"CLINICOPATHOLOGICAL ANALYSIS OF PLACENTA IN TERM LOW BIRTH WEIGHT INFANTS IN COMPARISON WITH TERM NORMAL BIRTH WEIGHT INFANTS - A CASE CONTROL STUDY AT TERTIARY CARE HOSPITAL, BELAGAVI"

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LIST OF ABBREVIATIONS USED

Abbreviation	Expansion
1. ACA	Acute Chorioamnionitis
2. AV	Avascular villi
3. AVM	Accelerated villous maturation
4. CH	Chorangiosis
5. CHI	Chronic histiocytic intervillositis
6. DA	Decidual arteriopathy
7. DVH	Distal villous hypoplasia
8. DVM	Delayed villous maturation
9. FGR	Fetal growth restriction
10. FPF	Focal perivillous fibrin
11. FS	Fibromuscular sclerosis
12. FVM	Fetal vascular malperfusion
13. GD	Gestational diabetes
14. H & E	Hematoxylin and eosin
15. IH	Intravillous hemorrhage
16. IUFD	Intrauterine fetal death
17. IUGR	Intrauterine growth restriction
18. K	Syncytial knots
19. LBW	Low birth weight
20. MPFD	Massive perivillous fibrin deposition
21. MVM	Maternal vascular malperfusion
22. NBW	Normal birth weight
23. OH	Oligohydramnios
24. PI	Placental infarction
25. PIH	Pregnancy induced hypertension
26. T	Thrombosis in fetal vessels
27. VE	Vascular ectasia
28. VEGF	Vascular endothelial growth factor
29. VIFD	Vascular intramural fibrin deposition
30. VSVK	Villous stromal vascular karyorrhexis
31. VUE	Villitis of unknown etiology

ABSTRACT

Background: Low birth weight is an indicator of multifaceted health care problem that causes two thirds of perinatal mortality. Fetal growth is largely determined by the availability of nutrients from the mother through the placenta. Hence, any pathology in the placenta can lead to adverse fetal outcomes like LBW.

Objective: This study aims to evaluate the placental histopathology and assess its clinical correlation in term LBW infants in comparison with term NBW infants

Methods: The study included placenta from 30 low birth weight infants (cases) and 60 normal birth weight infants (controls) . Clinical findings from the mother were obtained. The placental histopathology was assessed following the Amsterdam classification system and results were analyzed.

Results: Both the case and control groups showed maternal age between 18 to 25 as the most frequently occurring age group. Gestational age and maternal weight gain during gestation were significantly lower in cases as compared to controls. Cases showed more frequency of maternal diseases like anemia, pregnancy induced hypertension, gestational diabetes and oligohydramnios. Fetal distress and fetal growth restriction were present more in cases as compared to controls. Among gross findings, eccentric and marginal umbilical cord insertion were more in cases. Also the placental weight and dimensions were significantly lower in cases. Among the microscopic parameters, increase in syncytial knot, chorangiosis, focal avascular villi and focal perivillous fibrin were found in more than 50 percent of the cases. Correlation of maternal clinical findings with placental pathology showed that

maternal anemia had association with most of the placental histopathological findings in cases as compared to controls.

Conclusion: Our study concludes that placental pathology occurs more frequently in cases as compared to controls with statistically significant correlation of the clinical and histopathological findings. Further research is needed to validate these findings and explore therapeutic implications.

Keywords: low birth weight, normal birth weight, Amsterdam classification of placenta pathology, anemia, pregnancy induced hypertension, gestational diabetes, maternal vascular malperfusion, fetal vascular malperfusion, chorioamnionitis, villitis of unknown etiology

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INTRODUCTION

Low birth weight (LBW) indicates a major multifaceted public health care problem which includes maternal malnutrition, illness and poor care in pregnancy. [1]

Irrespective of the period of gestation, birth weight less than 2.5 kgs is defined as LBW by international consensus. LBW is a because of preterm birth (PTB; less than 37 weeks of pregnancy), intrauterine growth restriction (IUGR) or both.[1] Fetal Growth Restriction [(FGR), also known as IUGR] is present in neonates whose birth weight is below 10th percentile of the birth weight for the gestational age. [2]

Nearly 15% of the infants born worldwide are LBW and about half of them are born in Southern Asia.[1] Infants with LBW are much more prevalent in countries like India which are a developing nation.[3] As per the research by Pusdekar et al., the prevalence of low birth weight in Belagavi is 19.8%.[4]

Various maternal and fetal factors contribute to LBW.[5] The maternal factors are anemia, nutritional deficiencies, genetic factors, heart diseases,[3] renal insufficiency, autoimmune diseases, endocrine or infectious disorders and multiple gestation.[5] Fetal factors include genetic, chromosomal anomalies and chronic infections.[3]

LBW is the cause for two thirds of perinatal mortality.[3] The mortality rate of LBW infants due to neonatal complications such as hypoglycemia, hypocalcemia, hyponatremia, hypothermia and polycythemia is eight times greater than normal birth weight (NBW) infants.[5] LBW infants are also three times more likely to have abnormal neurodevelopment and congenital anomalies.[5]

Fetal growth is largely determined by the availability of nutrients as it is last step in the supply chain. Placenta delivers the nutrients from maternal circulation to the fetal circulation.[7,8] Hence, its function is providing the fetus with nutrients, gas exchange and immunity.[10] Human placenta is a unique organ that connects the fetus and the mother via the umbilical cord.[11]

Placenta is narrated as being the diary of intrauterine life.[12] It plays a central role in maintaining the well being of the fetus and the mother, and has a lifelong impact on their future health.[13]

Placental changes like infarct, massive perivillous fibrin deposition, increase in syncytial knots and basement membrane thickening lead to impaired intervillous space circulation which are linked with retarded fetal growth.[3]

Balasubramanian et al. in their study found that macroscopic and histologic features of placenta like appearance of hard areas, increase in syncytial knots, fibromuscular sclerosis, focal avascular villi and hyaline degeneration and are present with more frequency in term LBW infants as compared to term NBW infants.[14] Hence, if the placenta is carefully examined, it can reveal many important facts, which may outline the past events, and potentially decide the final pregnancy outcome.[3]

AIMS AND OBJECTIVES

Objective

- To evaluate the placental histopathology and assess its clinical correlation in term LBW infants in comparison with term NBW infants.

REVIEW OF LITERATURE

The term "Placenta" is obtained from Latin which means flat cake.[15] Placenta is the first fetal organ to develop and is the largest.[13] Throughout gestation, it changes in shape, dimensions, weight, volume and works continuously to maintain the fetus.[8] Placental pathology entails abnormalities that affect the placenta during the gestation which can jeopardize both maternal and fetal well being.[16]

Development of Placenta (Fig.1)-

1. Pre-lacunar stage - From the day of conception to 8th day post fertilization[17]

Post fertilization, at about the 3rd day, the ovum undergoes mitotic divisions to become morula (16 celled stage). At about 4-5th day, the cleaving blastomeres divide into an inner cell mass called embryoblast and an outer cell mass called trophoblast along with a central cavity known as the blastocyst. Implantation takes place between 6 to 12th day post fertilization. The cells of trophoblast invade the uterine endometrium which begins the process of implantation. The proteolytic enzymes which are secreted by the trophoblast and uterine epithelium erode the uterine endometrium. The blastocyst completely burrows itself into uterine mucosa and lies within the thickness of endometrium.[18]

By about the 8th day, blastocyst has partially embedded in the uterine stroma. Trophoblast divides into 2 layers namely, the syncytiotrophoblast and the cytotrophoblast.[18] At site of implantation, the syncytial mass gives finger like projections that branch and invade into the uterine endometrium and is known as the trophoblastic shell.[17]

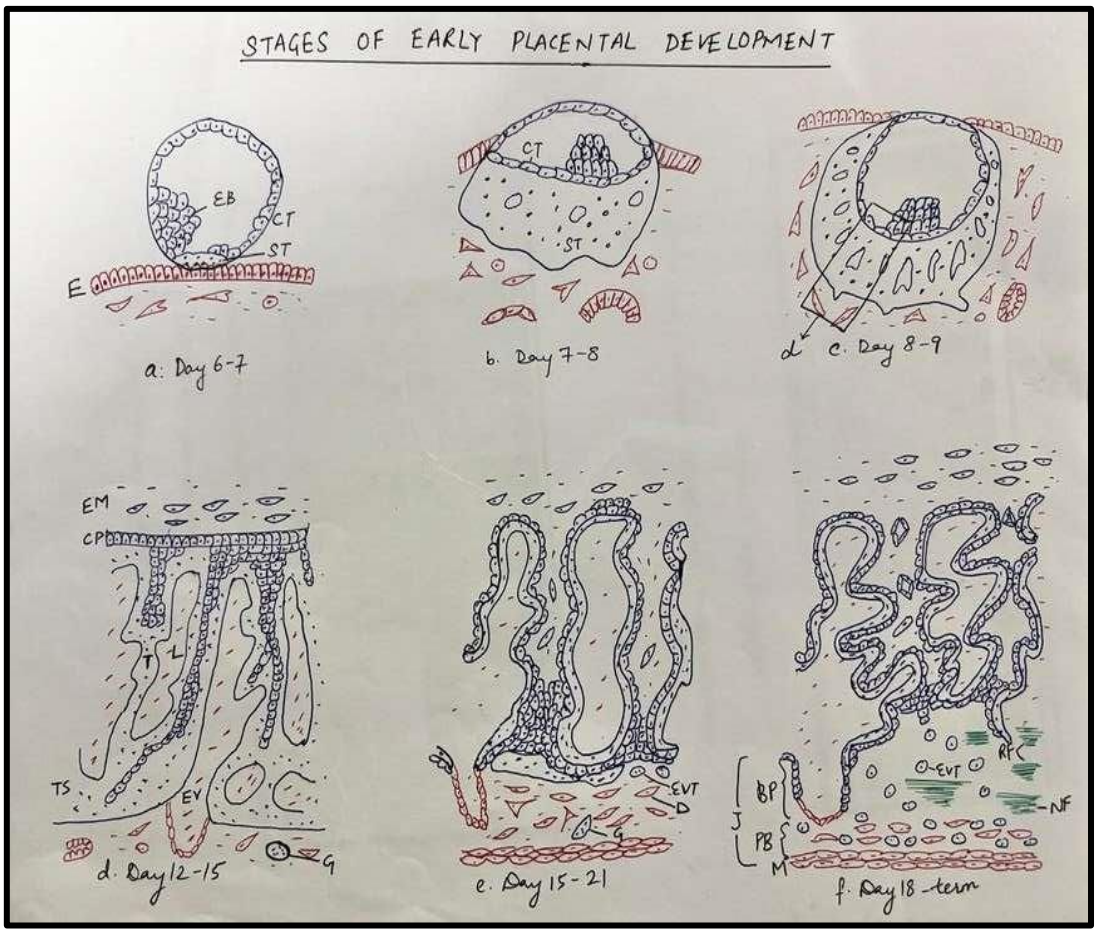


Fig 1.- Stages of placental development

(a,b) Pre-lacunar stage (c) Lacunar stage (d) Transition from lacunar to primary villous stage. (e) Secondary villous stage (f) Tertiary villous stage

The maternal tissue are colored in red and fetal tissues are colored in blue.

