IMMUNOHISTOCHEMICAL EXPRESSION E-CADHERIN IN THE BASEMENT MEMBRANE OF CYTOTROPHOBLAST, SYNCYTIOTROPHOBLAST AND BLOOD VESSELS OF PLACENTA OF PRE-ECLAMPSIA

BY
DR. SUKKA SAHITI, MBBS

DISSERTATION SUBMITTED TO
SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION & RESEARCH
TAMAKA, KOLAR, KARNATAKA
IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR IN MEDICINE
IN
PATHOLOGY

UNDER THE GUIDANCE OF
DR. HEMALATHA.A, M.D
PROFESSOR
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DEPARTMENT OF PATHOLOGY

SRI DEVARAJ URS MEDICAL COLLEGE, KOLAR

JULY 2024

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Date: Signature of the Candidate

Place: KOLAR **Dr. Sukka Sahiti**

LIST OF ABBREVIATIONS

PE – Pre-eclampsia

EMT – Epithelial to mesenchymal transition

IHC – Immunohistochemistry

E-Cadherin – Epithelial Cadherin

VE-Cadherin – Vascular endothelial Cadherin

EPM – Extraplacental membranes

H&E – Haematoxylin and Eosin

PAS – Periodic acid Schiff

IUGR – Intrauterine Growth Reduction

BP – Blood Pressure

HDP – Hypertensive disorders of Pregnancy

WHO – World Health Organisation

US – United States of America

ACOG – American College of Obstetricians and Gynaecologists

VEGF – Vascular endothelial growth factors

VEGFR1 - Vascular endothelial growth factor receptor 1

PIGF – Placental growth factors

uNK – Uterine natural killer cells

sEng – Soluble endoglin

TGFβ – Transforming growth factor β

MI – Myocardial Infarction

BMI – Body Mass Index

IBD – Inflammatory bowel disease

ROS – Reactive oxygen species

HIFs – Hypoxia inducible factors

qRT-PCR - Quantitative Real-Time Polymerase Chain Reaction

ELISA – Enzyme Linked Immunosorbent Assay

TABLE OF CONTENTS

LIST OF TABLES

LIST OF CHARTS

LIST OF FIGURES

ABSTRACT

BACKGROUND:

Pre-eclampsia, a severe pregnancy condition which is evident by increased blood pressure and proteinuria after 20 weeks. Affecting 2-5% of all the pregnancies globally, it carries significant risks for both mother and baby.[1] During pregnancy in the initial months there is a temporary decrease in E-cadherin expression within trophoblastic cells as they invade placenta, nevertheless the function of E-cadherin in regulation of placental vascularity is not fully understood. Hence this study aims to analyse the intensity and distribution of E-cadherin staining within the trophoblastic villi in healthy and pre-eclampsia placenta patients.

AIMS & OBJECTIVES:

1. To determine the Immunohistochemistry (IHC) expression of E-cadherin in the placenta of healthy normal pregnancy and the placenta of pre-eclampsia.
2. To study the correlation of intensity of expression of E-cadherin and the severity of pre-eclampsia.

MATERIALS & METHODS:

This study was performed in Department of Pathology in association with Department of Obstetrics & Gynaecology, Sri Devaraj Urs Medical College attached to RLJH and Research Center, Tamaka, Kolar during the period of September 2022 to December 2023. The study included a total of 160 placenta cases that included 80 pre-eclampsia placentas and 80 normal healthy controls. IHC was performed using antibodies against E-cadherin and expression of E-cadherin was analysed and interpreted. E-cadherin expression was compared among the cases and the controls and was also correlated with clinicopathological parameters. Statistical

analysis was performed using Chi-square test and mean along with standard deviation was also calculated. A p value of <0.05 was considered significant.

RESULTS:

The average median age of cases and controls was 26 years. Not only the age of females but also gestational age of the pregnant women along with gross weight of placenta, weight of baby, apgar score of the baby all these clinicopathological parameters were correlated among the pre-eclampsia cases and the healthy pregnant controls. The gross and microscopic findings that is necrosis, calcification, and thrombosis when compared among the pre-eclampsia cases and the healthy controls, these findings were more evident in the pre-eclampsia placentas compared to normal healthy controls and were statistically significant. The immunohistochemical expression of e-cadherin was measured in both healthy controls and pre-eclampsia cases and it showed high (grade 3) and continuity of expression e-cadherin in majority of the normal healthy placental villi and there was predominantly varied expression (grade 0,1,2&3) along with discontinuity in the staining of the placental villi in pre-eclamptic placentas and these findings were statistically significant.

CONCLUSION:

This study indicates that the reduced intensity and discontinuity of E-cadherin staining in pre-eclampsia cases point to a defect in placental barrier function. This defect likely contributes to the development of pre-eclampsia and associated pregnancy complications.

KEYWORDS:

Pre-eclampsia placenta, E-cadherin, Immunohistochemistry, Indian population

INTRODUCTION

INTRODUCTION

Pre-eclampsia, a severe pregnancy condition which is evident by increased blood pressure and proteinuria after 20 weeks. Affecting 2-5% of all the pregnancies globally, it carries significant risks for both mother and baby.[1]While the exact cause remains unclear, growing evidence suggests an imbalance in factors regulating blood vessel growth might contribute.[2]E-cadherin is a protein linking structure that associates cells together which is crucial for early development, cell to cell interaction and its expression is known to be aberrant in various cancers. During pregnancy in the initial months there is a temporary decrease in E-cadherin expression within trophoblastic cells as they invade placenta, nevertheless the function of E-cadherin in regulation of placental vascularity is not fully understood. Hence this study aims to analyse the intensity and distribution of E-cadherin staining within the trophoblastic villi in healthy and pre-eclampsia placenta patients.

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REVIEW OF LITERATURE

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HISTORICAL ASPECTS:[3]

The Old Testament doesn't directly mention the placenta, but some scholars believed there might be symbolic references to it as part of the "bundle of life," that likely included the umbilical cord. This concept suggests a connection between mother and child.

Historically, the earliest insights into this organ can be traced back to depictions in illustrations by figures like Andreas Vesalius. The term "placenta" was officially introduced by Gabriele de Falloppi, although some argue that Realdus Columbus in 1559 may have played a role in coining this designation.

The origin of the term's "chorion" and "chori," signifying "separate" or "distinct," are credited to Aristotle. Galen, in Greek, coined the term "amnion," which translates to "lamp." In 1564, Arantius proposed the concept of association between maternal and fetal vascular systems, while Harvey, in 1651, asserted interconnection of fetal arterial and venous circulation with the placenta.

John Mayow (1643-1679) provided a detailed description of placental circulation and simultaneously, in 1660, Malpighi recognized that the capillary network formed the anatomical foundation for placental regional circulation.

In mid-18th century, brothers John and William Hunter described the intricate network of blood vessels connecting mother and fetus within the placenta's intervillous spaces. William Hunter further classified the lining of the pregnant uterus (decidua) into two distinct layers namely - decidua parietalis and decidua capsularis while John Hunter focused his detailed studies on the decidua basalis.

Our understanding of the placenta advanced significantly in the late 19th century. In 1889, Hubrecht coined the term "trophoblast" to identify the cells that form the placenta, separate from those that build the embryo itself.

This distinction highlighted the unique role of these placental cells, another key discovery came with the realization that outer layer of the chorionic villi, now called syncytiotrophoblast, is a syncytium – a multinucleated giant cell formed by the fusion of individual cells.

Finally, in 1950, electron microscopy by Wislochi and Dempreyin provided a revolutionary view of the placenta's intricate cellular structure.

FUNCTIONS OF PLACENTA:[4]

The placenta plays a vital role in protecting and supporting the growing fetus. It doesn't just react to the mother's environment; but acts as a physical barrier, releases various hormones, growth factors, and signalling molecules.

The various important functions of placenta are as follows:

a) **Nutritive Function**: Facilitating the exchange of nutrients between the fetus and the mother.
b) **Excretory Function**: Enabling the transfer of metabolic wastes, like urea, uric acid, and creatinine, from fetus to the maternal circulation, also regulates pH and water balance which is later managed by the kidneys.
c) **Respiratory Function**: Plays a crucial role in the exchange of oxygen and carbon dioxide.

d) **Endocrine Function**: Forms glycoprotein and steroid hormones that contribute to maintaining overall homeostasis.

e) **Barrier Function**: Shielding the fetus in opposition to pathogens and maternal immune system.

f) **Haematopoiesis of Bone Marrow**: Engaging in the early-stage haematopoiesis of the fetal bone marrow.

g) **Placental transfer of Heat**: Influencing fetal heat loss through the regulation of umbilical blood flow.

h) **Immunologic Function**: Ensuring the immunological acceptance of the fetus.

i) **Metabolic and Secretory Functions**: Placenta acts like a liver for the developing baby which processes nutrients and releases hormones.

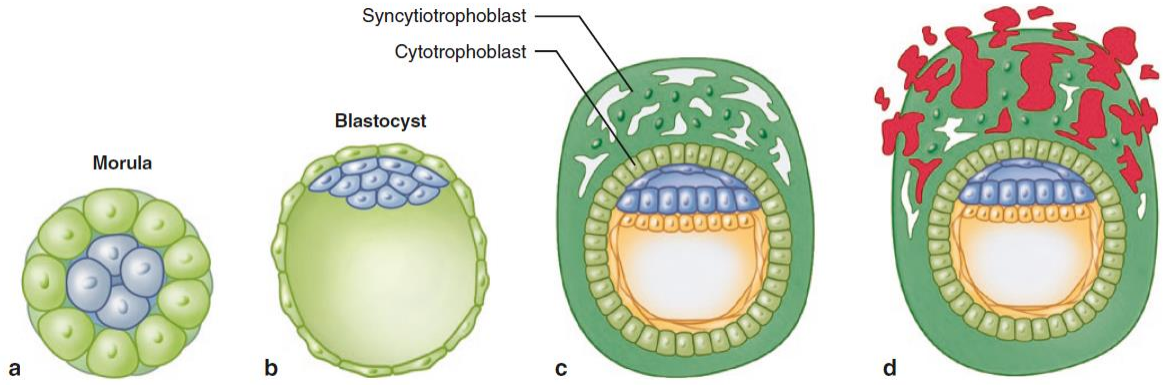
In conclusion, the placenta is a dynamic and multifunctional organ that plays a vital role for the health and progression of both fetus and the mother.

DEVELOPMENT OF PLACENTA: [4]

The proper formation, implantation, and development of placenta are essential for facilitating an effective interchange of nutrients and waste products between the mother and fetus. Despite its relatively short lifespan, the placenta undergoes diverse changes in appearance throughout pregnancy during various trimesters.

Following fertilization, the blastocyst establishes attachment to the endometrium at the implantation pole. This attachment is achieved through the proliferation of a trophoblastic cell mass, which firmly embeds itself into the endometrial stroma. This initial interaction sets the stage for the subsequent stages of placental development and the crucial exchange of substances essential for fetal growth and maturation.

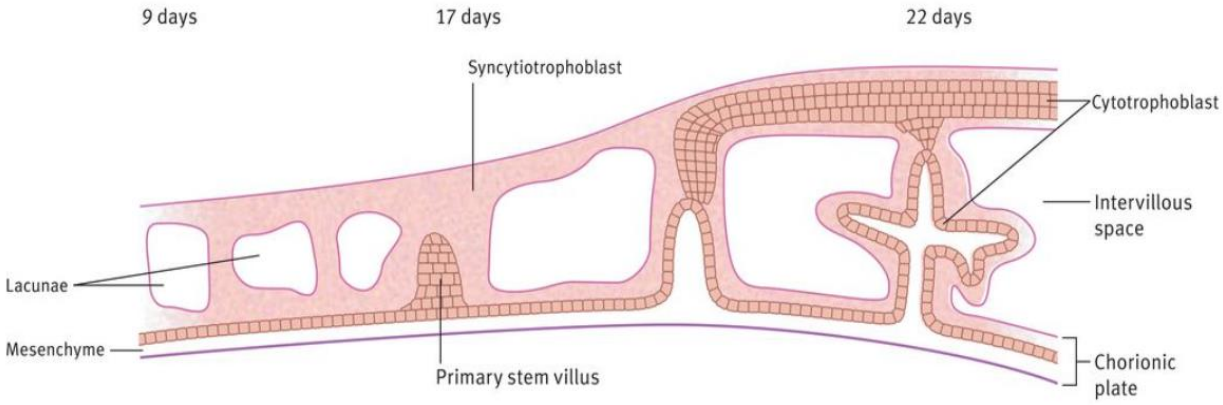
Fig 1: Shows formation and development of placenta -



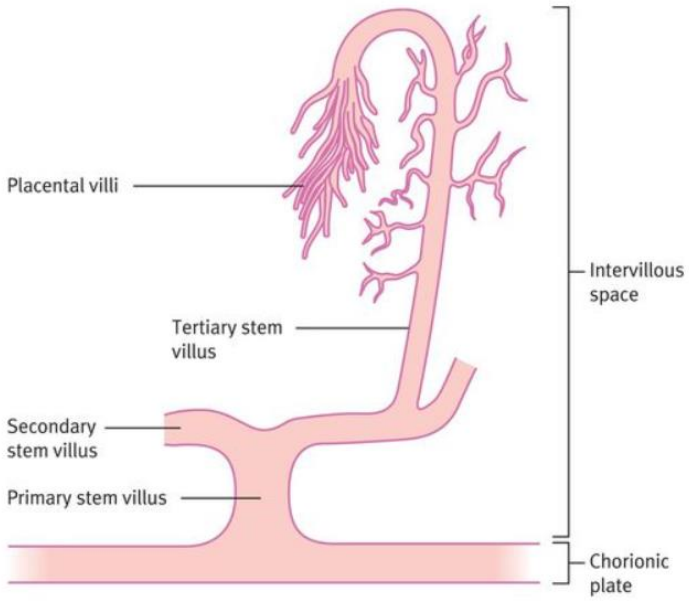
Placenta development in the early stage. (**a**) The Morula 3-4 days post fertilization contains inner cell mass that is destined to form the embryo (blue) and outer cell mass that forms placenta (green). (**b**) During the blastocyst stage, cells of outer cell mass trophoblast (green), forms the placenta. (**c**) Trophoblast differentiation begins shortly after blastocyst implantation on the endometrium. Outer layer is syncytiotrophoblast (dark green), and inner is cytotrophoblast (light green). (**d**) As blastocyst continues to penetrate endometrium, lacunae form within syncytiotrophoblast layer and fills with maternal blood (red).[5]

Table 1: Shows following ovulation, a sequential process -

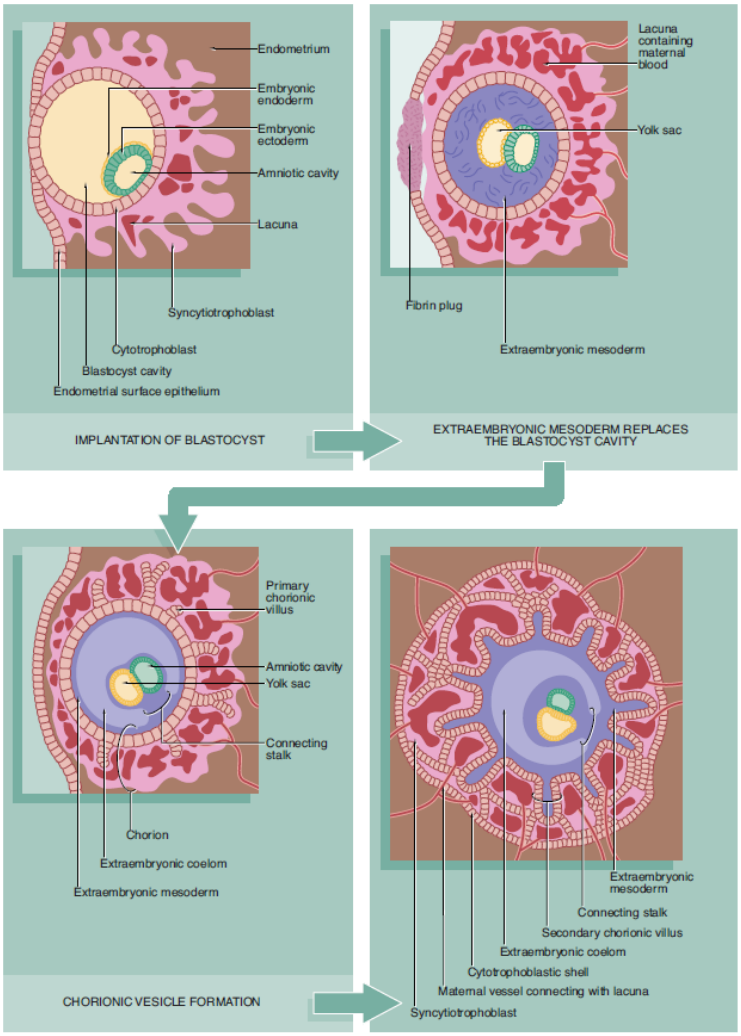
Stage	Key Events	Outcome
Day 7	Trophoblast differentiates into cytotrophoblast (inner) and syncytiotrophoblast (outer) layers.	Formation of developing cell mass
Day 10-13	Lacunae (spaces) form within the cell mass are filled with maternal plasma. Trabeculae (columns) separate lacunae.	Formation of intricate structure for exchange. No true maternal blood flow forms yet.
Day 14-21	Trabeculae become radially oriented, forming primary villous stems and cytotrophoblastic cells form the core.	Radially oriented villi form the framework for future primary villi. Labyrinthine structure of placenta is formed.
By day 21	Cytotrophoblast extends, forming a trophoblastic shell. Syncytium divides into peripheral and definitive layers. Peripheral syncytium on the decidual side degenerates and becomes Nitabuch's layer. Primary villi sprout and become vascularized.	Rapid growth of placenta occurs. Increased intervillous space is seen. Formation of primary villi starts.
Day 21 - 4th month	Villi near cavity degenerates. Chorion separates leaving thin rim of decidua. Villi towards basalis side of chorion forms the chorionic frondosum (future placenta). Placental septa emerge from the basal plate into the intervillous space, separating maternal space into 15-20 lobes.	Definitive formation about placenta occurs.
4^{th} month onwards	Further growth of villous tree for the development of placenta occurs	Complete formation of placenta occurs.



The Fig 2: Shows formation of the intervillous space and primary stem villi.[6]



The Fig 3: Shows formation of tertiary stem villi, which provide the architecture of the placenta. [6]



The Fig 4 shows: Comprehensive fertilization, development and implantation. [7]

VILLOUS DEVELOPMENT AND VILLOUS TYPES:[8]

Development of villous structures is a complex process, categorized based on factors such as stromal vasculature, function and location within the villous tree, and overall development. The distinct types of villi are as follows:

Mesenchymal Villi:

Beginning its development in the initial stages of 5th week, the mesenchymal villi establish a foundational structure. These villi consist of a primitive stromal core which has loosely arranged collagen and exhibit weakly developed fetal capillaries, showing highest mitotic

index among villous types. Furthermore, the presence of Hofbauer cells is minimal at this stage. As the developmental process advances, these mesenchymal villi undergo a transformation into immature mature intermediate villi.

Immature and Mature intermediate villi:

Around eighth week of pregnancy, a specific type of placental villus starts to dominate. These villi are called anchoring villi, which are bulbous in shape and have a thick outer layer called the trophoblast. This trophoblast layer contains prominent cytotrophoblast cells. Inside the villus, there's a reticular-type stroma with fluid-filled channels. Eventually, these anchoring villi develop further to become the mature stem villi. The mature intermediate villi diminish significantly by term, leaving only a few clusters. The stromal structure is of a reticular type, complemented by fluid-filled stromal channels. This reflects the dynamic changes and maturation that occur within the villous tree during the course of pregnancy.

Stem Villi:

Emerging around the eighth week, stem villi expand to constitute a significant portion approximately 20-25% of the placental volume by term. These are branch formations prominently located beneath the cord insertion, mainly within the central subchorionic region of the placenta. The primary role is to offer essential structural support to the entire villous tree.

These have a thick outer layer (trophoblast), but only about 20% of this layer contains actively dividing cytotrophoblast cells and fibrinoid necrosis covers most of the surface, indicating their maturity. Inside, the core (stroma) contains bundles of collagen fibres for strength, along with scattered fibroblasts, mast cells, and a few macrophages. Most importantly, stem villi have a complex network of blood vessels (arteries, veins, arterioles,

venules and capillaries) that allows for vital exchange of materials between the mother's and baby's blood circulation.

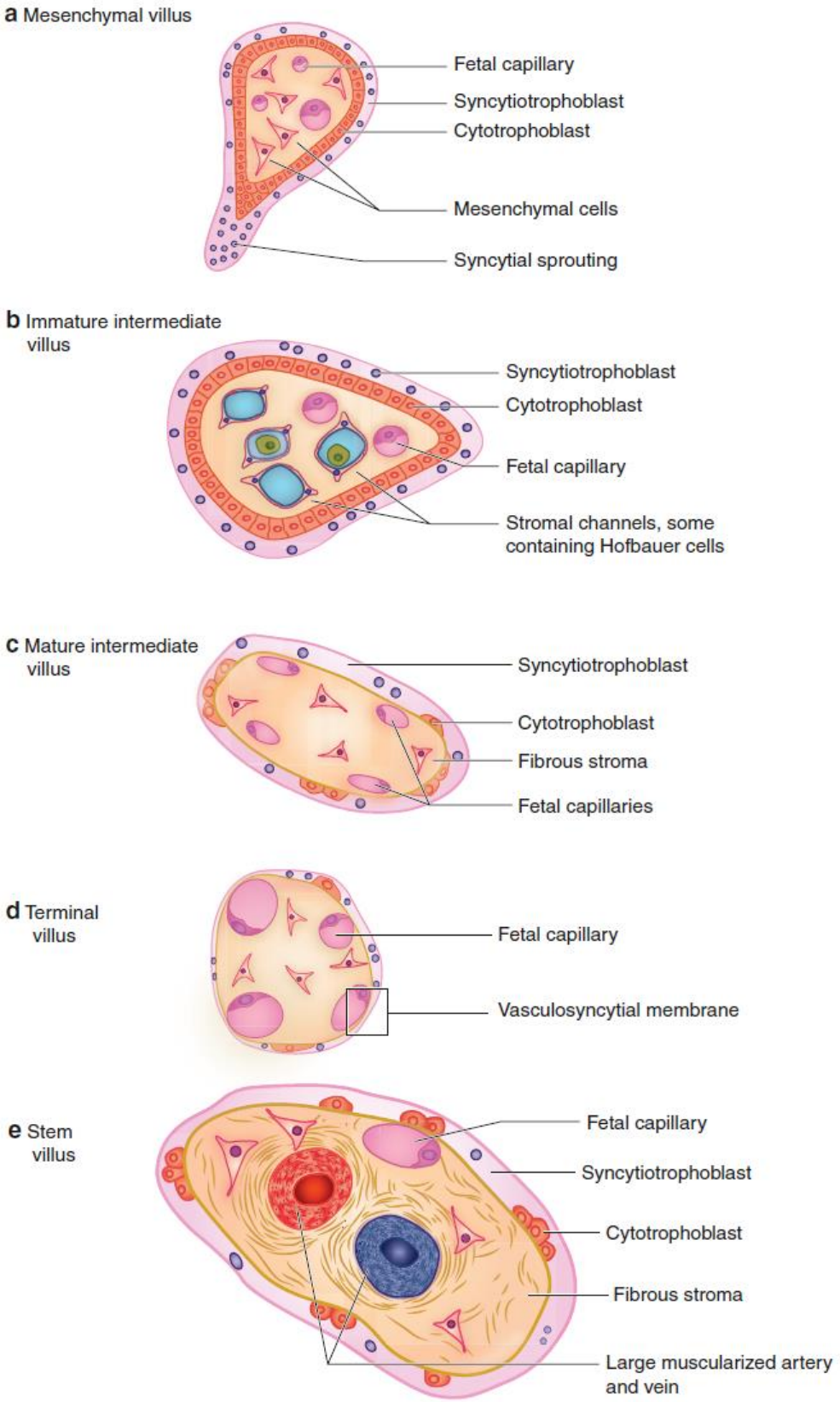
Terminal Villi:

Terminal villi represent the terminal or end branches of villous tree, resembling grape like outgrowths derived from the peripheral branching of mature intermediate villi. These structures have a network of connective tissue fibres along with a sparse presence of macrophages with trophoblasts closely associated with capillaries. Terminal villi are distinguished by their abundant fetal capillaries, supporting to the formation of the vasculo-syncytial membrane with syncytiotrophoblast cells. This architecture plays a pivotal role in facilitating essential exchange of substances between maternal and fetal circulatory systems within the placenta.

