerus (mm)</td>
<td>Gestation (weeks)</td>
</tr>
<tr>
<td>------------------</td>
<td>----------</td>
<td>----------</td>
<td>-------------------------</td>
<td>----------------------------</td>
<td>------------</td>
<td>-------------</td>
<td>------------------</td>
</tr>
<tr>
<td>20</td>
<td>47 (4.0)</td>
<td>61 (3.5)</td>
<td>170 (20)</td>
<td>151 (15)</td>
<td>32 (6.0)</td>
<td>31 (5.0)</td>
<td>20</td>
</tr>
<tr>
<td>21</td>
<td>49 (4.0)</td>
<td>63 (4.0)</td>
<td>176 (20)</td>
<td>164 (20)</td>
<td>34 (6.0)</td>
<td>32 (6.0)</td>
<td>21</td>
</tr>
<tr>
<td>22</td>
<td>52 (5.0)</td>
<td>68 (3.5)</td>
<td>188 (20)</td>
<td>176 (20)</td>
<td>37 (5.0)</td>
<td>35 (6.0)</td>
<td>22</td>
</tr>
<tr>
<td>23</td>
<td>57 (5.0)</td>
<td>76 (4.0)</td>
<td>210 (20)</td>
<td>186 (20)</td>
<td>43 (5.0)</td>
<td>38 (4.0)</td>
<td>23</td>
</tr>
<tr>
<td>24</td>
<td>60 (6.0)</td>
<td>79 (4.0)</td>
<td>220 (20)</td>
<td>201 (20)</td>
<td>45 (4.0)</td>
<td>40 (6.0)</td>
<td>24</td>
</tr>
<tr>
<td>25</td>
<td>64 (6.0)</td>
<td>82 (4.5)</td>
<td>231 (20)</td>
<td>212 (20)</td>
<td>48 (5.0)</td>
<td>43 (5.0)</td>
<td>25</td>
</tr>
<tr>
<td>26</td>
<td>67 (4.0)</td>
<td>84 (4.5)</td>
<td>238 (20)</td>
<td>223 (25)</td>
<td>49 (5.0)</td>
<td>44 (4.0)</td>
<td>26</td>
</tr>
<tr>
<td>27</td>
<td>68 (5.0)</td>
<td>86 (4.5)</td>
<td>250 (20)</td>
<td>230 (25)</td>
<td>50 (5.0)</td>
<td>47 (4.0)</td>
<td>27</td>
</tr>
<tr>
<td>28</td>
<td>72 (4.0)</td>
<td>95 (5.0)</td>
<td>263 (20)</td>
<td>242 (25)</td>
<td>54 (4.0)</td>
<td>50 (5.0)</td>
<td>28</td>
</tr>
<tr>
<td>29</td>
<td>75 (4.0)</td>
<td>97 (5.5)</td>
<td>269 (25)</td>
<td>259 (25)</td>
<td>55 (5.5)</td>
<td>51 (5.0)</td>
<td>29</td>
</tr>
<tr>
<td>30</td>
<td>76 (4.0)</td>
<td>98 (5.5)</td>
<td>274 (25)</td>
<td>262 (25)</td>
<td>58 (6.0)</td>
<td>52 (5.0)</td>
<td>30</td>
</tr>
<tr>
<td>31</td>
<td>80 (6.0)</td>
<td>101 (5.0)</td>
<td>284 (25)</td>
<td>272 (30)</td>
<td>59 (5.5)</td>
<td>54 (5.0)</td>
<td>31</td>
</tr>
<tr>
<td>Gestation (weeks)</td>
<td>BPD (mm)</td>
<td>OFD (mm)</td>
<td>Head circumference (mm)</td>
<td>Abdominal circumference (mm)</td>
<td>Femur (mm)</td>
<td>Humerus (mm)</td>
<td>Gestation (weeks)</td>
</tr>
<tr>
<td>------------------</td>
<td>-----------</td>
<td>-----------</td>
<td>-------------------------</td>
<td>----------------------------</td>
<td>-------------</td>
<td>-------------</td>
<td>------------------</td>
</tr>
<tr>
<td>32</td>
<td>81 (4.0)</td>
<td>102 (5.0)</td>
<td>288 (25)</td>
<td>283 (30)</td>
<td>62 (6.0)</td>
<td>56 (5.0)</td>
<td>32</td>
</tr>
<tr>
<td>33</td>
<td>84 (6.0)</td>
<td>107 (5.5)</td>
<td>300 (25)</td>
<td>294 (30)</td>
<td>65 (4.0)</td>
<td>57 (6.0)</td>
<td>33</td>
</tr>
<tr>
<td>34</td>
<td>86 (6.0)</td>
<td>108 (5.5)</td>
<td>305 (25)</td>
<td>305 (30)</td>
<td>66 (4.0)</td>
<td>59 (5.5)</td>
<td>34</td>
</tr>
<tr>
<td>35</td>
<td>88 (6.5)</td>
<td>109 (5.5)</td>
<td>310 (25)</td>
<td>315 (30)</td>
<td>67 (6.0)</td>
<td>60 (6.0)</td>
<td>35</td>
</tr>
<tr>
<td>36</td>
<td>90 (6.0)</td>
<td>112 (5.5)</td>
<td>317 (25)</td>
<td>325 (35)</td>
<td>69 (6.0)</td>
<td>62 (5.0)</td>
<td>36</td>
</tr>
<tr>
<td>37</td>
<td>92 (6.5)</td>
<td>113 (6.0)</td>
<td>321 (25)</td>
<td>333 (35)</td>
<td>72 (5.0)</td>
<td>63 (6.0)</td>
<td>37</td>
</tr>
<tr>
<td>38</td>
<td>93 (6.0)</td>
<td>116 (5.5)</td>
<td>328 (25)</td>
<td>342 (35)</td>
<td>73 (5.5)</td>
<td>64 (6.0)</td>
<td>38</td>
</tr>
<tr>
<td>39</td>
<td>95 (8.0)</td>
<td>119 (6.0)</td>