EB embryoblast, E endometrial epithelium, ST syncytiotrophoblast, CT cytotrophoblast, CP primary chorionic plate, EM extraembryonic mesoderm, L maternal blood lacunae, T trabeculae and primary villi, EV endometrial vessel, TS trophoblastic shell, D decidua, EVT Extravillous Trophoblast, NF Nitabuch's or uteroplacental fibrinoid, RF Rohr's fibrinoid, G trophoblastic giant cell, PB placental bed, BP basal plate, M myometrium, J junctional zone

2. Lacunar stage – Day 8 to day 13 post fertilization[17] (Fig. 2)-

On 8th day, small vacuoles crop up in the syncytiotrophoblastic mass, which grow and merge with each other and form a system of lacunae. The trabeculae, which are syncytiotrophoblastic bands separate the lacunae from one another.[17]

After the lacunar development, placenta can be differentiated into three zones-

a. Facing the embryo- the early Chorionic plate
b. The lacunar system along with trabeculae forms the intervillous space
c. The primitive basal plate in contact with maternal endometrium[19]

By 12th day, the blastocyst gets implanted into the uterine epithelium which covers the site of implantation.[17] Extraembryonic mesoderm cells which are derived from primitive streak begin to move on the upper side of the internal surface of the cytotrophoblastic cells. The cytotrophoblast and extraembryonic mesoderm are together known as chorion.[20,21] The cytotrophoblastic cells of the chorion plate extend further into the trabeculae. At about 13th day, they arrive at the trophoblastic shell and reach the uterine endometrium. The maternal capillaries are eroded by the syncytiotrophoblast cells and they become congested and dilated and form the sinusoids.[17]

3. Villous stage- 13th to 28th post fertilization[17] (Fig.3)-

By 13^{th} day, the trabeculae develop side branches which are syncytiotrophoblast protrusions and contain a core of cytotrophoblasts.[22,23] These two structures together form the primary villi and extend into the lacunae. Then, the extraembryonic mesodermal cells penetrate into the trabeculae. These cells do not get as far into the maternal surface but they end early leaving the distal trabeculae

covered only with the cytotrophoblast. The mesodermal cells penetrate the primary villi forming a mesodermal core and transforms them into secondary villi. Then, the hematopoetic stem cells differentiate within the mesoderm of the secondary villi.

By 20th day post fertilization, first placental blood vessels develop[22,23] and transforms the secondary villi into the tertiary villi.[24]

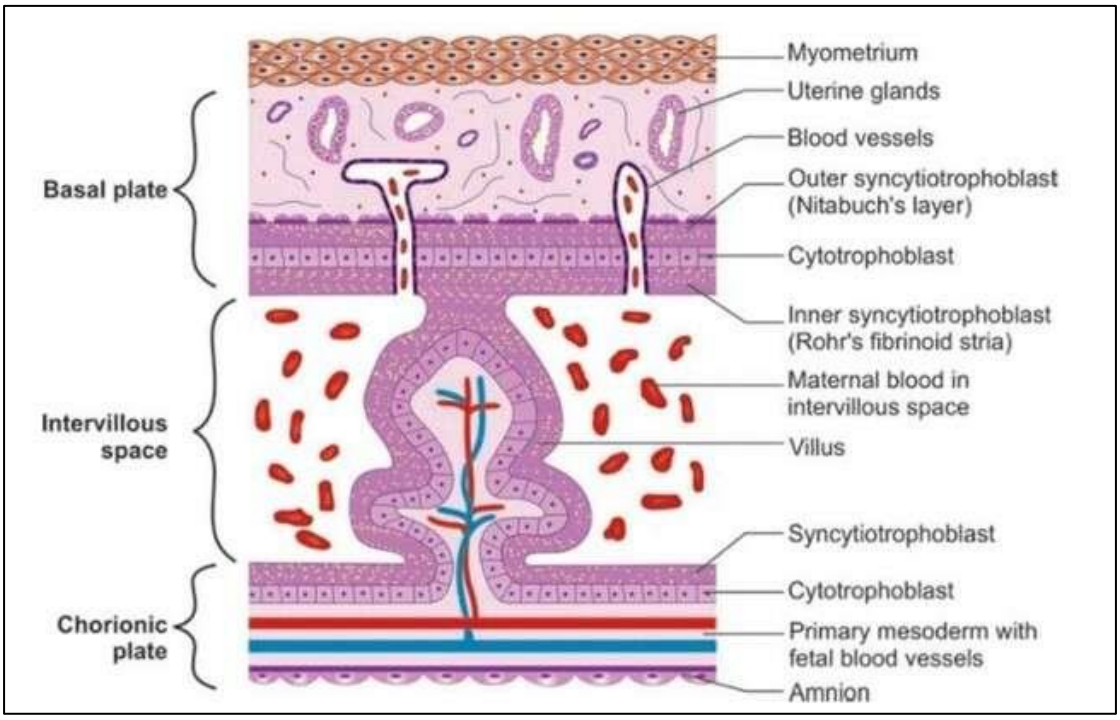


Fig.2- Structural components of placenta.[18]

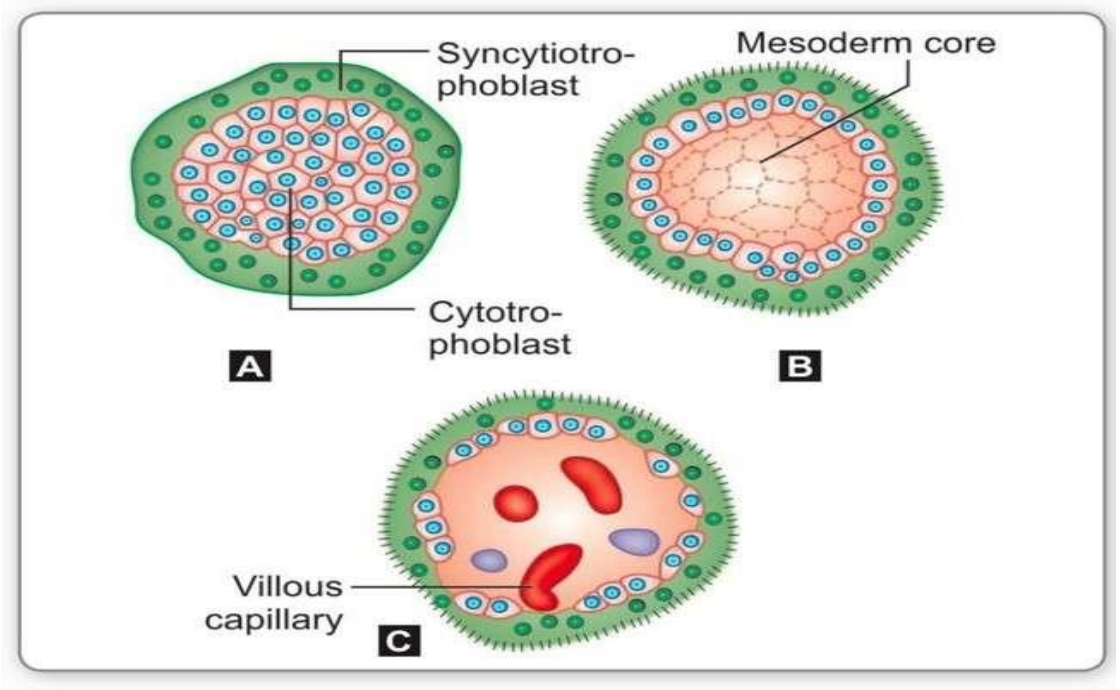


Fig.3- Structure of placental villi A. Primary villi, B. Secondary villi, C. Tertiary villi.[2]

Development of Umbilical cord and fetal membranes-

In the earliest stages of prenatal development, a unique fluid-filled space known as the extraembryonic coelom initially envelops the developing embryo. As gestation progresses, this space gradually diminishes, giving way to the expanding amniotic cavity that encompasses the growing fetus. Further the amnion's exterior mesenchymal layer fuses with the chorion's interior mesenchymal layer ultimately forming the chorioamnion or fetal membranes. At birth these two membranes are difficult to separate from each other.[25]

The umbilical cord begins to develop once the developing embryo is surrounded by extraembryonic coelom. The connecting stalk of the embryonic mesenchyme attaches the embryo to the chorion. During further embryonic development, this attachment point of the connecting stalk shifts more ventrally and comes to lie almost adjacent to the junction at which the vitello-intestinal duct joins the mid-gut and the yolk sac.[25]

The expanding amniotic environment exerts a compressive force on surrounding embryonic structures, gradually condensing the remnants of the yolk sac and its associated ductal systems up against the connecting stalk. These embryonic components progressively consolidate, ultimately forming the distinctive umbilical cord.[25]

By the fifth month of gestation, provisional elements such as the vitello-intestinal duct and yolk sac remnants gradually break down and disintegrate. What emerges is a more specialized structure: the mature umbilical cord with its two

arteries and one vein, all nestled within a protective cushion of specialized connective tissue which is the Wharton's jelly.[25]

Functions of the Placenta-

Placenta has an important role in maternal and fetal physiological functions.[26] It has various duties which are:

1. Implantation: Syncytiotrophoblast directly invades the uterine endometrium thus facilitating implantation and it later grows as a part of the placenta.[27]
2. Maintenance of pregnancy: The syncytiotrophoblast synthesizes and releases Human chorionic gonadotropin (hCG), which in turn helps in production of luteal progesterone that maintains the pregnancy.[28]
3. Exchange of nutrients: At the terminal villi, nutrient and gas exchange between the fetal and maternal circulation takes place. Maternal blood provides water, oxygen, hormones, electrolytes, vitamins, glucose and other important nutrients to the fetal circulation. The fetus throws out urea, carbon dioxide, hormones, water and waste products into its circulation which are then transported into the maternal circulation.[29,30]
4. Protective function of placenta : The placenta processes various substances and thus protects the fetus from various infections. Macrophages which are present in the villus stroma and syncytiotrophoblastic cells play an important function in protecting the fetus against various pathogens. Also, numerous leukocytes are there in the decidua to protect the pregnancy.[31,32]
5. Prevent Antigenic reaction: As placenta allows the transfer of different substances from maternal to fetal blood circulation and vice versa, it acts as a physical protective barrier, thereby preventing antigenic reactions between them.[18]

6. Endocrine function of Placenta: Various hormones are produced and liberated from the placenta to sustain pregnancy.
7. Placental growth hormone is given out by the placenta which prepares the mother for gestation in regards to cardiovascular adaption. Also, this hormone helps in fetal maturity and growth. Human chorionic somatomammotropin (HCS), which is also called human placental lactogen (HPL) promotes development of the breast and controls maternal metabolism. To make more glucose available to the fetus ,it decreases insulin sensitivity of the maternal circulation.[27,33]
8. Immunity against infections : Maternal antibodies like immunoglobulin G, Gamma globulins and Immunoglobulins reach the fetus through the placental circulation . Thus it provides the fetus with immunity against different infections.[18]

Anatomy (Fig. 4,5)-

The human placenta has a discoid shape, a diameter of about 15-25 cm, thickness of about 3 cm and weight of approximately 500-600 gms.[34] It has two surfaces: fetal surface and maternal surface.[18]

1. Fetal surface:

The placental fetal surface is represented by the chorionic plate and covered by amnion.[19] It is smooth[18] and light blue or pink in color.[35] The umbilical cord inserts near the centre into the chorionic plate.[18] Chorionic vessels are present in the chorion mesenchyme. Chorionic vessels are in continuation with the umbilical cord vessels. The chorionic arteries derive from the two umbilical arteries. They branch in a centrifugal pattern thus forming their final branches and supply the villous trees. The

veins of the villous trees form the chorionic veins which in turn gives rise to a single umbilical vein.[19]

2. Maternal surface of the Placenta-

The maternal surface of the placenta is represented by the basal plate. It is an artificial surface which emerges when the placenta separates from the uterine wall at the time of delivery. Maternal side of placenta has an uneven and rough surface. It has flat grooves that subdivide the basal plate into 10 to 40 slightly elevated regions called the lobes or maternal cotyledons. The flat grooves correspond to the placental septa inside the placenta. The lobes or cotyledons correspond to the same position from where the villous trees arose from the chorionic plate into the intervillous space.[19] There are about 60-70 villous trees (or fetal lobules) that arise from the chorionic plate in a full term placenta. Each maternal lobe comprises of one to four lobules.[36,37] At the placental margin both the basal plates and chorion merge to form the smooth chorion, the fetal membranes or the chorion laeve.[19]