Table 2: Shows the contrasting and similar features of all the villi -

Villous Type	Development	Shape	Trophoblast	Stroma	Function	Other features
Mesenchymal Villi	Early stages of 5th week	None	None	None	None	Structure: Primitive stromal core with loosely organized collagen, under-developed fetal capillaries with highest mitotic index
Immature and Mature Intermediate Villi	Around 8th week	Bulbous	Thick and robust outer layer with prominent cytotrophoblasts	Reticular type with fluid-filled channels	Reflects dynamic changes and maturation of the villous tree	Mature intermediate villi diminish by term
Stem Villi	Around 8th week	Large trunk and branch structures	Robust cover with 20% identifiable cytotrophoblasts, surface covered by fibrinoid necrosis	Bundles of collagen, occasional fibroblasts, mast cells, limited macrophages	Provides crucial structural support	Proportion of placental volume: 20-25% by term
Terminal Villi	Derived from peripheral branching of mature intermediate villi	Grape-like outgrowths	Trophoblasts are closely associated with capillaries and in conjunction with synctiotrophoblast	Network of connective tissue fibers along with sparse macrophages	Abundant fetal capillaries for forming vasculo-syncytial membrane.	Facilitate exchange between maternal and fetal circulation

The Fig 5: Shows main villous types of placentae. (a) The mesenchymal villous has a high concentration of mesenchymal cells and displays unusual vasculature, a thick, double layered trophoblast, primitive stroma and syncytial sprouting. (b) The immature intermediate villus has poorly established capillaries, reticular stroma, stromal channels that are home to a large number of macrophages or Hofbauer cells. (c) Smaller capillaries and vessels make up less than 50% of the mature intermediate villus's villous stroma, which is starting to turn collagenous. (d) Fetal capillaries make up more than 50% of the villous stroma in the terminal villus, which has a thin trophoblastic layer and the creation of vasculosyncytial membrane, indicating a shorter diffusion distance between the fetal and maternal circulations. (e) The largest villous form, the stem villus, is made up of a thick layer of collagenous stroma that surrounds massive, mascularized arteries, veins and uncommon capillaries.[7]


a Mesenchymal villus
Fetal capillary
Syncytiotrophoblast
Cytotrophoblast
Mesenchymal cells
Syncytial sprouting
b Immature intermediate villus
Syncytiotrophoblast
Cytotrophoblast
Fetal capillary
Stromal channels, some containing Hofbauer cells
c Mature intermediate villus
Syncytiotrophoblast
Cytotrophoblast
Fibrous stroma
Fetal capillaries
d Terminal villus
Fetal capillary
Vasculosyncytial membrane
e Stem villus
Fetal capillary
Syncytiotrophoblast
Cytotrophoblast
Fibrous stroma
Large muscularized artery and vein

NORMAL ANATOMY OF PLACENTA:[4]

Human placenta has unique discoid shape, connecting the upper part of uterine body, either on its posterior or anterior wall. Upon delivery, the placenta detaches along the intermediary spongy layer of the decidua basalis (decidua spongiosum).

It has a flesh-like texture, weighing around 500-700 grams and occupies 30% of the uterine wall. It measures between 15-20 cm in diameter and 1.6-3.5 cm in thickness.

Mature placenta has fetal side where umbilical cord attaches and maternal side.

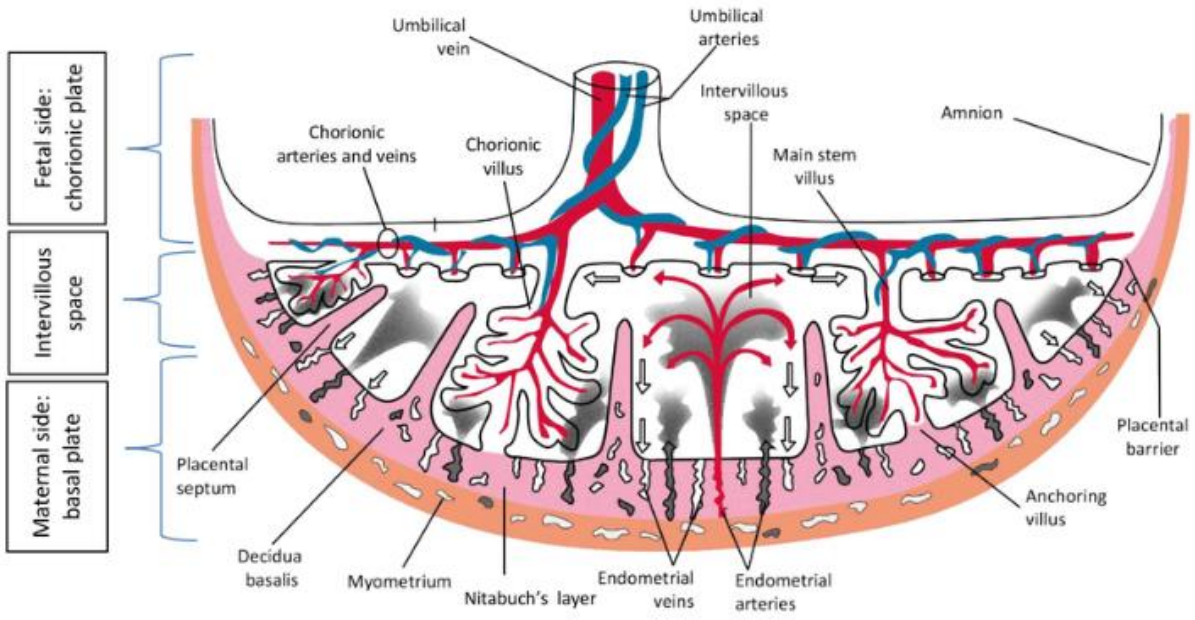
Fetal side of placenta is covered by glossy and transparent amnion layer.

Umbilical cord is centrally attatched, with visible branches of umbilical vessels beneath the amnion on the fetal side, it contains two arteries and one vein and is spongy to the touch, normal length on average is between 55 to 65 cm (average is 32 cm). True knots in the umbilical cord are normal when they cause adverse outcomes but tight knots can potentially lead to fetal demise. False knots, or vascular tortuosities, are frequently seen but infrequently have clinical relevance.

The maternal side of placenta is rough and spongy in texture. It is reddish hue in color due to maternal blood and is partly covered by decidua basalis that gives the shaggy appearance. This surface is divided into 15-20 cotyledons by septa. Placental margins are defined by fused chorionic and basal plate.

OVERVIEW OF COMPONENTS OF PLACENTA:[4,8]

Fetal Side



Maternal Side

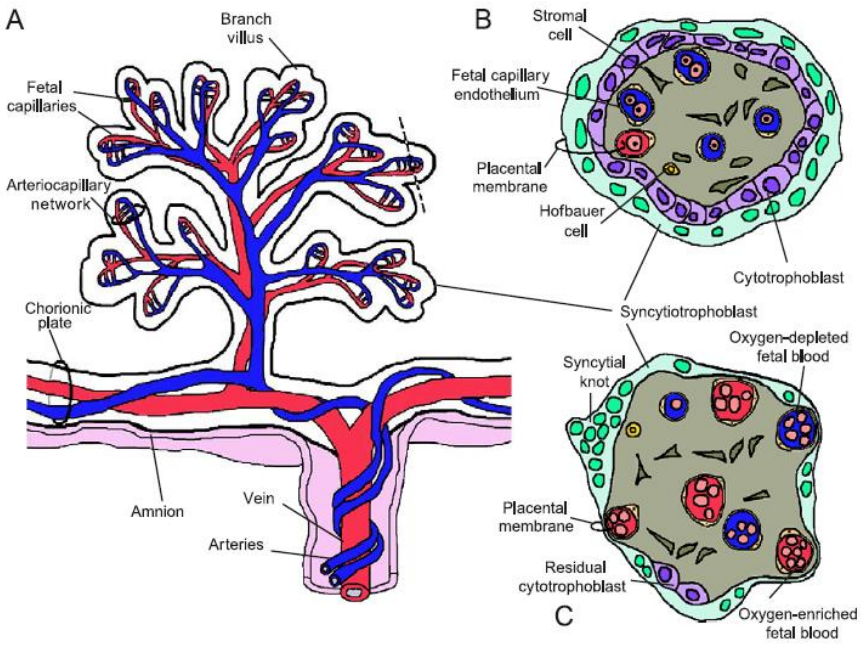
The Fig 6: Shows overview of the anatomy of placenta. The extraplacental membranes (EPM), composed of amnion (A), chorion (C), and parietal decidua (PD); the umbilical cord; the chorionic plate; the basal plate; and the villous parenchyma. [5]

The placenta is bounded by the fetal amniotic membrane and the maternal basal plate, comprising of the intervillous space an area filled with maternal blood and intricate stem villi. Histological examination reveals distinct functions of each component in facilitating nutrient and waste products exchange between maternal and fetal circulatory systems.

Histology of the placenta as follows-

- **Amniotic membrane** – This is lined by single layer of cuboidal epithelium delicately connected to the adjacent chorionic plate. It does not actively contribute to the formation of the placenta itself.
- **Chorionic plate** – Composed of chorionic villi which is in the intervillous space.

  The chorionic villi lined by fetal capillary endothelium that is comprised of syncytiotrophoblasts, cytotrophoblasts, trophoblastic basement membrane, connective tissue and endothelial basement membrane. It also has branches of umbilical vessels extending from the outer periphery towards the center.



The Fig 7: Shows typical representation of fetal placental circulation (a), in which the dotted line represents the location from which a drawing of a section through the chorionic villus (b). Section through the chorionic villus at full term is also depicted (c). [9]

- **Basal plate –** This forms the structural base of the placenta, consists of several distinct layers that are arranged from outermost to innermost layers. These include:

    a) Compact and spongy layer of decidua basalis

    b) Nitabuch layer

    c) Shell of Cytotrophoblasts and Syncytiotrophoblasts

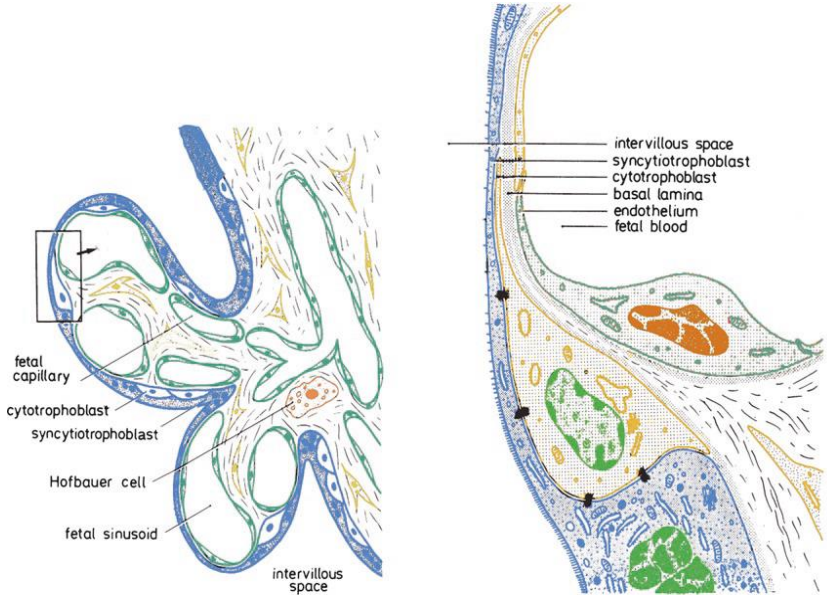
a) Compact and spongy layer of decidua act as an essential characteristic of the basal plate and the presence of perforations created by spiral arteries. These perforations serve as entry points for maternal blood into the intervillous space.

b) Layer of Nitabuch serves as a fibrinous barrier and is situated at the junction of the cytotrophoblastic shell and the decidua. Its formation is a result of the fibrinoid degeneration of syncytiotrophoblast. This layer plays an important role in preventing excessive trophoblast penetration into the decidua. This membrane is absent in conditions such as placenta accreta and morbidly adherent placentas.

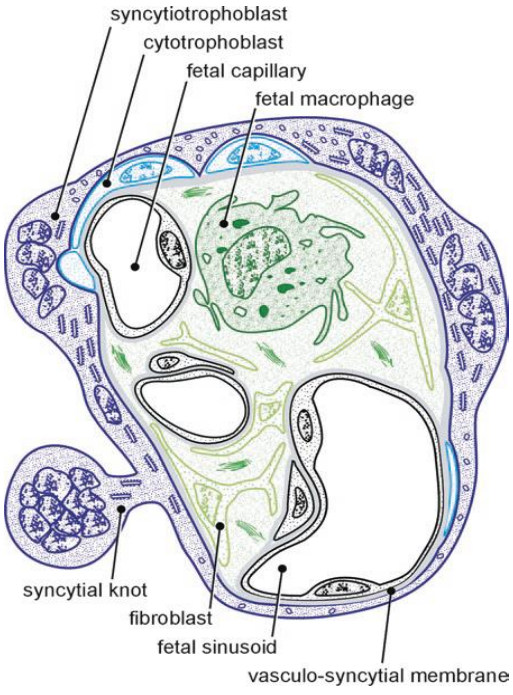
Table 3: Shows microscopic features of the cells that line mature chorionic villus -

Structure	**Function**
Syncytiotrophoblast (Syncytium)	These are multinucleated giant cells that form syncytial knots in term placenta. They facilitate exchange between maternal and fetal circulatory systems.
Syncytial Knots	These are aggregates of syncytiotrophoblast within placental tissue that undergo apoptotic changes and sheds into maternal circulation It contributes to dynamic turnover of placental tissues during pregnancy.

Villous Cytotrophoblasts	These are cuboidal to polyhedral cells with well-defined cell borders that contain dispersed chromatin in vesicular nucleus has clear or slightly granular and basophilic cytoplasm with occasional mitotic figures that indicate cellular activity.
Trophoblastic Basement Membrane	This causes separation between villous trophoblast and underlying stroma with fibrillary structure that is composed of collagen IV, laminin, and heparin sulphate, contributing to structural integrity and functional interactions within placental tissue.
Villous Stroma	It includes fixed connective tissue cells and fibers including pre-collagen and collagen containing Hofbauer cells and fetal vessels. It undergoes differentiation into fibroblasts and myofibroblasts during pregnancy trimesters
Hofbauer Cells	These are the placental tissue macrophages which round, ovoid, or reniform shape with eccentrically positioned nucleus. They contain vacuoles (early pregnancy) or intracytoplasmic granules (later pregnancy), act as immune defenders and chemical messengers



The Fig 8: Shows human placental villi structure. An enlarged light microscopic segment of two terminal villi branching of a mature intermediate villus can be seen on the left. A schematic electron-microscopic segment of the placental barrier, illustrating typical layers, is displayed on the right for a more detailed view. [10]



The Fig 9: Shows a simplified illustration of a terminal villus's cross section. The syncytial knot, fetal sinusoid, cytotrophoblast, syncytiotrophoblast with well-developed

smooth and rough endoplasmic reticulum, fetal sinusoid and other cells within the villus, such as macrophage and fibroblast are all depicted. [11]

HISTOPATHOLOGICAL FINDINGS IN ABNORMAL PLACENTA: [12–15]

Some of the grossly evident findings:

I. Calcification & Infarction:

Normally placental calcification seen in 15-36% of term placentas which tends to become more noticeable following 36 weeks of gestation and increases as gestational age advances. These calcifications show up on the maternal surface as small, sporadic, white, firm to hard plaques that have a grainy feeling while sectioning. The mild calcifications are thought to be a normal part of the placenta's ageing process. Extensive or severe calcifications indicate underlying pathological conditions in pre-term placentas. This phenomenon is attributed to the deposition of calcium salts within the placental tissue and is well-known to be associated with pathological factors like maternal age, elevated blood pressure, diabetes, and foetal growth restriction.

Histologically calcifications are identified as basophilic material on H&E staining and appears darkened when subjected to Von Kossa stain. They are detectable more in term placentas. Dystrophic calcification which affects the deceased or degenerative villi is also present in the placenta.[12]

Infarction results from the sudden cutoff of arterial blood flow. It occurs in approximately 25% of pregnancies which often affects only a limited area i.e. less than 5%. An abundance of infarcts with retroplacental hematoma bleeding behind the placenta indicates issues with the arteries supplying the placenta and these issues raise the possibility that there is intrauterine growth restriction of the growing child. A recent infarct is dark red in colour and

has a triangle shape, with the base pointing towards the direction of the basal plate. An older infarct has a white or yellow colour. The infarcts or tiny artery blockages in the placenta are occasionally caused by blood clots.[12]

II. Retroplacental hematoma:

Accumulation of blood behind the placenta that separates the placenta from the uterus is called a retroplacental hematoma. It is typically observed during delivery, feels soft to touch and appears crimson red in colour. This occurs in pathological conditions like pre-eclampsia, placental abruption, early delivery and when there are patches of dead tissue inside the placenta.[13]

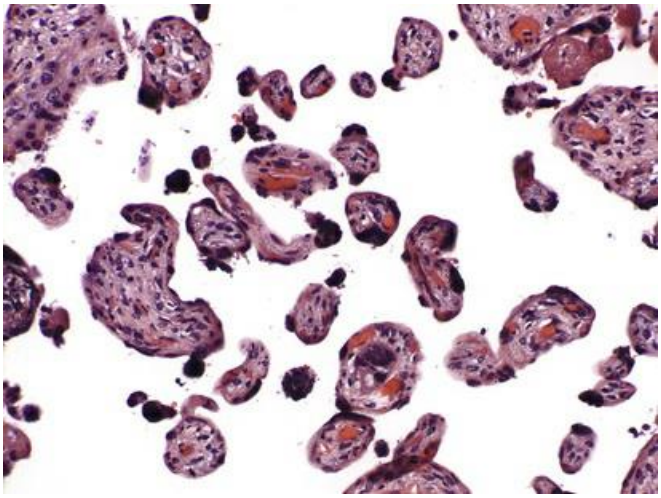
III. Perivillous and subchorionic fibrin deposit:

Perivillous fibrin-deposition-characterized by plaques that are primarily found in the placenta's periphery. There is significant poor foetal outcome when these deposits cover more than 30% of the villous surface. The perivillous fibrin deposition is a marker for possible issues that could impair the developing fetus's health.[14,15]

Some of the microscopic findings:

I. Abundant syncytial knots:

Syncytial knots are the degenerative process consisting of a collection of apoptotic nuclei that emerge from the villi's surface and extend into the intervillous region. These are typically rare before to 32 weeks of gestation and 10-30% villi will have knots at term.[16] They occur as a result of foetal stem artery obliterative lesion that is induced by villous hypoperfusion. Reduced intra placental oxygenation is known to cause an increase in syncytial knotting.[17] Syncytial knots are more common in IUGR, gestational diabetes, and preeclampsia.



The Fig 10: Shows characteristics of villous ischemia, such as terminal villi that are abnormally tiny and sparse.[18]

II. Vasculo-syncytial membranes:

These are attenuated anuclear syncytiotrophoblast that are stretched in close proximity to a capillary that make up the vasculo-syncytial membrane. Before 32 weeks, these membranes are rare, between 32 weeks and term, they quickly expand and 20% of villi exhibit vasculo-syncytial membrane at term.[16] Placentas of women with pre-eclampsia, diabetes, and Rh incompatibility had a deficiency of the vasculo-syncytial membranes.

III. Villi with fibrinoid necrosis:

Fibrinoid necrosis has few defective syncytial nuclei which manifests as homogenous PAS-positive deposits. Fibrinoid necrosis typically manifests in 3% of the villi in mature placentas. It contains fibronectin, laminin and collagen IV.[16] Conditions affecting more that 3% of fibrinoid necrosis of villi are materno-fetal rhesus incompatibility, diabetes, and preeclampsia. This is a telltale sign of an immune response in the tissue of the trophoblast.[19]

IV. Stromal fibrosis:

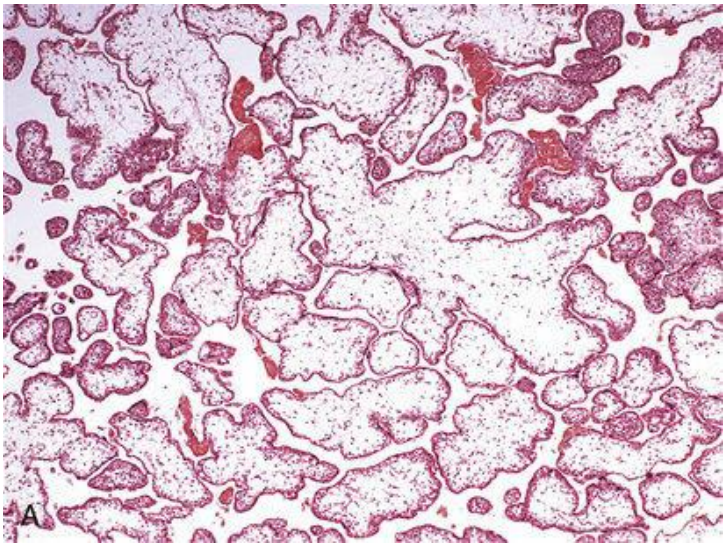
The stroma displays a delicate network of fibrous tissue at term as stromal collagen gradually accumulates throughout pregnancy.[16] Extended pregnancies, pre-eclampsia, and placentas from diabetic mothers are associated with stromal fibrosis of >3% and is a morphological indicator of decreased villous perfusion.[19]

V. Thickening of basement membrane:

Cytotrophoblast basement membranes precise thickness is unknown due to variability in measurement. Using specific stain such as PAS and IHC for collagen 4 or laminin, the basement membrane can be seen. Conditions causing thick basement membranes in placenta are pre-eclampsia, essential hypertension or IUGR, diabetes, materno-fetal rhesus incompatibility, and smoking have placentas that have thick basement membranes.[20]

VI. Villous edema

Typically, term pregnancy does not result in villous edema. A transparent, fluid, comparatively hypocellular stroma surrounds the widely expanded villi.[21] Conditions associated with villous edema are - Pre-eclampsia, diabetes, placental infections such as syphilis, toxoplasmosis, parvovirus, and cytomegalovirus, placentas with large haemangiomas or metastases from congenital nephrotic syndrome, foetal cardiac disorders, fetal anaemia and hydatidiform mole.[22]



The Fig 11 shows diffuse villous edema.[18]

PREGNANCY-RELATED HYPERTENSIVE DISORDERS:

Four primary forms of hypertensive disorders of pregnancy (HDP) exist:

1. Chronic hypertension

2. Gestational hypertension

3. Pre-eclampsia with or without severe features

4. Pre-eclampsia superimposed on chronic hypertension[23]

1. CHRONIC HYPERTENSION

It is defined as systolic bp ≥ 140 mm Hg and/or diastolic bp ≥ 90 mm Hg before pregnancy or before 20 weeks of gestation, or the persistence of hypertension longer than 12 weeks following delivery.

2. GESTATIONAL HYPERTENSION

It is defined as systolic bp ≥ 140 mm Hg and/or diastolic bp ≥ 90 mm Hg after 20 weeks of gestation in a woman who was at the baseline of normotensive before pregnancy. Blood

pressure usually returns to normal within 12 weeks after delivery. A woman should be classed as having chronic hypertension, if she has a sustained postpartum elevation in blood pressure after being diagnosed with gestational hypertension.

3. PRE-ECLAMPSIA WITH OR WITHOUT SEVERE FEATURES

The term "pre-eclampsia" refers to proteinuria and new onset hypertension that often develops after 20 weeks of pregnancy. According to ACOG, proteinuria is defined as (a) 300 mg or more of urine collected every 24 hours; (b) Protein to creatinine ratio of at least 0.3 mg/dl; or (c) A dipstick reading of 2+ in the absence of quantitative methods.

In the absence of proteinuria, pre-eclampsia can also present with the following additional diagnostic criteria: (a) Thrombocytopenia (platelet count $<1,00,000x10^9/L$); (b) Impaired hepatic function (transaminase level > 2 times the upper limit of normal); (c) Severe pain in the right upper quadrant or epigastric area that is not related to any other diagnosis; (d) Renal insufficiency (serum creatinine >1.1 mg/dl); (e) Pulmonary oedema; (f) New-onset headache that is not acetaminophen responsive and is not accompanied by any other symptoms or visual symptoms.

A systolic blood pressure of 160 mm Hg or higher and a diastolic blood pressure of 110 mm Hg or higher on two separate occasions spaced at least 4 hours apart are considered symptoms of pre-eclampsia with severe characteristics. A severe form of pre-eclampsia known as HELLP syndrome (haemolysis, raised liver enzyme levels and low platelet count) typically manifests in the 3^{rd} trimester and has been linked to higher rates of maternal morbidity and mortality. Elevated lactate dehydrogenase to 60 IU/L or more; elevated aspartate aminotransferase and alanine aminotransferase levels > 2 times the upper limit of normal; and platelet count $<1,00,000x10^9/L$ are the diagnostic criteria of HELLP.

4. CHRONIC HYPERTENSION WITH SUPERIMPOSED PRE-ECLAMPSIA

The diagnosis of chronic hypertension with superimposed pre-eclampsia is made up of two factors: history of pre-eclampsia during prior pregnancy and a diastolic bp >100 mm Hg for more than 4 years. Superimposed pre-eclampsia is difficult to differentiate from deteriorating chronic hypertension in women with baseline proteinuria and chronic hypertension; new-onset thrombocytopenia or significant increase in liver enzyme values are frequently the first indicators of superimposed pre-eclampsia.

