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COLLEGE OF HEALTH SCIENCES, SCHOOL OF MEDICINE

DEPARTMENT OF ANATOMY

EFFECTS OF PREECLAMPSIA AND INTRAUTERINE GROWTH RESTRICTION ON MORPHOLOGY OF THE PLACENTA AND BIRTH WEIGHT OF FETUS IN TIKUR ANBESSA SPECIALIZED HOSPITAL, ADDIS ABABA, ETHIOPIA.

A THESIS SUBMITTED TO ANATOMY DEPARTMENT, SCHOOL OF MEDICINE ADDIS ABABA UNIVERSITY FOR PARTIAL FULFILLMENT OF THE REQUIREMENT OF MASTER'S DEGREE IN ANATOMY.

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DECLARATION

By my signature below, I declare and affirm that this thesis is my work. I have followed all ethical principles of scholarship in the preparation, data collection, data analysis, and completion of this thesis. All scholarly matter that is included in the thesis has been given recognition through citation. I affirm that I have cited and referenced all sources used in this document. Every effort has been made to avoid plagiarism in the preparation of this thesis. This thesis is submitted in partial fulfillment of the requirement for a Master's degree in Anatomy from Addis Ababa University at the College of Health Sciences, School of medicine. The thesis is deposited in the Addis Ababa University Digital Library and is made available to local, national, and international scientific communities.

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TABLE OF CONTENTS

ACRONYMS AND ABBREVIATIONS

ANC _____Antenatal Care

ANOVA_____ Analysis of Variance

FGR_____ Fetal Growth Restriction

HDP_____ Hypertensive Disorders of Pregnancy

HELLP_____ Hemolysis Elevated Liver Function Enzymes and Low Platelets

IUGR_____ Intrauterine Growth Retardation/ Restriction

LBW_____ Low Birth Weight

PE_____ Preeclampsia

PIH_____ Pregnancy Induced Hypertension

SD_____ Standard Deviation

SE_____ Standard Error

SGA_____ Small for Gestational Age

SPSS_____ Statistical Package for Social Sciences

WHO_____ World Health Organization

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

Background: The placenta is a unique characteristic of higher mammals that develops in the uterus during pregnancy. It is connected with the fetus through the umbilical cord. Preeclampsia (PE) and Intrauterine growth restriction (IUGR) influence the normal function of the placenta which in turn affects the birth weight of the fetus.

Objective: To comparethe Effects of Preeclampsia and IUGR on Morphology of Placenta and Birth Weight of Fetus in Tikur Anbessa Specialized Hospital from May 2019 to June 2019.

Method:A comparative cross-sectional study was conducted on 54 pregnant women consisting of 22 mothers with PE, 10 with IUGR, and 22 without any complication. Maternal, fetal, and placental data were recorded after delivery. The micro/macroarchitecture of the placenta was examined by inspection, measuring and microscopically. The data were entered using EPI data version 4.2.0 and analyzed by SPSS version 21. One way ANOVA was performed to compare the mean differences of the placenta and the newborn's weight across the groups. P values less than 0.05 were assumed as statistically significant.

Results: The findings showed that placental weight was 485.45gm in the normotensive, 422.27gm in the PE, and 328.00gm in IUGR groups ($p<0.002$). The mean placental diameter was 19.05cm, 17.07cm, and 15.08cm in uncomplicated, PE, and IUGR mothers respectively ($p<0.001$). The mean placental thickness was 21.16mm in uncomplicated, 19.42mm in PE, and 17.06mm in IUGR mothers ($p<0.001$). The mean placental number of cotyledons in the uncomplicated group was 19.00 whereas it was 17.18 and 15.10 in PE and IUGR participants respectively ($p<0.001$). Histological results; placental calcification was observed in 60% of IUGR and 36.4% of PE, infarction in 40% of IUGR and 36.4% of PE, thrombosis in 30% of IUGR, cytotrophoblast proliferation in 31.8% PE, syncytial knots in 36.4% of PE, basement membrane thickening in 30% of IUGR and fibrinoid necrosis in 22.7% of PE groups.

Conclusion: Preeclampsia and IUGR significantly decreased the weight, diameter, thickness, and the number of cotyledons of the placenta. The weights of the babies also were significantly smaller in IUGR. Even though it was not statistically significant histological abnormalities of the placenta was more common among IUGR and PE patients than the uncomplicated pregnancies. Using the current study as a baseline, investigations should be conducted on the effects of specific types of preeclampsia on morphology of placenta.

Keywords: Birth weight, Intrauterine growth restriction, Morphology, Placenta, Preeclampsia

1. INTRODUCTION

1.1. Background

The placenta is a unique characteristic of higher mammals which is attached to the uterus and is connected to the fetus through the umbilical cord(1). It develops from chorion frondosum and decidua basalis. The placenta begins to meet the demand of the embryo as early as the third week of intrauterine life(2). It is an organ that transfers vital nutrients from mother to embryo and the waste products from embryo to mother(3).

The placenta is also a major endocrine organ, secreting more than 100 peptide and steroid hormones that modulate maternal physiology(4). Its weight is approximately 1/6th of the fetal weight(5). At term, 1/5th part of the placenta is of maternal origin and 4/5th part of the placenta is of fetal origin which is dark reddish-blue and discoid organ, 15- 25cm in diameter, 400- 600gm in weight, 2- 3cm in thickness, and 15 - 20 cotyledons(6).

No organ can match the placenta for the diversity of its functions because it performs the actions of all the major organ systems while these differentiate and mature in the fetus but also it is the principal cause of maternal and perinatal mortality if it is abnormal(4, 5).

Various clinical conditions such as anemia, diabetes, hypertension, and others have a detrimental effect on the placenta occasionally resulting in morphological change. Some researchers observed thatplacenta has compensatory mechanism which tends to limit ill-effects of both tissue and unfavorable maternal situations like hypertension(7). The placenta depicts the most accurate record of the prenatal experience of an infant(8). It undergoes different changes in weight, volume, structures, shape, and function continuously throughout the gestation to support perinatal life(8).

HDP (Hypertensive disorders of pregnancy) affect about 10% of all pregnant women around the world(9). Preeclampsia is a pregnancy-related metabolic disease that affects the placenta macroscopically as well as microscopically which in turn will impact maternal health as well as the fetus(10, 11).

PE (Preeclampsia) usually occurs after 20 weeks of gestation (or earlier with trophoblastic diseases). It is characterized by increased blood pressure ≥140/90 mmHg and proteinuria (≥300mg/24hr or ≥+2 dipstick) in a woman normotensive before 20 weeks(12).

The pathogenesis of PE is complex; numerous genetic, immunologic, and environmental factors interact. It has been suggested that PE is a two-stage disease. The first stage is asymptomatic, characterized by abnormal placental development during the first trimester resulting in placental insufficiency and the release of excessive amounts of placental materials into the maternal circulation. This in turn leads to the second, symptomatic stage, wherein the pregnant woman develops characteristic hypertension, renal impairment, and proteinuria and is at risk for the HELLP syndrome (hemolysis, elevated liver function enzymes, and low platelets), eclampsia, and other end-organ damage(13).

Obesity, chronic hypertension, and diabetes are among the risk factors for PE, which also include nulliparity, adolescent pregnancy, and conditions leading to hyperplacentation and large placentas (e.g. twin pregnancy)(14).

PEand IUGR (intrauterine growth restriction) are pregnancy complications that substantially contribute to both perinatal morbidity and mortality. Their etiologies are unknown, but clinically they are interrelated, with PE often accompanying IUGR and small for gestational age (SGA) infants(15).

IUGR is defined as the failure of the fetus to reach normal growth potential at a particular gestational age(16). Fetal growth impairment is seen in about 10% of pregnancies, but most of such pregnancies will have a physiologically normal fetus called SGA babies (birth weight is below the tenth percentile for a given gestational age). But IUGR is a pathological condition leading to prematurity, prenatal mortality, neurological and respiratory morbidities, and immediate problems of hypothermia, hypoglycemia, pulmonary hemorrhage, and encephalopathy. It has many possible causes and placental abnormality could be one of them(17).

The gross and microscopic measurements of a placenta offer a good way to get proper information about IUGR by predicting its etiology using its effects on it. The weight of the IUGR placenta was less than the normal placenta.Infarction rate, thrombosis, tissue ischemia, increased thickness of membranes and intervillous fibrin were significantly higher in the IUGR group(18).

As the placenta is the direct link between mother and fetus, the examination of the placenta should give a clear idea of what had happened with it, when it was in the mother’s womb, and what is going to happen with the fetus in the future. It can provide much insight into the prenatal health of the baby and the mother.

1.2. Statement of the Problem

While motherhood is a positive and enjoyable experience, many women are experiencing suffering, illness, and death. Around 15% of pregnant women are expected to develop life-threatening complications during pregnancy, at delivery, or post-partum. HDP are significant contributors to these complications(19).

Although maternal mortality has been reduced significantly, the perinatal mortality remains very high even in the developed countries (7–10%). In the developing countries, the perinatal mortality remains to the extent of about 20%, 50% of which being stillborn(20).

Around 40,000 women, mostly from developing countries, die each year due to preeclampsia or eclampsia. Preeclampsia alone is estimated to account for about 40% to 60% of maternal deaths in developing countries(19, 21).

A hospital-based study conducted in South Africa showed that HDP contributed to 20.7% of maternal deaths in the country(21). HDP accounts for 19% of maternal deaths in Ethiopia(22).

A cross-sectional study done by Teklu and Gaym in 2006 implies that the prevalence of preeclampsia among pregnant mothers attending antenatal clinics in Tikur Anbessa Hospital was 5.3% and in Addis Ababa city it was 5.41%(23).

The most common abnormalities preeclampsia causes are poor growth as a result of inadequate blood supply through the damaged placenta, and the problems of prematurity(9).