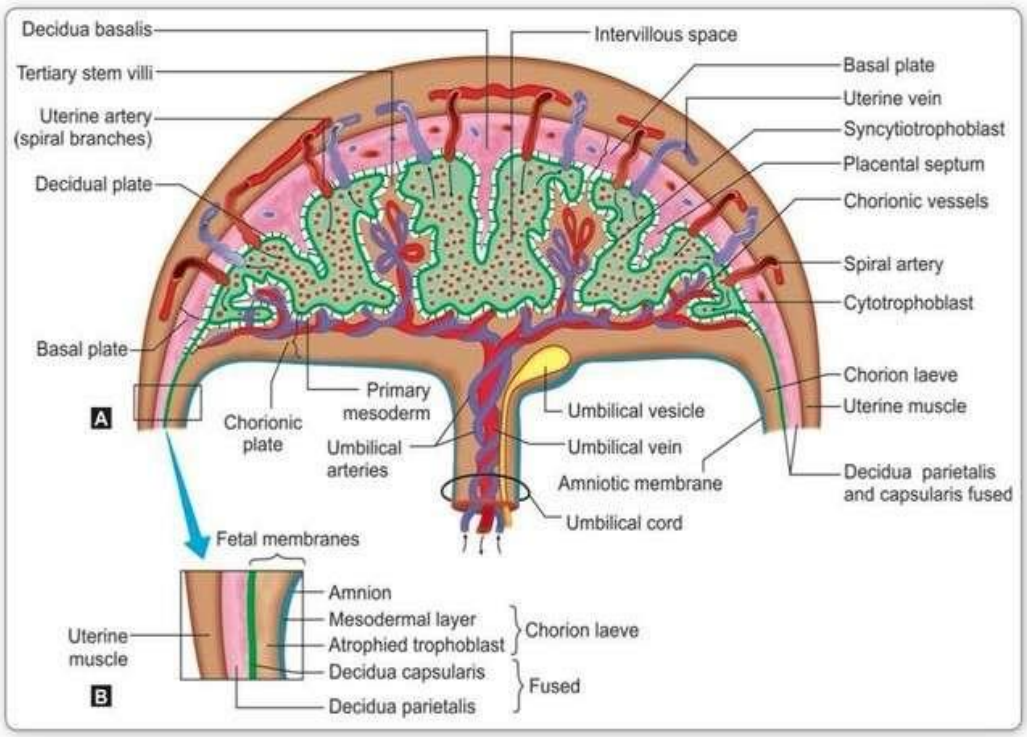


Fig 4.- A. Structure of placenta at term, B. Structure of membranes in relation to decidua.[2]

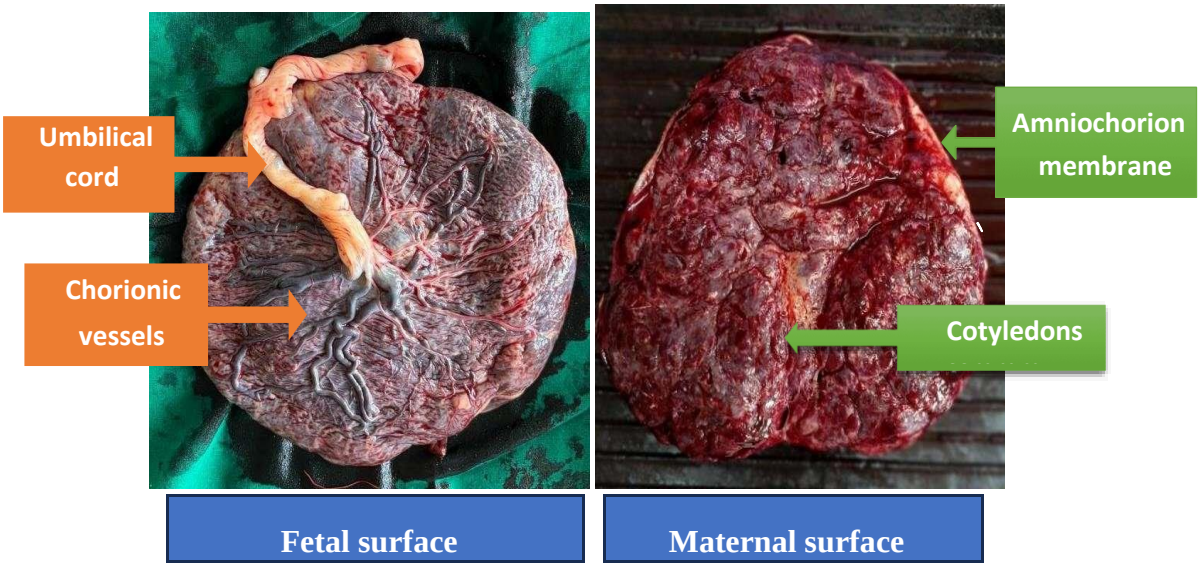


Fig. 5- Gross appearance of placenta

The chorion leave has three layers-

1. The amnion with its mesenchyme and epithelium,
2. The chorion and its layer of mesenchyme and extravillous trophoblast
3. The decidua capsularis.[19]

- Fetal membranes and umbilical cord-

Normal fetal membranes are translucent, tan with insertion at the edge of the placental disc.[35]

Normal color of umbilical cord is white tan and is about 50-70 cm in length.[35]

Histology-

1. Early Placenta (Fig. 6,7)-

Early Placenta has a large number of villi (V), protruding into the lacunar system (L). The lacunar system is likely to be filled with maternal blood seen at lower magnification.[25]

Higher magnification shows villi with a core of primitive mesenchyme (M). The villi are enclosed by two layers – an internal layer of cytotrophoblast (C) and external layer of syncytiotrophoblast (**S**).[38] Cytotrophoblast is the inner layer of cells which is cuboidal to columnar and mononucleated. Syncytiotrophoblast is the outer layer of multinucleated cells that are formed when the dividing cells of cytotrophoblast migrate to the periphery and fuse.[18]

2. Term placenta (Fig. 8,9)-

Term placenta demonstrates the branching nature of villi. Villi show marked vascularity as compared to early placenta. Syncytial knots (**K**) that are aggregates of

syncytiotrophoblast nuclei are seen, which are a feature of term placenta. Figure 9 shows a small branch villus and also highlights that fetal capillaries (C) lie close to maternal blood in surrounding lacunae (L). The trophoblast changes into a thin layer of syncytiotrophoblast only.

There are 5 layers in the diffusion barrier which is present between maternal and fetal circulation – trophoblast basement membrane, trophoblast, endothelial basement membrane, villous core supporting tissue and endothelium. Sometimes, the basement membranes of the fetal capillaries and the trophoblast fuse (F), so then the diffusion barrier consists of three layers.[25]

3. Fetal membranes (Fig.10)-

Amniotic membrane (Am) is composed of a layer of epithelial cells (E) which arises from extraembryonic ectoderm and rests on a thick basement membrane (BM). Below it lies the delicate avascular mesenchymal layer (M). This layer is a remnant of the extraembryonic mesoderm. Chorionic membrane (Ch) comprises of three layers-

a. Inner layer (I)- It is a vascular collagenous layer which arises from extraembryonic mesoderm. There is an intermediate zone (In) which divides the inner layer and the amnion and is a representative of extraembryonic coelom remnant.
b. Middle layer- It represents the trophoblast (T) of chorion laeve
c. Outermost layer- It is a vascular collagenous layer (D) which represents decidua capsularis.[25]

4. Umbilical cord (Fig.11)-

Consists of one vein (V) and two arteries (A) which are embedded in a specialized connective tissue called Wharton's jelly (**W**).[25]

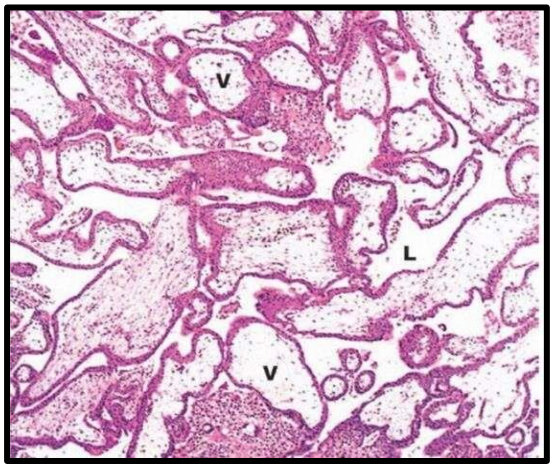


Fig. 6- Early placenta[25] (H & E, 100X)

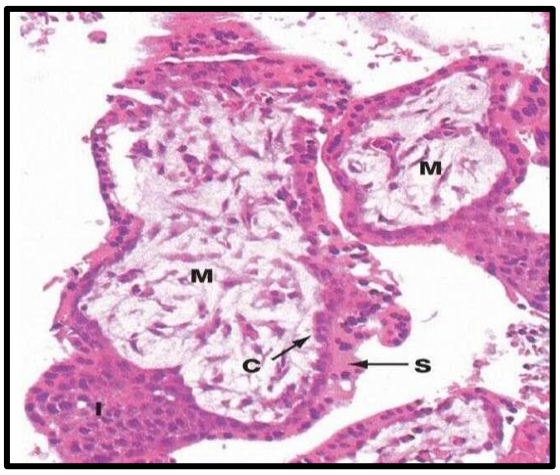


Fig. 7- Early placenta[25] (H & E, 400X)

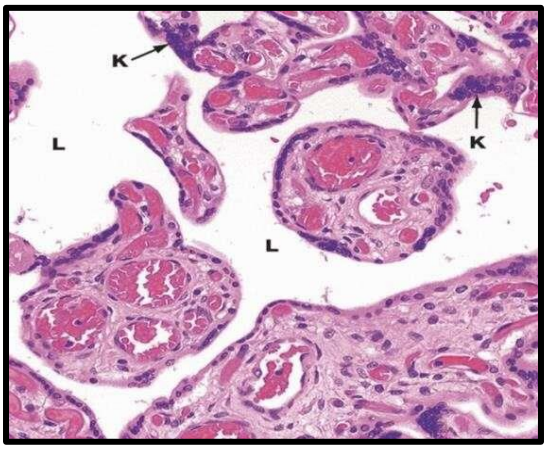


Fig. 8- Term placenta[25] (H & E, 100X)

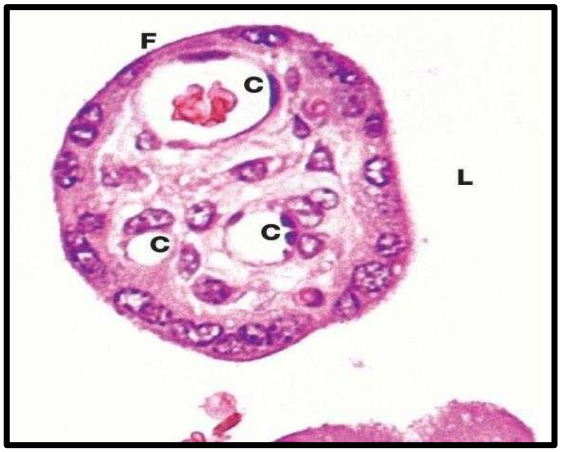


Fig. 9- Term placenta villus[25] (H & E, 400X)

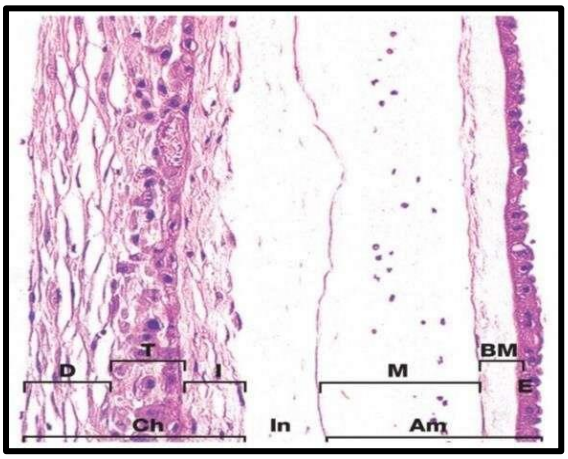


Fig. 10- Fetal membrane[25] (H & E, 100X)

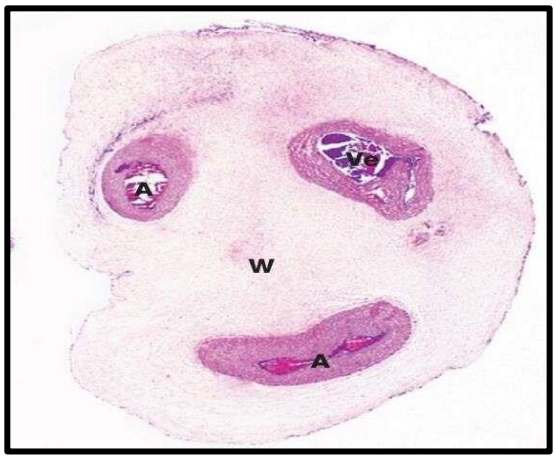


Fig. 11- Umbilical cord[25] (H & E, 100X)

Placental pathology-

Placental pathology is divided into four broad categories based on the 2016 Amsterdam classification system. These are

1. Maternal vascular malperfusion (MVM)
2. Fetal vascular malperfusion (FVM)
3. Acute chorioamnionitis (ACA)
4. Villitis of unknown etiology (VUE)[39]

MVM and FVM is a diffuse process affecting almost all the structures of placenta.