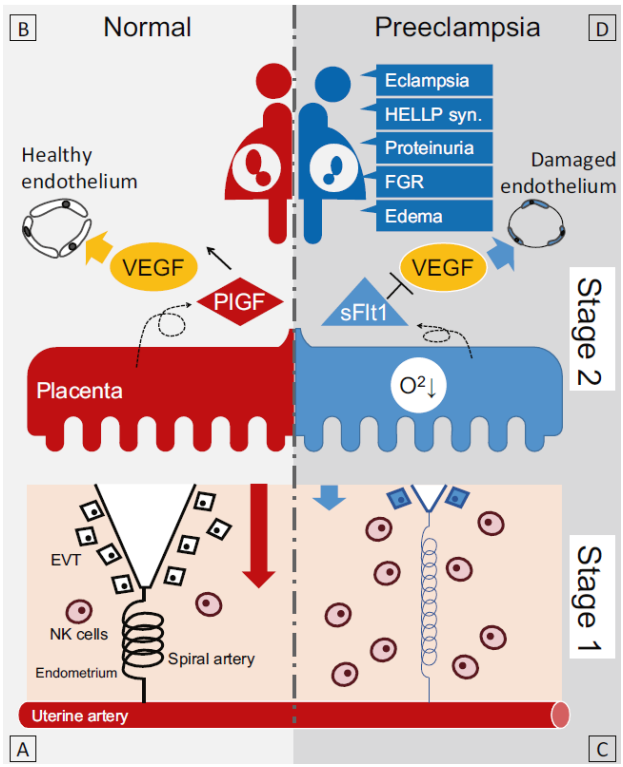
PHYSIOLOGY OF NORMAL PREGNANCY

During normal pregnancy, spiral artery remodelling takes place, involving the invasion of trophoblastic cells into the decidua. These cells replace the endothelial cells and vascular smooth muscle of the spiral arteries. Consequently, maternal blood vessels begin to perfuse into the interchorionic space, leading to increased oxygen partial pressure in the placenta and decreased systemic vascular resistance. Angiogenic factors, including vascular endothelial growth factors (VEGFs) and placental growth factors (PIGFs), modulate angiogenesis intracellularly via the receptor VEGFR-1. Uterine natural killer (uNK) cells and regulatory T cells play vital roles in maintaining pregnancy and supressing allogeneic responses toward the fetus. [14,15] By releasing chemokines such interleukin-8, interferon-inducing protein-10, and other angiogenic factors, decidual uNK cells control trophoblast invasion.[16] The uterine spiral arteries are in close proximity to early vascular alterations, including desquamation - induced intimal vacuolation, disintegration, and tunica media weakening.[17]

PATHOPHYSIOLOGY OF PREECLAMPSIA

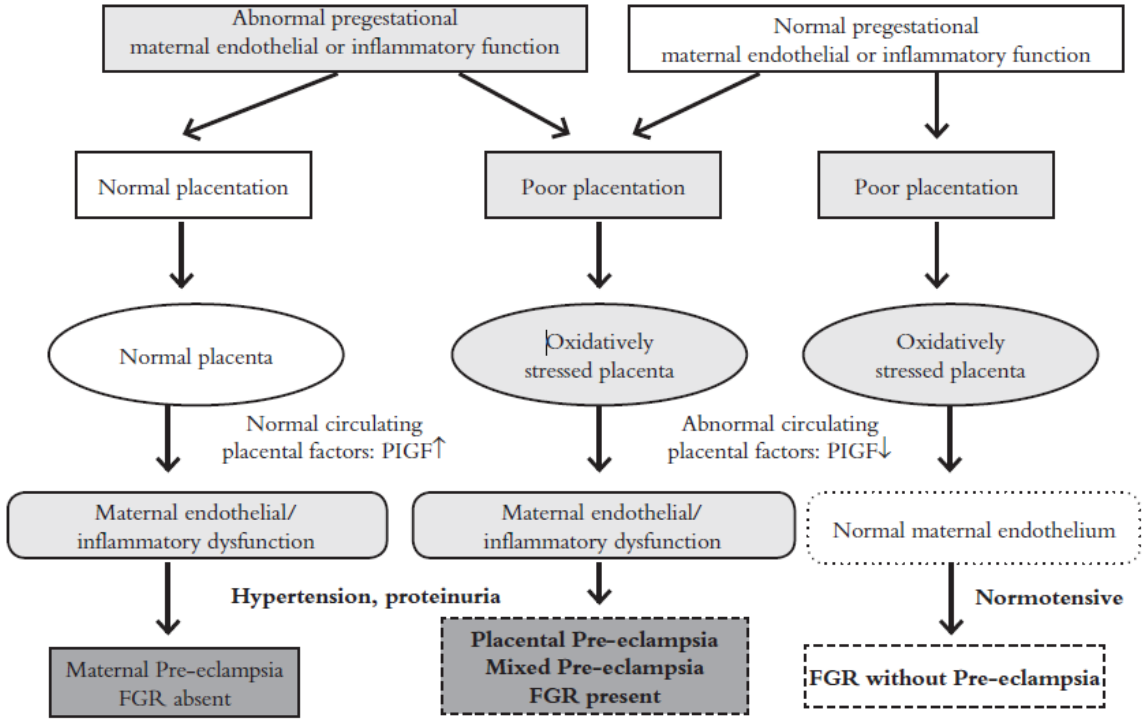
Inadequate angiogenesis and remodelling lead to a partial increase in fetal placental circulation oxygen pressure, causing placental ischemia and damage.[24] Trophoblast cells produce (sFlt-1) or simulated soluble VEGFR-1, inhibiting PlGF and production of soluble

endoglin (sEng).[25] The sFlt-1 mediated suppression of PIGF and VEGF hampers trophoblastic cell invasion into the placental membrane and damaged vascular endothelial cells, sEng binds to TGF-β causing further inhibition of cytotrophoblast cell invasion. These variables cause pre-eclamptic symptoms in mothers when they enter the bloodstream.[26] Early pregnancy placental anomalies cause local ischemia, inflammatory cytokine release, and chronic uteroplacental insufficiency, which all contribute to early-onset maternal hypertension in pre-eclampsia.[27] Placental dysfunction brought on by long-term oxidative stress from maternal metabolic problems including obesity and insulin resistance is frequently linked to late-onset pre-eclampsia.[28]



The Fig 12: Demonstrates the tow-stage theory of pre-eclampsia. Sufficient maternal blood flow from the spiral artery (A) results from proper EVT invasion into the maternal endometrium (red arrow) in normal pregnancy. The placenta secretes PIGF, which stimulates VEGF and keeps the endothelium in good condition (B). Conversely, partial invasion of the

EVT (blue arrow) in pre-eclamptic pregnancy results in inadequate blood flow from the spiral artery to the mother and consequent placental hypoxia (C). Following this, the placenta secretes sFlt-1, which inhibits VEGF and causes systemic endothelial dysfunction as well as the emergence of numerous clinical symptoms (D). NK cells, natural killer cells, EVT extra-villous trophoblast, PIGF placental growth factor, sFlt-1 soluble fms-like tyrosine kinase-1, VEGF vascular endothelial growth factor, HELLP syndrome. haemolysis, high fever, high liver enzymes, low platelet count and FGR fetal growth restriction.[29]



The Fig 13: Shows flow chart model of pre-eclampsia, FGR (fetal growth restriction) and PIGF (placental growth factor).[30]

EPIDEMIOLOGY

Hypertension is recognized as prominent contributor to the maternal mortality in high-income countries.[31] Hypertensive disorders of pregnancy (HDP) confound approximately to 5-10% of

all pregnancies. World Health Organization (WHO) research identified hypertension as primary cause of maternal mortality in high-income nations, responsible for 15% of deaths.[31]

In United States, the incidence of hypertensive disorders of pregnancy (HDP) heightened from 12% in 2017 to 16% in 2019.[32] Pre-eclampsia affects approximately 3% of all pregnancies in US.[33] Healthy women with singleton gestations and no prior history of HDP have an overall rate of HDP of less than 10% and are classified as low risk.[34]Women who have experienced chronic hypertension or HDP in the past are 25-50% are more likely to develop HDP.[34]

In India, prevalence of eclampsia is 1.5% while that of pre-eclampsia ranges from 5-15%.[35] An estimated 62,000-77,000 people die from HDP each year, making up roughly 18.1% of all maternal deaths.[31]

Untreated hypertension during pregnancy can cause significant complications for both fetus and the mother. It is associated with premature delivery (birth occurring before 37 weeks of gestation) and low birth weight (when baby is born weighing < 5 pounds 8 ounces). These outcomes are often due to chronic inadequate blood flow to the uteroplacental unit, which can result in fetal growth restriction.

Untreated hypertension, particularly preeclampsia, can lead to various complications for the mother. Women with untreated hypertension are at higher risk of experiencing acute sequelae such as pulmonary edema, renal injury and posterior reversible encephalopathy syndrome. Additionally, a history of hypertensive disorders of pregnancy (HDP) significantly increases woman's risk of future cardiovascular disease, including myocardial infarction and stroke, by 2 to 8 times compared to those with normotensive pregnancies.[36]

Pre-eclampsia plays a role in around 12-25% of cases involving fetal growth restriction and infants classified as small for gestational age. Additionally, it contributes to 15-20% of all

pre-term births and is linked for complications associated with prematurity, leading to neonatal morbidity and mortality.

RISK FACTORS

A. Pre-conceptional and/or chronic risk factors:

• Nulliparity/primiparity/teenage pregnancy - Nulliparity significantly increases the risk of preeclampsia, making it an important risk factor.

• History of prior pre-eclampsia

• Family history – The development of preeclampsia is tripled when there is a family history of pre-eclampsia.[37]

B. Presence of specific underlying disorders:

• Pre-existing medical condition such as hypertension, obesity (BMI >35 kg/m^2) and vascular disorders (renal disease) are linked to the occurrence of preeclampsia. [38,39] Women with underlying chronic hypertension, have 10-25% increased risk of developing pre-eclampsia.[40,41] The overall risk of pre-eclampsia in individuals with pre-gestational diabetes is approximately 21%, and the risk associated with obesity increases by approximately 2 to 3-fold.

Advancing age is an additional risk factor, especially as individuals increasingly delay pregnancy. This increases the risk of comorbidities, including the use of assisted reproductive technologies and illnesses including hypertension, diabetes and cardiovascular disease.[42,43] Maternal mortality rates for patients over 40 years are 4-5 times greater than for those in their 20's. [44]

• Autoimmune diseases – Pregnant women with autoimmune diseases such as antiphospholipid antibody syndrome and systemic lupus erythematosus are more likely to develop pre-eclampsia.[42]

• Hyperhomocysteinemia

• Protein S deficiency, Activated protein C resistance

• Sickle cell disease and trait

C. External Influences

• Smoking

• Stress, psychosocial strain related to work

D. Pregnancy-Related Risk Factors

• Congenital structural anomalies

• Hydrops fetalis

• Chromosomal abnormalities (trisomy)

E. Placental factor

• Abnormal placental volume seen in conditions like hydatidiform moles and multiple-fetal gestations.[45]

E-CADHERIN:

Cadherins were first discovered by Takeichi as cell surface molecules that are that are involved in Ca^{2+} dependent adhesion mechanism in Chinese hamster V79 cells.[46] They comprise a large family of transmembrane or membrane-associated glycoproteins that

mediate specific cell to cell adhesion in Ca2+-dependent manner, functioning as a key molecule in the morphogenesis of a variety of organs. [47]

The cadherin family consists of five major subfamilies:

a) Classical cadherins of Type I,
b) Closely related cadherins of Type II
c) Desmosomal cadherins (desmocollins and desmogleins)
d) Protocadherins
e) Variety of cadherin-related molecules.[48]

E-cadherin is a type -I cadherin surface protein of about 150kDa and is protected by Ca^{2+} against iodination and trypsinization. This is the first report on E-cadherin and its Ca2+ dependent adhesion potential. Francois Jacobs group in Paris 1980 described E-cadherin as an 84-kDa glycoprotein (gp84) that was identified by an immunological approach on the membranes of mouse embryonic carcinoma cells.[49]

NORMAL FUNCTIONS OF E-CADHERIN:[50]

a) Cell to Cell Adhesion:

E-cadherin is primarily expressed in epithelial tissues where it mediates interactions between adjacent cells by forming calcium dependent adhesive complexes. The adhesive interactions contribute to the formation of adherens junctions, which are specialized cell-cell junctions found in epithelial tissues

b) Tissue Morphogenesis and Development:

During embryonic development, E-cadherin is essential for tissue morphogenesis and the formation of epithelial structures. It regulates cell migration, and tissue patterning

processes by mediating cell-cell adhesion and communication. This is particularly important in the formation of the ectoderm during gastrulation and the establishment of epithelial layers in various organs and tissues.

c) Maintenance of Epithelial Polarity:

E-cadherin contributes to the establishment and maintenance of epithelial polarity, which is essential for the proper functioning of epithelial tissues. By promoting cell-cell adhesion and forming adherens junctions, E-cadherin helps to establish apical-basal polarity and maintain the asymmetric distribution of proteins and lipids within epithelial cells. Loss of E-cadherin function can disrupt epithelial polarity and lead to aberrant cell behaviours, such as epithelial-to-mesenchymal transition (EMT).

d) Regulation of Cell Signalling:

E-cadherin is involved in the regulation of intracellular signalling pathways that control cell proliferation, differentiation, and survival. Through its cytoplasmic domain, E-cadherin interacts with various intracellular proteins, including β-catenin and p120-catenin, which are implicated in Wnt signalling, cytoskeletal dynamics, and gene expression regulation.

E-cadherin expression levels vary in both benign and malignant conditions and alterations in its expression have been implicated in various diseases.

BENIGN CONDITIONS:

Inflammatory Conditions:

In benign inflammatory conditions, such as inflammatory bowel disease (IBD) or gastritis there is increased E-cadherin is seen as part of the tissue repair process. E-cadherin

overexpression contributes to the restoration of epithelial integrity following damage caused by inflammation.

Tissue Regeneration:

During tissue regeneration and wound healing, E-cadherin expression may be upregulated to facilitate the re-establishment of epithelial barriers and the formation of adherens junctions between regenerating cells.

MALIGNANT CONDITIONS:

Early Tumorigenesis:

In early stages of tumorigenesis, some cancers may exhibit increased E-cadherin expression. This phenomenon is often associated with well-differentiated tumors and is thought to reflect the retention of epithelial characteristics by tumor cells.

Tumor Progression and Metastasis Suppression:

In certain advanced malignancies, such as invasive ductal carcinoma of the breast, overexpression of E-cadherin has been linked to the suppression of tumor progression and metastasis. High E-cadherin levels can inhibit tumor cell invasion and dissemination by promoting cell to cell adhesion and maintaining epithelial characteristics.

Table 4: Shows the E-cadherin expression and its consequences in various cancers –

Cancer type	Expression of E-cadherin	Consequences
Breast Lobular Carcinoma	Loss/downregulation	Cell to cell adhesion is lost, increased tumor invasiveness
Gastric Carcinoma	Downregulated	Tumor invasion, lymph node metastasis, poor prognosis
Colorectal Carcinoma	Reduced	Tumor progression, lymph node metastasis, worse clinical outcomes
Prostate Cancer	Downregulated	Increased tumor aggressiveness, metastasis
Ovarian Carcinoma	Reduced	Tumor progression, poor prognosis
Lung Carcinoma	Decreased	Tumor invasion, metastasis, poor patient outcome

E-CADHERINS ROLE AND FUNCTION IN NORMAL PLACENTA

1. **Epithelial Barrier Formation:**

E-cadherin is primarily expressed in the trophoblastic cells in placenta, which are responsible for forming the outer layer of the placental villi. E-cadherin mediates interactions between adjacent trophoblast cells, leading to the formation of tight junctions and establishment of an intact epithelial barrier.

2. **Syncytiotrophoblast Formation:**

E-cadherin is associated in the differentiation and fusion of cytotrophoblast cells to form the syncytiotrophoblast which is the outermost layer of the placental villi. Proper regulation of E-cadherin expression and function is essential for syncytiotrophoblast formation and maintenance.

3. **Placental Development and Function:**

E-cadherin is crucial for the placental development and function. It helps in preserving the structural integrity of placenta, facilitates nutrient and gas exchange among the fetal and maternal circulations, and supports fetal growth and development.

4. **Regulation of Trophoblast Invasion:**

E-cadherin expression is tightly regulated during trophoblast invasion into maternal decidua and spiral arteries. Dynamic changes in E-cadherin expression and activity are required for trophoblast cells to undergo epithelial-to-mesenchymal transition (EMT) and invade maternal tissues.

5. **Angiogenesis:**

E-cadherin plays a role in regulating angiogenesis in the placenta, as it interacts with vascular endothelial cadherin that is expressed in endothelial cells. Interaction between trophoblast and endothelial cells is crucial for the development of functional placental vasculature.

ROLE OF E-CADHERIN IN PREECLAMPSIA: [51]

1. Reduced Trophoblast Invasion:

In preeclampsia, there is often inadequate invasion of trophoblast cells into the maternal decidua and spiral arteries. Dysregulated E-cadherin expression impairs trophoblast invasion by disrupting cell-cell adhesion and inhibiting the transition to an invasive phenotype.

2. Abnormal Placental Morphology:

Placentas from preeclamptic pregnancies frequently exhibit structural abnormalities, including reduced villous branching and decreased syncytiotrophoblast surface area. Dysregulated E-cadherin expression contributes to these morphological changes by affecting trophoblast differentiation and fusion.

3. Placental Hypoxia and Oxidative Stress:

Placental ischemia/hypoxia and oxidative stress are key features of preeclampsia and can further dysregulate E-cadherin expression and function. Reactive oxygen species (ROS) and Hypoxia inducible factors (HIFs) generated under hypoxic conditions may alter E-cadherin expression and disrupt trophoblast function.

4. Endothelial Dysfunction:

Dysregulated E-cadherin expression in trophoblast cells also contribute to endothelial dysfunction in preeclampsia. Abnormal trophoblast-endothelial interactions mediated by E-cadherin impairs vascular remodelling and contributes for development of hypertension and proteinuria.

Various techniques for detection of E-cadherin:

1. Immunohistochemistry
2. Western blot test
3. Immunofluorescent method
4. Flow Cytometry
5. Quantitative Real-Time Polymerase Chain Reaction (qRT-PCR)

In the study done by ***Irtegun S. et al,***[52] to evaluate the expression of levels of Endothelin-1, CD68 and E-cadherin using the western blot method in both preeclamptic and normal placentas to understand the mechanisms contributing to preeclampsia. The results revealed that E-cadherin was not detectable in normal placentas but was highly expressed in preeclamptic placentas. Similarly, endothelin-1 was undetectable in normal placentas but showed high expression in preeclamptic ones. Additionally, CD68 exhibited low expression in normal placentas, with significantly increased levels in preeclamptic placentas.

In the study done by ***Osman SE. et al,***[53] to evaluate the expression of N-cadherin, E-cadherin and cytokeratin 18 and 19 in the placentas of women with severe preeclampsia by immunohistochemical method showed that there is no significant difference in the expression of N-cadherin, E-cadherin, cytokeratin 18, and cytokeratin 19 between the placentas of women with severe pre-eclampsia and those of healthy controls.

In Study done by ***Acikgöz, A. S. et al,***[54] to evaluate the serum levels of soluble vascular endothelial (sVE)-Cadherin in early- and late-onset preeclampsia by venous sampling of the blood showed that the mean serum sVE-cadherin levels were significantly higher in females with early onset pre-eclampsia correlated with gestational aged-matched controls. In the same

way, sVE-cadherin levels were higher in women with late onset pre-eclampsia compared to gestational aged-matched controls. There was also a significant difference between the groups with early onset pre-eclampsia and late onset pre-eclampsia groups, with higher levels of sVE-cadherin in early onset pre-eclampsia.

Serum sVE-cadherin levels positively correlated with both systolic and diastolic blood pressure. There was negative association between sVE-cadherin levels and gestational age indicating that higher sVE-cadherin levels were associated with early onset of preeclampsia.

In the study done by ***Atigan A. et al,***[55] to evaluate the role of specific cell to cell adhesion molecules like N-cadherin, E-cadherin, CD97and integrin beta-4, in preeclampsia by using immunohistochemical staining method and also measuring maternal serum 97 levels by ELISA method. The results showed that the maternal serum level of CD97 was significantly lower in the Pre-eclampsia group compared to healthy group. Immunohistochemical staining showed that CD97 expression in placental sections was also significantly decreased in the PE group. N-cadherin expression was significantly lower in the PE group compared to healthy group. There was no statistically substantial difference in the expression of integrin beta-4 among the PE group and the healthy group. On contrary E-cadherin expression was significantly increased in the PE group compared to healthy group.

In the study done by ***Pęksa M. et al,***[2] to know the loss of e-cadherin staining continuity in the trophoblastic basal membrane that associates with higher resistance in uterine arteries and proteinuria in individuals with pregnancy-induced hypertension by using immunohistochemical staining method. The study showed that there is loss of e-cadherin continuity in basal membrane of syncytiotrophoblast and was significantly more frequent in the study group, both in the maternal and fetal parts of placenta. The intensity of E-cadherin

expression was not differed significantly among the study and healthy groups. Loss of E-cadherin staining continuity was significantly correlated with the presence of a bilateral early diastolic notch in the uterine arteries. A relevant correlation was found between loss of E-cadherin continuity and the presence of proteinuria. Lower Apgar scores were significantly associated with discontinuous E-cadherin expression in the maternal part of the placenta.

MATERIALS & METHODS

MATERIALS & METHODS

STUDY DESIGN: Cross-sectional observational study.

SOURCE OF DATA: All the placenta specimens which were sent from Department of Obstetrics and Gynaecology of RLJ Hospital and Research Centre to the Department of Pathology, Sri Devaraj Urs Medical College. A detail of the procedure was explained to the patient in their own language and consent was taken.

STUDY DURATION: September 2022 – December 2023

SAMPLE SIZE:

$$n = \frac{Z_{1-\propto}^2 * p * q}{d^2}$$

- Z = Standard normal variant (1.96)
- p = prevalence = 8%
- q = 1 – prevalence
- d = absolute error (6%)
- Therefore n = 79.65

Sample size is estimated based on 8% prevalence of pre-eclampsia.[56] Considering an absolute error of 6% with 95% confidence interval the estimated minimum sample size for each group of the present study was 80 and the total sample size was **160**.

COLLECTION OF DATA:

A total of 80 placentas with > 28 weeks of gestational age with pre-eclampsia was included in the study and 80 placentas from normal antenatal cases attending at RLJH & Research

Centre in Sri Devaraj Urs Medical College, Kolar from 2022 – 2024 was included in this study.

INCLUSION CRITERIA:

All patients diagnosed with pre-eclampsia > 28 weeks of gestation age complying with criteria of pre-eclampsia who underwent delivery (normal and caesarean section) at R L Jalappa Hospital & Research Centre between 2022-2024.

EXCLUSION CRITERIA:

1. Chronic hypertension
2. Congenital abnormality in new born
3. Twin pregnancy
4. Hypothyroid patient
5. Clinically detected other medical conditions like Heart disease, Systemic lupus erythematous, Rh incompatibility.

METHODOLOGY

METHOD OF COLLECTION:

1. The placenta was collected immediately after delivery from mild, moderate, severe pre-eclampsia cases and healthy groups and is washed in tap water to eliminate any blood clots.
2. Gross inspection was done noting weight, diameter, thickness, no.of cotyledons on the maternal surface, calcification, infarction and umbilical cord vessels and knots.
3. The placenta is sliced at regular intervals of 0.5cm and gross abnormalities were detected (Bread and slice method)

4. The whole specimen was left for fixation in 4% formalin for more than 48 hrs.

SAMPLING PROCEDURE:

1. Five sections were taken from each central and peripheral areas.
2. Additional sections were taken from abnormal areas.
3. Tissue sections 5 micrometre thickness were cut from paraffin embedded blocks and stained by conventional H&E stain.
4. Placental changes were compared with the severity of the pre-eclampsia (mild, moderate and severe) with that of control group.

TISSUE PROCESSING:

Table 5: Tissue processing steps -

Formalin	7 Hours
Water	20 Minutes
60% Isopropyl alcohol	1 Hour
70% Isopropyl alcohol	1 Hour
80% Isopropyl alcohol	1 Hour
90% Isopropyl alcohol	1 Hour
100% Isopropyl alcohol	1 Hour
100% Isopropyl alcohol	1 Hour
Chloroform I	1 Hour
Chloroform II	1 Hour
Paraffin Wax I	1 Hour
Paraffin Wax II	1 Hour
Total	**17 Hours 20 Minutes**

After processing the sections were embedded and tissue section of 5 um were cut by the routine histopathological procedure of our department. The slides were stained with haematoxylin and eosin using by following steps:

1. The section was deparaffinized and hydrating through grading of alcohols to water
2. It was kept in Harris haematoxylin for 4 mins
3. Rinsed in running tap water for 5 mins
4. Differentiated in 1% acid alcohol for 5 secs
5. Washed well in Tap water for 5 mins (Until Blueing)
6. Dipped in Eosin for1 min
7. Rinsed in tap water for 5 mins.
8. Dehydrated in grading of alcohols in ascending order.
9. Dipped in Xylene (Clearing)
10. Mounted in DPX

HAEMATOXYLIN AND EOSIN STAINING:

In H&E staining, calcification appeared as areas of dense, thick dark blue staining. Fibrosis is a result from the formation of excess fibrous connective tissue due to chronic inflammation or injury and this is seen as regions of increased collagen deposition. Necrosis is identified as acellular, eosinophilic areas with a loss of tissue architecture. Excessive syncytial knots, clusters of syncytial cells, are indicative of placental hypoxia. Peri-villous edema is seen as widened spaces between the villi, caused due to fluid accumulation.

IMMUNOHISTOCHEMICAL STAINING:

PROTOCOL:

IHC staining was performed on 4% formalin-fixed (fixed for >48hrs at 25 degree Celsius) paraffin-embedded 4 micro meter tissue sections which were taken on coated slides. Tissue sections were deparaffinized in xylene and were rehydrated through a descending ethanol

series (100,95,90,80 and 70%) at room temp for 5 minutes, followed by a wash in distilled water after allowing to cool for 10 mins.