Preeclampsia is an antecedent for up to 12% of infants born SGA and $1/5^{th}$ of those born preterm. Perinatal mortality is high after preeclampsia and even higher after eclampsia. One-quarter of stillbirths and neonatal deaths in developing countries are associated with PE and eclampsia. In low and middle-income countries, many public hospitals have little or no access to neonatal intensive care, and so the mortality and morbidity associated with preeclampsia and eclampsia are likely to be considerably higher than in settings where such facilities are available(9).

Preeclampsia and IUGR are of uncertain etiology, complicate a significant proportion of all pregnancies, and contribute to maternal and perinatal morbidity and mortality(24).

The following hazards may occur due to preeclampsia; Intrauterine fetal death, IUGR, Asphyxia, and Prematurity(20).Besides prematurity, fetal growth restriction (FGR) is the second leading cause of perinatal mortality and morbidity, affecting about 5% of all pregnancies(25).

Studies suggest that both PE and IUGR pregnancies are associated with reduced fetal weights. PE alone had little effect on placental weight or composition. In marked contrast, IUGR had substantial effects on placental weight and composition regardless of whether or not this was complicated further by PE.

The examination of placental anatomy has been useful in utero as well as after parturition. After delivery, if the placenta is inspected meticulously, it can provide much insight into the prenatal health of the baby and the mother. Morphometric features of the placenta can be correlated to fetal wellbeing. The growth of the fetus depends on the adequate functionality of the placenta. It shares the same stress and strain to which the fetus is exposed. Thus any disease which affects the mother has a great impact on the placenta. The anatomical structure of the placenta greatly influences function. Thus a study of placental morphology is considered essential.

This study was conducted to put some baseline data on effects of PE and IUGR on morphology of the placenta and birth weight of fetus. Even though studies on this area are being carried outglobally it has differences in races, economic status and health care standards. Since PE and IUGRare public health important diseases in Ethiopia, there are a lot of mothers who suffered from it. One of the reason is, they didn't get full antenatal care follow up and they went to the health center without being recorded. Therefore, examining the placenta thoroughly is helpful for health professionals to predict the etiology of the disease and to save the newborn's life.

1.3. Significance of the Study

The human placenta plays a key role to support the growing fetus. The mother, placenta, and fetus constitute the triad for the perinatal outcome. So it is an effective index by examination of which we can predict the status of the fetus in utero as well as in neonatal life. It may act as an indicator of the overall development of the fetus in cases of PE and IUGR. Therefore examination of the placenta in cases of maternal disorders provides vital information to both obstetricians and neonatologists by explaining the biology of the disease, predicting recurrence, and identifying specific disorders.

It becomes more and more obvious that preeclampsia and FGR are different entities affecting different cells and tissues within the placenta, although both may be associated with impaired placentation. Only a thorough analysis and comparison of both syndromes can decipher their similarities and differences.

In the case of idiopathic intrauterine growth-restricted babies where there are no apparent maternal and fetal reasons, the placenta might hold the key to its etiology. So, this study was undertaken to quantitatively evaluate various dimensions of the placenta and analyze their relationship with fetal birth weight, and to note the abnormalities in the placenta with PE and IUGR.

In mothers who had no previous antenatal checkup, a thorough examination of the placental morphology will help in the early diagnosis of the fatal complications, soon after parturition, and guide post-partum management of mother and newborn, especially in a rural setup.

This study will help inunderstanding the types and degrees ofeffects that PE and IUGR causes on the placenta and birth weight of fetus,which will lead to specific treatment and preventive measures for those with risk for recurrence in subsequent pregnancies.

Moreover, few investigations have been conducted globally regarding this important issue. No similar study has been conducted in Ethiopia. Therefore, the findings of this research will offer baseline data for future detailed investigations in Ethiopia as well as in the world.

2. LITERATURE REVIEW

2.1. What is Placenta?

The term placenta means ‘flat cake’ in Latin(26). The placenta is a feto-maternal organ that has afetal part that develops from the chorionic sac, and a maternal part that is derived from the endometrium(27).

2.2. Morphology of Placenta

In the human placenta, the primary barrier to maternal-fetal exchange is the syncytiotrophoblast, a transporting epithelium covering the placental villi which project into the maternal blood of the intervillous space. Villi contain capillary networks derived from fetal circulation(28).

Any pathological event that concerns the mother or the fetus will influence the normal function of the placenta, occasionally resulting in morphological change(29).

Morphology of the placenta is characterized by its shape, weight, diameter, thickness, lobes/cotyledons, and microarchitecture. Research studies have employed quantitative descriptions of placental morphology by stereology and morphometry to describe differences in placental structure in clinical conditions.

2.2.1. Shape of Placenta

The shape of the placenta is determined by the persistent area of chorionic villi. Usually, this is a circular area, giving the placenta a discoid shape. The definitive shape of the human placenta is a result of the disappearance of villi from all but a circumscribed locus on the chorion(30). Deviation from the round or oval shape such as an irregularly shaped, bilobed or multilobed placenta can be attributed to disturbed implantation or uterine abnormalities, but it can be assessed only in the clinicopathological context(29).

A research conducted in West U. P. India, on 60 mothers with an uncomplicated pregnancy and 60 mothers with pregnancy with hypertensive disorder shows that majority of the placenta is discoidal in shape (90% and 86% in control and hypertensive group respectively), out of which prevalence of oval shape placentae is 73.3% and 80% in control and hypertensive group respectively, while the prevalence of circular-shaped is 16.6 and 6.6% in control and hypertensive groups. Irregularly shaped placentae were present only in 10% and 13.3% cases in control and hypertensive groups respectively(31).

Kishwara et al., (2009) observed that discoidal shape placenta (76.69%& 73.3%) is more prevalent over irregularly shaped placenta (23.3%& 26.7%) in control as well as hypertensive groups. In the study of amongst the discoidal placenta, circular-shaped placenta (circular 43.3%& oval 33.3%) were the most common type seen in the control group and oval placenta (circular 33.3%& oval 40%) were the most common type shape found in the hypertensive group(32).

These shape anomalies reflect a failure or disturbance in the pattern of orderly villous atrophy and proliferation that generally results in a single circular or oval placental disc with a transition to fetal membranes at the disk edge(33).

2.2.2. Weight of Placenta

Placental weight is one of several standard placental measurements by which placental growth can be characterized. It is a summary of different dimensions of growth, including placental thickness, shape,the number of blood vessels, cord insertion, and arborization of the villous and vascular nutrient exchange surface reflected in increased thickness of the disk(34).

The weight of the placenta is functionally significant as it is related to villous surface area and fetal metabolism(10). It is around 400–600gm usually one-sixth of the fetal weight(6).

The relationship between placental weight and birthweight is sometimes expressed as the feto-placental ratio, a proportion with fetal weight in the numerator and placental weight in the denominator. This ratio is influenced by exogenous signals in the fetus, the mother, or both(35).

The weight of the placenta gives an idea of the amount of substance that is exchanged between the mother and the fetus(36). Early in the second trimester, the placenta approximates the fetus in size and continues to grow until term. As pregnancy advances, it becomes relatively smaller and by term, the ratio of its weight to that of the fetus is about 1:6 to 1:7(37).

Kmbale et al., (2016) reported the feto-placental weight ratio in the normal group as 5.68 and Pregnancy-induced hypertension (PIH)group as 5.38:1(38). Majumdar (2005) reported values of 6.23±0.87:1 and observed reduced feto-placental weight ratio with an increasing degree of PIH(39).

According to research conducted in India, the mean placental weight was 495gm in the control group, 435.63gm in mild hypertension, and 371.43gm in severe hypertension. Thus there is a significant lowering of placental weight in PIH. As the severity of hypertension increases, placental weight

decreases as confirmed by minimum placental weight of 250gm in mild hypertension and 200gm in severe hypertension. A significant increase in the incidence of intrauterine growth retardation and stillbirth is found with lower placental weight(40).

Chakravorty (1967) in his study of PIH found the mean placental weight of 435±25gm in mild and 371±25gm in severe preeclampsia(41).

Research conducted in Belgium implies placental weight and the fetal-placental weight ratio in the IUGR group is significantly lower than controls. The average placental weights were 440gm and 585gm in the IUGR and control groups respectively (P=0.000). The placenta of the IUGR group is smaller than the normal group(18).

2.2.3. Diameter and Thickness of Placenta

The diameter of the placenta may give an idea about the size of the placenta which may intend to give indirect information about the fetal-placental ratio. The diameter of the placenta will affect the number of nutrients, oxygen, and carbon dioxide that will pass from the mother to the child and vice versa.

The thickness of the placenta may give indirect information on the fetal-placental ratio as well. It may indicate the number of substances that are exchanged between the fetus and the mother(36).

The term placenta is 15cm to 20cm in diameter and 2cm to 3cm in thickness(6).

A study conducted on morphological Changes of the placenta in preeclampsia observed that the mean diameter of the placenta was 18.64±1.81cm in mild PE, and 17.94±1.96cm in severe PE and in comparison with a non-PE group which was 20.33±1.45cm, whereas, the mean central thickness of the placenta area was 1.96±0.2cm, 1.77±0.42cm and 2.02±0.2 in mild PE, severe PE, and non-PE mothers respectively(42).

Another study conducted in India noted that the mean placental diameter and thickness were 17.2cm and 1.8cm in preeclamptic placentas and 18.7cm and 2.3cm in normotensive placentas. Preeclamptic placentas were smaller and thinner as compared to normotensive(10).

2.2.4. Number of Cotyledons of Placenta

The functional unit of the placenta is the fetal cotyledon and the mature human placenta has about 120 cotyledons, which are sometimes grouped into visible lobes. Each cotyledon contains a primary villous stem arising from the chorionic plate and supplied by primary branches of fetal vessels(43).

After birth, when the placenta is viewed from the maternal side, 15 to 20 slightly bulging areas, the cotyledons, covered by a thin layer of decidua basalis are recognizable. Grooves between the cotyledons are formed by decidua septa(44).

According to a study in Sudan, the mean number of cotyledons was 18.88 with SD 1.73 and ranged from 12 to 22, and also a study in India the average number of cotyledons was 18(1, 45).