<td>336 (25)</td>
<td>356 (35)</td>
<td>75 (6.0)</td>
<td>65 (5.5)</td>
<td>39</td>
</tr>
<tr>
<td>40</td>
<td>96 (8.0)</td>
<td>120 (6.0)</td>
<td>340 (25)</td>
<td>362 (35)</td>
<td>76 (4.0)</td>
<td>66 (6.0)</td>
<td>40</td>
</tr>
<tr>
<td>41</td>
<td>98 (8.0)</td>
<td>122 (6.0)</td>
<td>344 (25)</td>
<td>367 (35)</td>
<td>77 (5.0)</td>
<td>68 (6.0)</td>
<td>41</td>
</tr>
<tr>
<td>Gestation (weeks/days)</td>
<td>CRL (mm)</td>
<td>Gestation (weeks/days)</td>
<td>CRL (mm)</td>
<td>Gestation (weeks/days)</td>
<td>CRL (mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------</td>
<td>----------</td>
<td>------------------------</td>
<td>----------</td>
<td>------------------------</td>
<td>----------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.2</td>
<td>1</td>
<td>8.3</td>
<td>20</td>
<td>11.4</td>
<td>52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.3</td>
<td>2</td>
<td>8.4</td>
<td>21</td>
<td>11.5</td>
<td>55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.4</td>
<td>3</td>
<td>8.5</td>
<td>22</td>
<td>11.6</td>
<td>56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.5</td>
<td>3</td>
<td>8.6</td>
<td>22</td>
<td>12.0</td>
<td>57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.6</td>
<td>4</td>
<td>9.0</td>
<td>23</td>
<td>12.1</td>
<td>58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.0</td>
<td>4</td>
<td>9.1</td>
<td>24</td>
<td>12.2</td>
<td>60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.1</td>
<td>5</td>
<td>9.2</td>
<td>26</td>
<td>12.3</td>
<td>61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.2</td>
<td>6</td>
<td>9.3</td>
<td>27</td>
<td>12.4</td>
<td>63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.3</td>
<td>7</td>
<td>9.4</td>
<td>28</td>
<td>12.5</td>
<td>64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.4</td>
<td>8</td>
<td>9.5</td>
<td>29</td>
<td>12.6</td>
<td>65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.5</td>
<td>9</td>
<td>9.6</td>
<td>31</td>
<td>13.0</td>
<td>68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.6</td>
<td>10</td>
<td>10.0</td>
<td>34</td>
<td>13.1</td>
<td>70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.0</td>
<td>11</td>
<td>10.1</td>
<td>36</td>
<td>13.2</td>
<td>72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.1</td>
<td>11</td>
<td>10.2</td>
<td>37</td>
<td>13.3</td>
<td>74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.2</td>
<td>12</td>
<td>10.3</td>
<td>38</td>
<td>13.4</td>
<td>76</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.3</td>
<td>12</td>
<td>10.4</td>
<td>39</td>
<td>13.5</td>
<td>77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.4</td>
<td>13</td>
<td>10.5</td>
<td>39</td>
<td>13.6</td>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----</td>
<td>----</td>
<td>------</td>
<td>----</td>
<td>------</td>
<td>----</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.5</td>
<td>14</td>
<td>10.6</td>
<td>40</td>
<td>14.0</td>
<td>81</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.6</td>
<td>15</td>
<td>11.0</td>
<td>44</td>
<td>14.1</td>
<td>84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.0</td>
<td>17</td>
<td>11.1</td>
<td>45</td>
<td>14.2</td>
<td>85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.1</td>
<td>18</td>
<td>11.2</td>
<td>47</td>
<td>14.3</td>
<td>86</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.2</td>
<td>19</td>
<td>11.3</td>
<td>48</td>
<td>14.4</td>
<td>87</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>