Table 6: Antibody, clone, species used in IHC staining -

Antibody	Clone	Species	Producer	Control	Stain
E-Cadherin	EP6 Monoclonal	Rabbit	Pathn Situ Biotechnologies	Colon Cancer	Membrane

THE PROCEDURE OF IHC IS AS FOLLOWS:

1. Tissue blocks were fixed in 10% formalin were used to create sections that were 3-5 µm thick.
2. These sections were placed on organosilane slides that had a positive charge.
3. Glass slides were incubated overnight at 58 degrees temperature on hot plate.
4. Deparaffinization was conducted by immersing the sections in Xylene I and Xylene II for 15 mins each.
5. Dexylnization was carried out using pure alcohol I and II with each step lasting for 1 min.
6. Dealcoholisation is done by immersing the slides in 90% and 70% alcohol for 1 minute each.
7. The slides were rinsed with distilled water to make sure that the sections did not dry at any point during the staining process.
8. Antigen Retrieval was achieved through enzymatic treatment in a microwave set at power 10 for 6 minutes, using TRIS EDTA buffer at a pH of 6.0, and repeated for two cycles.
9. The slides were rinsed with distilled water for 5 minutes.

10. The sections were washed in Tris Buffer Solution (TBS) at a pH of 7.6 for two consecutive 5-minute periods.

11. A peroxidase block was applied for 10-15 minutes to inhibit endogenous peroxidase enzyme activity.

12. TBS buffer washes were performed for three separate 5-minute intervals.

13. A power block was applied for 10-15 minutes to prevent non-specific reactivity with other tissue antigens.

14. The sections were incubated with a specific primary antibody for 45 minutes to detect tissue markers by antigen-antibody reaction.

15. The sections were rinsed in Tris buffer (pH 7.6) for 5 mins before processing. This was repeated 3 times with gentle agitation to remove unbound antibodies.

16. A super enhancer was introduced for 20 mins to enhance the interaction between the primary and secondary antibodies.

17. TBS buffer washes were performed for 5 mins intervals to remove unbound antibodies.

18. A highly responsive polymer horseradish peroxidase (poly HRP) was applied for 30 minutes to extend the chain and mark the enzyme.

19. The inclusion of DAB for 5-8 minutes leads to the production of a chromogen, leading to antigen coloration.

20. TBS buffer washes were performed for three 5-minute intervals.

21. The sections were rinsed with tap water for 5 minutes, then counterstained with haematoxylin for 1 minute.

22. The slides was dehydrated with 90% alcohol and absolute alcohol for 2 minutes each.

23. The slides were then cleared with a mixture of alcohol and xylene for 2 minutes each.

24. Finally, the slides were mounted with DPX.

Table 7: After the process of IHC the slides were interpreted and documented as below -

Basement Membrane of	Grading			
Cytotrophoblast	-	+	++	+++
Syncytiotrophoblast	-	+	++	+++
Blood vessels	-	+	++	+++

The expression was graded as –

- - = 0
- + = 1
- ++ = 2
- +++ = 3

STATISTICAL ANALYSIS

All the data collected was entered into Microsoft excel data sheet and was analyzed by SPSS 24 (Statistical Package for Software Sciences 24) version software. Quantitative data was represented using mean and standard deviation. Independent t test was performed as test of significance to see the mean difference. All the Qualitative data was demonstrated in the form of frequencies and proportions. Chi square test was used to look for difference between the groups. P value <0.05 at 95% CI was considered statistically significant.

RESULTS

RESULTS

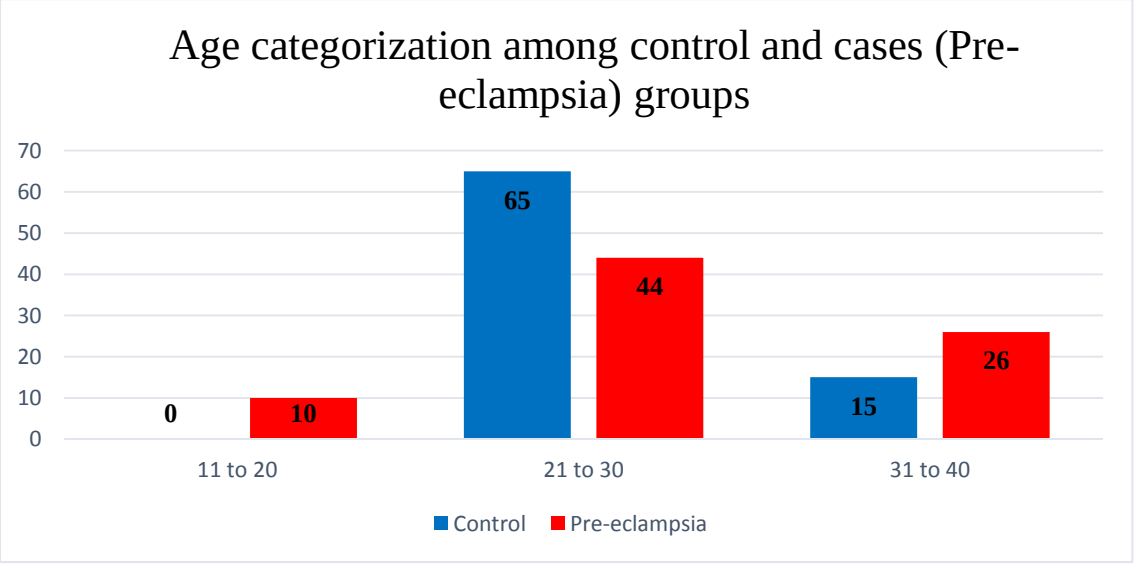
A total of 160 placentas were included out of which 80 (50%) placentas were from normal term pregnancy which formed healthy control group and 80 (50%) placentas were from pregnancy with pre-eclampsia (BP>140/80). Of these 20 cases were of mild preeclampsia, 20 cases of moderate preeclampsia and 40 cases were of severe pre-eclampsia. All the mothers in the control group and the pre-eclampsia group fulfilled the selection criteria.

Table 8: Age categorization among healthy controls and cases groups

Age group	Control (n=80)	Pre-eclampsia (n=80)	Pre-eclampsia		
			Mild (n=20)	Moderate (n=20)	Severe (n=40)
11-20	0	10(13%)	2(10%)	4(20%)	4(10%)
21-30	65(81%)	44(55%)	16(80%)	12(60%)	16(40%)
31-40	15(19%)	26(32%)	2(10%)	4(20%)	20(50%)

* Age >18 was considered.

Chart 1: Age categorization among healthy control groups and cases groups

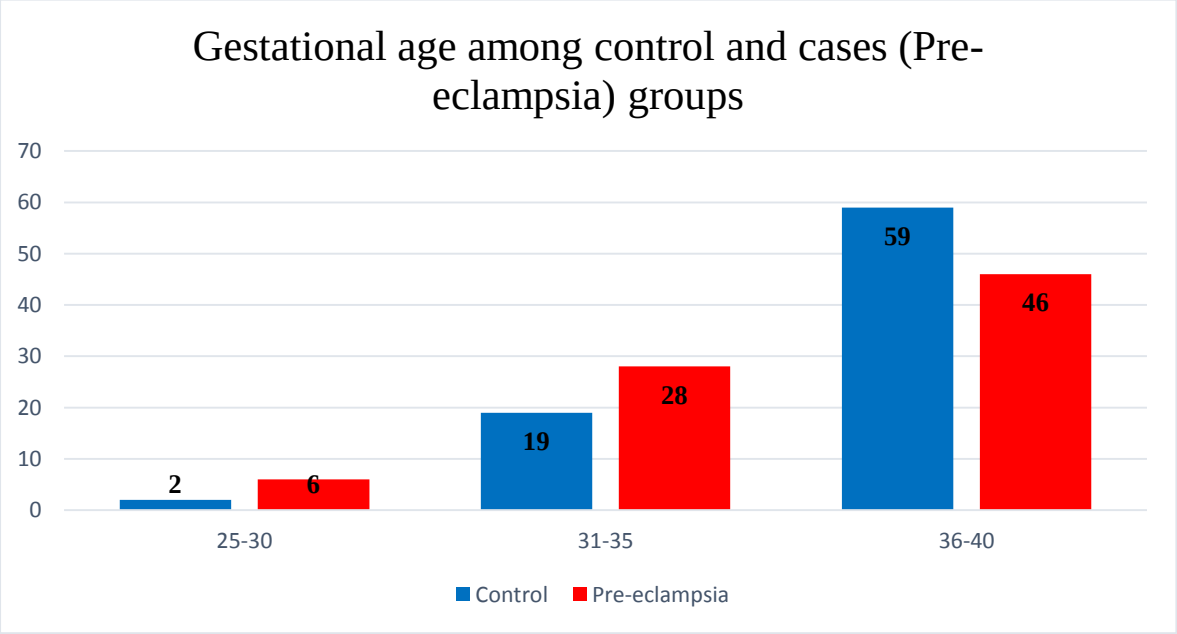


Majority of the cases and controls were linked to the age group 21 to 30 years. Mean age of the mothers was 26.28 ± 3.16 years in the control group and 26.12 ± 4.12 in pre-eclampsia.

Table 9: Gestational age among control groups and cases groups

Gestational age	Control (n=80)	Pre-eclampsia (n=80)	Pre-eclampsia		
			Mild (n=20)	Moderate (n=20)	Severe (n=40)
25-30	2(2.5%)	6(7%)	2(10%)	1(5%)	3(7%)
31-35	19(24%)	28(36%)	8(40%)	10(50%)	10(25%)
36-40	59(74%)	46(57%)	10(50%)	9(45%)	27(68%)

Chart 2: Gestational age among healthy control and cases groups



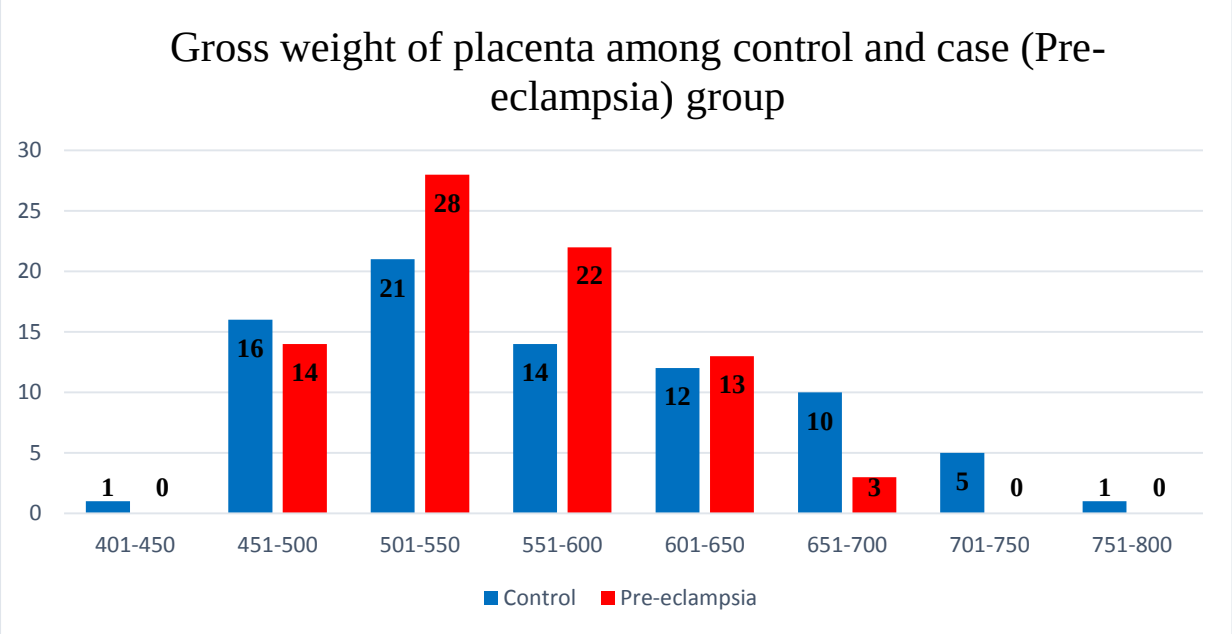
Predominant of the cases and controls were in the gestational age group between 36-40 years. The mean gestational age is 37.12±2.84 weeks in the control group and 36.02±2.8 weeks in pre-eclampsia.

When compared the severity of preeclampsia with gestational age of patients the result among the 2 groups was not statistically significant (p-value is 0.36).

Table 10: Gross weight of placenta among control groups and cases groups

Gross weight of placenta	Control (n=80)	Pre-eclampsia (n=80)	Pre-eclampsia		
			Mild (n=20)	Moderate (n=20)	Severe (n=40)
401-450	1(1%)	0(0%)	0(0%)	0(0%)	0(0%)
451-500	16(20%)	14(17%)	6(30%)	3(15%)	5(13%)
501-550	21(26%)	28(35%)	5(25%)	7(35%)	16(40%)
551-600	14(17%)	22(35%)	3(15%)	4(20%)	15(38%)
601-650	12(15%)	13(17%)	5(25%)	5(25%)	3(7%)
651-700	10(13%)	3(4%)	1(5%)	1(5%)	1(2%)
701-750	5(7%)	0(0%)	0(0%)	0(0%)	0(0%)
751-800	1(1%)	0(0%)	0(0%)	0(0%)	0(0%)

Chart 3: Gross weight of placenta among control and cases groups



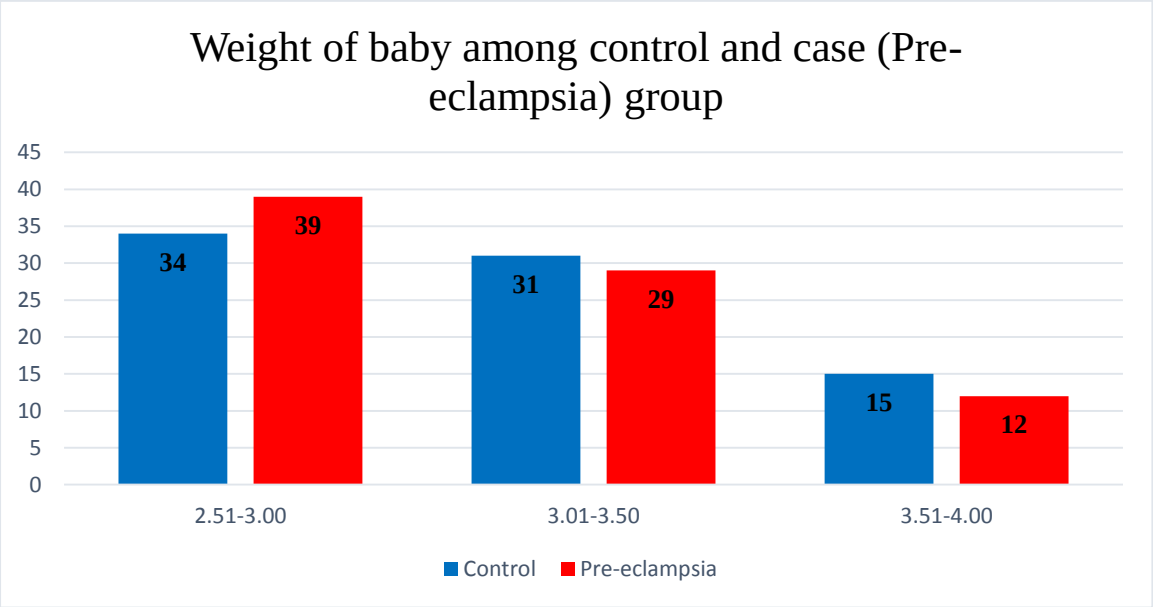
Predominant cases and controls belong to the group between 501-550 grams of weight of placenta. The mean gross weight of placenta was 558.5±78.66 grams in the control group and 543.0±51.5 in pre-eclampsia.

When compared the severity of preeclampsia with gross weight of the placenta the result among the 2 groups was not statistically significant (p-value is 0.98).

Table 11: Weight of baby among control groups and cases groups

Weight of baby	Control (n=80)	Pre-eclampsia (n=80)
2.51-3.00 kgs	34(42%)	39(48%)
3.01-3.50kgs	31(38%)	29(36%)
3.51-4.00 kgs	15(20%)	12(16%)

Chart 4: Weight of baby among control and cases groups



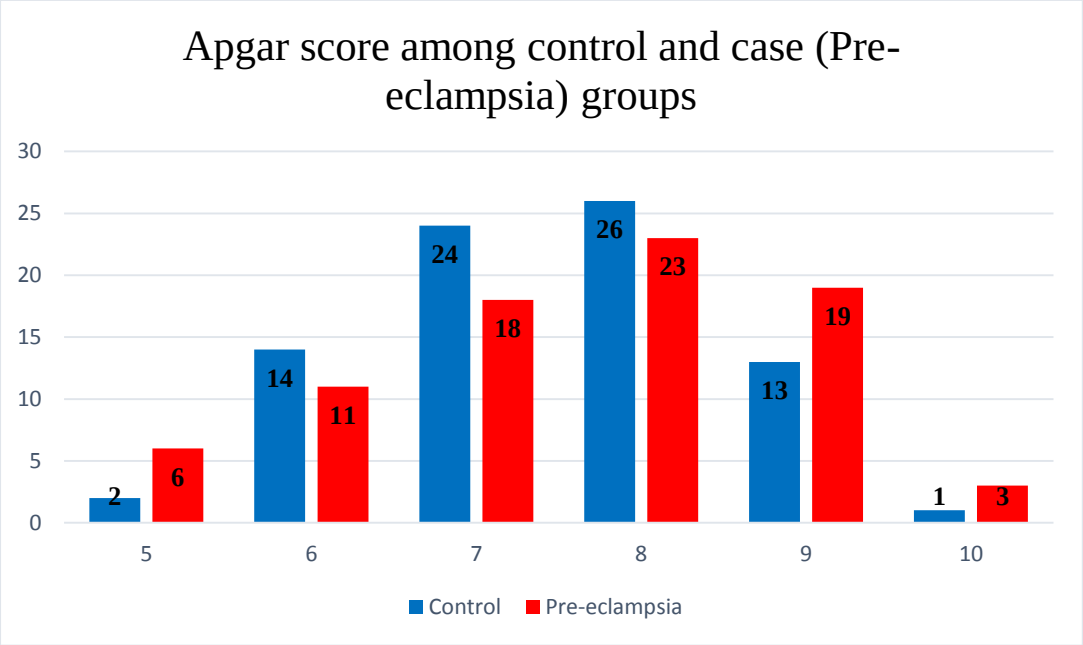
Predominance of cases and controls belonged to the group between 2.51-3.00 kgs of weight of the baby. The mean gross weight of baby is 3.08±0.34 kgs in the control group and 3.02±0.36 kgs in pre-eclampsia.

When compared the weight of the baby of pre-eclamptic mothers with the weight of the baby of the normal healthy mothers the result between the two groups was not statistically significant.

Table 12: Apgar score among control groups and cases groups

Apgar score of babies	Control (n=80)	Pre-eclampsia (n=80)
5	2(5%)	6(8%)
6	14(18%)	11(14%)
7	24(30%)	18(23%)
8	26(32%)	23(28%)
9	13(14%)	19(24%)
10	1(1%)	3(3%)

Chart 5: Apgar score among control groups and cases groups



Majorly the cases and controls were in the group 8 of Apgar score. Mean apgar score of the babies is 7.46±1.07 in the control group and 7.33±1.30

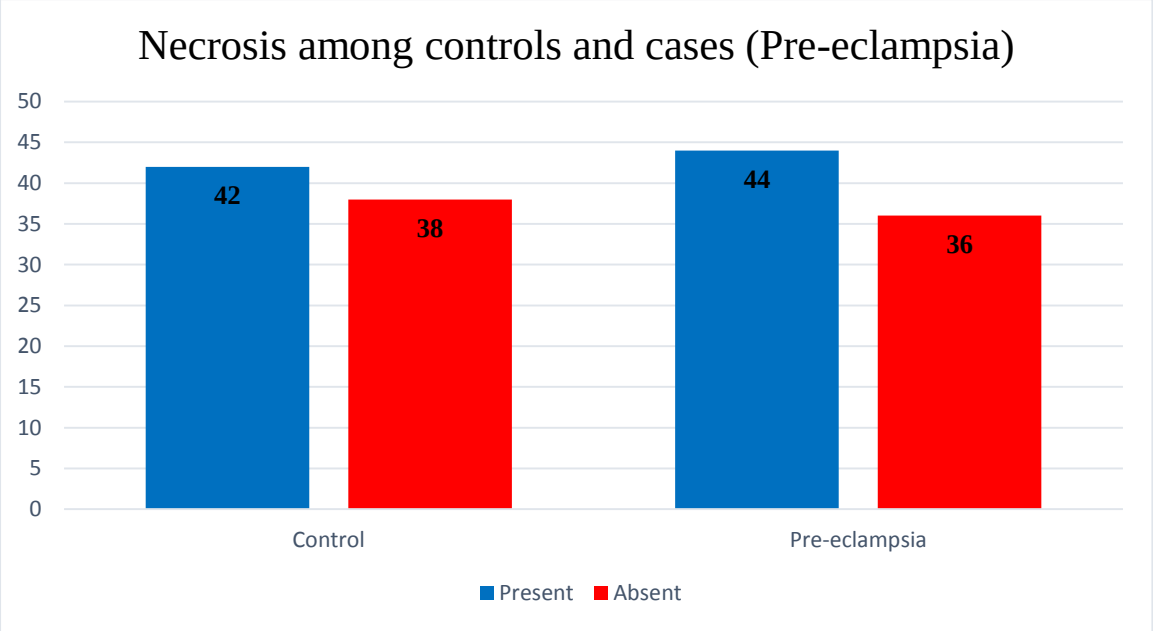
in pre-eclampsia.

When compared the apgar score of the cases and the controls the result was not statistically significant.

Table 13: Gross and microscopic findings – Necrosis among cases and control groups

Necrosis	Control (n=80)	Pre-eclampsia (n=80)	Pre-eclampsia		
			Mild (n=20)	Moderate (n=20)	Severe (n=40)
Present	42(52%)	44(55%)	8(40%)	6(30%)	30(75%)
Absent	38(48%)	36(45%)	12(60%)	14(70%)	10(25%)

Chart 6: Necrosis among healthy controls and cases groups

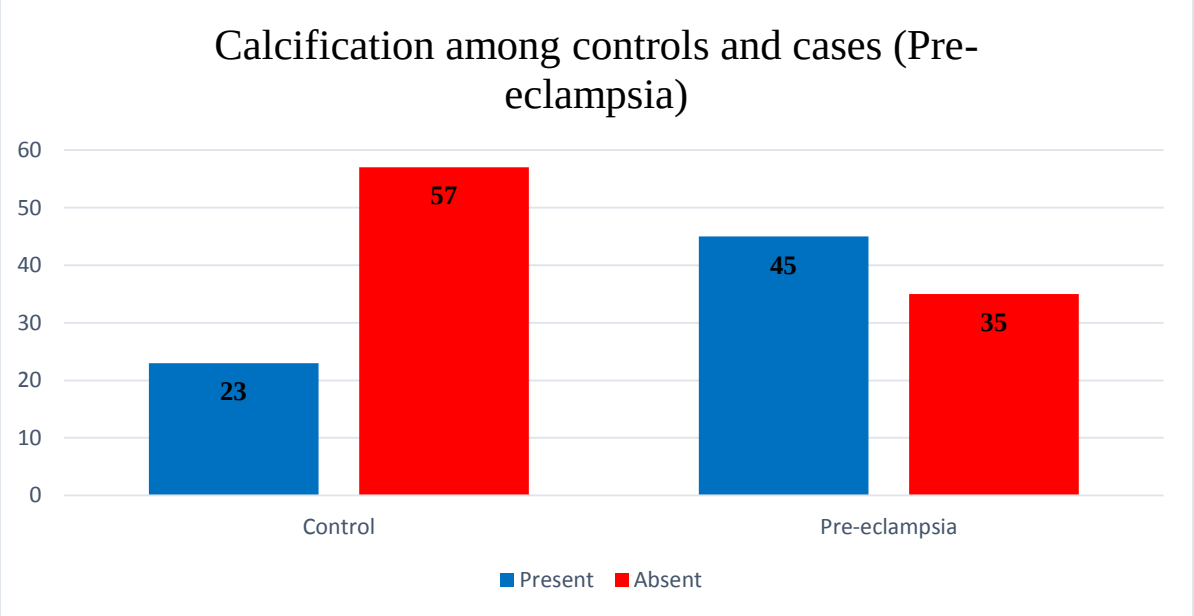


Majority of the cases and controls showed that necrosis was present that is almost 45-55%. When compared the severity of pre-eclampsia with the gross and microscopic findings i.e, necrosis of the placenta the result among the two groups was statistically significant (p value is 0.001273) ($p<0.5$).