ACA and VUE form localized lesions and show focal changes, which means placenta is locally infiltrated by inflammatory infiltrate.[39]

1. Maternal vascular malperfusion (MVM)-

Maternal vascular malperfusion (MVM) is an umbrella term replacing "uteroplacental underperfusion" and has been used to refer to maternal disorders with a component of vascular disease, which result in placental pathology of ischemia.[35]

MVM signifies reduced blood flow in maternal circulation which results in alteration in the morphology of placenta and distal villi.[40] Malperfusion describes the pathophysiology of the placental ischemia and the theory that, in many cases, the placental damage includes hypertensive pressure effects (the shear force of the high-pressure maternal perfusion prevents villous growth into the flow often fragmenting the trophoblast from the villi).[41,42]

The diagnosis of MVM is made when features are present that have been associated with maternal vascular disease and/or placental ischemia.[35]

It develops when the required differentiation signals fail to reach to the extravillous fetal trophoblast for endometrial invasion and spiral artery remodelling.[43,44]

When this happens there is abnormal blood supply in the intervillous space which causes oxidative stress thus resulting in decreased growth of the villi, accelerated maturation of the villi and sometimes elevated release of antiangiogenic mediators which are soluble VEGF-1 receptor within the maternal circulation.[45-48]

Risk factors for MVM include- type 1 diabetes, preeclampsia, chronic kidney diseases, oligohydramnios, low PAPP-A (pregnancy associated plasma protein A), abnormal Doppler studies of umbilical or uterine vessels.[49-53]

Detrimental results linked to MVM are- indicated preterm birth, FGR, abruptio placenta, IUFD and elevated risk of cardiovascular ailments in the mother as well as the child.[54-58]

Macroscopic features-

- Placental hypoplasia-
    - Occurs when weight of the placenta is lower than 10th percentile for the stated gestational age[59]
- Thin umbilical cord-
    - Occurs when the diameter of the cord is lower than 10th percentile for the gestational age or is less than 8 mm at term[60]

- Placental infarct (Fig.12) -
    - In usual type or hypertensive infarcts - Firm, gritty parenchymal masses are seen
    - In villous infarcts- lesions are well circumscribed, hard, wedge shaped, are present on basal plate and have a granular surface [39]
- Infarction hematomas-
    - Multiple hemorrhagic masses are seen with peripheral firm parenchyma[35]
- Focal perivillous fibrin deposition-
    - Large regions of firm, white/tan, smooth masses of fibrin involving less than 25% of the disc[35]
- Features of acute or subacute abruption-
    - Retroplacental or marginal hemorrhage/ hematoma with parenchymal indentation and/or infarction[35]

7. Peripheral insertion of umbilical cord[39]
8. Irregular placental contour[39]

Microscopic features-

1. Placental infarcts (Fig. 13) -

- In early placental infarction, the intervillous space is obliterated, stromal nuclear basophilia of the villi are lost and there are smudgy syncytiotrophoblastic cells.
- In late placental infarction, the nuclear trophoblastic integrity is lost and it may show pyknosis, karyorrhexis or full loss of basophilia resulting in "ghost" villi.[61]

2. Accelerated villous maturation-

- AVM shows alternate pattern of villous scarcity and crowding.
- In areas of crowding, these foci are seen near to the stem villi, and are rooted in place by intervillous fibrin, dense syncytial knots and agglutination of the villi.
- In the areas of scarcity, the villi are very small and also demonstrate loss of branching[62]
- There is presence of syncytial knots in more than one third of the villi at term[63] (Fig. 14)

3. Distal villous hypoplasia (Fig.17) -

- Distal villous is characterized by scarcity of villi focally in comparison to the parenchyma surrounding it
- It is seen in basal two thirds of the placental thickness
- These villi are abnormal morphologically, show less branching, are thin and elongated rather than round.[64]

4. Decidual arteriopathy with or without acute atherosis (Fig. 16) -

- These are found in the maternal blood vessels
- The findings are: arterial fibrinoid necrosis, retention of musculoelastic structures in arterial wall, arterial thrombosis, chronic perivasculitis, and persistent intramural trophoblast.[64,65]

5. Focal perivillous fibrin deposition-

- It is defined as fibrin deposition occupying less than 25% of the placental mass[35]

6. Histologic features of acute abruption:

a. Intravillous hemorrhage (Fig. 15)

b. Adherent hematoma with dissection into the underlying parenchymal tissue[35]

The Amsterdam consensus has not given any clear instructions or criteria as to how many of these findings should be present to diagnose MVM.[61] Some authors have recommended that the diagnosis of MVM will be confirmed when there is low placental weight and at least two histological features are present.[39]

There are many other histopathologic findings that have been ascribed to MVM, including laminar necrosis of the decidua capsularis or parietalis, cystic change of the chorion laeve[66,67], immature extravillous trophoblast and increased giant cells at the placental site.[40]

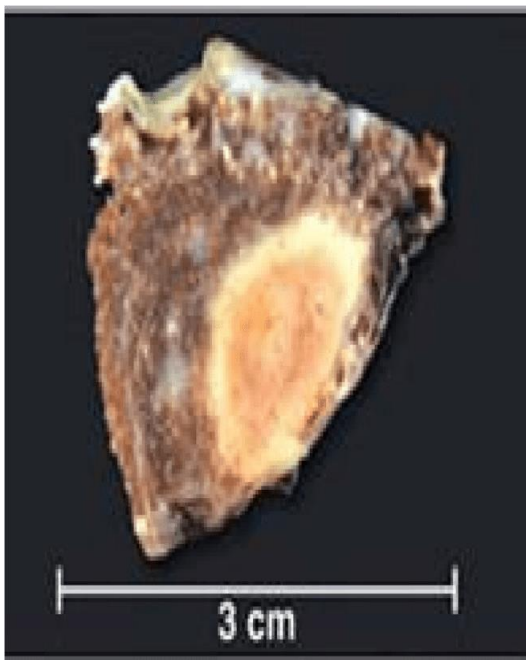


Fig. 12- Placental infarct- Firm, tan, pale in appearance on the maternal surface of placental parenchyma[35]

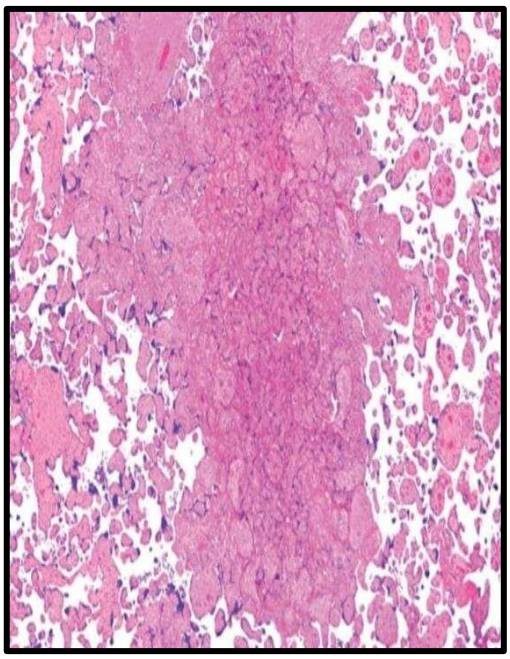


Fig.13- Placental Infarct [35] (H & E, 100X)

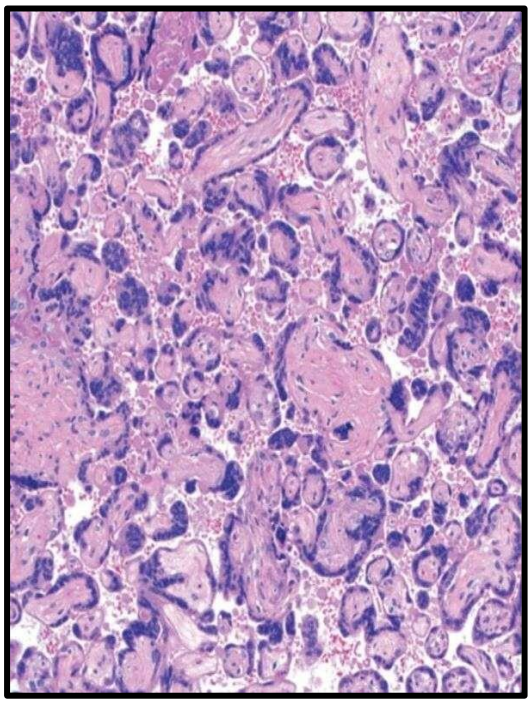


Fig.14- Increased syncytial knots[35] (H & E, 400X)

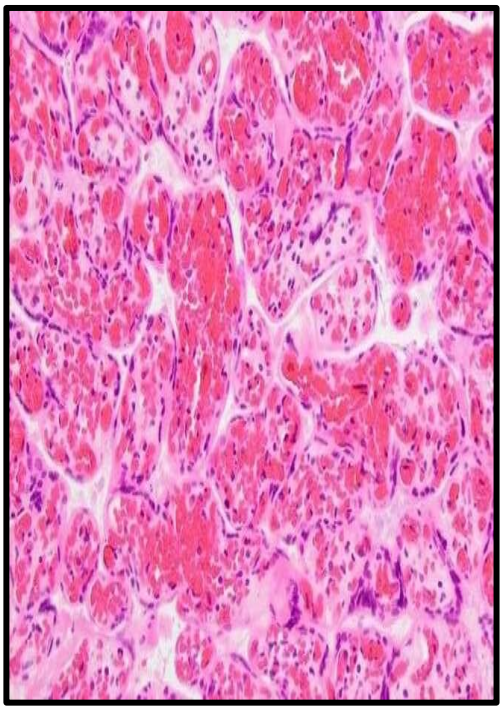


Fig.15- Intravillous hemorrhage[61] (H & E, 400X)

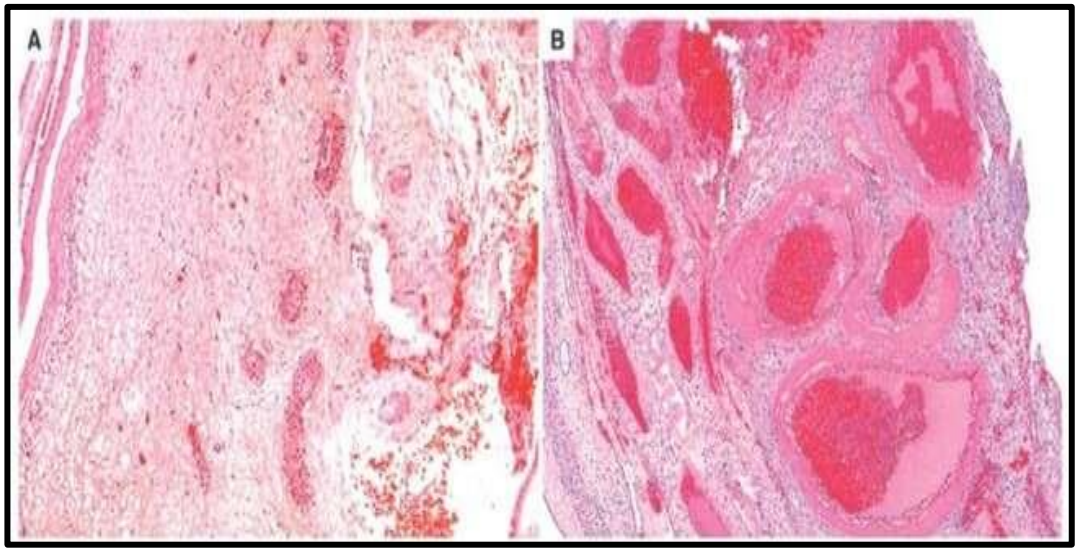


Fig.16 - Decidual Arteriopathy

A) Mild retention of smooth muscle (H & E, 100X)