The number of cotyledons is less in preeclamptic placentae as compared to normotensive. A study reported the mean number of cotyledons was 18.9 in normotensive placentae and 16 in preeclamptic placentae and intercotyledonous vasculature is altered in hypertensive placentae resulting in low birth weight babies(10, 46).

2.2.5. Histology of Placenta

The placental histology can add useful information in ascertaining the cause and mechanism involved in adverse pregnancy outcomes. Although an interpretation of histological lesions is complex and requires skill and insight into clinical-pathologic correlation (47), histological placental evaluation provides valuable features that are useful to parents in understanding the cause of an adverse outcome(48), and useful to health care providers both for parent counseling and as a legal defense in cases of medical malpractice allegations(47).

A study conducted in India reported an increase in the incidence of infarction (28.8%) and retroplacental hematoma (15.5%) in the hypertensive group. Percentage of the cytotrophoblastic proliferation of villi, syncytial knots formation (64.5%), basement membrane thickening of villi (37.8%), and fibrinoid necrosis of villi (46.7%) increased in the placentae from the PIH group as compared to the normal group. This research concluded, HDP adversely influences the morphology of the placenta which then affects the perinatal and fetal outcome(38).

Ghomian N et al. (2014) found that infarction rate, thrombosis, tissue ischemia, increased thickness of membranes and intervillous fibrin was significantly higher in the IUGR group than normal placentas(18). Similar to this study Vedmedovska et al. (2011) reported the thickening of the villous

trophoblastic basal membrane, incidence of villous infarction, presence of thrombi, or hematomas, and the incidence of villitis were more common in the FGR group than in the controls ($p<0.05$). There were, however, no significant differences in peri-villous fibrin deposition, stromal fibrosis, and cytotrophoblast proliferation between the groups(49).

2.3. Factors Contributing to Differences in Fetal Weight

Fetal weight can be influenced by many factors, both endogenous and extrinsic factors. These factors include gestational age at delivery, maternal factors, paternal factors, environmental influences, physiological factors, pathological factors (hypertension, uterine malformation), and complications of pregnancy (gestational diabetes mellitus, preeclampsia)(50).

A lot of work has been done to find out the effect the placenta has on the well-being of the baby. Some studies conducted in this area revealed so many relationships between the placenta and the baby that come out of the placenta. According to the work done by Luz et al. (2001) on 300 live newborns with a gestational age of 37 weeks or older, the mean of birth weight was 3369±445gm. Placenta weight was a mean of 537±96gm. The relation between the weight of the placenta and the birth weight was significant, and it was found that for each gram increase in placenta weight, birth weight is increased by 1.98gm (SE = 0.25, $p<0.01$) and this relation are not linear since the quadratic term is significant. Placenta weight has a non-linear relation to birth weight and is an important predictor of birth weight(51).

2.4. Effect of PE on Placenta and Birth Weight of the Fetus

Preeclampsia is one of the pregnancy-induced metabolic diseases that may jeopardize the health of the mother and the fetus(52). PE contributes to complications like preterm birth, perinatal death, IUGR, and is directly associated with 10 to 15 % of maternal deaths(53). Pregnancy complications like PE are reflected in the placenta both macro and microscopically. The fetus depends on the placenta for normal development, thus pathological changes in the placenta result in reduced blood flow across the placenta and cause uteroplacental insufficiency(54).

A research conducted on Morphological Changes of Placenta in Preeclampsia reported that all values related to the diameter, thickness, number of cotyledons, and volume of placentae in the PE group were found lower than that of the control group and this was contributed to the insufficient blood supply due to PE(32, 38).

Udania (2001), there was a significant lowering of placental weight in PIH and it was directly proportional to the severity of the disease. The mean weight of the newborn baby was 2640gm in the control group, 2480gm in mild hypertension, and 2050gm in severe hypertension. This indicates that the weight of newborn babies is significantly low in PIH and it decreases with an increase in the severity of hypertension(40).

2.5. Effect of IUGR on Placenta and Birth Weight of the Fetus

IUGR is a term applied to infants who are at or below the 10^{th}percentile for their expected birth weight at a given gestational age. Approximately 1 in 10 babies have IUGR(44). Risk factors that cause IUGR are; Maternal (Anemia, hypertension, thrombotic diseases, heart disease, chronic renal disease, collagen vascular disease), placental (The causes include cases of poor uterine blood flow which leads to chronic placental insufficiency with inadequate substrate transfer), and fetal (multiple gestation, chromosomal and structural abnormalities) are the important causes(20).

In the placentas of IUGR infants, the mean surface area and the capillary surface area were reduced, implying a diminished diffusing capacity. It had been found that the terminal villi from the IUGR cases were smaller in diameter than controls, had increased syncytial nuclei relative to cytotrophoblastic nuclei, thickened basal lamina, and increased stromal deposition of collagens and laminin. Villous capillary loops in IUGR cases were relatively sparse in number and significantly longer than in control cases(55). Ghomian N et al. (2014) concluded that the placenta of the IUGR group was smaller than the normal group. The fetal-placental weight ratio in the IUGR group was lower than controls. Important pathologic findings were infarction, thrombosis, ischemia, avascular villi, increased placental membranes thickness, and intervillous fibrosis(18).

3. OBJECTIVES

3.1. General Objective

To comparethe Effects of Preeclampsia and IUGR on Morphology of Placenta and Birth Weight of Fetus in Tikur Anbessa Specialized Hospital from May 2019 to June 2019.

3.2. Specific Objectives

- To compare the morphology of placenta between normal and PE mothers.
- To compare the morphology of placenta between normal and IUGR pregnancies.
- To compare the birth weight of the baby between normal andPE mothers.
- To compare the birth weight of the baby between the normal and IUGR pregnancies.

4. MATERIALS AND METHODS

4.1. Study Design and Study Period

A comparative cross-sectional study design was conductedfrom May 2019–June 2019.

4.2. Study Area

The study was conducted in Tikur Anbessa Specialized Hospital; Obstetrics and Gynecology ward, Addis Ababa, Ethiopia. The ward has antepartum, intrapartum, and postpartum services for obstetric patients. The delivery ward has six laboring beds, one neonatal resuscitation room which has a radiant warmer, oxygen, and suction machine. It has an average monthly delivery of 300-400 babies.

Addis Ababa the capital city of the Federal Democratic Republic of Ethiopia, is located at the Centre of a country, it is the home of the African Union, Economic Commission for Africa, and international organizations. Addis Ababa has an aggregate population density of 4,847.8 persons per square kilometer. The city has 10 sub-city and 116 woredas. There are 51 hospitals of which 6 are owned by the Addis Ababa City Administration Health Bureau, 4 by the Federal Ministry of Health, 1 by Addis Ababa University, 3 by Non-governmental organization, 3 by Defense Force, and Police, and 34 by private owners.

4.3. Source Population

- All term pregnant mothers who attend their delivery at Tikur Anbessa Specialized Hospital.

4.4. Study Population

- Pregnant mothers at term with uncomplicated pregnancies as control, mothers with PE, and mothers with IUGR as case groups, who were attended their delivery at Tikur Anbessa Specialized Hospital during our data collection period.

4.5. Eligibility Criteria

4.5.1. Inclusion Criteria

Group I

- All pregnant mothers who were diagnosed with PE and delivered in between 37-42 weeks of gestation.

Group II

- All pregnant mothers who were diagnosed with IUGR and delivered in between 37-42 weeks of gestation.

Group III

- All normotensive mothers who delivered in between 37-42 weeks and not complicated by IUGR, PE or other conditions such as diabetes mellitus and renal disease.

4.5.2. Exclusion Criteria

Any pathological condition which affectsthe placenta as well as the fetus, for instance, pregnant mothers who experience any complication during pregnancy like Gestational Hypertension, Chronic Hypertension, pre-existing Diabetes Mellitus, Gestational Diabetics Mellitus, Eclampsia, Intrauterine Fetal Death, Chronic Intrauterine Infection, Fetal Hydrops, Retroviral Infections, Anemia, Multiple Pregnancies, Placenta Accereta, Placenta Percreta, Placenta Previa, Abruption of Placenta, Rh Iso-immunization, Incomplete delivery of the placenta, diagnosed Single Umbilical Artery, Pre and Post-term pregnancies were excluded from this study.

4.6. Sample Size Determination and Sampling Method

The sample size of 22 was calculated with the mean difference formula.

$$n_1 = \frac{(\sigma_1^2 + \sigma_2^2)\,(Z_{\alpha/2} + Z_{\beta})^2}{(\mu_1 - \mu_2)^2}$$

Using the assumption of an average size of 497.95gm (SD=89.1) and 417.6gm (SD=102.41) (56)for the normal and placenta from a woman with PE, 5% level of significance ($Z_{a/2}$=1.96), power of 80% (Z_{β}=0.84), and a ratio of 1:1 for both groups.

And, another sample size of 10 was calculated with the same formula by using an assumption of the average size of 585.7gm (SD=149.4) and 440gm (SD=64.5) (18)for the normal and placenta from a woman with IUGR, 5% level of significance ($Z_{a/2}$=1.96), power of 80% (Z_{β}=0.84) and a ratio of 1:1 for both groups.

Note: The final sample size for placental morphology was54 which is10 for IUGR, 22 for PE, and since we can compare normal placentas with both cases We choose the largest one which is 22.

4.7. Sampling Technique and Procedure

A purposive sampling technique was employed to conduct this research; during the data collection period, the number of mothers who delivered at Tikur Anbessa Hospital was expected to be 350. From those 350 mothers who delivered in the hospital, the sample was taken purposively until the total sample size is achieved. And, for those 22 control groups, a systematic random sampling with a skip interval of 7 (N/n=350/54~6.5) was used.

4.8. Variables

4.8.1. Dependent Variables

- Gross morphology: weight, shape, thickness, diameter, and number of cotyledons
- Microscopic morphology
- Birth weight of the fetus

4.8.2. Independent Variables

- Maternal preeclampsia: mild and severe
- IUGR
- Socio-demographic characteristics: age, sex of the fetus and parity.