Table 14: Gross and microscopic findings – Calcification among cases and healthy control groups

Calcification	Control (n=80)	Pre-eclampsia (n=80)	Pre-eclampsia		
			Mild (n=20)	Moderate (n=20)	Severe (n=40)
Present	23(28%)	45(56%)	9(45%)	8(40%)	28(70%)
Absent	57(72%)	35(44%)	11(55%)	12(60%)	12(30%)

Chart 7: Calcification among controls and cases groups



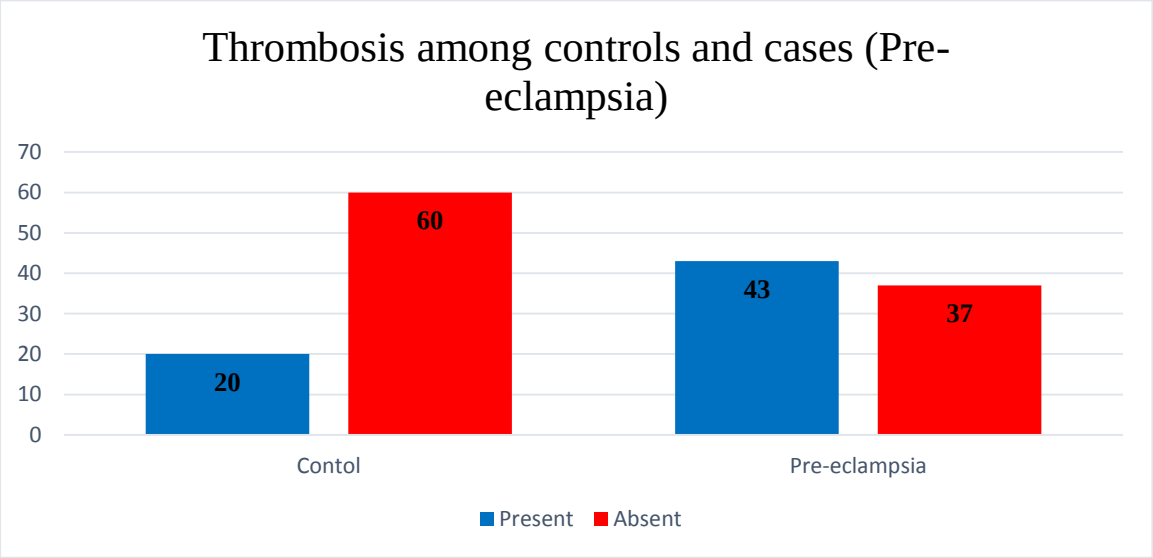
Compared with the controls group the pre-eclampsia group showed increased presence of calcification.

When compared the severity of pre-eclampsia with the gross and microscopic findings i.e, calcification in the placenta the result among the two groups was statistically significant (p-value is 0.043989) ($p<0.5$).

Table 15: Gross and microscopic findings – Thrombosis among cases and control groups

Thrombosis	Control (n=80)	Pre-eclampsia (n=80)	Pre-eclampsia		
			Mild (n=20)	Moderate (n=20)	Severe (n=40)
Present	20(25%)	43(54%)	7(35%)	8(40%)	28(70%)
Absent	60(75%)	37(46%)	13(65%)	12(60%)	12(30%)

Chart 8: Thrombosis among controls and cases groups



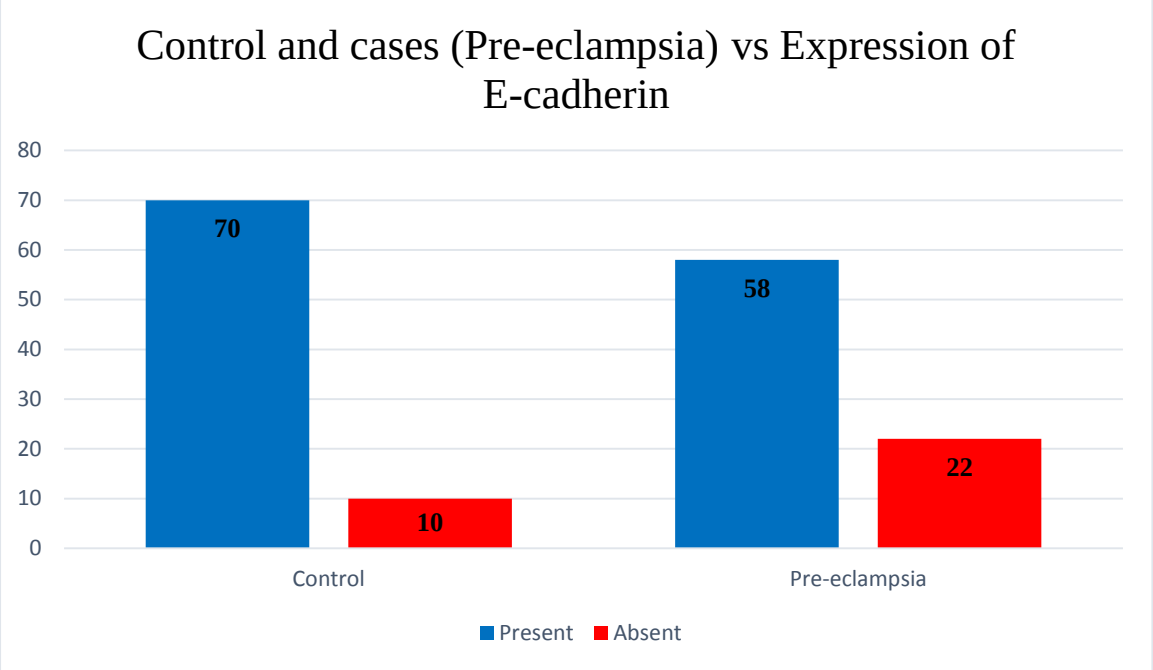
Compared with the controls group the pre-eclampsia group showed presence of increased thrombosis.

When compared the severity of pre-eclampsia with the gross and microscopic findings i.e, thrombosis in the placenta the result among two groups was statistically significant (p-value is 0.01358) ($p<0.5$).

Table 16: Expression of E-cadherin among cases and control groups

Expression of E-cadherin	Control (n=80)	Pre-eclampsia (n=80)
Present	70(88%)	58(73%)
Absent	10(12%)	22(27%)

Chart 9: Expression of E-cadherin among healthy control groups and cases



The table compares the presence and absence of E-cadherin expression between control and pre-eclampsia groups.

Higher Presence of E-cadherin in Healthy Group: In the healthy group majority of cases (88%) showed presence of E-cadherin with continuous staining among the placental villi and only a small percentage (12%) showing its absence.

Lower Presence of E-cadherin in Preeclampsia Group: In the preeclampsia group less number of cases showed the presence of E-cadherin with discontinuous staining compared to the healthy group. Absence of E-cadherin was more in the pre-eclampsia group than in the control group.

This indicates that E-cadherin expression is significantly decreased in preeclampsia cases compared to the healthy group and indicates that preeclampsia is linked with decreased E-cadherin expression.

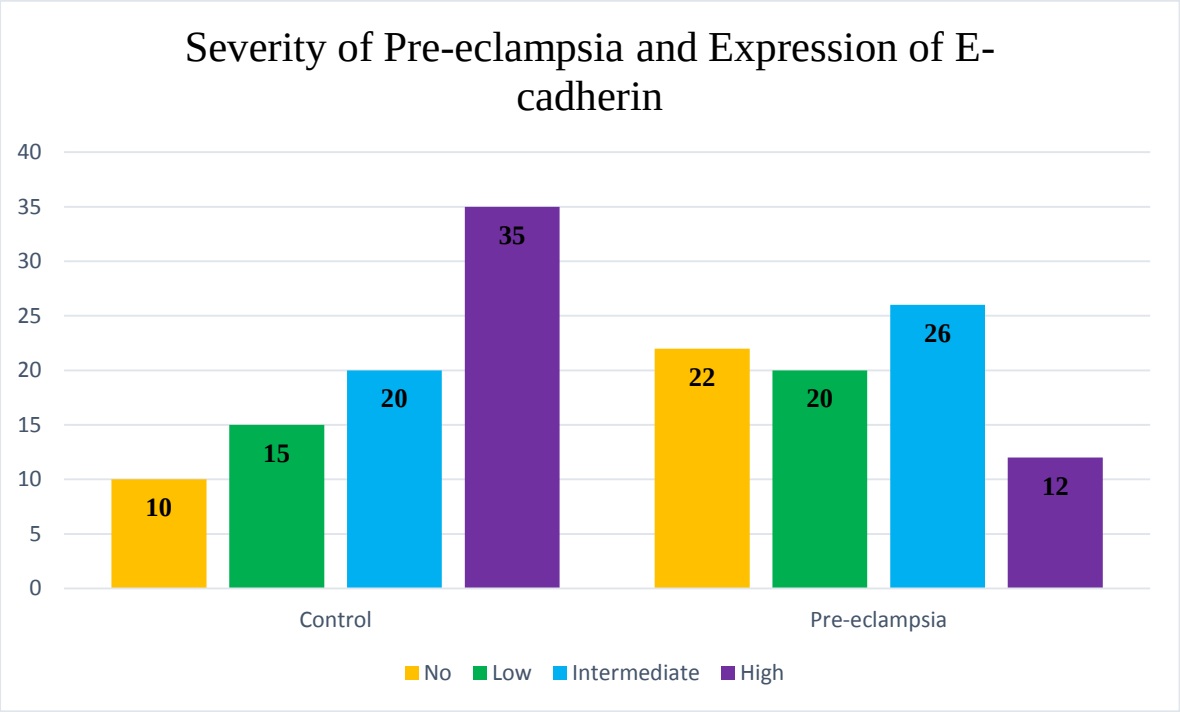
The chi square data analysis is done for the presence of expression of E-Cadherin in normal placenta (healthy groups) and the pre-eclampsia placentas.

Overall, it showed a significant association between them with the p value of 0.017706 ($p < 0.05$) which is statistically significant.

Table 17: Severity of expression of E-cadherin among cases and healthy control groups

Expression of E-cadherin	**Control (n=80)**	**Pre-eclampsia (n=80)**	**Pre-eclampsia**		
			Mild (n=20)	**Moderate (n=20)**	**Severe (n=40)**
No	10(12%)	22(28%)	2(10%)	5(25%)	15(38%)
Low	15(19%)	20(24%)	5(25%)	5(25%)	10(25%)
Intermediate	20(25%)	26(32%)	8(40%)	8(40%)	10(25%)
High	35(44%)	12(6%)	5(25%)	2(10%)	5(12%)

Chart 10: Severity of expression of E-cadherin among control groups and cases



The intensity of expression of E-cadherin was measured in control group and pre-eclampsia. The intensity of expression graded as –

- 0 or Negative = No expression
- 1 = Low expression
- 2 = Intermediate expression
- 3 = High expression

This grading is according to the IHC scoring expression as mentioned above.

When the intensity of expression of E-cadherin was seen in the control group, predominant cases that is (44%) showed high expression which is relating to grade 3 (Fig 22) of intensity of expression of E-cadherin. Similarly (25%) of the cases showed intermediate expression with which is corresponding to grade 2 (Fig 25) of intensity of expression of E-cadherin. Finally, the remaining (19%) and (12%) of the cases showed low and no expression which is

corresponding to grade 1 (Fig 21) and 0 (Fig 23) respectively of intensity of expression of E-cadherin.

However, in overall preeclampsia, a higher percentage of cases (28%) showed no E-cadherin expression which is correlating to grade 0 (Fig 23) of intensity of expression of E-cadherin, when compared to the control group. Only a small percentage (6%) showed high expression which is corresponding to grade 3 (Fig 22) of intensity of expression of E-cadherin.

In Mild Pre-eclampsia majority of cases (65%) showed intermediate or high expression which is grade 2 and 3 (Fig 25 and 22 respectively).

In Moderate Pre-eclampsia the intermediate expression that is grade 2 (Fig 25) was most common (40%), but there was a significant proportion with no (25%) or low (25%) expression which is grade 0 and 1 (Fig 23 and 21) respectively.

In Severe Pre-eclampsia majority of cases (63%) showed no or low expression which is grade 0 and 1(Fig 23 and 21) respectively and only 12% showing high expression which is correlating to grade 3 (Fig 22) of intensity of expression of E-cadherin.

The chi square data analysis is done for the level expression of E-cadherin and the severity of pre-eclampsia showed a significant association between them with the p value of 0.003108 ($p < 0.05$) which was statistically significant.

Therefore, the table suggests that E-cadherin expression tends to decrease with increasing severity of pre-eclampsia, with the most severe cases having the lowest levels of E-cadherin expression.

IMAGES

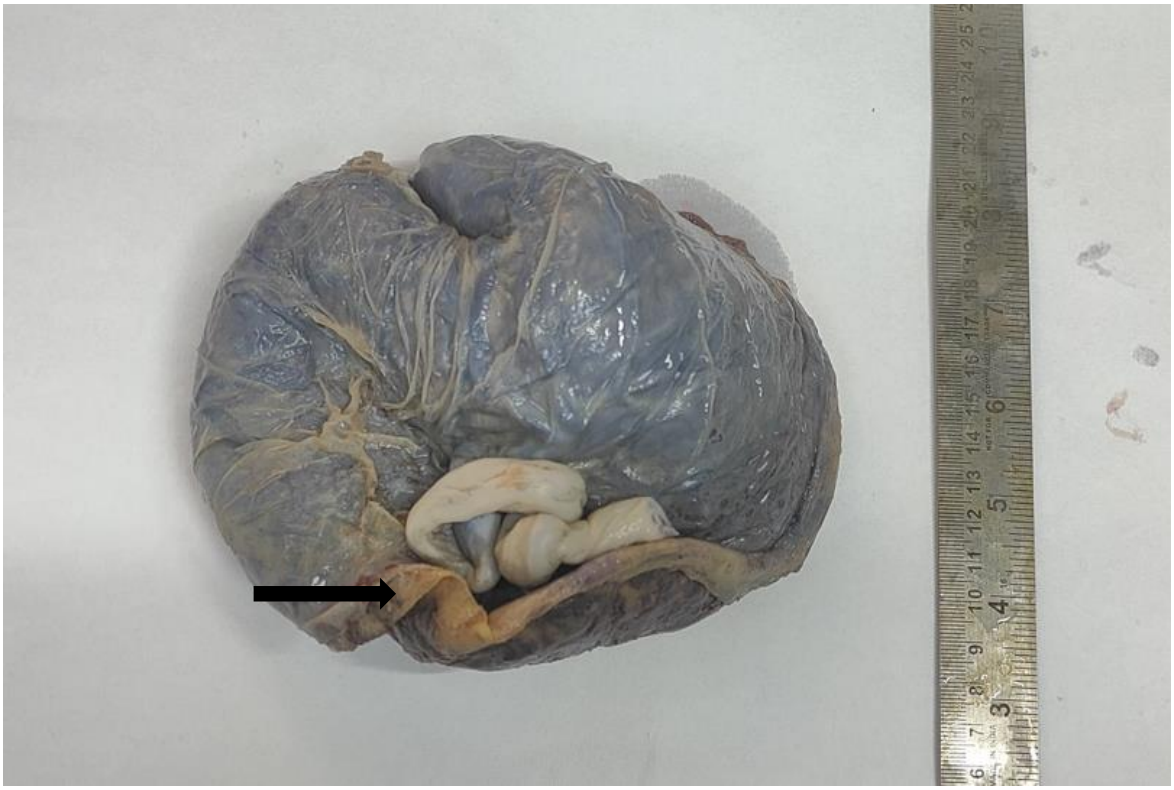


Fig 14: Shows gross image of placenta. The shiny glistening surface is the fetal surface with centrally placed umbilical cord (shown by arrow).

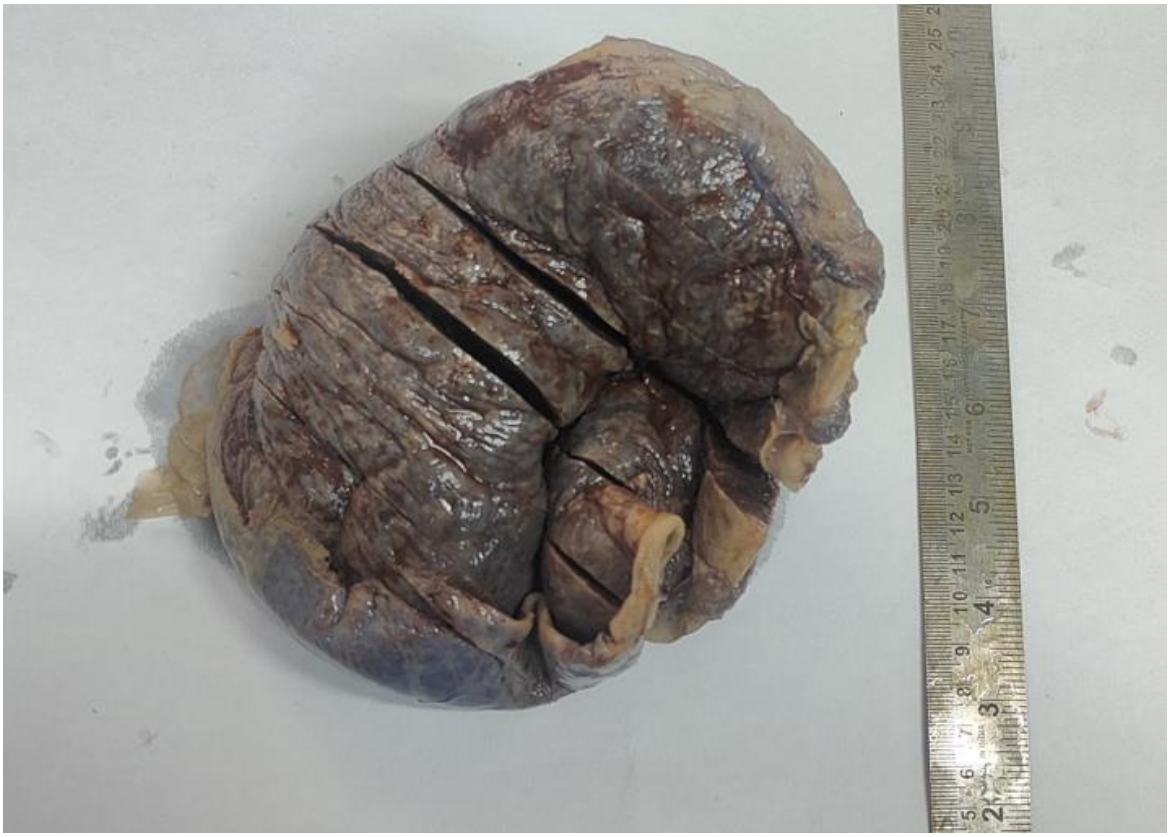


Fig 15: Shows the gross image of placenta. The ragged surface is the maternal surface.

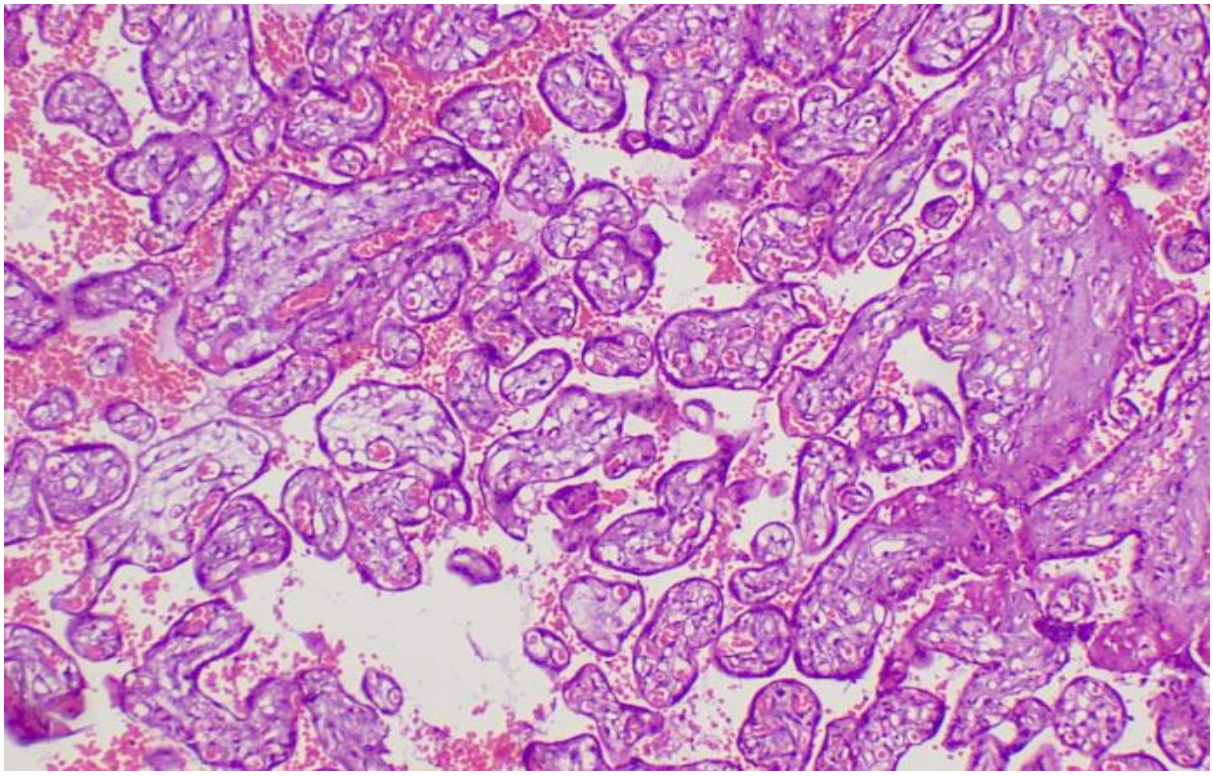


Fig 16: H&E image shows normal placental chorionic villi comprising of outer syncytiotrophoblast and inner cytotrophoblast under 100x magnification.

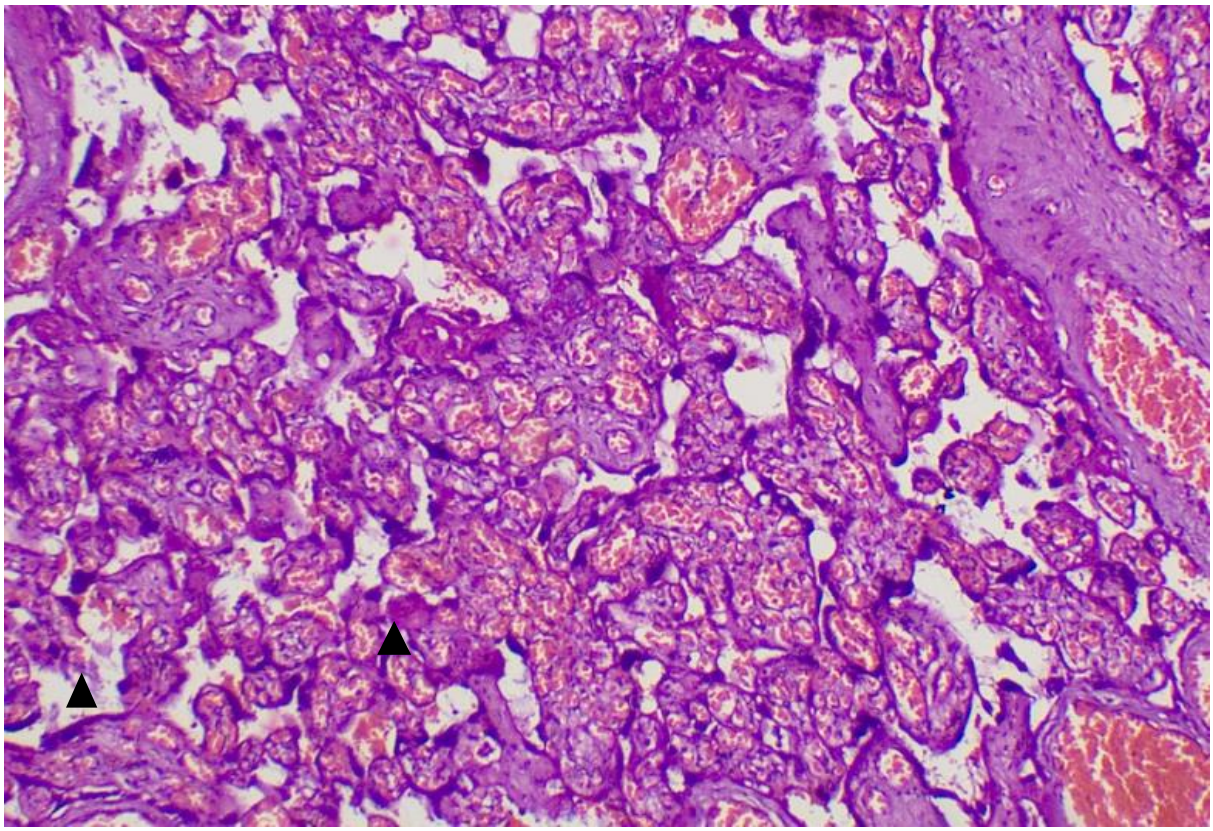


Fig 17: H& E image shows the overcrowded placental villi and excessive syncytial knots (shown by arrow head) which are seen in pre-eclampsia placenta under 100x magnification.