B) Severe fibrinoid necrosis[35] (H & E, 400X)

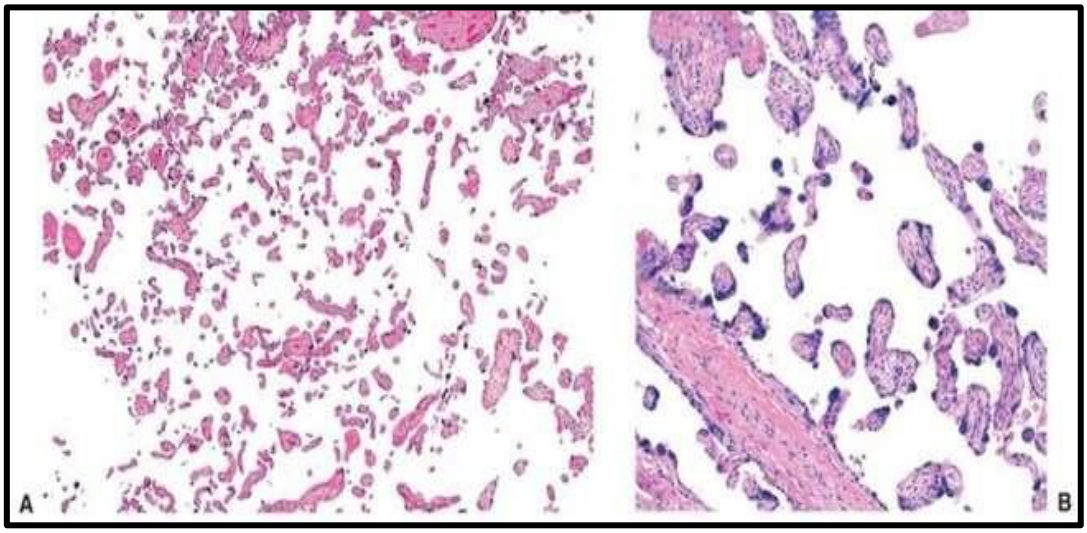


Fig.17 - Distal villous hypoplasia

A) low power view showing villous paucity, (H & E, 100X)

B) High power view showing long and slender villi with increased syncytial knots[35], (H & E, 400X)

2. Fetal Vascular Malperfusion (FVM)-

Fetal vascular malperfusion is described as a condition when there are lesions that occur as a result of impaired /obstructed fetal blood flow[61] in the umbilical cord . It is linked to changes in the vessels of chorion and villi.[68]

Causes:

- Umbilical cord obstruction
- Insufficiency of the fetal heart
- Hyperviscosity syndrome
- Maternal diabetes
- Acquired or inherited thrombophilia[69]

Pathological findings of FVM:

1. Thrombosis (Fig. 18):

- Whether fetal arterial or venous circulations are affected should be specified when possible
- Within chorionic plate, as chorionic arteries lie over chorionic veins, we can grossly differentiate thrombosed vessels from one another.
- Location of thrombosis is important to verify its clinical significance with thrombosis anywhere else in the fetal vascular tree – if umbilical level, chorionic plate level, stem vessel level or any other combination is affected.[64]

2**.** Avascular villi (Fig. 19):

- Avascular villi can be differentiated as follows-

1. Small foci : If three or more foci of two to four terminal villi are affected and there is complete loss of capillaries of villi and also stromal hyaline fibrosis
2. Intermediate foci: Five to ten villi are affected.
3. Large foci : More than ten villi are affected.[64]

3. Vascular Intramural Fibrin Deposition (Fig. 20, 21):

- It is termed as isolated when there is single lesion present per slide
- Criteria for intramural fibrin deposition is: fibrin or fibrinoid deposition when accumulated either in subendothelium or intramurally in large fetal vessels with calcification .[64]

4. Villous Stromal -Vascular Karyorrhexis (Fig.22):

- The criteria for villous stromal-vascular karyorrhexis are: three or more foci of two to two terminal villi which show karyorrhexis of fetal cells like leukocytes, nucleated erythrocytes, endothelial cells and stromal cells with surrounding trophoblastic preservation.[64]

5. Fibromuscular sclerosis (Fig. 23):

- This is synonymous with obliteration of the stem vessel
- This lesion is characterized by thickened vessel wall which causes obliteration of its lumen.[64]

6. Vascular Ectasia (Fig. 24):

- When the luminal diameter of chorionic vessel is four times more than that of the surrounding corresponding vessels, it is said to have vascular ectasia.[70]
- The cause of vascular ectasia may be nonspecific or it may be related to mbilical cord compromise in combination with FVM.[64]

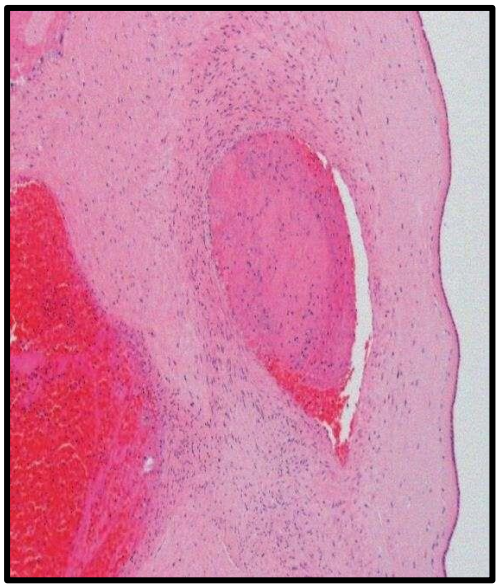


Fig. 18- Thrombosis of a fetal artery (overlying a vein) in the chorionic plate.[64] (H & E, 400X)

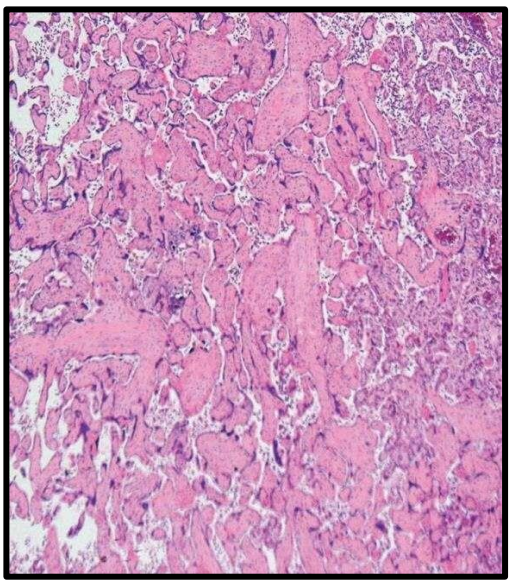


Fig. 19- A large foci of avascular villi.[64] (H & E, 100X)

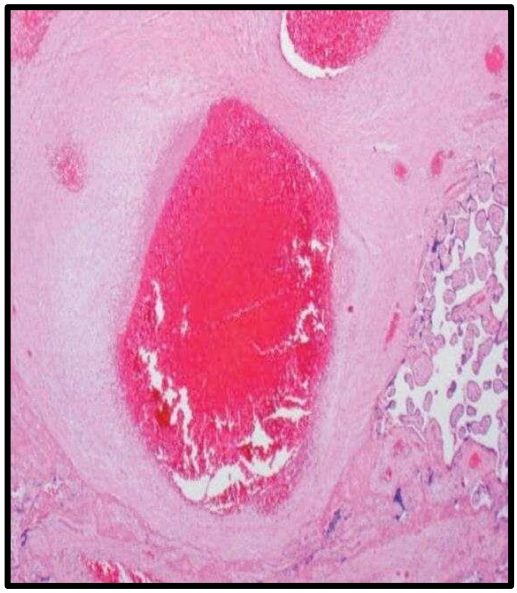


Fig. 20- Intramural Fibrin Deposition.[64] (H & E, 400X)

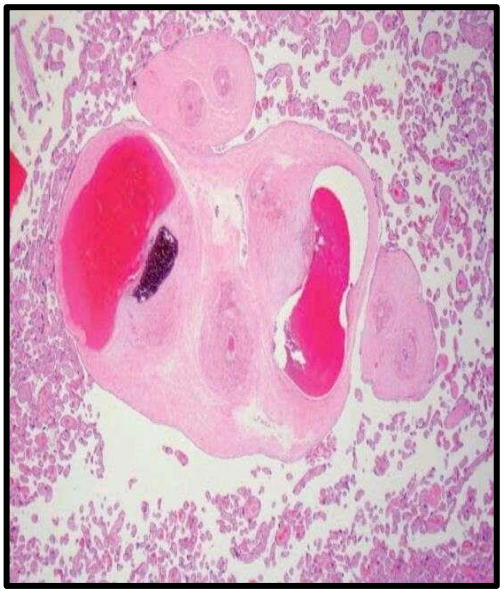


Fig. 21- Intramural Fibrin Deposition with Calcification[64] (H & E, 100X)

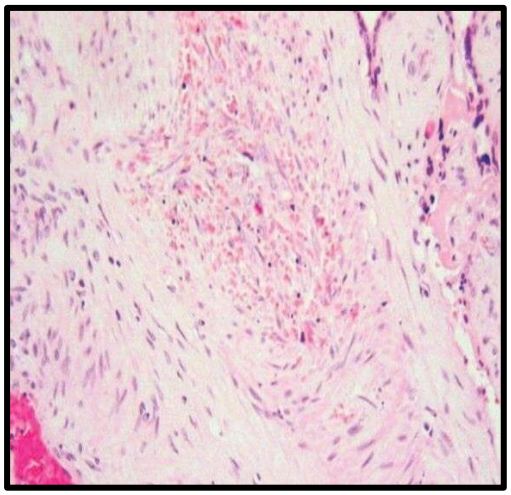


Fig. 22- Villous stromal-vascular karyorrhexis: karyorrhexis of fetal cells with preservation of surrounding trophoblast. (H & E, 100X)

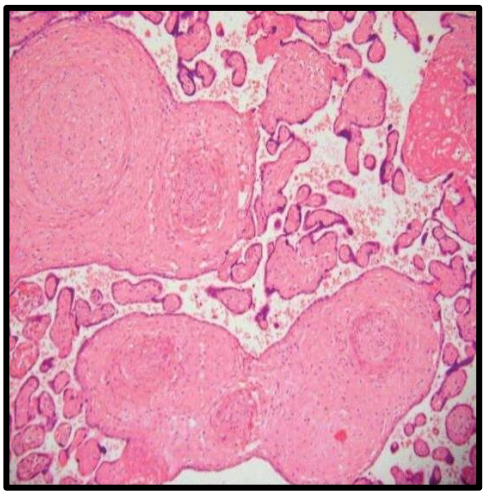


Fig. 23- Fibromuscular sclerosis: there is marked thickening of the vessel wall with consequent obliteration of the vessel lumen.[64] (H & E, 200X)