4.9. Operational Definitions

- **Preeclampsia:** ≥300 mg/L proteinuria in a 24-hour collection or >2+ on avoided random sample of urine (in the absence of urinary tract infection) together with blood pressure in a previously normotensive woman of ≥140/90mmHg on two or more occasions(12).
- **Severe preeclampsia:** with severe hypertension (blood pressure ≥160/110mmHg), severe proteinuria (≥5gms in 24hours), or other signs/symptoms of end-organ injury are present.
- **Mild preeclampsia:** in the absence of any of the severe signs it is classified as 'mild'
- **IUGR:** is a fetus whose estimated weight is below the 10^{th} percentile for its gestational age on ultrasound scan(57).
- **Birth weight:** bodyweight of babies recorded post-delivery immediately after placental delivery.
- **The irregular shape of the placenta:** all shape of the placenta except circular or oval.

4.10. Data Collection Tool and Procedure

4.10.1. Materials

To conduct the study we used a standard weight scale, flat tray, measuring cylinder, wooden block, gloves, towels, plastic sheet, sponge, blade holder and blade, metallic ruler, embedding cassette, tissue block, hematoxylin and eosin, glass slide with its cover, paraffin wax, xylene, needle, digital camera, alcohol, and formalin solution.

4.10.2. Data Collection Procedure

After getting ethical approval from the institutional review board of Addis Ababa University, a letter of cooperation was written by Anatomy Department to the Head of Obstetrics and Gynecology department and other concerned bodies. Written informed consent was obtained from the study participants. Data were collected by a trained BSc Midwifery nurse who works in the delivery room. Data collection was accomplished within 1 month.

For each case, a preliminary history was taken from the mother and from her clinical sheets regarding her current and past Medical, Surgical, Obstetric, and Gynecologic histories which affect the morphology of the placenta. Then, the fresh placenta wascollected as soon as delivery and checked for its completeness; secondly, the umbilical cord was cut 5cm away from its site of insertion and trimming of a membrane. Then it was washed by running water, clean up witha towel, and label with code numbers. After doing this the following placental parameters were observed and measured.

1. **Shape:** The shape of the placenta and the presence of the accessory lobe were recorded after proper inspection. Each placenta was categorized as an oval, circular or irregular in shape.

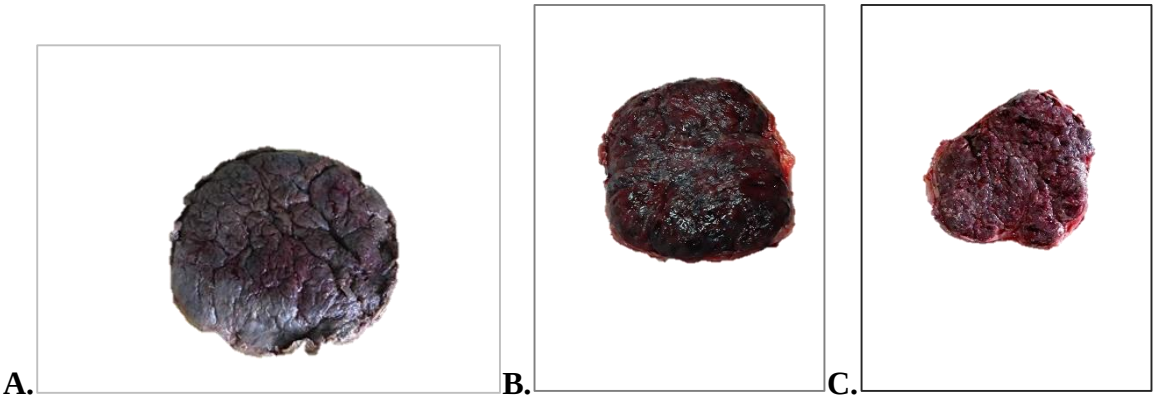

Figure 1: ***Different shapes of the placenta (A. circular, B. Oval, C. Irregular)***

2. **Weight:** The weight of each placenta was recorded in grams by using a standard weighing scale after the removal of membranes, umbilical cord, and blood clots inside it(46)**.**

Figure 2: ***Weighting placenta by Standard Weight Scale***

3. **Diameter:** The placenta wasplaced in a flat tray after trimming and mopping. At first, the maximum diameter was measured with a metallic scale graduated in centimeters. Then a second maximum diameter was taken at right angles to the first one. The mean of two measurements was considered as the diameter of the placenta express in centimeter(58).

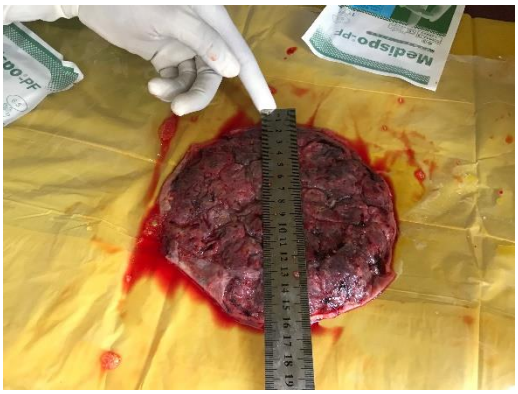

Figure 3: Maximum diameter measured on the maternal surface in two axes

4. **Thickness:** With a long needle placental thickness was measured at five points of each placenta. Each placenta was placed on a fetal surface. The placenta was divided arbitrarily into three zones of equal parts by drawing two circles on the maternal surface. These circles cut the radius of the placenta into three equal parts. One thickness was measured from the center of the central zone, two from the middle, and two from the peripheral zone. The peripheral points were taken within the outer zone on a line perpendicular to the previous

imaginary line. Finally, the mean of all five measurements was calculated and considered as the thickness of the placenta(59).

Figure 4: Measurement techniques and points for placental thickness

5. **Number of Cotyledons:** After measuring and inspecting the above parameters placenta was fixed by 10% formalin for 24 hours to make the placental septum separation visible to count the cotyledon. Each formalin-fixed placenta was taken on both hands. Then gentle pressure was applied on the central part of the fetal surface with the thumbs of both hands while holding the periphery of the placenta with the other fingers. As a result, the cotyledons on the maternal aspect become prominent after the separation between them. Then the placenta was put on a flat tray with the maternal side facing upward by placing a wood block on the fetal side. Then counting was started from the left side of the one end of the placenta going rightward and again turning back to the left in a manner of the loop. This counting procedure was repeated until the other end of the placenta is reached. The total number of cotyledons was recorded(60).

Figure 5: Number of cotyledons

6. **Birth weight:** Birth weight of fetuses was noted from the clinical sheets.
7. **Placental Histology:** After performing the above parameters placental tissue for microscopy was taken as follows,

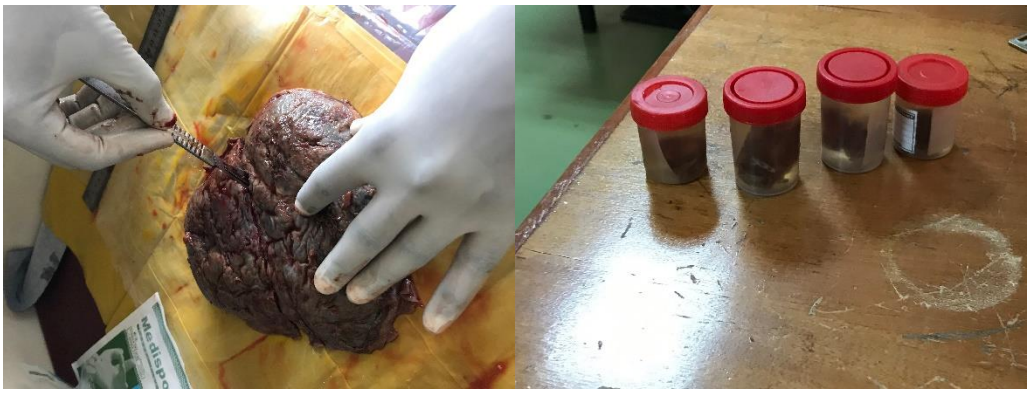

Figure 6: Taking samples for histological examination

Full-thickness of fresh placental tissue for microscopy was taken from the following sites,

I. Margins-peripheral area

II. Centre of the placenta

III. Between center and margin

IV. Pathologic area, if any

Then, after taking the tissue it was labeled and kept in 10% formalin for fixation. Each selected tissue again was cut in small pieces of 5mm × 2mm. Finally, tissue was processed as routine (Annex III). To avoid bias, the pathologist was blind to all samples (cases or controls).

Maximum possible fields were examined for each slide to assess the following parameters:

- Placental infarction, hematoma, basement membrane and fibrinoid necrosis(38)
- Abnormalities of intervillous space
    - Intervillous thrombosis
- Placental calcification
- Abnormality of cytotrophoblast proliferationin villi and presence of syncytial knots; for instance, focal (> 30% of 1 full-thickness slide) and Diffuse (≥2 full-thickness slides) (61)

4.11. Data Quality Assurance

Data were collected and recorded on the checklist by a BSc midwifery staff member working in the delivery room. She was trained by the principal investigator for 2 days concerning the placental gross morphology, measurements, how to take tissue from it, and appropriate disposal of the placenta. Finally, the collected data were checked for completeness by the principal investigator.

4.12. Data Processing and Analysis

Data were entered by using EPI-data Version 4.2.0 and exported to SPSS Version 20 for analysis. Descriptive statistics like frequency, ratio, mean and standard deviation were computed to describe the study variable and were presented by tables and graphs. The Association of dependent and independent variables was confirmed by the chi-square test and F-test. Comparisons of the morphology of placenta (weight, shape, diameter, thickness and number of cotyledons) and birth weight of fetus in PE, IUGR,and normal mothers were analyzed using one way ANOVA. Differences at $p<0.05$ was considered as statistically significant.