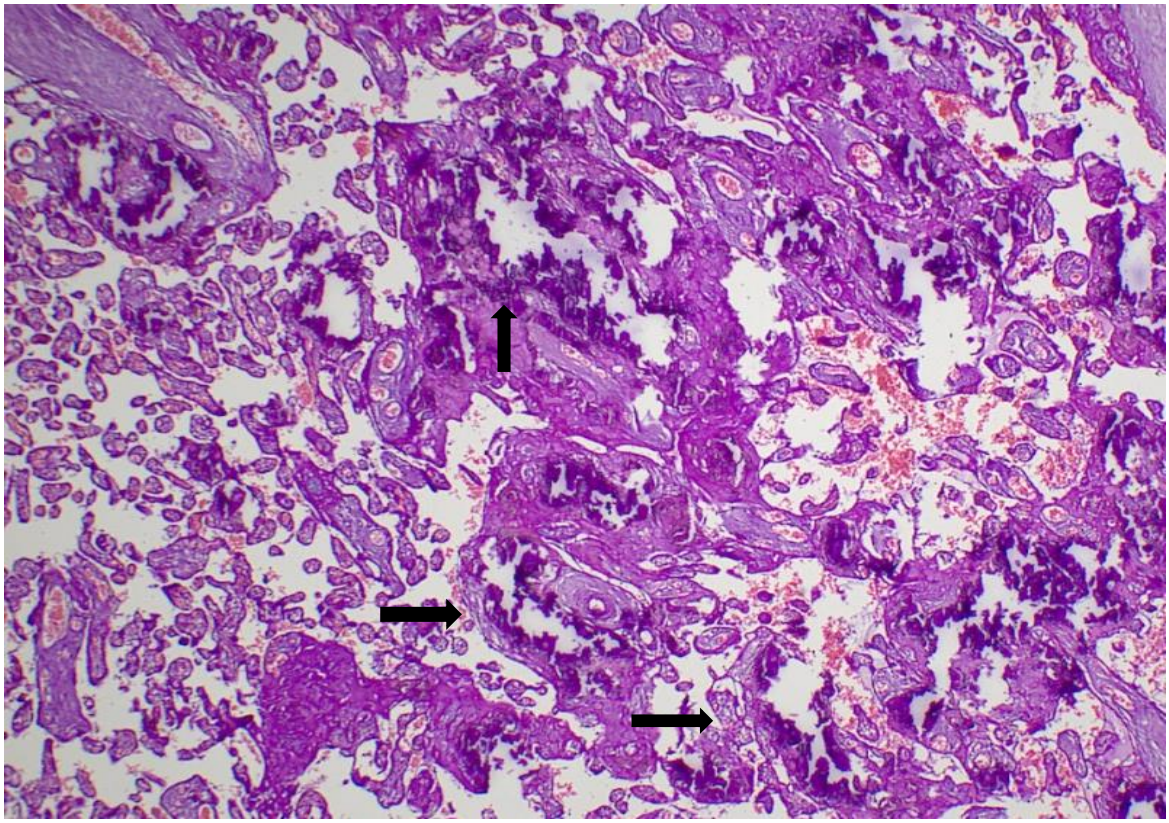


Fig 18: H& E image shows areas of calcifications (shown by arrows) which are mostly seen in pre-eclampsia placentas under 100x magnification.

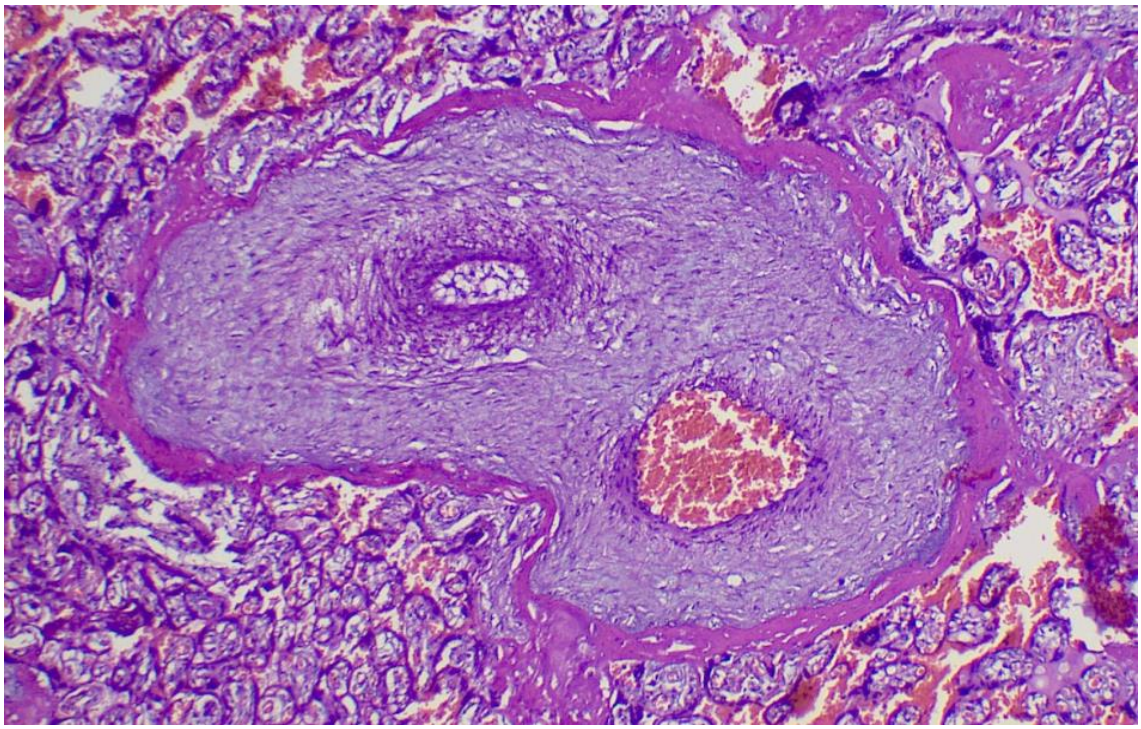


Fig 19: H&E image shows vascular medial coat of blood vessel seen predominantly in pre-eclampsia placentas and occasionally in normal placentas under 100x magnification.

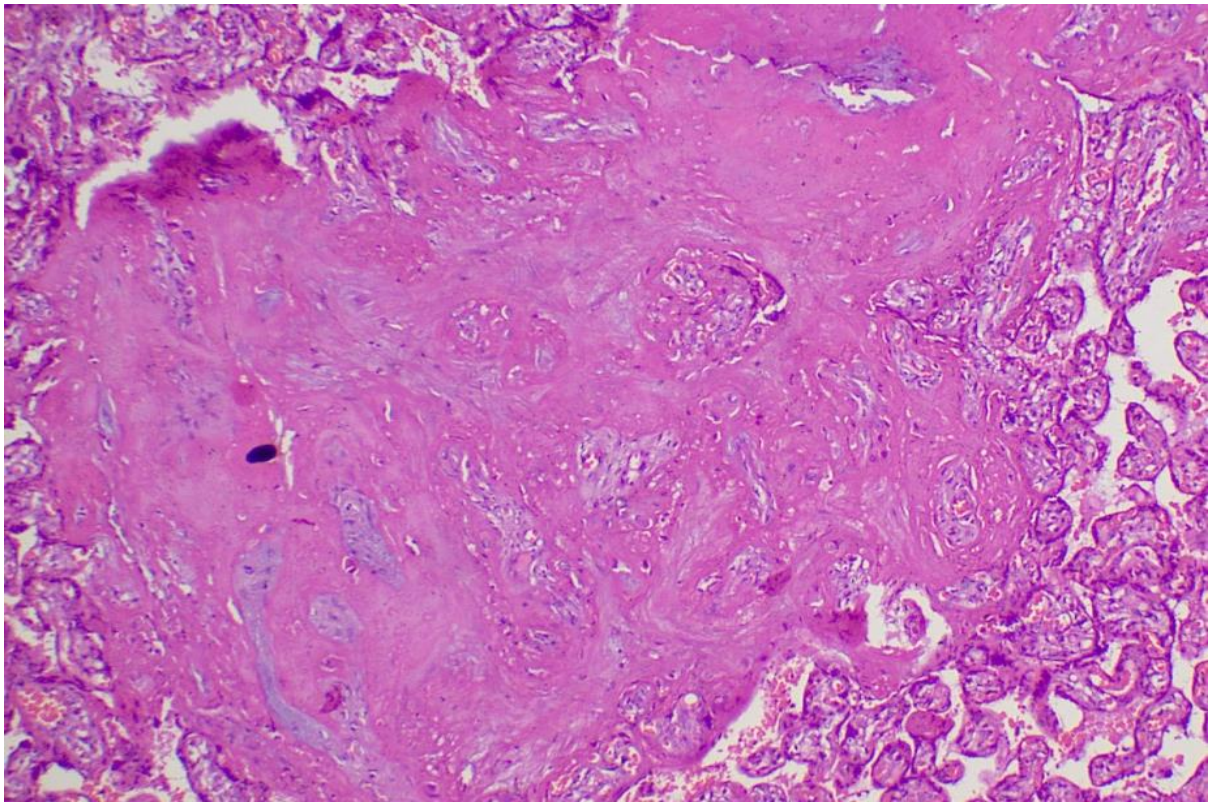


Fig 20: H&E slide shows abundant area stromal fibrosis seen more evidently in preeclampsia placentas under 100x magnification.

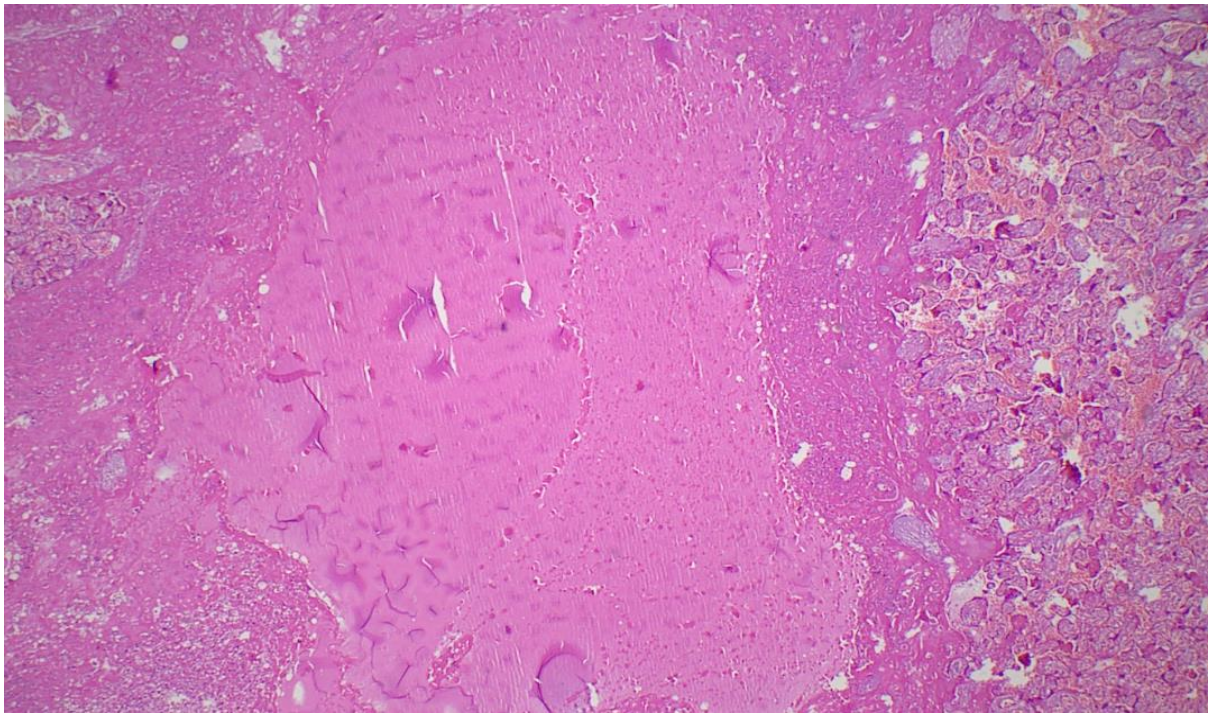


Fig 21: H& E slide shows major area of necrosis which acellular and eosinophilic that is seen in pre-eclampsia placentas under 100x magnification.

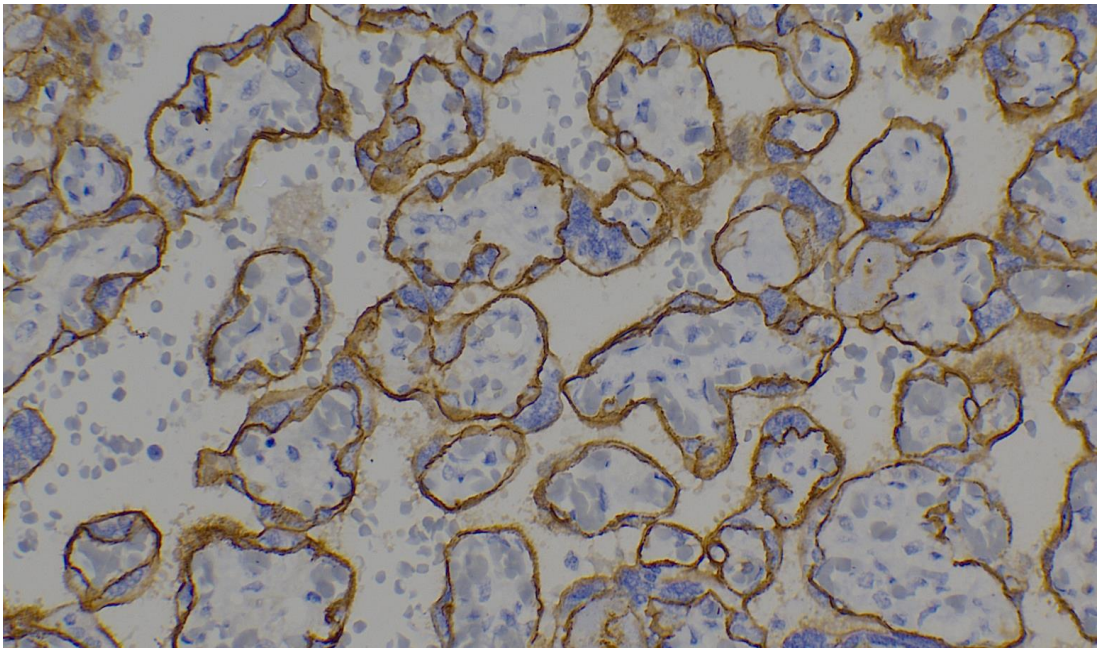


Fig 22: Shows strong IHC expression which is grade 3 of intensity of expression of E-cadherin in placenta in 100x magnification.

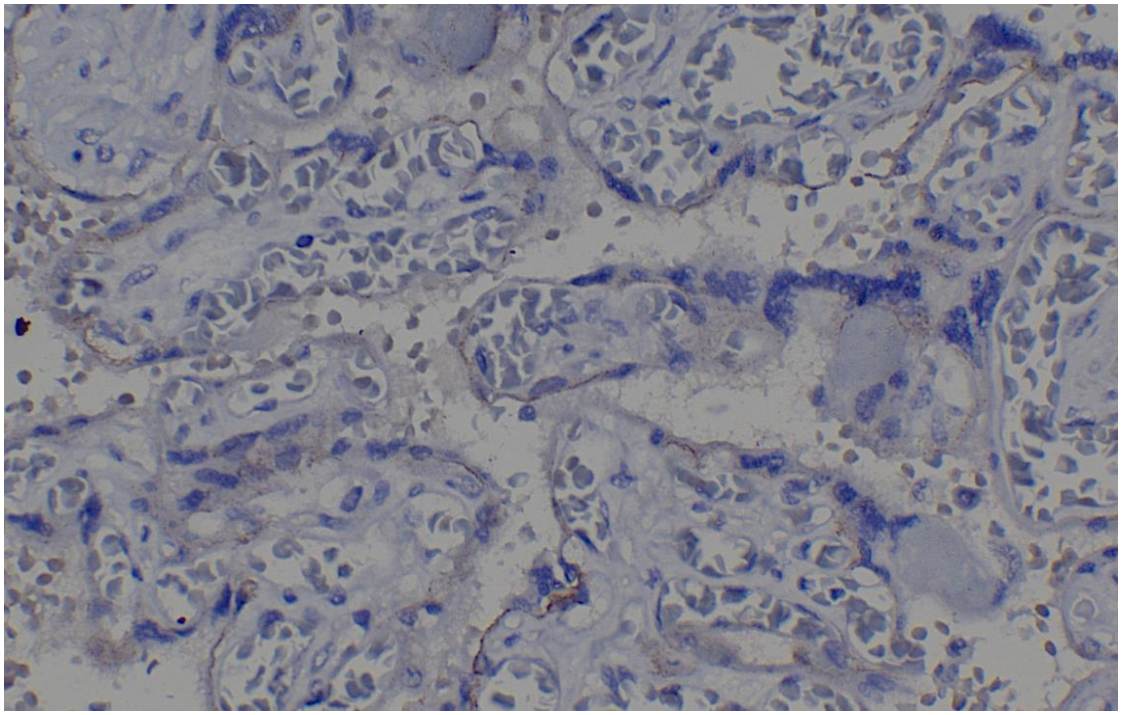


Fig 23: Shows no IHC expression which is grade 0 of intensity of expression of E-cadherin in pre-eclampsia placenta in 100x magnification.

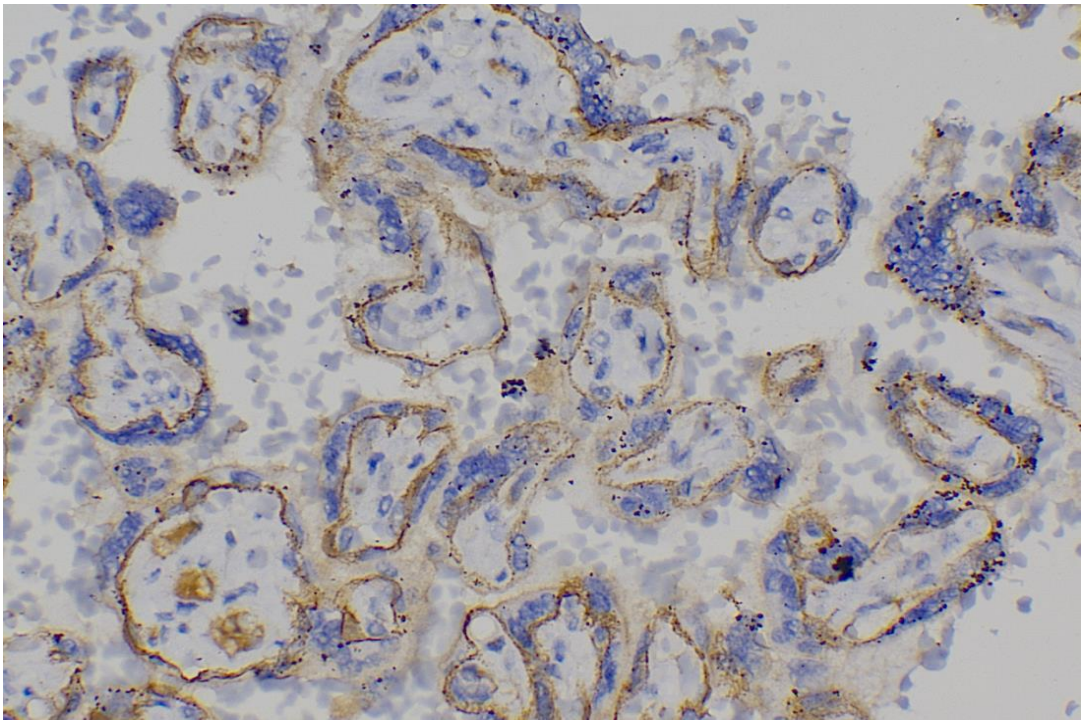


Fig 24: Shows the mild IHC expression which is grade 1 of intensity of expression of E-cadherin in pre-eclampsia placenta in 100x magnification.

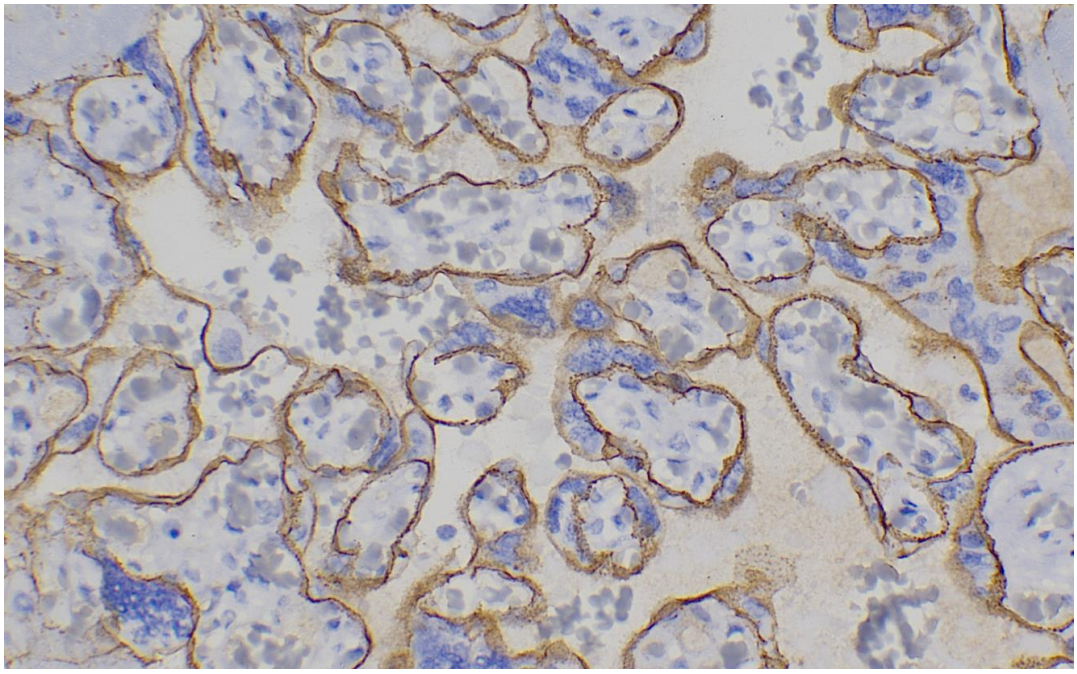


Fig 25: Shows the moderate IHC expression which is grade 2 of intensity of expression of E-cadherin in pre-eclampsia placenta in 100x magnification.

DISCUSSION

DISCUSSION

The placenta is a complex organ that connects mother & fetus, and its function is highly influenced by its anatomical structure. The morphology and cellular architecture of the placenta are crucial for adequate oxygen transport from the mother to the baby. Successful placental development is essential for fetal growth and well-being greater than 20 weeks of gestation and is necessary for adequate maternal blood supply to the placenta.[57]The placental architecture is altered in diseases like pre-eclampsia, gestational hypertension, gestational diabetes mellitus that affects the mother and the fetus as well.

This study aims to investigate the causes of pre-eclampsia, as its pathogenesis remains incompletely understood. One of the factors implicated in the pathogenesis of pre-eclampsia is E-cadherin. The study examines the degree of E-cadherin expression in both normal and pre-eclamptic cases. A total of 160 cases were analyzed, including 80 normal placentas and 80 pre-eclamptic placentas. The pre-eclamptic cases were further subdivided into 20 mild, 20 moderate, and 40 severe pre-eclampsia cases.

In addition to assessing E-cadherin expression, the study also evaluated other parameters. These included gross findings such as identification of necrosis and thrombosis in majority of pre-eclampsia placentas. The microscopic findings were areas of calcification, intervillous haemorrhage, abundant areas of necrosis, syncytial knots, peri-villous edema and stromal fibrosis (Fig 17,18,19,20 and 21). The various clinical parameters which were used in the study were the age of patient, gestational age of the patient, gross weight of placenta, weight of the baby and apgar score of the baby. The comprehensive analysis aimed to provide a clearer understanding of the role of E-cadherin and other factors in the development of pre-eclampsia.

Majority of our cases were in the age group of 21-30 years in both the control and pre-eclampsia. This age group is significantly represented in mild (80%) and moderate (60%) pre-eclampsia, but is less represented in severe cases (40%). Conversely, the age group of 31-40 years showed an increase in severe pre-eclampsia cases (50%), indicating a higher severity of pre-eclampsia in older patients within the pre-eclampsia group. Comparison of age groups with the severity of pre-eclampsia showed statistical significance, with a p-value of less than 0.05. Similarly, in the study conducted by **Peska M** the mean age of the control group was 28.1 years, which is similar with our findings.[2] In the study by **Poon LC,et al.** it was demonstrated that as age advances the development of pre-eclampsia increases.[1] As age advances, women experience significant physiological changes that can impact vascular health that is increasing the likelihood of developing pre-existing conditions such as chronic hypertension, diabetes, and renal disease. These conditions are well known risk factors for pre-eclampsia. Additionally, older women tend to have higher baseline levels of inflammatory markers, which contribute to an enhanced inflammatory response. This heightened inflammation plays a critical role in the pathogenesis of pre-eclampsia, further elevating the risk of developing this condition.

When gestational age was taken into consideration majority of the cases were between 36-40 weeks in both control and the pre-eclampsia groups. The mean gestational age is 37.12±2.84 weeks in the control group and 36.02±2.8 weeks in pre-eclampsia. These findings suggest that pre-eclampsia commonly manifests towards the later stages of pregnancy.

When comparing the severiety of pre-eclampsia with the gestational age of the patients, the results between the two groups were not statistically significant (p-value = 0.36). Our study's findings are consistent with those of **Atigan A.** who also reported similar results regarding gestational age, with a non-significant p-value.[55] These findings suggest that while

gestational age is an important factor in pregnancy outcomes, it may not be the primary determinant of pre-eclampsia onset or severity.[58]

The ideal weight of the placenta ranges between 400 and 800 grams. In the current study, the majority of cases in both the control and pre-eclampsia groups had placental weights in the range of 501-550 grams. When the weight of the placenta was compared with the severity of pre-eclampsia, the results did not show any statistical significance, with a p-value of 0.98. The relationship between placental weight and pre-eclampsia is complicated as it is affected by multiple factors such as maternal health, genetic conditions, and environmental factors. These factors can cause variability in the weights of the placentas.