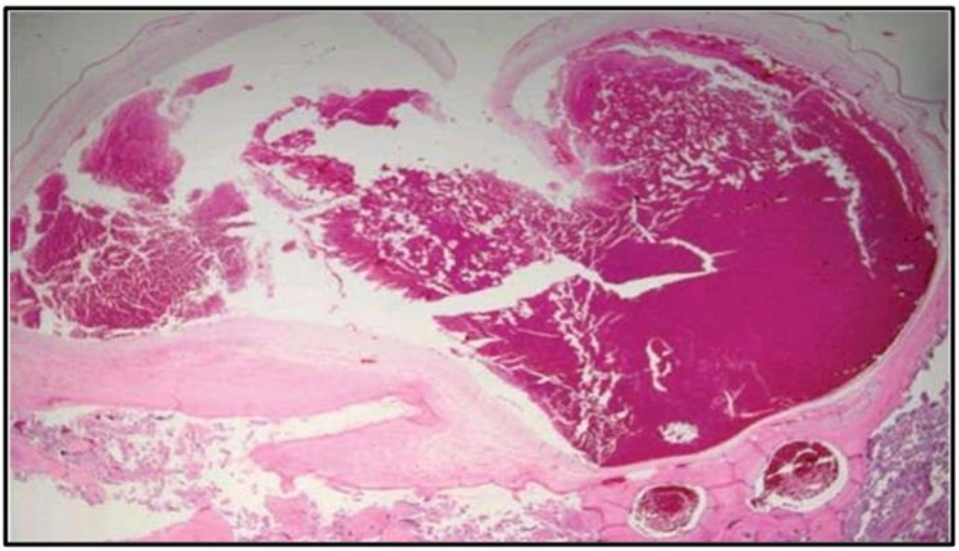


Fig. 24- Vascular ectasia: the luminal diameter of the chorionic vessel is more than four times that of the adjacent vessels[64] (H & E, 400X)

3. Acute Chorioamnionitis (ACA)-

Amniotic fluid infection is an important cause of preterm birth and neonatal morbidity and mortality. It is the histologic hallmark of ascending amniotic fluid infection and is considered the gold standard for the diagnosis.[35]

The gravid uterus has to protect the developing fetus and also halt the rejection of allogenic fetus, but it is not well equipped to prevent entry of fungal and bacterial pathogens as they cross the anatomic barriers that are formed by the cervix and fetal membranes.[39,71]

The immune system – activation of complement system and adaptive immunity are under expressed in the placenta during pregnancy, and hence there is only neutrophilic dominant innate immunity which protects the developing fetus from bacterial and fungal infections.[72] This neutrophilic response to the ascending infection describes the lesion known as Acute Chorioamnionitis (ACA).[39]

ACA is identified as amniotic fluid infection which is a consequence of an acute inflammatory response that affects fetal membranes, umbilical cord and chorionic plate.[73]

Maternal inflammatory response (MIR): In ACA, there is movement of maternal neutrophils from the veins in decidua into the fetal membranes which takes place due to chemotactic factors released in the amniotic fluid.[39] (Fig. 25)

Fetal inflammatory response (FIR): Then fetal neutrophils add to the maternal response by moving from fetal vessel into the umbilical cord and the chorionic plate.[39] (Fig. 26)

In ACA, the maternal response can result in premature labor.[39] The fetal immune system may be overactivated by the fetal response which may lead to serious effects on the organs of the fetus like the central nervous system, respiratory tract and gastrointestinal tract.[74-77]

Clinical symptoms of infection are - maternal fever greater than 37.8 degree celsius in labor, tachycardia in mother or fetus, foul odour in amniotic fluid, uterine tenderness and leukocytosis.[39,78,79]

Clinical factors that cause ACA are :

Preterm rupture of membranes, prolonged labour , cervical insufficiency, marginal abruption of placenta, history of miscarriage or prior history of delivery before term or lower APGAR score.[80]

Macroscopy-

Gross examination: Amnion may appear dull gray, cloudy or sometimes green (purulent)[39]

Umbilical cord may shows gray-white areas surrounding the vessels and yellow plaques may be seen on the cord which may suggest candidial infection. [81,82] Sometimes, the parenchyma may show formation of abscess suggesting infection by listeria.[39]

Microscopy-

The subchorionic fibrin may be diffusely infiltrated by the neutrophils which is also known as acute subchorionitis.

Low power findings are: umbilical cord may show abscesses in the peripheral areas in case of infection by candida (Fig. 27), acute inflammation of intervillous space along with abscess in case of infection by listeria, a mixture of neutrophilic and histiocytic infiltrate in case of chronic infection by mycoplasma, and foci of acute inflammation of villus and intervillous space in cases of sepsis in the mother and fetus.[71,83]

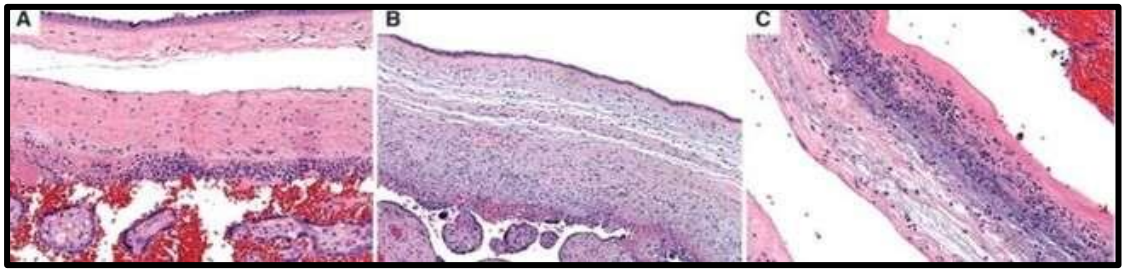


Fig. 25- Maternal inflammatory response in amniotic fluid infection Subchorionitis in the chorionic plate (H & E, 100X) (A); chorioamnionitis with neutrophils in fibrous chorion and amnion (H & E, 100X) (B); necrotizing chorioamnionitis (H & E, 100X) (C)[35]

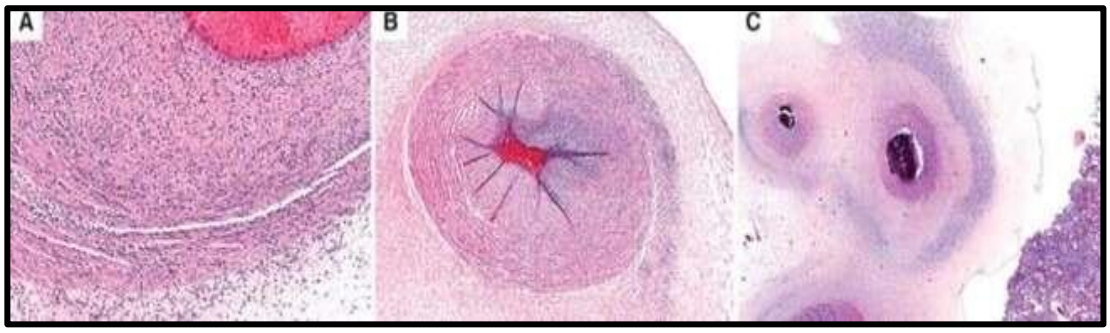


Fig. 26- Fetal inflammatory response in amniotic fluid infection. Umbilical phlebitis (H & E, 400X) (A); umbilical arteritis (H & E, 200X) (B); concentric umbilical vessel inflammation (H & E, 100X) (C)[35]

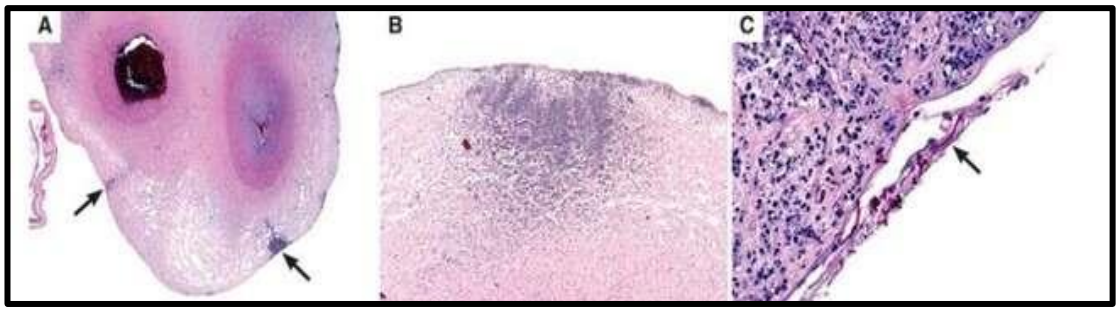


Fig. 27- Candida umbilical cord microabscesses. Microabscess at peripheral aspect of cord [arrows A (H & E, 100X), B (H & E, 400X)]; Candida organisms on PAS with diastase stain (H & E, 400X) (C)[35]

4. Villitis of unknown etiology (VUE)-

Chronic villitis is currently classified as villitis of unknown etiology (VUE).[35]

It is characterized by lymphohistiocytic or sometimes giant cells or lymphoplasmacytic infiltrate within the terminal and /or stem villi.[35] VUE is due to a maternal T cell mediated immune response to antigens in the fetal villous stroma which leads to inflammation centered on the distal villi.[84-86]

Although a specific infectious etiology that occurs via hematogenous spread can be demonstrated in a small proportion of cases, most VUE is relatively common and is seen in 5 % to 15 % of placentas.[35]

It is due to maternal T lymphocytes that cross over into the stroma of villi. Later, the transplantation antigens which are seen on the surface of fetal Hofbauer cells activate them.[39]

There are two theories known to be causing VUE:

1 The first theory is that VUE is represented by an inflammatory response in the mother against the alloantigens of fetus[84,85] Evidence to support this hypothesis are the increased frequency of VUE cases in pregnancies through donation of egg in multipara women because of risk of recurrence in subsequent pregnancies[84,87-89]

2 In the second theory fetal or maternal response to the infection is seen by the presence of chronic inflammatory infiltrate[90,91] Evidence to support this mechanism are occurrence of the infection seasonally and linkage between chronic villitis and various pathogens (Rubella, Toxoplasma, Cytomegalovirus

and Herpes (TORCH) pathogens and others like syphilis, varicella-zoster, parvovirus B19.)[84,92-94]

Macroscopy-

- Placenta can be small in size with a normal ratio of fetoplacental weight
- In severe cases, cut section may show areas of pale, ill defined and firm parenchyma
- Sometimes, a necrotic or infarct like mass can be seen.[39]

Microscopy (Fig.28)-

- The characteristic feature of VUE is the villous stroma shows small lymphocytes which are haphazardly and asymmetrically arranged along with features which show secondary damage to the tissue damage like edema, obliteration of the vessels and fibrosis.[39]

It can be differentiated into three groups:

a. Primary changes are increased basophilia in the villi which are more adherent as compared to the surrounding parenchyma. They are usually well circumscribed, being surrounded by normal villi and affect less than fifty percent of villi even in severe cases. Secondary changes which are seen include large amounts of perivillous fibrin deposition and areas of avascular villi.

b. Associated lesions in other areas include chronic deciduitis which shows the presence of plasma cells. Other lesions are chorionic histiocytic hyperplasia, lymphocytic chorioamnionitis and eosinophilic fetal vasculitis.[39]

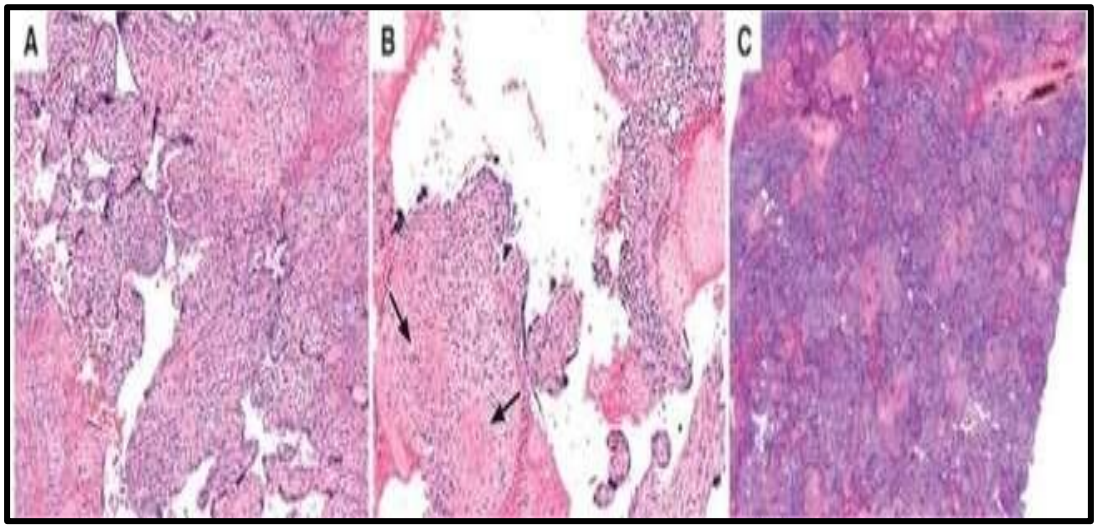


Fig. 28- Villitis of unknown etiology (VUE), lymphohistiocytic (H & E, 400X) (A); VUE with obliterative vasculitis (arrows indicate obliterated stem villous vessels) (H & E, 400X) (B); diffuse pattern of VUE (H & E, 100X) (C)[35]