4.13. Ethical Considerations

Ethical clearance was obtained from the Institutional Review Board of the College of Health Science, Addis Ababa University. Each study participant was adequately informed about the objective, benefit, and risk of the study. Individual verbal informed consent was obtained from every study participant and those who agreed werealso included in the study. Then, giving due respect, confidentiality, and appropriate disposal of the placenta was observed/done by the data collector and the supervisor. The raw data obtained was secured and accessed only by the principal investigator.

4.14. Dissemination and Utilization of results

The findings of the study was presented to the Department of Anatomy and Obstetrics & Gynecology of the College of Health Science, Addis Ababa University. The results will be disseminated through publication in local or international journals, presentations on annual scientific seminars, conferences, and meetings.

5. RESULTS

5.1. Socio-demographic characteristics

Among 54 mothers who participated in this study 22(40.74%), 10(18.52%), and 22(40.74%) were preeclamptic, IUGR, and uncomplicated mothers, respectively. The mean age of the participants was 25.55±4.84 years in PE, 24.02±3.95 years in IUGR, and 27.09±4.71 in uncomplicated groups, respectively. In this study gestational age of the mothers was 38.55±1.03 in PE, 38.02±0.97 in IUGR, and 39.52±0.89 in uncomplicated groups.

Mothers who give birth vaginally were 39; which includes 17 of uncomplicated, 17 of PE and 5 of IUGR deliveries. Regarding the sex of the babies, 24 of them were males and 30 females out of 54.

The majority of the study participants 36(66.67%) were from urban areas whereas 18(33.33%) were from rural areas. The mean body mass index of mothers was 23.07±2.26 (Kg/m^2), 22.59±1.89 (Kg/m^2), and 23.15±2.92 (Kg/m^2) and in PE, IUGR, and uncomplicated mothers respectively.

Table 1: Socio-demographic and related characteristics of mothers delivered in Tikur Anbessa Specialized Hospital, Addis Ababa Ethiopia, May-June, 2019.

Socio-demographic variables	**Uncomplicated**		**Preeclampsia**		**IUGR**	
	Frequency	*Percent*	*Frequency*	*Percent*	*Frequency*	*Percent*
Educational status						
Can't read or write	*4*	*18.2*	*6*	*27.3*	*0*	*0*
Read and write	*3*	*13.6*	*5*	*22.7*	*4*	*40*
Primary education	*4*	*18.2*	*3*	*13.6*	*1*	*10*
Secondary education	*6*	*27.3*	*5*	*22.7*	*5*	*50*
College and above	*5*	*22.7*	*3*	*13.6*	*0*	*0*
Occupational status						
Housewife	*9*	*40.9*	*12*	*54.5*	*2*	*20*
Governmental	*1*	*4.5*	*3*	*13.6*	*1*	*10*
Non-governmental	*1*	*4.5*	*2*	*9.1*	*6*	*60*
Private	*11*	*50*	*5*	*22.7*	*1*	*10*
Parity						
Para-0	*10*	*45.5*	*12*	*54.5*	*4*	*40*
Para-1	*7*	*31.8*	*7*	*31.8*	*4*	*40*
Para-2	*3*	*13.6*	*2*	*9.1*	*0*	*0*
Para>2	*2*	*9.1*	*1*	*4.5*	*2*	*20*

5.2. Gross placental morphology and birth weight of the fetus

As shown in the table below circular placental shapes were mostly found in uncomplicated and IUGR mothers followed by oval and irregular shapes whereas oval shapes were more common in PE mothers followed by circular and irregular shapes.

Table 2: Fisher's Exact Test of placental shapes with maternal status in Tikur Anbessa Specialized Hospital, Addis Ababa Ethiopia May-June 2019.

Diagnosis	Placental shape			Total	F-test	P-value
	Oval	Circular	Irregular			
Uncomplicated	6(27.3%)	13(59.1%)	3(13.6%)	22(100%)	*6.552*	*0.145*
PE	11(50.0%)	6(27.3%)	5(22.7%)	22(100%)		
IUGR	2(20%)	7(70%)	1(10%)	10(100%)		
Total	19(35.2%)	26(48.1%)	9(16.7%)	54(100%)		

The placental shape has no significant association with maternal status (p = 0.145, which is >0.05).

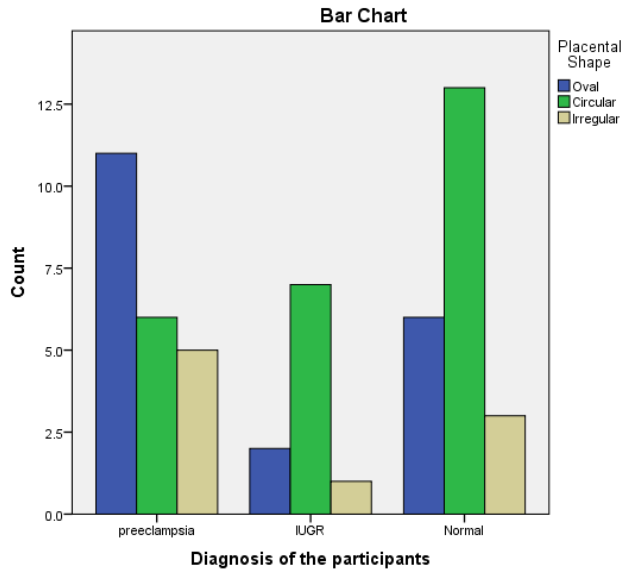

Figure 7: Shapes of the placenta in Preeclampsia, IUGR, and Normal mothers at Tikur Anbessa Specialized Hospital, Addis Ababa Ethiopia May-June 2019.

The mean placental weight ofthe uncomplicated group was heavier than the other groups. It has a significant difference between PE and IUGR by a mean difference of 63.18gm and 157.46gm respectively.

Table 3: Placental weight in grams with their mean and standard deviation in 95% Confidence Interval for Mean in Tikur Anbessa Specialized Hospital, Addis Ababa Ethiopia May-June 2019.

Diagnosis	Mean ± SD in gm	95% CI for mean		Minimum	Maximum
		Lower Bound	Upper Bound		
Uncomplicated	485.45 ± 66.67	455.89	515.01	350	620
PE	422.27 ± 44.07	402.73	441.81	350	480
IUGR	328.00 ± 60.33	284.84	371.16	200	400
Total	430.56 ± 80.08	408.70	452.41	200	620

The mean placental diameter was 19.05±1.27cm, 17.07±1.35 cm, and 15.08±1.48 cm in uncomplicated, preeclamptic, and IUGR mothers respectively. There was a significant difference between uncomplicated and PE and between uncomplicated and IUGR mothers by a mean difference of 1.98, with a 95%CI (1.00, 2.98) and 3.25 with a 95% CI (2.01, 4.48) respectively.

Table 4: Placental diameter in cm with their mean and standard deviation in 95% Confidence Interval for Mean in Tikur Anbessa Specialized Hospital, Addis Ababa Ethiopia May-June 2019.

Diagnosis	Mean ± SD in cm	95% CI for mean		Minimum	Maximum
		Lower Bound	Upper Bound		
Uncomplicated	19.05 ± 1.27	18.48	19.61	17.00	22.00
PE	17.07 ± 1.35	16.47	17.67	15.00	19.50
IUGR	15.08 ± 1.48	14.74	16.86	13.00	17.50
Total	17.64 ± 1.82	17.14	18.14	13.00	22.00

The mean placental thickness was 21.16 ± 1.78 mm in uncomplicated, 19.42 ± 1.07 mm in preeclamptic and 17.06 ± 2.56 mm in IUGR mothers. Placental thickness in uncomplicated and PE mothers was significantly thicker than IUGR mothers by 4.1mm & 2.36mm respectively.

Table 5: Thickness of placentas in mm with their mean and standard deviation in 95% Confidence Interval for Mean in Tikur Anbessa Specialized Hospital, Addis Ababa Ethiopia May-June 2019.

Diagnosis	**Mean ± SD in mm**	**95% CI for mean**		**Minimum**	**Maximum**
		Lower Bound	**Upper Bound**		
Uncomplicated	21.16 ± 1.78	20.37	21.95	15.60	23.40
PE	19.42 ± 1.07	18.95	19.90	18.00	21.80
IUGR	17.06 ± 2.56	15.23	18.89	13.00	21.60
Total	19.69 ± 2.25	19.08	20.31	13.00	23.40

The mean placental number of cotyledons in the uncomplicated group was 19.00 ± 0.82; whereas it was 17.18 ± 1.10 and 15.10 ± 1.73 in preeclampsia and IUGR participants respectively.

Table 6: Number of cotyledons of placentas with their mean and standard deviation in 95% Confidence Interval for Mean in Tikur Anbessa Specialized Hospital, Addis Ababa Ethiopia May-June 2019.

Diagnosis	**Mean ± SD**	**95% CI for mean**		**Minimum**	**Maximum**
		Lower Bound	**Upper Bound**		
Uncomplicated	19.00 ± 0.82	18.64	19.36	17	20
PE	17.18 ± 1.10	16.70	17.67	14	19
IUGR	15.10 ± 1.73	13.86	16.34	13	18
Total	17.54 ± 1.82	17.04	18.03	13	20

Table 7: Multiple comparison (post-hoc) test: gross morphology of placentas in TikurAnbessa Specialized Hospital, Addis Ababa Ethiopia May-June 2019.

Placental characteristics	Diagnosis of the participants		Mean difference	Significance	95% confidence interval	
					Lower Bound	Upper Bound
Placental Weight	Uncomplicated	PE	63.182*	.002	21.55	104.82
		IUGR	157.455*	.000	104.79	210.12
	PE	IUGR	94.273*	.000	41.61	146.94
Diameter of Placenta	Uncomplicated	PE	1.97727*	.000	1.0013	2.9533
		IUGR	3.24545	.000	2.0109	4.4800
	PE	IUGR	1.26818*	.043	0.337	2.5027
Thickness of Placenta	Uncomplicated	PE	1.74091*	.004	0.4935	2.9883
		IUGR	4.10364*	.000	2.5258	5.6815
	PE	IUGR	2.36273*	.002	0.7849	3.9406
Number of cotyledons	Uncomplicated	PE	1.818*	.000	0.99	2.65
		IUGR	3.900*	.000	2.85	4.95
	PE	IUGR	2.082*	.000	1.03	3.13

**. The mean difference is significant at the 0.05 level.*

In this study, the mean birth weight of the fetus was significantly smaller in IUGR groups ($p<0.0001$).