On comparing the gross and microscopic features of the placentas showed a significant association between the presence of infarction, calcification, and thrombosis in the control group and the pre-eclampsia cases. In the present study majority of cases and controls showed the presence of necrosis in approximately 45%. When comparing the severity of pre-eclampsia with the gross findings of placental necrosis, the results between the two groups were statistically significant (p-value = 0.001273, $p < 0.05$). But when compared to the control group, the pre-eclampsia group exhibited a higher presence of calcification and thrombosis which were also statistically significant (p-value = 0.043989, $p < 0.05$ and p-value = 0.01358, $p < 0.05$) respectively. When compared to the study done by **CR Gore et al.** showed that the gross and microscopy findings of necrosis, calcification and thrombosis were similar to the present study and were statistically significant.[59]

In Pre-eclampsia is there is endothelial dysfunction and abnormal placentation, causing decreased blood flow and increased oxidative stress within the placenta. These factors lead to the formation of infarctions, calcifications, and thromboses as the placenta tries to

compensate for the impaired blood flow. The degree of necrosis is mainly due to the increased placental hypoxia and ischemia associated. Calcification and thrombosis in the placenta can decrease the maternal-fetal exchange of nutrients and oxygen, leading to the adverse outcomes causing pre-eclampsia.[59]

In the current study the expression of e-cadherin was assessed in the normal placenta and the pre-eclampsia placenta. E-cadherin in healthy placentas was more positively expressed that is nearly 88% showed the presence of e-cadherin, a protein that is involved in cell-to-cell adhesion and only a small portion (12%) lacked it. E-cadherin expression is less common in pre-eclampsia placentas when compared to healthy placentas that is almost 73% cases and the absence of e-cadherin expression was seen in 27% of the cases in this group. Therefore, pre-eclampsia likely reduces E-cadherin expression and this difference suggests that pre-eclampsia is associated with a decrease in E-cadherin levels in the placenta. A statistical analysis (chi-square test) confirmed a significant association (p-value = 0.017706, less than 0.05) between E-cadherin expression in the normal and pre-eclampsia placenta.

During pregnancy, E-cadherin, a cell-to-cell adhesion molecule is important for maintaining epithelial integrity and plays a crucial role in the development and functioning of the placenta. E-cadherin expression in trophoblastic cells temporarily decreases during the process of placental invasion in the first and second trimesters. This temporary decrease of E-cadherin enables the invasive capability of trophoblasts, allowing them to permeate and remodel the maternal uterine tissue effectively.[60]

However, as the pregnancy progress E-cadherin is expressed strongly and circumferentially in the placental villi, which is essential for maintaining the structural and functional integrity of the placental barrier and helps in completion of the trophoblast invasion and the

establishment of the placental villous architecture, which in turn helps in nutrient and gas exchange between the mother and the fetus.

Shallow trophoblast invasion is due to downregulation of E-cadherin and other invasion-related mechanisms, which is a hallmark for pregnancy-induced hypertension (PIH) and pre-eclampsia (PE). Here, the spiral arteries stay narrow and high-resistance causing reduced placental perfusion. This inadequate blood flow leads to placental hypoxia, oxidative stress, and the release of antiangiogenic factors into the maternal circulation, contributing to the systemic manifestations of PE, such as hypertension and proteinuria.[61]

In the study conducted by **Pęksa M**, E-cadherin expression was significantly higher in the control group (normal placentas) and was less or weakly expressed in the pre-eclampsia placentas, these findings are similar to those of the present study. In study by **Zeynep Bayramoğlu** stated that expression of e-cadherin was higher in pre-eclampsia cases when realted to the normal control cases which was not similar with present study. In the study by **Sevgi İrtegun** stated that e-cadherin expression by western blot technique was not detectable in normal placentas but was highly expressed in preeclamptic placentas which was not correlating with the present study. In the study conducted by **Atigan A**, IHC staining showed that the expression of E-cadherin was increased in the pre-eclampsia group compared to the control group which was not similar with present study.

Table 18: Comparison study of expression of E-cadherin

Study	Year	No of cases	Methodology	Result
Zeynep Bayramoğlu[62]	2023	Total of 60 cases (32 pre-eclampsia and 28 healthy)	Immunohistochemistry	The study showed E-cadherin expression was higher in pre-eclampsia cases compared to normal control cases
Sevgi İrtegun[52]	2016	Total 20 cases (10 pre-eclampsia and 10 normal)	Western blot analysis	E-cadherin expression was not detectable in normal placentas but highly expressed in preeclamptic placentas
Atigan A[55]	2022	Total 36 cases (20 pre-eclampsia and 16 normal healthy)	Immunohistochemistry	E-cadherin expression was significantly higher in pre-eclampsia group compared to control group
Pęksa M[2]	2022	Total 92 cases (55 pre-eclampsia and 37 normal healthy)	Immunohistochemistry	E-cadherin expression was significantly higher in control group (normal placentas) and less or weakly expressed in pre-eclampsia placentas
Present Study	2024	Total 160 cases (80 pre-eclampsia and 80 normal healthy)	Immunohistochemistry	The E-cadherin expression was significantly higher in control group (normal placentas) and less or weakly expressed in pre-eclampsia placentas

In present study, intensity of expression e-cadherin was evaluated in both control and pre-eclamptic groups. The expression levels were graded from no expression to high expression that is grade 0 to 3.

In the control group, major cases exhibited high E-cadherin expression that is grade 3. On the contrary in pre-eclampsia group a higher number of cases that is 28% showed no E-cadherin expression (grade 0) compared to control group.

Among the mild pre-eclampsia cases, a higher number of cases that is 65% showed intermediate and high expression (grade 2 and 3). In moderate pre-eclampsia cases, intermediate expression that is grade 2 was most common. For severe pre-eclampsia, highest number of cases that is 63% showed no and low expression that is grade 0 and 1.

Chi-square data analysis showed positive correlation between that level of E-cadherin expression and severity of pre-eclampsia with a p-value of 0.003108 ($p<0.05$) which is showing statistical significance.

In the study conducted by **Pęksa M**, a detailed examination of E-cadherin staining patterns revealed significant differences between patients with pregnancy-induced hypertension and pre-eclampsia compared to the normal pregnant control group[2]. Specifically, the study found that patients with pregnancy-induced hypertension and pre-eclampsia exhibited a loss of E-cadherin staining continuity. This means that the staining of E-cadherin, a protein crucial for cell-to-cell adhesion, was disrupted in these patients.

Furthermore, **Pęksa M's** study noted that in the pre-eclampsia and PIH groups, there was a distinct discontinuity in the staining at the basement of the villi.[2] The villi are important in gaseous exchange and nutrition between mother and fetus. In normal pregnancies, the basement membrane of these villi showed continuous, uninterrupted staining for E-cadherin, indicating a healthy and intact cellular architecture.

In healthy control groups, the e-cadherin expression is predominantly continuous causing the structural integrity of normal placenta and supports cell to cell adhesion leading to normal function of placenta and nutrition to fetus. In pre-eclampsia cases, especially the severe forms there is marked discontinuity in the E-cadherin expression in the villi. This loss of continuity is associated with increased vascular resistance of uterine arteries leading to disruption in cell-to-cell adhesion and impaired placental function.

However, in the pre-eclampsia and pregnancy-induced hypertension groups, this continuous staining was disrupted, suggesting a compromised structural integrity of the placental tissue. This disruption in E-cadherin staining continuity could potentially contribute to the pathological mechanisms causing underlying pre-eclampsia and pregnancy-induced hypertension, affecting the proper functioning of the placenta.

These findings from **Pęksa M's** study are consistent with the results seen in present study, which also showed a significant reduction in expression of E-cadherin and staining continuity in pre-eclampsia cases compared to normal pregnancies. [2]The similarity in these findings between the two studies underscores the important role of E-cadherin disruption in the pathogenesis and progression of preeclampsia and pregnancy-induced hypertension. Additionally, the observed differences in E-cadherin staining patterns between the groups were statistically significant, further supporting the correlation between reduced expression of E-cadherin and severity of these conditions. The evaluation of e-cadherin expression can be a potential marker to know the development of pre-eclampsia.

CONCLUSION

CONCLUSION

This study indicates that the reduced intensity and discontinuity of E-cadherin staining in pre-eclampsia cases point to a defect in placental barrier function. This defect likely contributes to the development of pre-eclampsia and associated pregnancy complications. The findings suggest that disruptions in E-cadherin expression may impair the structural integrity of the placenta, thereby playing a critical role in the pathogenesis of pre-eclampsia. However, in pre-eclampsia cases with positive e-cadherin other mechanisms causing disruption of vasculosyncytial membrane needs to be investigated.

SUMMARY

SUMMARY

- The placenta is a vital organ that is necessary for the growth and development of the fetus.
- In the current study the placentas from normal healthy pregnancy and pre-eclampsia pregnancies were evaluated by gross, microscopy and Immunohistochemical expression of E-cadherin was demonstrated in the placental villi.
- The gross findings were calcification, necrosis and thrombosis. Whereas in the microscopy excessive syncytial knots, stromal fibrosis, necrosis, peri-villous edema and overcrowding of placental villi were seen predominantly in pre-eclamptic placentas.
- When the immunohistochemistry of E-cadherin expression was evaluated in the healthy and pre-eclamptic placentas, there was a very high expression (grade 3) and continuity of staining of E-cadherin in normal healthy placentas.
- However, in preeclampsia placentas the expression of E-cadherin was varied that is, majority of severe pre-eclampsia placentas showed no expression (grade 0) and no staining of the e-cadherin in the placental villi. Whereas the mild and moderate pre-eclampsia placentas showed intermediate expression (grade 2) and discontinuity in the staining of e-cadherin in placental villi.
- Overall, the continuous and high expression of e-cadherin suggests healthy functioning and development of placenta. The discontinuity and varied expression of e-cadherin in pre-eclampsia placentas implied disruption of the placental architecture leading to disease progression and severity.

LIMITATIONS

LIMITATIONS

We did not investigate whether similar E-cadherin alterations occur in placental disruptions associated with other gestational diseases. This means that our findings are specific to pre-eclampsia and cannot be used to other conditions affecting pregnant women. Future research should be done on larger demographic areas.

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BIBILIOGRAPHY

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ANNEXURE

PATIENT PROFORMA

Name:

Age:

Hospital Number:

Biopsy Number:

Chief Complaint:

History of Presenting Illness:

Past History:

Personal History:

Local Examination:

Histopathological Diagnosis:

Gross:

Microscopy:

Mild/Moderate/Severe Pre-eclampsia:

Proteinuria:

Weight of Baby:

APGAR Score:

INFORMED CONSENT FORM

Study Title: **Immunohistochemical Expression of E-Cadherin in Cytotrophoblast, Syncytiotrophoblast and Blood Vessels in Placenta of Pre-Eclampsia**.

I, _____ have read or have been read to me the patient information sheet and understand the purpose of the study, the procedure that will be used, the risk and benefits associated with my involvement in the study and the nature of information will be collected and disclosed during the study.

I have had my opportunity to ask my questions regarding various aspects of the study and my questions are answered to my satisfaction.

I, the undersigned, agree to participate in this study and authorize the collection and disclosure of my personal information for the dissertation.

Name and Signature / Thumb Impression (Subject)	Date: Place:
Name and Signature / Thumb Impression (Witness/Parent/ Guardian/ Husband)	Date: Place:

PATIENT INFORMATION SHEET

Study Title: **Immunohistochemical Expression of E-Cadherin in Cytotrophoblast, Syncytiotrophoblast and Blood Vessels in Placenta of Pre-Eclampsia.**

Place Of Study: Department of Pathology, Sri Devaraj Urs Medical College, Kolar.

The main aim of the study is to find the Immunohistochemical expression of E-Cadherin in Cytotrophoblast, Synctiotrophoblast and Blood vessels in the Placenta of Pre-Eclampsia . The specimens will be collected from the department of Obstetrics and Gynaecology , SDUMC, Kolar. This study will be approved by the institutional ethical committee. The information collected will be used only for dissertation and publication. There is no compulsion to agree to participate. You are requested to sign / provide thumb impression only if you voluntarily agree to participate in the study. All information collected from you will be kept confidential and will not be disclosed to any outsider. Your identity will not be revealed. You will not receive any monetary benefits to participate in this research. This informed consent document is intended to give you a general background of study. Please read the following information carefully and discuss with your family members. You can ask your queries related to study at any time during the study. If you are willing to participate in the study you will be asked to sign an informed consent form by which you are acknowledging that you wish to participate in the study and entire procedure will be explained to you by the study doctor. You are free to withdraw your consent to participate in the study any time without explanation and this will not change your future care. All the cost will be borne by me.

For any clarification you are free to contact the investigator.

Principal Investigator : Dr Sukka Sahiti

Phone Number: 7386799759

ರೋಗಿಯ ಮಾಹಿತಿ ಹಾಳೆ:

ಕ್ರಮ ಸಂಖ್ಯೆ :

ರೋಗಿಯ ಹೆಸರು :

ಮೊಬೈಲ್ ನಂಬರ್ :

ಅಧ್ಯಯನದ ಶೀರ್ಷಿಕೆ: ಪ್ರೀ ಎಕ್ಲಾಂಪ್ಸಿಯಾ ಜರಾಯುವಿನ (placenta)ದಲ್ಲಿನ ಸಿಂನ್ಸಿಷಟ್ರೋಫೋಬ್ಲಾಸ್ಟ್ , ಸೈಟೊಟ್ರೋಫೋಬ್ಲಾಸ್ಟ್, ರಕ್ತನಾಳಗಳು ಮತ್ತು ಇಮ್ಯುನೊಹಿಸ್ಟೋಕೆಮಿಸ್ಟ್ರಿ ಬಳಸಿ ಇ ಕೆಡರಿನ್ ಅಭಿವ್ಯಕ್ತಿಯನ್ನು ಕಂಡುಹಿಡಿಯುವುದು ಅಧ್ಯಯನದ ಮುಖ್ಯ ಗುರಿಯಾಗಿದೆ

ಅಧ್ಯಯನದ ಸ್ಥಳ: ರೋಗಶಾಸ್ತ್ರ ವಿಭಾಗ, ಶ್ರೀ ದೇವರಾಜ್ ಅರ್ಸ್ ವೈದ್ಯಕೀಯ ಕಾಲೇಜು, ಕೋಲಾರ.

ಪ್ರೀ ಎಕ್ಲಾಂಪ್ಸಿಯಾ ಜರಾಯುವಿನ (placenta)ದಲ್ಲಿನ ಸಿಂನ್ಸಿಷಟ್ರೋಫೋಬ್ಲಾಸ್ಟ್ , ಸೈಟೊಟ್ರೋಫೋಬ್ಲಾಸ್ಟ್, ರಕ್ತನಾಳಗಳು ಮತ್ತು ಇಮ್ಯುನೊಹಿಸ್ಟೋಕೆಮಿಸ್ಟ್ರಿ ಬಳಸಿ ಇ ಕೆಡರಿನ್ ಅಭಿವ್ಯಕ್ತಿಯನ್ನು ಕಂಡುಹಿಡಿಯುವುದು ಅಧ್ಯಯನದ ಮುಖ್ಯ ಗುರಿಯಾಗಿದೆ. ಕೋಲಾರದ ಎಸ್‌ಡಿಯುಎಂಸಿಯ ಪ್ರಸೂತಿ ಮತ್ತು ಸ್ತ್ರೀರೋಗ ವಿಭಾಗದಿಂದ ಜರಾಯುವನ್ನು ಸಂಗ್ರಹಿಸಲಾಗುವುದು. ಈ ಅಧ್ಯಯನವನ್ನು ಸಾಂಸ್ಥಿಕ ನೈತಿಕ ಸಮಿತಿಯು ಅನುಮೋದಿಸುತ್ತದೆ. ಸಂಗ್ರಹಿಸಿದ ಮಾಹಿತಿಯನ್ನು ಪ್ರಬಂಧ ಮತ್ತು ಪ್ರಕಟಣೆಗೆ ಮಾತ್ರ ಬಳಸಲಾಗುತ್ತದೆ. ಭಾಗವಹಿಸಲು ಒಪ್ಪಿಕೊಳ್ಳಲು ಯಾವುದೇ ಒತ್ತಾಯವಿಲ್ಲ. ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ನೀವು ಸ್ವಯಂಪ್ರೇರಣೆಯಿಂದ ಒಪ್ಪಿದರೆ ಮಾತ್ರ ಹೆಬ್ಬೆರಳಿನ ಗುರುತನ್ನು ಸಹಿ ಮಾಡಲು/ಒದಗಿಸಲು ನಿಮ್ಮನ್ನು ವಿನಂತಿಸಲಾಗಿದೆ. ನಿಮ್ಮಿಂದ ಸಂಗ್ರಹಿಸಿದ ಮಾಹಿತಿಯನ್ನು ಮತ್ತು ನಿಮ್ಮ ಗುರುತನ್ನು ಗೌಪ್ಯವಾಗಿ ಇರಿಸಲಾಗುತ್ತದೆ ಮತ್ತು ಹೊರಗಿನವರಿಗೆ ಬಹಿರಂಗಪಡಿಸುವುದಿಲ್ಲ. ಈ ಸಂಶೋಧನೆಯಲ್ಲಿ ಭಾಗವಹಿಸಲು ನೀವು ಯಾವುದೇ ಹಣಕಾಸಿನ ಪ್ರಯೋಜನಗಳನ್ನು ಸ್ವೀಕರಿಸುವುದಿಲ್ಲ. ಈ ಮಾಹಿತಿಯುಕ್ತ ಸಮ್ಮತಿ ಡಾಕ್ಯುಮೆಂಟ್ ನಿಮಗೆ ಸಾಮಾನ್ಯ ಅಧ್ಯಯನದ ಹಿನ್ನೆಲೆಯನ್ನು ನೀಡಲು ಉದ್ದೇಶಿಸಿದೆ. ದಯವಿಟ್ಟು ಕೆಳಗಿನ ಮಾಹಿತಿಯನ್ನು ಎಚ್ಚರಿಕೆಯಿಂದ ಓದಿ ಮತ್ತು ನಿಮ್ಮ ಕುಟುಂಬ ಸದಸ್ಯರೊಂದಿಗೆ ಚರ್ಚಿಸಿ. ಅಧ್ಯಯನದ ಸಮಯದಲ್ಲಿ ನೀವು ಯಾವುದೇ ಸಮಯದಲ್ಲಿ ಅಧ್ಯಯನಕ್ಕೆ ಸಂಬಂಧಿಸಿದ ನಿಮ್ಮ ಪ್ರಶ್ನೆಗಳನ್ನು ಕೇಳಬಹುದು. ನೀವು ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ಸಿದ್ಧರಿದ್ದರೆ, ತಿಳುವಳಿಕೆಯುಳ್ಳ ಸಮ್ಮತಿಯ ನಮೂನೆಗೆ ಸಹಿ ಹಾಕಲು ನಿಮ್ಮನ್ನು ಕೇಳಲಾಗುತ್ತದೆ ಮತ್ತು ಅದರ ಮೂಲಕ ನೀವು ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ಬಯಸುತ್ತೀರಿ ಎಂದು ಒಪ್ಪಿಕೊಳ್ಳುತ್ತೀರಿ ಮತ್ತು ಸಂಪೂರ್ಣ ಕಾರ್ಯವಿಧಾನವನ್ನು ಅಧ್ಯಯನ ವೈದ್ಯರು ನಿಮಗೆ ವಿವರಿಸುತ್ತಾರೆ. ವಿವರಣೆಯಿಲ್ಲದೆ ಯಾವುದೇ ಸಮಯದಲ್ಲಿ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ನಿಮ್ಮ ಸಮ್ಮತಿಯನ್ನು ಹಿಂಪಡೆಯಲು ನೀವು ಸ್ವತಂತ್ರರಾಗಿದ್ದೀರಿ ಮತ್ತು ಇದು ನಿಮ್ಮ ಭವಿಷ್ಯದ ಚಿಕಿತ್ಸೆಯನ್ನು ಬದಲಾಯಿಸುವುದಿಲ್ಲ. ಯಾವುದೇ ಸ್ಪಷ್ಟೀಕರಣಕ್ಕಾಗಿ ನೀವು ತನಿಖಾಧಿಕಾರಿಯನ್ನು ಸಂಪರ್ಕಿಸಲು ಮುಕ್ತರಾಗಿದ್ದೀರಿ. ಅಧ್ಯಯನದ ವೆಚ್ಚವನ್ನು ಪ್ರಾಥಮಿಕ ತನಿಖಾಧಿಕಾರಿ ಭರಿಸುತ್ತಾರೆ.

ಪ್ರಮುಖ ಸಂಶೋಧಕರ ಹೆಸರು ಮತ್ತು ರುಜು: **ಡಾII ಸುಕ್ಕ ಸಾಹಿತಿ**

Phone number

ತಿಳಿಸಲಾದ ಒಪ್ಪಿಗೆ ನಮೂನೆ

ಅಧ್ಯಯನದ ಶೀರ್ಷಿಕೆ: ಪ್ರೀ ಎಕ್ಲಾಂಪ್ಸಿಯಾ ಜರಾಯುವಿನ (placenta)ದಲ್ಲಿನ ಸಿಂನ್ಸಿಷಟ್ರೋಫೋಬ್ಲಾಸ್ಟ್ , ಸೈಟೊಟ್ರೋಫೋಬ್ಲಾಸ್ಟ್, ರಕ್ತನಾಳಗಳು ಮತ್ತು ಇಮ್ಯುನೊಹಿಸ್ಟೋಕೆಮಿಸ್ಟ್ರಿ ಬಳಸಿ ಇ ಕೆಡರಿನ್ ಅಭಿವ್ಯಕ್ತಿಯನ್ನು ಕಂಡುಹಿಡಿಯುವುದು

ನಾನು __ ಮಾಹಿತಿ ಹಾಳೆಯನ್ನು ಓದಿದ್ದೇನೆ ಅಥವಾ ನನಗೆ ಓದಿ ತಿಳಿಸಿದ್ದಾರೆ ಮತ್ತು ಅಧ್ಯಯನದ ಉದ್ದೇಶ, ಬಳಸಲಾಗುವ ವಿಧಾನ, ಅಧ್ಯಯನದಲ್ಲಿ ನನ್ನ ಪಾಲ್ಗೊಳ್ಳುವಿಕೆಗೆ ಸಂಬಂಧಿಸಿದ ಅಪಾಯ ಮತ್ತು ಪ್ರಯೋಜನಗಳು ಮತ್ತು ಮಾಹಿತಿಯ ಸ್ವರೂಪವನ್ನು ಸಂಗ್ರಹಿಸಲಾಗುತ್ತದೆ ಮತ್ತು ಅಧ್ಯಯನದ ಸಮಯದಲ್ಲಿ ಬಹಿರಂಗಪಡಿಸಲಾಗುತ್ತದೆ.ಅಧ್ಯಯನದ ವಿವಿಧ ಅಂಶಗಳಿಗೆ ಸಂಬಂಧಿಸಿದಂತೆ ನನ್ನ ಪ್ರಶ್ನೆಗಳನ್ನು ಕೇಳಲು ನನ್ನ ಅವಕಾಶವನ್ನು ನಾನು ಹೊಂದಿದ್ದೇನೆ ಮತ್ತು ನನ್ನ ಪ್ರಶ್ನೆಗಳಿಗೆ ನನ್ನ ತೃಪ್ತಿಗೆ ಉತ್ತರಿಸಲಾಗಿದೆ. ಈ ಕೆಳಗೆ ಸಹಿಮಾಡಿರುವ ನಾನು ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ಒಪ್ಪಿರುತ್ತೆನೆ ಮತ್ತು ಪ್ರಬಂಧಕ್ಕಾಗಿ ನನ್ನ ವೈಯಕ್ತಿಕ ಮಾಹಿತಿಯ ಸಂಗ್ರಹಣೆ ಮತ್ತು ಬಹಿರಂಗಪಡಿಸುವಿಕೆಯನ್ನು ಅಧಿಕೃತಗೊಳಿಸುತ್ತೇನೆ.