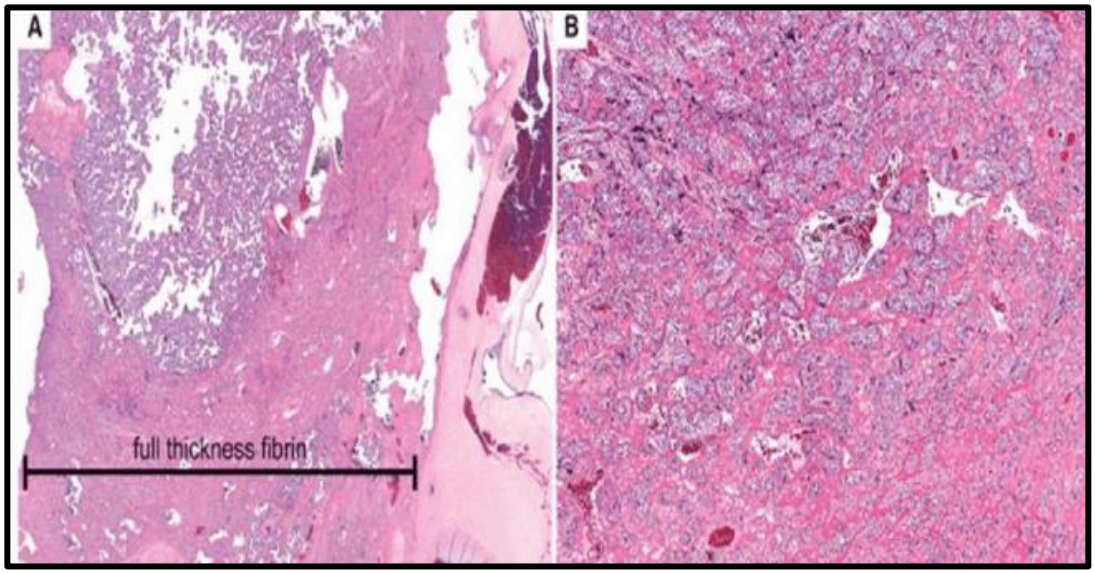


Fig. 29- Full thickness involvement (H & E, 100X) (A) in massive perivillous fibrin deposition (H & E, 200X) (B)[35]

Other placental pathologies are-

- Lesions which have an increased risk of recurrence:
  - ○ Chronic histiocytic intervillositis
  - ○ Massive Perivillous Fibrin Deposition
- Villous capillary lesions:
  - ○ Chorangiomatosis
  - ○ Chorangiosis
  - ○ Chorangioma
- Miscellaneous:
  - ○ Amnion nodosum
  - ○ Delayed villous maturation
  - ○ Erythroblastosis
  - ○ Meconium staining
  - ○ Squamous metaplasia[95]

5. Chronic histiocytic intervillositis (CHI)-

   - Chronic histiocytic intervillositis (CHI) is a disorder which is linked to recurrent miscarriages , FGR, neonatal alloimmune thrombocytopenia, preterm delivery skeletal anomalies resembling osteogenesis imperfecta, and intrauterine fetal death (IUFD)[35,96-98.]

   - CHI is associated with maternal hypertension, autoimmune disease, and elevated maternal serum alkaline phosphate levels.[31,98-100]

   - Microscopically, the intervillous space is diffusely infiltrated by a population of mononuclear inflammatory cells, mostly macrophages with scattered lymphocytes occasionally with a lesser associated VUE.[35]

6. Maternal Floor Infarction/ Massive Perivillous Fibrin Deposition (Fig.29)-
   - Maternal floor infarction and massive perivillous fibrin deposition probably describe the spectrum of the same disorder. In both conditions, there is a very significant increase in perivillous fibrin deposition such that uteroplacental blood flow is presumably compromised and leads to increased risk of FGR and intrauterine death.
   - Studies have demonstrated that placentas with maternal floor infarction have a high rate of prior miscarriages and stillbirth.[101,102]
   - Risk factors include maternal thrombophilia and autoimmune diseases. Some cases have been associated with coxsackie virus infection.[103,104] Both disorders tend to recur in subsequent pregnancies.[35,101]
   - Maternal floor infarction is grossly apparent as a thick orange-rind–like layer of fibrin along the maternal surface.
   - Katzman and Genest define the disorder as placentas in which the villi of the whole of maternal floor are encased in at least 3 mm of fibrin on at least one slide.[105]
7. <u>Chorangiosis, Chorangioma, Chorangiomatosis-</u>
   - Chorangiosis is described when capillaries increase in number in the terminal villi and is noted in conditions arising due to chronic hypoxia. As per Altshuler , chorangiosis consists of at least 10 fields with 10 or more villi with 10 or more capillaries per villus.[35]
   - Chorangiomas are mass lesions of vascular proliferation within one or more stem villi. Grossly, they often appear as glassy, myxoid red brown oval masses in the placenta.[35] Microscopically, it is a well defined mass comprising of fetal

capillaries with surrounding stroma and trophoblast. Trophoblast proliferation may be present.[106]

- Chorangiomatosis can be seen microscopically similar to a chorangioma, as both show a proliferation of capillaries within a stem villus. However, in chorangiomatosis , there is stromal proliferation in between the capillaries and may be seen in intermediate and terminal villi.[35]

As per The College of American Pathologists, IUGR forms specific antepartum indication for pathological evaluation of the placenta. Placental findings associated with IUGR include features of maternal vascular malperfusion (MVM), fetal vascular malperfusion (FVM), chronic villitis (infective or villitis of unknown etiology [VUE]), maternal floor infarction/massive perivillous fibrin deposition, thin umbilical cords, single umbilical artery, mesenchymal dysplasia, chronic placental abruption, chronic histiocytic intervillositis (CHI), and chorangiomas/ chorangiomatosis.[35]

MATERIALS AND METHODS

1) **Study Design:** A Case Control Study

2) **Study Period:** One year from 1st June 2023 to 31st May 2024

3) **Source of Data:** Placenta of term low birth infants and term normal birth weight infants which were received for histopathological examination at Department of Pathology, KAHER's J.N. Medical College, Belagavi from KLE'S Dr. Prabhakar Kore Hospital and MRC, the attached teaching hospital.

4) **Sample Size:** 90 samples,

   30 - cases (Placenta of term LBW infants)

   60 - controls (Placenta of term NBW infants)

5) **Sampling technique:** Consecutive sampling

   One case followed by two consecutive controls were taken and this was continued for the rest of the sample collection.

6) **Inclusion Criteria:**

   Women more than 18 years of age, giving birth to live infant of birth weight less than 4000 g and gestational age from 37 weeks to 41 weeks 6 days [term gestation].

7) **Exclusion Criteria:**

1. Women giving birth to infant of birth weight more than 4000 g (macrosomia)
2. Women giving birth to stillborn fetus or having intrauterine fetal demise (IUFD)
3. Women having multifetal gestation

4. Participants not consenting for the study

8) Ethical Clearance:

The ethical clearance was acquired from Institutional Ethics Committee, JNMC, Belagavi prior to the commencement of study.

9) Methodology:

The present study was conducted on women giving birth to term babies with low birth weight (cases) and term babies with normal birth weight (controls) at tertiary care hospital, Belagavi. [LBW infants - weight less than 2500 g, NBW infants - weight between 2500 and 4000 g] Matching between cases and controls was done for gestational age and sex of the infant.

The participants were briefed in detail regarding the study. Also informed consent was taken from the ones who were willing to participate in the study.

Clinical case details of each case was taken like birth weight of the infant, gestational age, sex of the infant, maternal age, method of delivery [Full term vaginal delivery (FTVD)/ Lower segment cesarean section (LSCS)/ Forceps or Vacuum assisted delivery], gravida, parity, number of live births, any previous abortion/ IUFD/ stillbirth, maternal anemia, pregnancy induced hypertension and/or its complications like preeclampsia, eclampsia, gestational diabetes, maternal infection during present gestation, oligo/polyhydramnios, placenta previa, placental abruption, maternal chronic health conditions like diabetes, heart disease, kidney disease, hypertension, history of any toxin intake (alcohol, smoking, drugs) and USG findings.

Placentas received for histopathological examination were assessed macroscopically and microscopically. Macroscopic examination will include evaluation of umbilical cord, membranes and placental disc. Umbilical cord length, diameter, attachment to placental disc, color, site of insertion, coils, number of vessels, appearance and consistency of sectioned surface and any other lesions were seen. Membranes were assessed for presence, complete or incomplete, insertion, color, opacity and any other significant findings. For the placental disc, the weight, dimensions, shape, presence or absence of accessory lobe, appearance of fetal and maternal surface, any missing cotyledons and appearance and consistency of sectioned surface were seen.

The specimens were taken and immediately fixed in a 10% formaldehyde solution for 48 hours. After that, serial sections of 0.3 to 0.5 mm were done and then fixed for 24 hours.

Following bits were given:

- Umbilical cord section
- Cross section was taken from membranes after rolling them into a swiss roll model.
- Fetal and maternal surface of the placenta.
- Abnormal areas, if any.

All the bits were processed and slides of 4 micron thickness were made.

Then staining with Hematoxylin and Eosin was done for the sections.

Microscopically, placental pathologies were grouped according to -The 2016 Amsterdam placental workshop statement on sampling and definition of placental lesions.

10) Statistical analysis:

Data obtained was entered in Microsoft Excel sheet, analysis was done using IBM SPSS software and expressed in percentages and proportions

Continuous variables were represented by Mean ± Standard deviation (SD) or median (range) and categorical variables were expressed in frequency and percentage. Two-sample t-test, one-proportion z-test and Chi-square test were conducted for the analysis of clinical and gross parameters. Chi-square test was done for the analysis of microscopic parameters. Multiple logistic regression and correlation was carried out. A p-value of less than 0.05 was considered statistically significant.

RESULTS

This study was conducted among 30 cases and 60 controls and compared various clinical, gross and microscopic parameters among them.

A. COMPARISON OF CLINICAL PARAMETERS

TABLE 1. Maternal Age Group Distribution-

Age Category	Case (Count & %)	Control (Count & %)
18-25	15 (50%)	26 (43.33%)
26-30	10 (33.33%)	22 (36.67%)
30-35	1 (3.33%)	12 (20%)
>35	4 (13.34%)	0 (0.0%)

The 18-25 age group represents highest proportion of both cases and controls among all age groups.

The 26-30 age group represents the second-largest proportion of both cases and controls.

The 30-35 age range represents a relatively small proportion of cases as compared to controls.

The more than 35 age category represents third highest proportion of cases. However, no controls were present in this group.

The p-value of **0.007** is less as compared to commonly used p-value of 0.05 which is considered significant. This shows that there is a statistically significant association between the age categories and the groups.

TABLE 2. Parity-

Parity	Case (Count & %)	Control (Count & %)
Primipara	14 (46.67%)	24 (40.00%)
Multipara	16 (53.33%)	36 (60.00%)

Both cases and controls were more in multipara women in comparison to primipara. However, it did not show any statistically significant difference between the two groups with a p value of 0.55.

TABLE 3. Gestational Age-

Group	Count	Mean (Weeks)	Standard Deviation (SD)	Min (Weeks)	25th Percentile (Q1)	Median (50th Percentile)	75th Percentile (Q3)	Max (Weeks)
Case	30	38.16	0.59	37.29	38.0	38.0	38.86	39.0
Control	60	38.76	0.99	37.0	37.86	38.86	39.57	40.57

The Case group show a lower gestational age as compared to the Control groups with a p value of **0.001**, making it statistically significant.