Table 8: The Birth weight of the babies in grams with their mean and standard deviation in 95% Confidence Interval for Mean in Tikur Anbessa Specialized Hospital, Addis Ababa Ethiopia May-June 2019.

Diagnosis of participants	Birth weight in gm (Mean ± SD)	95% Confidence Interval for Mean		Minimum	Maximum
		Lower Bound	Upper Bound		
Uncomplicated	3304.55 ± 367.07	3141.80	3467.30	2800	4200
PE	3213.64 ± 339.88	3062.94	3364.33	2600	3700
IUGR	2250.00 ± 374.91	1981.81	2518.19	1600	2700
Total	3072.22 ± 530.67	2927.46	3216.98	1600	4200

The birth weight of the babies in uncomplicated mothers was greater than IUGR by 1054.55gm with 95% CI (725, 1383.74). There was also a significant difference between PE and IUGR fetuses by 963.66gm with 95% CI (634.44, 1292.83).

Table 9: Multiple comparison (post-hoc) test: the birth weight of babies in Tikur Anbessa Specialized Hospital, Addis Ababa Ethiopia May-June 2019.

Diagnosis of the participants		**Mean difference**	**Significance**	**95% confidence interval**	
				Lower Bound	**Upper Bound**
Uncomplicated	PE	90.909	.678	-169.34	351.16
	IUGR	1054.545*	.000	725.35	1383.74
IUGR	PE	-963.636*	.000	-1292.83	-634.44
	Uncomplicated	-1054.545*	.000	-1383.74	-725.35
PE	IUGR	963.636*	.000	634.44	1292.83
	Uncomplicated	-90.909	.678	-351.16	169.34

**. The mean difference is significant at the 0.05 level.*

5.3. Microscopic morphology

In the table shown below 36.4% of uncomplicated, 27.3% of PE, and 60% of IUGR mothers' placentas were calcified. The p-value was (>0.05) and it was not significant.

Table 10: Chi-square distribution of placental calcification at Tikur Anbessa Specialized Hospital, Addis Ababa Ethiopia May-June 2019.

Diagnosis	**Calcification**		**Total**	**$\chi 2$- statistic**	***P-value***
	Yes	**No**			
Uncomplicated	4(18.8%)	18(81.2%)	22(100%)	5.564	*.062*
PE	8(36.4%)	14(63.6%)	22(100%)		
IUGR	6(60%)	4(40%)	10(100%)		
Total	18(37.0%)	36(63.0%)	54(100%)		

Placental infarction was observed in 40% of IUGR cases whereas it was 36.4% and 18.8% among preeclamptic and uncomplicated deliveries. But there was no statistically significant difference.

Table 11: Chi-square distribution of placental infarction at Tikur Anbessa Specialized Hospital, Addis Ababa Ethiopia May-June 2019.

Diagnosis	**Infarction**		**Total**	**χ2- statistic**	***P-value***
	Yes	**No**			
Uncomplicated	4(18.8%)	18(81.2%)	22(100%)	2.377	*.305*
PE	8(36.4%)	14(63.6%)	22(100%)		
IUGR	4(40%)	6(60%)	10(100%)		
Total	16(29.63%)	38(70.37%)	54(100%)		

Regarding placental thrombotic findings, 13.6% of uncomplicated and 22.7% PE mothers' haveshown thrombosis. There was no statistically significant difference.

Table 12:Chi-square distribution of placental intervillous thrombosis at Tikur Anbessa Specialized Hospital, Addis Ababa Ethiopia May-June 2019.

Diagnosis	**Thrombosis**		**Total**	**χ2- statistic**	***P-value***
	Yes	**No**			
Uncomplicated	3(13.6%)	19(86.4%)	22(100%)	*1.262*	*.532*
PE	5(22.7%)	17(77.3%)	22(100%)		
IUGR	3(30%)	7(70%)	10(100%)		
Total	11(20.4%)	43(79.6%)	54(100%)		

There was no hematoma seen except one data which was from preeclamptic mothers.

In this study, we observed 31.8%,10%, and 13.6% of PE,IUGR, and uncomplicated mothers have cytotrophoblast proliferation greater than 20% respectively. There was no statistical difference.

Table 13: Fisher's Exact Test of Cytotrophoblast proliferation of placentas with maternal status in Tikur Anbessa Specialized Hospital, Addis Ababa Ethiopia May-June 2019.

Diagnosis	**Cytotrophoblast proliferation**		**Total**	***P-value***
	Greater than 20%	**Less than 20%**		
Uncomplicated	3(13.6%)	19(86.4%)	22(100%)	*.356*
PE	7(31.8%)	15(68.2%)	22(100%)	
IUGR	1(10.0%)	9(90%)	10(100%)	
Total	11(20.4%)	43(79.6%)	54(100%)	

Syncytial knots were observed in 18.2% of uncomplicated, 36.4% of PE, and 10% of IUGR mothers' placenta. But it was not statically significant.

Table 14: Fisher's Exact Test of Syncytial knots of placentas with maternal status in Tikur Anbessa Specialized Hospital, Addis Ababa Ethiopia May-June 2019.

Diagnosis	**Syncytial knots**		**Total**	***P-value***
	Greater than 30%	**Less than 30%**		
Uncomplicated	4(18.2%)	18(81.8%)	22(100%)	*.241*
PE	8(36.4%)	14(63.6%)	22(100%)	
IUGR	1(10%)	9(90%)	10(100%)	
Total	13(24.1%)	41(75.9%)	54(100%)	

As shown below 30% of IUGR mothers' placentas basement membrane was greater than 3%.

Table 15: Fisher's Exact Test of Basement membrane of placentas with maternal status in Tikur Anbessa Specialized Hospital, Addis Ababa Ethiopia May-June 2019.

Diagnosis	**Basement membrane**		**Total**	***P-value***
	Greater than 3%	**Less than 3%**		
Uncomplicated	2(9.1%)	20(90.9%)	22(100%)	.366
PE	3(13.6%)	19(86.4%)	22(100%)	
IUGR	3(30.0%)	7(70%)	10(100%)	
Total	8(14.8%)	46(85.2%)	54(100%)	

Wefound 22.7% and 20% of >3% fibrinoid necrosis in preeclamptic and IUGR groups respectively.

Table 16: Fisher's Exact Test of Fibrinoid necrosis of placentas with maternal status in Tikur Anbessa Specialized Hospital, Addis Ababa Ethiopia May-June 2019.

Diagnosis	**Fibrinoid necrosis**		**Total**	***P-value***
	Greater than 3%	**Less than 3%**		
Uncomplicated	2(9.1%)	20(90.9%)	22(100%)	*.503*
PE	5(22.7%)	17(77.3%)	22(100%)	
IUGR	2(20.0%)	8(80.0%)	10(100%)	
Total	9(16.7%)	45(83.3%)	54(100%)	

6. DISCUSSIONS

This study was conducted to compare the Effects of Preeclampsia and Intrauterine Growth Restriction on Morphology of Placenta and Birth Weight of Fetus in Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia. We found statistically significant decrement in weight, diameter, thickness, and the number of cotyledons in PE and IUGR compared to uncomplicated pregnancies.

6.1. Gross morphology of placenta

Even though there was no statistically significant difference in the shape of the placenta among the study participants, the majority of the irregular and oval placentas were seen among the preeclamptic placentas. This finding is supported by studies conducted by Navbir (2012) and Kishwara et al. (2009) who reported that the majority of circular shapes of the placenta were observed in the uncomplicated group, and oval shapes in PE mothers(32, 62). In contrary to this study, a research conducted in West India observed that oval shape placentas were the most common ones in the control and preeclamptic mothers. While irregular placentas were more common than circular shapes in preeclampsia(31). The main reason for this discrepancy could be a failure or disturbance in the pattern of orderly villous atrophy and proliferation, which generally results in a single circular or oval placental disc with a transition to fetal membranes at the disk edge(33).

The weight of the placenta gives an idea of the amount of substance that is exchanged between the mother and the fetus(36). There was a statistically significant difference in weight of the placenta between control and PE groups by a mean difference of 36.182gm. This study was in line with the finding reported by Yibeltal Wubale, a research done at Ghandi and Tikur Anbessa Hospitals (2016), which was 456.20±19.13 gm and 499.4±11.89 gm. However, in the present study placental weight was way more decreased in preeclamptic mothers which is similar with other studies(10, 39, 40, 42, 56, 63). In the date reported by Udainia and Jain (2001), the mean placental weight was 495 gm in the control group, 435.63 gm in mild hypertension, and 371.43 gm in severe hypertension. Thus, there was a significant lowering of placental weight in PIH. Contrary to our finding Ravi K, Sadasivan S (2018) found the mean placental weight has shown no significant difference between normal and preeclamptic pregnancy(64). The placental weight was less affected in preeclampsia because the placenta grows more rapidly than the fetus before mid-gestation. So since PE occurs after the 20^{th} week of pregnancy its effect on the weight of the placenta decreased.

There was also a statistical difference in placental weight between normal and IUGR deliveries. In agreement with this study, Sharmistha Biswas (2007) reported the placental weights of the IUGR group which ranged from 180gm to 458gm with a mean of 333.32gm (SD±75.59). These values were significantly lower (p-value<0.001) than the placental weights of the control group, which ranged from 340gm to 545gm with a mean of 416.77gm (SD±63.03)(65). Another similar study in Belgium reported that the placental weight of the control group with 641±133gm and the IUGR group with 412±117gm(49). The reason might be due to placental insufficiency caused by any reason that causes IUGR, poor ANC follows up, genetics, or under-nutrition of the mothers.