ಹೆಸರು ಮತ್ತು ಸಹಿ / ಹೆಬ್ಬೆರಳಿನ ಗುರುತು

(ವಿಷಯ)

ಹೆಸರು ಮತ್ತು ಸಹಿ / ಹೆಬ್ಬೆರಳಿನ ಗುರುತು

(ಸಾಕ್ಷಿ/ಪೋಷಕ/ಗುರು/ಪತಿ)

ಮತ್ತಷ್ಟು ಸ್ಪಷ್ಟೀಕರಣಕ್ಕಾಗಿ ನೀವು ಅಧ್ಯಯನಶೋಧಕವನ್ನು ಸಂಪರ್ಕಿಸಬಹುದು

ಡಾII **ಸುಕ್ಕ ಸಾಹಿತಿ**

MASTER CHART

KEYS TO MASTER CHART

Sev of PE	Severity of Pre-Eclampsia
Ges	Gestational weeks
Gross – Wt of Pla	Gross – Weight of Placenta
Gross – Meas	Gross – Measurements
Wt of baby	Weight of baby
G&M – Nec	Gross & Microscopy – Necrosis
G&M – Cal	Gross & Microscopy – Calcification
G&M – Throm, mas	Gross & Microscopy – Thrombi, masses
IHC E-cadherin	Immunohistochemistry expression of E-cadherin
Syncytio	Syncytiotrophoblast
Cyto	Cytotrophoblast
BV	Blood vessels
Clin Dia	Clinical diagnosis

Biopsy no	Name	Age	Hosp no	Sev of PE	Ges	Gross - Wt of Pla (in gms)	Gross - Meas	APGAR Score (Out of 10)	Wt of baby (in kgs)	G&M - Nec	G&M - Cal	G&M - Throm, mas		IHC E cadherin		Continuity
													Syncytio	Cytotrpho	BV	
B/2778/22	Malika	26	154845	Mi	39	580	15x12x8cm	9	3	No	No	Yes	2+	2+	2+	Partially present
B/2955/22	Nagamani.J.V	26	163169	Sev	36	460	12x10x77cm	5	3.5	Yes	Yes	Yes	0	0	0	Absent
B/2971/22	Amrutha	22	163391	Sev	38	500	13x11x9cm	6	3.94	No	Yes	No	3+	3+	3+	Present
B/537/22	Nelamma	25	165166	Mi	30	560	17x15x9cm	6	3.32	Yes	No	No	1+	1+	1+	Partially present
B/3146/22	Pushpa	25	167824	Sev	33	460	10x8x5cm	5	3.66	Yes	Yes	Yes	1+	1+	0	Partially present
B/537/23	Kavitha	30	198787	Mi	40	480	11x10x8cm	8	2.97	No	No	No	1+	1+	1+	Partially present
B/397/22	Muskan taj	20	194608	Sev	38	500	12x10x9cm	5	2.6	Yes	Yes	Yes	2+	2+	1+	Partially present
B/449/23	Siddhiqua	28	186797	Sev	34	470	11.5x10x9cm	7	3.27	Yes	No	No	1+	1+	0	Partially present
B/426/23	Shamsunab	36	196384	Sev	29	510	13x12x10cm	6	3.8	Yes	Yes	Yes	0	0	0	Absent
B/427/23	Sania Mizra	23	194601	Sev	38	560	11x10x9cm	8	3.33	No	Yes	No	3+	3+	3+	Present
B/606/22	Chaitra	19	200175	Mi	36	500	12x11x9cm	9	3.52	No	Yes	No	1+	1+	0	Partially present
B/915/23	Sunitha	35	21176	Sev	35	480	11.5x10x9cm	6	2.81	Yes	Yes	Yes	0	0	0	Absent
B/932/23	Chaitra	33	212592	Sev	34	520	13x11x10cm	7	2.5	Yes	No	No	3+	3+	3+	Present
B/905/23	Hemavathi	22	211045	Sev	38	600	17x15x12cm	8	3.95	No	No	Yes	2+	2+	1+	Partially present
B/965/23	Sunita	35	213270	Sev	34	550	15x13x10cm	6	2.6	Yes	Yes	No	0	0	0	Absent
B/967/23	Sharmila	26	213735	Mi	35	500	12x10x10cm	8	2.8	No	No	No	1+	1+	0	Partially present
B/987/23	Vinnetha	29	214158	Sev	39	530	14x11x10cm	7	3.73	Yes	No	No	0	0	0	Absent
B/1522/23	Ruhani	30	230638	Mi	35	650	12x10x5cm	7	3.2	No	Yes	Yes	1+	1+	0	Partially present
B/1555/23	Savitha	23	236742	Sev	36	580	12x10x7cm	9	3.25	Yes	No	No	2+	2+	1+	Partially present
B/1560/23	Deepa	30	230695	Mod	39	530	15x9x7cm	7	2.5	No	No	No	2+	2+	2+	Partially present
B/1567/23	Nagaveni	28	231834	Sev	38	520	13x8x5cm	5	3	No	Yes	No	3+	3+	3+	Present
B/1732/23	Hamesha	31	236742	Mi	34	530	15x10x8cm	8	2.85	Yes	No	Yes	1+	1+	1+	Partially present
B/1771/23	Rupa	27	238124	Mod	35	620	15x9x6cm	9	2.75	No	Yes	Yes	0	0	0	Absent
B/1768/23	Amitha	23	237178	Mi	39	580	14x9x6cm	9	2.95	No	Yes	No	2+	2+	1+	Partially present
B/1782/23	Anushree	24	238451	Mi	40	650	15x9x5cm	7	3.25	Yes	No	No	0	0	0	Absent
B/1856/23	Bindhu	28	237985	Sev	37	530	14x9x6cm	9	3.3	No	No	Yes	0	0	0	Absent
B/1868/23	Divya	37	241436	Sev	35	550	15x9x5cm	7	3.2	No	Yes	No	0	0	0	Absent
B/2028/23	Renuka	25	246418	Mi	35	630	15x9x4cm	6	3.4	No	No	No	1+	1+	0	Partially present
B/2040/23	Bharthi	33	247563	Mi	39	590	16x10x7cm	7	3.25	Yes	Yes	No	2+	2+	0	Partially present
B/2051/23	Manjula	30	242368	Mi	37	540	13x8x5cm	9	3.3	No	No	Yes	2+	2+	1+	Partially present
B/2042/23	vasantha	20	247668	Mi	39	550	15x10x7cm	8	2.7	No	Yes	No	3+	3+	3+	Partially present
B/2195/23	chowdamma	36	251989	Sev	34	580	13x9x4cm	7	3.1	No	Yes	Yes	2+	2+	1+	Partially present
B/2217/23	nethravathi	28	246202	Mod	40	600	13x10x6cm	9	2.5	No	No	No	2+	2+	0	Partially present
B/2219/23	bhagyamma	36	253216	Sev	39	550	15x8x5cm	8	3.2	No	No	No	2+	2+	2+	Partially Present
B/2226/23	thimakka	19	244834	Sev	38	540	13x10x4cm	8	3.45	Yes	Yes	No	1+	1+	1+	Partially present
B/2236/23	vanja	35	254484	Sev	39	540	15x9x5cm	6	3.2	Yes	Yes	No	3+	3+	3+	Fully present
B/2238/23	ashwini	18	254759	Mod	37	520	15x11x7cm	9	2.5	No	Yes	Yes	0	0	0	Absent
B/2243/23	swomya	28	254609	Mi	36	510	15x9x7cm	7	3.2	Yes	No	Yes	2+	2+	0	Partially present
B/2251/23	roopashree	27	255055	Mod	39	580	12x9x6cm	7	2.5	No	No	Yes	3+	3+	3+	Present
B/2268/23	mounika	32	255565	Mod	37	550	15x10x6cm	7	2.75	No	No	No	3+	3+	1+	Fully Present
B/2280/23	devaki	25	251090	Mi	38	590	14x10x8cm	8	3	Yes	Yes	No	2+	2+	0	Partially present
B/2287/23	meghana	20	255289	Mod	39	510	15x11x6cm	8	3	No	No	No	2+	2+	1+	Partially present
B/2293/23	meenakshi	22	255704	Mi	38	480	12x8x6cm	7	3.2	No	Yes	Yes	3+	3+	3+	Fully present
B/2300/23	dhanushree	20	256644	Mod	37	530	15x11x7cm	8	2.75	No	Yes	Yes	0	0	0	Absent
B/2105/23	kavya	26	225747	Mod	39	510	15x12x8cm	8	3	No	No	Yes	1+	1+	0	Partially present
B/2108/23	anusha	23	249663	Sev	38	590	13x10x5cm	9	3.45	No	No	Yes	2+	2+	2+	Partially present
B/2340/23	bhavya	36	257662	Sev	35	520	15x12x9cm	10	2.85	No	Yes	Yes	1+	1+	1+	Partially present
B/2215/23	chandhini	34	253958	Mod	34	530	12x10x7cm	8	3.6	No	No	No	1+	1+	1+	Partially present
B/2304/23	geethama	32	256688	Sev	36	610	14x12x10cm	8	3.5	Yes	Yes	Yes	1+	1+	0	Partially present
B/95/23	vanajkshi	30	126227	Sev	37	460	13x11x9cm	7	3.75	Yes	Yes	Yes	0	0	0	Absent
B/822/23	kousalya	33	207994	Mod	32	630	15x12x9cm	7	2.75	No	Yes	No	1+	1+	0	Partially present
B/718/23	jothi	31	203945	Mod	35	550	18x14x10cm	8	3.1	No	No	No	0	0	0	Absent
B/1458/23	Hemavathi	28	228032	Mod	36	670	14x11x10cm	8	3	Yes	Yes	Yes	1+	1+	1+	Partially present
B/1446/23	uma	25	227117	Mi	34	540	11x9x7cm	5	2.6	No	No	No	2+	2+	2+	Partially present
B/1444/23	divya	27	227215	Sev	37	500	18x15x12cm	9	2.8	Yes	No	Yes	0	0	0	Absent
B/1050/23	gayathri	22	216113	Mi	38	570	17x14x10cm	9	3.35	Yes	Yes	No	0	0	0	Absent
B/1439/23	savithri	33	228397	Sev	39	550	12x10x8cm	8	3	Yes	Yes	Yes	2+	2+	2+	Partially present
B/3117/23	nagamma	24	275668	Mod	33	600	16x8x10cm	10	3.7	Yes	Yes	Yes	2+	2+	2+	Partially present
B/3460/23	prabhavathi	30	253041	Mi	40	620	13x10x8cm	9	3	Yes	Yes	Yes	1+	1+	1+	Partially present
B/3253/23	sumathi	32	284782	Sev	35	600	15x8x7cm	6	3.6	Yes	No	Yes	2+	2+	2+	Partially present
B/3368/23	ganga	33	287961	Sev	36	560	14x7x9cm	8	3.3	Yes	Yes	Yes	2+	2+	2+	Partially present
B/3348/23	asha	20	287866	Sev	37	580	16x9x7cm	9	2.95	Yes	No	Yes	0	0	1+	Absent
B/3631/23	kavitha	26	295857	Mi	32	590	12x9x7cm	9	3.1	No	No	No	2+	2+	2+	Partially present
B/3628/23	sirisha	35	295898	Sev	30	580	17x14x10cm	6	3.3	Yes	No	Yes	0	0	0	Absent
B/3735/23	veena	32	299211	Sev	31	620	15x12x8cm	5	3.65	Yes	Yes	Yes	1+	1+	1+	Partially present
B/3927/23	kamala	30	303564	Mod	33	620	12x10x7cm	7	3.75	Yes	No	Yes	2+	2+	2+	Partially present
B/4013/23	chaitra	38	307140	Sev	35	610	13x11x10cm	8	3	Yes	Yes	Yes	0	0	0	Absent
B/4167/23	sindhu	27	311730	Sev	36	680	15x13x11cm	9	3.4	Yes	Yes	Yes	1+	1+	1+	Partially present

Biopsy no	Name	Age	Hosp no	Sev of PE	Ges	Gross - Wt of Pla (in gms)	Gross - Meas	APGAR Score (Out of 10)	Wt of baby (in kgs)	G&M - Nec	G&M - Cal	G&M - Throm, mas		IHC E cadherin		Continuity
B/4255/23	haritha	22	314695	Mod	32	550	16x14x12cm	9	2.9	Yes	Yes	No	0	0	0	Absent
B/4662/23	hema	32	311469	Sev	30	640	14x9x8cm	6	3.1	Yes	Yes	Yes	0	0	1+	Absent
B/636/23	hamsaveni	22	201177	Mod	35	530	15x13x11cm	8	2.7	No	No	No	2+	2+	2+	Partially present
B/847/23	anitha	36	207106	Sev	37	680	14x13x11cm	8	2.65	Yes	Yes	Yes	0	0	0	Absent
B/1039/23	sumalatha	26	215802	Sev	38	480	11x9x8cm	10	2.8	Yes	Yes	Yes	3+	3+	3+	Fully present
B/1713/23	ramya	35	236195	Sev	39	600	12x10x9cm	7	2.6	Yes	Yes	Yes	2+	2+	2+	Partially present
B/1072/23	pooja	21	238457	Mod	28	570	15x8x7cm	8	2.9	Yes	Yes	No	3+	3+	3+	Partially present
B/1768/23	arthi	20	237178	Sev	35	500	16x14x11cm	9	3	Yes	Yes	Yes	3+	3+	3+	Present
B/1793/23	rajamma	33	227392	Sev	30	630	17x15x12cm	7	3.1	Yes	Yes	Yes	1+	1+	1+	Partially present
B/1806/23	pranathi	30	239611	Sev	39	650	15x14x11cm	6	3.3	Yes	Yes	Yes	2+	2+	2+	Partially present
B/1821/23	purvi	21	240171	Mod	34	510	16x14x12cm	8	2.6	No	No	No	2+	2+	2+	Partially present
B/2129/23	deeksha	20	243988	Mod	32	590	12x10x9cm	9	2.5	Yes	No	No	0	0	0	Absent

Biopsy no	Age	Hosp no	Clin diag	Ges	Gross - Wt of Pla (in gms)	Gross - Measurments	APGAR Score	Wt of Baby	G&M - Nec	G&M - Cal	G&M - Throm, mas		IHC E-cadherin		Continuity
												Syncytiotropho	Cytotropho	Blood vessels	
B/376/23	27	154845	Normal Placenta	40 weeks	520	18x15x7 cm	8	3.91	No	No	Yes	3+	3+	3+	Present
B/388/23	23	194920	Normal Placenta	39 weeks	490	15x11x8 cm	7	3.05	Yes	Yes	Yes	2	2	2	Present
B/406/23	29	195225	Normal Placenta	39 weeks	500	13x10x8 cm	6	3.03	No	No	No	3+	3+	3+	Present
B/612/23	24	200226	Normal Placenta	40 weeks	500	13x11x7cm	7	3.3	Yes	No	No	0	0	0	Present
B/535/22	24	198612	Normal Placenta	38 weeks	540	17x14x9 cm	7	2.62	Yes	Yes	Yes	2	2	2	Present
B/408/23	21	83582	Normal Placenta	28 weeks	490	10x9x8 cm	9	3.65	No	No	No	2	2	2	Present
B/605/23	28	210660	Normal Placenta	40 weeks	600	10x9x5 cm	7	3.29	Yes	Yes	Yes	0	0	0	Present
B/857/23	28	208962	Normal Placenta	30 weeks	450	10x9x5 cm	6	3.88	Yes	No	No	3+	3+	3+	Present
B/897/23	21	206483	Normal Placenta	39 weeks	520	10x9x4 cm	8	2.88	Yes	No	No	3+	3+	3+	Present
B/836/23	24	208005	Normal Placenta	39 weeks	480	12x10x7 cm	7	3.84	No	No	No	1	1	1	Present
B/848/23	21	20849	Normal Placenta	40 weeks	650	18x14x10 cm	7	2.47	No	No	No	3+	3+	3+	Present
B/849/23	22	209053	Normal Placenta	40 weeks	560	15x14x9 cm	6	3.42	Yes	Yes	Yes	2	2	2	Present
B/834/23	30	208097	Normal Placenta	39 weeks	700	18x16x10 cm	6	3.75	Yes	No	No	0	0	0	Present
B/833/23	23	207835	Normal Placenta	39 weeks	550	12x10x5 cm	8	2.53	No	No	Yes	3+	3+	3+	Present
B/846/23	26	205804	Normal Placenta	40 weeks	650	18x13x9cm	7	2.67	Yes	Yes	No	1	1	1	Present
B/888/23	23	207380	Normal Placenta	40 weeks	760	20x18x12cm	9	3.69	No	No	No	2	2	2	Present
B/923/23	28	209982	Normal Placenta	40 weeks	510	14x12x17 cm	9	3.14	Yes	No	No	3+	3+	3+	Present
B/933/23	22	212711	Normal Placenta	32 weeks	600	14x11x7cm	5	3.72	No	Yes	Yes	0	0	0	Present
B/930/23	27	212674	Normal Placenta	36 weeks	500	12x10x6cm	7	3.33	Yes	No	No	3+	3+	3+	Present
B/919/23	24	212011	Normal Placenta	33 weeks	530	14.5x10x5cm	8	2.89	No	No	No	2	2	2	Present
B/904/23	25	199613	Normal Placenta	38 weeks	680	18x15x9cm	8	3.75	No	No	No	1	1	1	Present
B/908/23	24	211218	Normal Placenta	35 weeks	650	17x12x8cm	5	2.81	Yes	No	No	3+	3+	3+	Present
B/934/23	27	188741	Normal Placenta	38 weeks	550	13x11x5cm	10	3.77	Yes	Yes	Yes	2	2	2	Present
B/966/23	26	213732	Normal Placenta	38 weeks	600	12x10xcm	9	3.5	No	No	No	0	0	0	Present
B/968/23	27	212573	Normal Placenta	34weeks	470	15x10x9cm	8	2.75	Yes	No	No	3+	3+	3+	Present
B/1521/23	25	222983	Normal Placenta	32 weeks	500	11x9x7cm	7	3.25	No	No	Yes	1	1	1	Present
B/1523/23	30	229892	Normal Placenta	32 weeks	650	13x9x6cm	8	3.5	No	No	No	2	2	2	Present
B/1527/23	28	230732	Normal Placenta	32 weeks	570	12x8x6 cm	6	2.85	No	No	No	3+	3+	3+	Present
B/1537/23	31	231221	Normal Placenta	31 weeks	540	12x10x9cm	7	3.1	Yes	Yes	No	1	1	1	Present

Biopsy no	Age	Hosp no	Clin diag	Ges	Gross - Wt of Pla (in gms)	Gross - Measurments	APGAR Score	Wt of Baby	G&M - Nec	G&M - Cal	G&M - Throm, mas		IHC E-cadherin		Continuity
B/1543/23	23	231165	Normal Placenta	33 weeks	520	13x9x6cm	8	3.25	No	No	Yes	3+	3+	3+	Present
B/1539/23	27	231232	Normal Placenta	39 weeks	560	12x8x5cm	9	3.5	No	No	No	3+	3+	3+	Present
B/1551/23	31	226523	Normal Placenta	33 weeks	550	15x11x6cm	8	3.25	No	Yes	No	0	0	0	Present
B/1553/23	28	231254	Normal Placenta	31 weeks	630	13x10x9cm	8	2.95	Yes	No	No	2	2	2	Present
B/1571/23	23	224188	Normal Placenta	31 weeks	720	10x9x6cm	6	3.5	No	No	No	3+	3+	3+	Present
B/1577/23	30	231802	Normal Placenta	32 weeks	590	13x10x8 cm	7	2.85	Yes	No	No	2	2	2	Present
B/1579/23	36	227278	Normal Placenta	39 weeks	570	16x9x5cm	6	3.01	Yes	Yes	No	1	1	1	Present
B/1591/23	31	232378	Normal Placenta	33 weeks	550	12x9x6 cm	8	3.5	No	No	Yes	3+	3+	3+	Present
B/1592/23	31	232412	Normal Placenta	40 weeks	610	11x9x7cm	8	2.75	Yes	No	No	1	1	1	Present
B/1594/23	33	229613	Normal Placenta	38 weeks	700	13x10x8cm	8	3.25	yes	No	No	3+	3+	3+	Present
B/1599/23	22	232701	Normal Placenta	36 weeks	580	12x9x7cm	9	2.75	No	No	No	0	0	0	Present
B/1582/23	32	208237	Normal Placenta	38 weeks	690	13x10x7cm	8	3.5	Yes	No	No	2	2	2	Present
B/1569/23	27	231803	Normal Placenta	39 weeks	480	15x10x7cm	7	3.8	No	No	No	3+	3+	3+	Present
B/1564/23	26	228179	Normal Placenta	36 weeks	700	11x9x5cm	6	2.95	No	No	No	1	1	1	Present
B/1584/23	24	232242	Normal Placenta	38 weeks	570	13x11x9cm	7	3.25	Yes	Yes	Yes	3+	3+	3+	Present
B/1566/23	31	197264	Normal Placenta	39 weeks	550	13x11x9cm	8	2.85	No	No	No	2	2	2	Present
B/1600/23	34	196338	Normal Placenta	36 weeks	680	15x12x11cm	7	3.6	No	No	Yes	3+	3+	3+	Present
B/1603/23	29	145038	Normal Placenta	37 weeks	710	13x9x7cm	9	2.95	No	Yes	Yes	0	0	0	Present
B/1726/23	30	236797	Normal Placenta	32 weeks	680	13x10x6cm	8	2.5	Yes	No	No	2	2	2	Present
B/1727/23	21	236794	Normal Placenta	38 weeks	470	15x10x6cm	6	3.65	Yes	No	Yes	3+	3+	3+	Present
B/1729/23	28	237223	Normal Placenta	37 weeks	580	15x9x6cm	9	3	No	Yes	No	2	2	2	Present
B/1740/23	30	23684	Normal Placenta	38 weeks	630	13x9x5cm	8	3.45	No	No	No	3+	3+	3+	Present
B/1743/23	35	226925	Normal Placenta	40 weeks	530	12x10x7cm	7	3.36	No	No	No	1	1	1	Present
B/1760/23	27	234139	Normal Placenta	38 weeks	730	13x10x9cm	9	3.3	Yes	Yes	Yes	3+	3+	3+	Present
B/1762/23	30	235036	Normal Placenta	37 weeks	660	11x8x5cm	7	2.95	No	No	No	2	2	2	Present
B/1764/23	22	225588	Normal Placenta	39 weeks	570	14x11x9cm	6	3.7	Yes	No	No	3+	3+	3+	Present
B/1773/23	28	238098	Normal Placenta	40 weeks	510	12x10x5cm	9	3.3	Yes	No	No	1	1	1	Present
B/856/23	29	240945	Normal Placenta	37 weeks	550	11x9x5cm	8	3	No	Yes	No	3+	3+	3+	Present
B/2038/23	28	247619	Normal Placenta	39 weeks	490	13x11x7cm	7	3.2	Yes	Yes	No	0	0	0	Present
B/2063/23	25	244752	Normal Placenta	37 weeks	510	13x10x8cm	6	2.8	Yes	No	Yes	3+	3+	3+	Present

Biopsy no	Age	Hosp no	Clin diag	Ges	Gross - Wt of Pla (in gms)	Gross - Measurments	APGAR Score	Wt of Baby	G&M - Nec	G&M - Cal	G&M - Throm, mas		IHC E-cadherin		Continuity
B/2050/23	23	229406	Normal Placenta	38 weeks	560	12x9x5cm	7	3	Yes	No	No	2	2	2	Present
B/2097/23	28	241254	Normal Placenta	38 weeks	660	15x9x5cm	8	3.25	No	Yes	No	3+	3+	3+	Present
B/2041/23	30	247596	Normal Placenta	37 weeks	560	12x9x6cm	7	2.75	No	No	No	0	0	0	Present
B/2095/23	25	249336	Normal Placenta	39 weeks	610	13x11x7cm	6	2.8	Yes	No	No	2	2	2	Present
B/2096/23	33	249479	Normal Placenta	40 weeks	500	12x10x6cm	7	2.8	Yes	No	No	3+	3+	3+	Present
B/2062/23	24	238452	Normal Placenta	38 weeks	490	13x9x5cm	6	2.75	Yes	Yes	No	1	1	1	Present
B/2045/23	31	247958	Normal Placenta	36 weeks	520	15x10x7cm	8	3	Yes	No	No	3+	3+	3+	Present
B/2107/23	33	239397	Normal Placenta	37weeks	500	12x8x5cm	7	3.2	No	Yes	No	3+	3+	3+	Present
B/2113/23	34	249884	Normal Placenta	35 weeks	710	11x9x5cm	8	3	Yes	No	No	3+	3+	3+	Present
B/2119/23	29	250253	Normal Placenta	38 weeks	670	13x8x5cm	6	3.1	Yes	No	No	1	1	1	Present
B/2128/23	25	250455	Normal Placenta	32 weeks	620	11x7x5cm	9	2.85	Yes	Yes	No	3+	3+	3+	Present
B/2143/23	30	251498	Normal Placenta	36 weeks	480	15x7x5cm	8	3.5	No	No	No	2	2	2	Present
B/2144/23	31	239053	Normal Placenta	38 weeks	500	12x8x5cm	7	3.9	No	Yes	No	3+	3+	3+	Present
B/2156/23	22	225488	Normal Placenta	40 weeks	550	11x9x6cm	8	3	No	No	No	1	1	1	Present
B/2171/23	28	252558	Normal Placenta	34 weeks	720	15x10x7cm	9	2.75	Yes	Yes	Yes	2	2	2	Present
B/2176/23	22	252022	Normal Placenta	39 weeks	630	15x9x5cm	8	3.2	Yes	No	No	2	2	2	Present
B/2178/23	23	252577	Normal Placenta	38 weeks	520	13x9x5cm	9	3	No	No	No	1	1	1	Present
B/2184/23	21	252754	Normal Placenta	36 weeks	630	15x9x7cm	7	2.75	Yes	No	Yes	3+	3+	3+	Present
B/2188/23	22	252750	Normal Placenta	35 weeks	550	12x8x5cm	8	4	Yes	Yes	No	3+	3+	3+	Present
B/2194/23	27	253202	Normal Placenta	39 weeks	610	11x7x4cm	7	3	No	No	No	1	1	1	Present
B/889/23	29	210721	Normal Placenta	36 weeks	550	14x10x8cm	8	3.5	Yes	No	Yes	3+	3+	3+	Present