The diameter and thickness of the placenta give an idea about the size of the placenta. The diameter of the placenta will affect the number of nutrients, oxygen, and carbon dioxide that will pass from the mother to the child, and vice versa(36).

The placenta in an uncomplicated mother is bigger and thicker than PE. This study was in line with Vijayalakshmi et al. (2015) who observed that the mean diameter of the placenta was 18.64±1.812cm in mild PE, and 17.94±1.963cm in severe PE in comparison with the control group which was 20.33±1.446cm, whereas, the mean thickness of the placenta area was 19.6±1.97 mm, 17.7±4.23mm and 20.2±1.99mm in mild PE, severe PE, and in control groups respectively(42). Another study conducted in India noted that the mean placental diameter and thickness were17.2cm and 18mm in preeclamptic placentae and 18.7cm and 23m in normotensive placentae(10).

Similar findings have been reported by Modi et al. (2013), Salmani et al. (2014), and Kishwara et al. (2009) reported that preeclamptic placentae were smaller than normal indicating an underlying pathological process that interferes with normal growth of the placenta(32, 54, 66). This reduction may be due to the small size of the placenta in preeclampsia.

Mean diameters in control placentas were 19.05±1.48cm; and in IUGR placentas mean diameter was 15.08±1.48cm. The placentas associated with IUGR were significantly (p<0.001) smaller and thinner than those of the control group of placentas. These results were similar to Woodling et al. (1976) and Sharmistha Biswas (2008)(65, 67).

In contrary to our study Vedmedovska et al. (2011) reported the placental thickness of control and IUGR groups were 18.9±4.6mm and 19.1±6.0mm respectively. They did not find any difference in the thickness of the placentas between the two groups(49). This can be explained by the induction of progressive branching and arborization of the villous tree to guarantee an adequate nutrient exchange

surface and support fetal growth(25). A thin placenta less than 20 mm is usually associated with possible placental insufficiency with intrauterine growth retardation.

The number of cotyledons was less in preeclamptic placentas as compared to normotensive. There was a significant difference between normal and PE placentas. This study was consistent with shaved et al. (2015), Londhe et al. (2011), and Kishwara et al. (2009) who reported that intercotyledonous vasculature is altered in hypertensive placentae resulting in low birth weight babies(10, 32, 68). In contrary to this study, the research studied by Majumdar et al. (2005) showed no significant difference between controls and cases(39). The present finding showed that the number of cotyledons of the control group was significantly ($P<0.001$) higher than IUGR groups by a mean difference of 3.90. Our finding was supported by Raghunath G et al. (2011) who revealed the paucity of cotyledon numbers in low birth weight mothers(1).

We have noted that all placental dimensions that are mean placental weight, thickness, and diameter show significantly lower values in preeclamptic and IUGR cases as compared to control. The main reason for the reduced placental weight in preeclampsia could be uteroplacental insufficiency. Sankar et al. (2013) reported reduced villous diameter,surface area, and vessel densities in preeclamptic placentae. Thus reduced proportional and absolute volume in preeclampsia could contribute to reduced morphological dimensions in preeclampsia(69).

IUGR is caused by any reason that affects the normal growth of the fetus usually by decreasing the blood flow from the mother to the fetus which also affects all the dimensions of the placenta.

6.2. Birth weight of the fetus

The main impact on fetuses is under-nutrition due to uteroplacental vascular insufficiency which leads to growth retardation(70). Odegard et al.(2000) observed that preeclampsia was associated with a 5% reduction in fetal weight(71). In the present study, there was a significant difference between normal and IUGR, and PE and IUGR babies. Although there was no statistical significance between the weight of babies of normotensive and PE mothers, control groups babies were bigger than PE by a mean difference of 90.64. The reason might be good antenatal care taken by the mothers or since some studies concluded it is very less in mild PE, and our study might not have much of severe PE. It was observed that smaller placentae usually accompanied low birth weight babies. Similar findings have been reported by Londhe et al. (2011), Udaina et al. (2001), Salmani et al. (2014), and Meyhew et al. (2004)(40, 54, 68, 72).

6.3. Microscopic morphology of placenta

Countless articles have been published on the pathology of the placenta in pre-eclampsia. Whereas there are no specific lesions that cannot be found in the placenta of a normotensive woman, there is general agreement that many types of lesions are significantly more extensive in pre-eclampsia.

Placental calcification is often found in pregnancy at term and is regarded as a physiological aging process(73). Although no statistical significance in placental calcification among the study participants, the majority of case participants showed calcification compared with control groups. In agreement with our study, Dutta and Dutta (74) found calcification in 4 out of 32 (12.5%) cases of normal pregnancy and 26 (44.3%) placentae from the PIH group. Vijayalakshmi et al. (2015) study incidence of calcification was increased in severe PE group 35% compared to mild PE 13% and controls 10% which was similar to the study by Narasimha and Vasudeva (2011) which showed the overall incidence was 26.9%, 22.2% in mild PE and slightly higher (33.3%) in severe PE(42, 75). This study also showed that placental calcification in IUGR groups was 60% which was significantly higher compared to control groups. There was a similar study in India, where calcification was higher in IUGR patients ($P<0.01$)(76). Some researches associate placental calcification with an incidence of IUGR(77). The reason could be uteroplacental insufficiency which makes narrowing of the lumen. Calcification is regarded as evidence of placental senescence or degeneration.

Thrombotic occlusion of maternal uteroplacental vessels is responsible for infarction(78). The result of this study in PE is comparable to the results of the study done by Kambale et al. (2016) (28.8%) and Kurdukar M et al. (2007) (28.7%)(38, 79).

H. Fox studied placental infarction was seen in 25% of placentae from normal pregnancies and hence in itself cannot be classified as strictly abnormal. This is comparable to our study which has 18.8% of normal placentae has infarction. In contrary to the present study, the control group did not show any placental infarction in Kambale et al. (2016)(38).

Microscopic infarction in IUGR placentas was 40%, compared to normotensive placentas which account for only 18.8%. This study was consistent with Ghomian N et al. (2014) 52.1% and 8.6 % of infarction in IUGR and control groups respectively(18). Krishna Rao G et al. (2018), Vedmedovska et al. (2011), and Mardi K & Sharma J (2003) agree with this finding(49, 80, 81). In contrary to this study Tomas S et al. (2010) reported placental infarction of 7.69% IUGR and 11.59% control(58). Chronic maternal "under perfusion" of fetal villi often results in a small ischemic placenta(82). Which

causes villous necrosis due to obstruction of the uteroplacental artery and ultimately results in placental infarcts(83).

Although there was no significant difference in placental thrombosis, there was a higher incidence in cases than control groups. This was in line with a study that found 19% of the placentas (66/350) and 19.2% of PIH placentas had thrombosis (39, 84, 85). Uncomplicated placentas were comparable to a study that found 19.2% of the normal placenta had intervillous thrombosis(85) but there was a study in Ethiopia, by Teshome who discovered none of his normal placentas had any thrombosis(86). Regarding IUGR placental infarction; Ghomian N et al. (2014) found placental infarction to be 34.7% in the IUGR group and 6% in the control group with the difference being statistically significant (18). Vedmedovska et al. (2011) revealed the presence of thrombi was more common in the FGR group than in the controls ($p < 0.05$) which were 22% in IUGR and 12% in the control group(49).
Intervillous thrombosis of the placenta is caused due to focal coagulation of maternal blood inside the intervillous space. Several studies have reported a higher incidence of infarction and placental vascular thrombosis in IUGR cases. The pathology of the uteroplacental circulation accounts for the majority of nutritional IUGR(87).

There was 1/22 of preeclampsia showed hematoma. Page (1972) observed 0.8% and 6.2% retroplacental hematoma in the normal and PIH groups respectively, whereas Kurdukar M et al. (2007) noted a percentage of 12% and 12.2%(79, 88). Gurdip K et al. (2017) and Mardi K et al. (2003) observed retroplacental hematoma in 1% and 4% cases of IUGR respectively(81, 89). In contrary to this study, intervillous hematomas were seen more often in FGR placentas, explaining the reduced feto-placental oxygen delivery(90). Extensive hematomas are associated with higher rates of fetal-growth restriction. The reason we found none amount of placental hematomas might be due to our small sample size.
In the present study cytotrophoblast proliferation greater than 20% was found in 31.8% of preeclamptic mothers' placenta, which was comparable to Kamabal et al.(2016) >50%, Sodhi et al. (1990), and Kurdukar M et al. (2016)(38,79, 91). It has higher numbers in other studies and they observedthe severe preeclampsia the more >20% cytotrophoblast proliferation, and there might be more mild preeclampsia in our study. Only 13.6% of normal placentas were greater than 20% cytotrophoblast proliferation and this is in agreement with a study in India, 15.6% of Kambale et al. (2016) but more than Teshome's 3%(38, 86). This may be because the tissue suffers from ischemic

damage. Abnormal cytotrophoblastic invasion leads to placental ischemia and endothelial dysfunction which characterizes preeclampsia.

In the present study, we observed cytotrophoblast proliferation (>20%) was less in IUGR than in control groups. In line with this study, Vedmedovska N et al. (2011) reported that it was 50% in IUGR and in control, it was 62%(49). Other studies concluded the incidence of cytotrophoblastic hyperplasia was higher in IUGR placentas(81). All the major histologic findings pointed towards reduced blood flow to the placentas resulting in the restriction of blood flow to the fetus.

Several authors stated that 30% of terminal villi at term possess syncytial knots under normal conditions(92). When more than 30% of terminal villi possess syncytial knots, it is considered diagnostic of perfusion comprise. Even though there was no statistical significance of syncytial knots it was higher in preeclamptic placentas which is consistent with Kurdukar M et al. (2007) 84% ofcases of severe PIH and 100% cases of eclampsia(79). Kambale et al. (2016) also found all the cases of severe PIH and eclampsia showing syncytial knot count more than 30%(38). Furthermore, studies done by Kalra et al. (1985) and Sodhi et al. (1990) showed increased syncytial knots in their studies(91, 93). The reason behind this study has less number of >30% syncytial knots may be due to the exclusion of eclampsia cases and lesser severe preeclampsia cases. A significant increase in syncytial knot formation in placental villi indicates the disturbance in the hormonal factors, which may probably lead to altered blood flow. Maternal uteroplacental blood flow is decreased in preeclampsia because of maternal vasospasm which leads to constriction of fetal stem arteries(94).

We found more >30% syncytial knots in control than IUGR groups. Contrary to our study research done in India reported a highly significant increase in the prevalence of syncytial knotting in IUGR placentas compared to full-term normal placentas(81). This might be due to the difference in the onset of the IUGR since early and late-onset has a different impact on the development of terminal villi, with an increase in syncytial knots(95). In our study, the onset of IUGR might be late; which means, it has less time to affect the placenta.

Despite no significant difference majority of preeclamptic cases basement membrane were thicker than the control groups. This study was supported by Kambale et al. (2016) who observed >3% thickening of the basement membrane in (15.4%) mild PIH, (60% cases) severe PIH, and (100% cases) eclampsia. However, it was only 4.4% in control groups. Kurdukar et al. (2007) also supported our finding(79). An increase in the number of villi with thickened basement membrane is the result of

ischemia of the uteroplacental circulation(82). The reason our study had less thickening the basement membrane might be due to less severe PIH cases.

The incidence of basement membrane thickening was higher in IUGR compared to control group placentas. Similar studies by Gurdip K et al. (2017) and Mardi K et al. (2003) reported that 32% and 40% cases of IUGR showed >3% Basement membrane thickening(81, 89).

Histopathological observations showed significant areas of fibrinoid necrosis in the hypertensive group of placentas. Kurdukar M et al. (2007) and Kambala et al. (2016) reported fibrinoid necrosis in the hypertensive group of placentas. Compared to the present research, Kambale et al. (2016) found a higher number (44%) of preeclamptic cases with fibrinoid necrosis. This may be due to higher number of severe than mild preeclampsia in their study(38, 79).

Similar to our study Gurdip K et al. (2017), Mardi et al. (2003), and Jain et al. (2006) observed 48%, 20%, and 34.4% respectively of placenta having significant fibrinoid necrosis(81, 89, 96). Fibrinoid necrosis was seen in placentae from patients only(76). Fibrinoid necrosis depicts the mosaicism of the placenta which probably leads to placental insufficiency and ultimately to fetal growth retardation. About 3% of the villi in mature placentae show fibrinoid necrosis. It is increased in PIH(97).

All the major histologic findings pointed towards reduced blood flow to the placentas resulting in the restriction of blood flow to the fetus which leads to FGR(81).

The reason for the discrepancy between these reports and our results could be in the study design: we investigated placentas solely from idiopathic IUGR pregnancies, whereas other studies investigated placentas from pregnancies complicated by IUGR combined with different disorders of pregnancies.

7. LIMITATIONS OF THE STUDY

In this study, certain limitations created constrains on the generalization of the results to the wider population. One of the major limitations of the study was the relatively low sample size.

Although the objective of the current study was to compare PE and IUGR with uncomplicated mothers, we did not identify and studied the specific types of PE, and IUGR caused by PE to see if findings are specific to both cases or can appear concomitantly.

8. CONCLUSIONS

From the present study, it can be concluded that the hypertensive disorders of pregnancy adversely influence the morphology of the placenta. The gross morphological changes observed in the placentae of patients with preeclampsia such as statistically significant increment in the weight, diameter, thickness and the number of cotyledons when compared with control group. In histological findings, even though there was no statistically significant difference, we have observed more calcification, infarction, thrombosis, cytotrophoblast differentiation, syncytial knots, basement membrane thickening, and fibrinoid necrosis of placenta in PE compared to uncomplicated mothers.

The placenta of IUGR was significantly decreased in weight, diameter, thickness, and number of cotyledons compared to uncomplicated placentas. Important pathological findings were placental calcification, infarction, thrombosis, basement membrane thickening and fibrinoid necrosis. Study of placenta can provide important information about pathophysiology and better treatment modality of IUGR.

The majority of the placental shape of uncomplicated and IUGR groups were circular whereas in preeclampsia it was oval. There was a significant decrement of the weight of the babies in IUGR compared to both PE and uncomplicated mothers but no significant difference between uncomplicated and PE.

9. RECOMMENDATIONS

To improve maternal and child health we recommend this to all concerned individuals and institutions;

- Researchers should conduct large scale studies, using the current study as baseline data, on the same or different clinical conditions' effects on the placenta.
- A study should be conducted on the effects of specific types of preeclampsia.
- Finally, Clinicians should carry out routine placental examination and measurement during the postpartum period; hence, this will provide better evidence for clinical decisions.

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11. ANNEXES

Annex I

English version information sheet and consent form

Department of Medical Anatomy, School of Medicine, College of Health Sciences, Addis Ababa University.

Title of the study: Morphological changes of placenta and birth weight of fetuses in pregnancies with and without preeclampsia and IUGR in TikurAnbesa Specialized Hospital.

Written Consent Form

Dear study participant, Good morning/afternoon, my name is_____ I am one of the data collector for the study being conducted by Addis Ababa University, School of Medicine and Health Sciences, Department of Anatomy, on morphological changes of placenta and birth weight of fetus with and without preeclampsia and IUGR. For this study, your permission is important to research your placenta and it will help policymakers to design strategies to prevent and control maternal and child morbidity and mortality secondary to preeclampsia and IUGR. Your name will not be written in this form and will never be used in connection with your placenta. All findings from your placenta will be kept strictly confidential. You are not obligated to permit without your interest. Your decline/refusal to participate will not affect any of the services you should obtain from the hospital. If you feel discomfort to give permission, please feel free to dropout at any time you want. If you have any question/concern time you can communicate me or the IRB on the following addresses;-

Principal investigator address -----0915860954

IRB address -----

Could I have your permission to continue?

1. Yes, signature_____ 2. No, skip to the next subject.

Informed consent certified by investigator

Name _____Signature_____

Date of permission given _____ Time_____

Amharic version information sheet and consent form

[illegible]

[illegible]

[illegible]:
[illegible]

[illegible]

[illegible]/ [illegible]
___________________________ [illegible]:
[illegible]

[illegible] ----- +251915860954

[illegible] -----

[illegible]**?**

1.[illegible] ________________________________ 2.[illegible]

[illegible] ____ [illegible]
____

[illegible] _______________________________________ [illegible] ___________________

Annex II

I. Sociodemographic characteristics

Serial no.	Variables	Response
1	Maternal age	_____years
2	Sex of the fetus	A. Male B. Female
3	Residence	A. Urban B. Rural
4	Educational status	A. Illiterate B. Read and write C. Primary education D. Secondary education E. College and above
5	Occupation	A. Housewife B. Governmental C. Non-governmental D. Private E. If any specify_____

II. Checklist related to mother and newborn

S. no	GA	Parity	Mode of Delivery (C/S,VD)	BP	Pro tein uria	Placental weight (gm)	Placental shape	Diameter (cm)	Thickness (mm)	No. of cotyledons	BW of fetus	BMI
1												
2												
-												
54												

III. Checklist related to placental Histopathology

Slide code	A Placental infarction	B Calcification	C Intervillous spaces	D Cytotrophoblast proliferation		E Syncytial knots		F Hematoma	G Basement membrane		H Fibrinoid necrosis	
	(P/A)	(P/A)	Thrombosis (P/A)	<20%	>20%	<30%	>30%	(P/A)	<3%	>3%	<3%	>3%
1												
01												
001												
0001												
-												
-												

Annex III

I. Methods of processing

1) **Fixation:** The tissue will be preserved/fixed in 10% formalin solution
2) **Dehydration:** The preserved tissue will be washed in running tap water for 4-6 minutes. Then, it will be passed through upgraded alcohol as follows:- 70% alcohol – 1hour, 85 % alcohol – 1hour, 96% alcohol – 1hour, Absolute alcohol I– 1hour, Absolute alcohol II – 1hour.
3) **Clearing:** Clearing of tissue will be done in xylene,-1hour in xylene -I, then after in xylene II for 1 hour.
4) **Infiltration:** Tissue will be infiltrated with paraffin wax I, for 1and 1/2 hrs., paraffin wax II for 2 and 1/2 hrs.and paraffin wax III for overnight.
5) **Embedding:** The cleared tissue will be put in molten wax (melting point 56-58degree Celsius) for 12 hours in a cryostat. The paraffin blocks of tissue will be made with the help of embedding cassettes.
6) **Sectioning:** The serial paraffin sections of 5-micron thickness will be cut by rotator microtome and floated in a water bath having temperatures 45-50 degrees Celsius. The section will be made spread on the slide smeared with an adhesive solution (a mixture of an equal amount of glycerol and egg albumin). The slide will be dried on a hot plate with having a temperature of 50 degrees Celsius.
7) **Deparaffinization of sections:** The slide will be put in xylene II, changes each for 5-10 min to remove the extracellular and intracellular wax.
8) **Rehydration:** The slide will be put in descending grades of alcohol i.e. absolute, 90 %, 70 %, and 50% alcohol for 2 min for each. The slide will be then washed in running tap water for 2 minutes and then taken for routine H & E staining.

II. Mode of staining

1) Stained with Hematoxyline for 10 minutes.
2) Washed in running tap water until the section becomes blue.
3) Stained in 1% eosin for 7- 10 min.
4) Washed in running tap water (5 minutes)
5) Dehydrated through 70 % and 95% Alcohol 3 minutes for each, then absolute alcohol I and Absolute alcohol II for 1 and 1/2 hour for each.
6) Cleaned by - Xylene I and XyleneII,5 minutes for each

Finally Mounted – By DPX