TABLE 4. Weight gain during gestation-

Group	Mean weight gain (in kg)	S.D. (in kg)	Minimum weight gain (in kg)	Q1 (25th Percentile) (in kg)	Median (in kg)	Q3 (75th Percentile) (in kg)	Maximum weight gain (in kg)
Case	8.88	0.76	7.5	8.43	9.0	9.2	11.0
Control	10.54	0.7	9.0	10.0	10.8	11.0	11.5

The study compares the mean weight gain during gestation between the LBW and NBW groups. The t-test performed to compare the two groups showed a statistically significant difference with p value less than **0.0001**. This suggests that maternal weight gain during pregnancy has a strong influence on the occurrence of LBW in infants.

TABLE 5. Maternal diseases in present pregnancy-

	PIH	GD	Anemia	OH	Hypothyroidism	No diseases
Case	6 (20.00%)	3 (10.00%)	21 (70.00%)	6 (20.00%)	4 (13.33%)	1 (3.33%)
Control	3 (5.00%)	0 (0.00%)	19 (31.67%)	3 (5.00%)	3 (5.00%)	34 (56.67%)
p-value	**0.025**	**0.013**	**0.0006**	**0.025**	0.16	-

Our study found that maternal diseases were present in 29 (96.67 %) of the cases and 26 (43.33%) of the controls. The findings which showed statistically significant occurrence in cases were Pregnancy induced hypertension (PIH), Gestational Diabetes (GD), maternal anemia and Oligohydramnios (OH). Maternal anemia showed overlap with 3 cases of PIH, one case of GD, 2 cases of OH and one case of hypothyroidism. However, presence of hypothyroidism did not show significant difference between the two groups.

Maternal infection in present pregnancy, maternal chronic diseases like hypertension, diabetes mellitus, heart diseases, kidney diseases and cerebrovascular diseases were not found in both cases and controls. Maternal placental diseases like placenta previa and placental abruption also were not found in both cases and controls.

The mode of delivery was also explored in the study; however, no direct statistical analysis was provided to assess its relationship with low birth weight (LBW). Standard delivery modes, such as Full Term Normal Delivery (FTND) and Lower Segment Cesarean Section (LSCS), were observed in both LBW and NBW groups.

TABLE 6. Infant Gender-

Group	Female (F) (Count & %)	Male (M) (Count & %)
Case	9 (30%)	21 (70%)
Control	24 (40%)	36 (60%)

Both the case and control groups showed a higher proportion of male gender in infants.

Since the p-value is 0.486, which is greater than 0.05, there is no statistically significant difference in the gender distribution between the Case and Control groups.

TABLE 7. Birth weight of Infant-

Group	Count	Mean BWI (in grams)	Most Frequent BWI (in grams)	Frequency of Most Frequent BWI
Case	30	2310	2300	15
Control	60	2920	2900	10

The Case group has a lower mean weight (2310 grams) compared to the Control group (2920 grams) with a p-value of **0.00000576**.

– Fetal distress (FD)–

Fetal distress was present in 8 (26.66%) of the cases and 4 (6.66%) of controls with p value of **0.0085**, showing statistically significant correlation between fetal distress and LBW.

– Other findings-

Fetal growth restriction (FGR) was present in 6 (20%) of cases and 2 (3.33%) of controls with p value of **0.009**, showing statistically significant correlation between FGR and occurrence of LBW.

B. COMPARISON OF GROSS PARAMETERS (Fig. 30 to 33)

TABLE 8. Insertion of umbilical cord

Parameter	Case (Count, %)	Control (Count, %)	p-value
Eccentric insertion	24 (80.00%)	47 (78.33%)	0.857
Marginal insertion	6 (20.00%)	1(1.67%)	**0.0042**
Central insertion	0 (0.00%)	12 (20.00%)	**0.0062**

Umbilical Cord Insertion was Eccentric in 80% cases, 78.33% controls, Marginal in 20% cases, 1.67% controls and Central in 20% controls. The p value for marginal cord insertion is 0.0042, showing statistically significant difference whereas eccentric insertion of umbilical cord showed no significant difference. Central umbilical cord insertion in controls is the normal finding and its absence in cases with a p value of 0.0062 suggests a statistically significant deviation in cases from what is considered normal.

TABLE 9. Color of fetal membrane

Parameter	Case (Count, %)	Control (Count, %)	p-value
Tan Color	28 (93.33%)	60 (100%)	0.143
Green Color	2 (6.67%)	0 (0.00%)	**0.044**

Color of fetal membranes was tan for 93.33% cases, 100% controls and green for 6.67% cases. The p value for green color of fetal membranes is 0.044 showing statistical significance whereas tan color showed no significant difference.

TABLE 10. Attachment of fetal membrane

Parameter	Case (Count, %)	Control (Count, %)	p-value
To the disc margin	28 (93.33%)	60 (100%)	0.143
Circumvallate	2 (6.67%)	0 (0.00%)	**0.044**

Attachment of the fetal membrane to the disc margin was found in 93.33% cases,100% controls and circumvallate attachment was found in 6.67% cases. The p value for circumvallate attachment is 0.044 showing statistical significance whereas attachment to disc margin showed no significant difference.

TABLE 11. Presence of cotyledons on maternal surface

Parameter	Case (Count, %)	Control (Count, %)	p-value
Intact cotyledons	28 (93.33%)	60 (100%)	0.143
Missing cotyledons	2 (6.67%)	0 (0.00%)	**0.044**

Maternal surface with presence of intact cotyledons were found in 93.33% cases,100% controls and with missing cotyledons were found in 6.67% cases. The p value for missing cotyledons is 0.044 showing statistical significance whereas presence of intact cotyledons showed no significant difference.

TABLE 12. Placental weight and dimensions

Parameter	Case (Mean ± SD) or	Control (Mean ± SD)	p-value
Trimmed placental Weight (TW) (gm)	370.00 ± 55.48	447.33 ± 91.58	**0.000179**
Placental Length (L) (cm)	14.55 ± 1.12	15.80 ± 1.86	**0.002837**
Placental Breadth (B) (cm)	13.00 ± 1.25	14.03 ± 1.64	**0.003236**
Placental Thickness (Th) (cm)	2.12 ± 0.30	2.48 ± 0.42 cm	**0.000005**

Trimmed placental Weight (TW), Placenta Length (L), Breadth (B) and Thickness (Th) showed significant differences between cases and controls with p value less than 0.05.

The presence of areas of infarction in the placental parenchyma were seen in 6 (20.00%) of cases and 2 (3.33%) of controls with a significant p value of **0.0152.**

Umbilical Cord Color and sectioned surface was white tan for both cases and controls, with no significant differences observed.

Umbilical Cord Attachment was to the Placental disc for both the groups, showing no significant difference.

Umbilical cord dimensions and Cord Coil Index (CCI) showed no significant differences between cases and controls.

Number of vessels in the umbilical cord were 3 for both cases and controls, showing no significant difference.

Fetal membranes were complete and translucent in appearance for both the groups and showed no significant difference.

Placental disc was discoid in shape for 80% cases, 86.67% controls and oval in shape for 20% cases, 13.33% controls, with p value of 0.436 showing no significant difference.

Fetal surface was smooth, glistening and pale blue in color for both the groups and showed no significant difference.

Maternal surface was grey brown in both the groups, showing no significant difference.

Sectioned surface of placental disc was spongy and dark red for both the groups, showing no significant difference.

C. COMPARISON OF MICROSCOPIC PARAMETERS (Fig. 34 to 45)

GRAPH 1. Comparison of microscopic findings in cases and controls

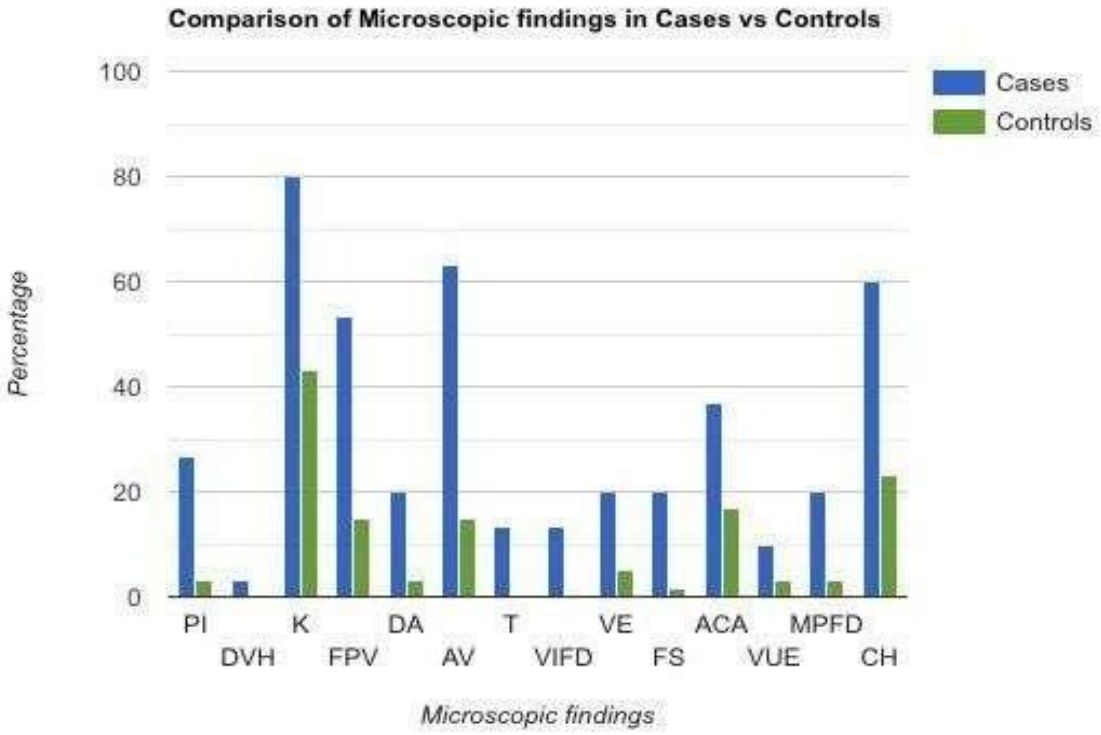


TABLE 13. Comparison of Maternal Vascular Malperfusion (MVM) findings between Cases and Controls

Microscopic Findings	Case (Count, %)	Control (Count, %)	p-value
PI	8 (26.66%)	2 (3.33%)	**0.0019**
AVM	0 (0.00%)	0 (0.00%)	0.62
DVH	1 (3.33%)	0 (0.00%)	0.333
K	24 (80.00%)	13 (43.33%)	**0.00083**
FPF	16 (53.33%)	9 (15.00%)	**0.00021**
IH	0 (0.00%)	0 (0.00%)	0.62
DA	6 (20.00%)	2 (3.33%)	**0.0152**

Among the parameters in the MVM (Maternal Vascular Malperfusion) category, Placental Infarction (PI), presence of Syncytial Knots (K), Focal Perivillous Fibrin (FPV) and Decidual Arteriopathy (DA) all yield statistically significant results, with p-values less than 0.05. These findings were overlapping for most of the cases. Distal Villous Hypoplasia (DVH), however, did not show a significant result. The findings of Accelerated villous maturation (AVM) and Intravillous Hemorrhage (IH) were not found in both cases and controls. This indicates a strong association between MVM and LBW.

TABLE 14. Comparison of Fetal Vascular Malperfusion (FVM) findings between Cases and Controls

Microscopic Findings	Case (Count, %)	Control (Count, %)	p-value
AV	19 (63.33%)	9 (15.00%)	**0.0000057**
T	4 (13.33%)	0 (0.00%)	**0.011**
VIFD	4 (13.33%)	0 (0.00%)	**0.011**
VE	6 (20.00%)	3 (5.00%)	**0.025**
VSVK	0 (0.00%)	0 (0.00%)	0.62
FS	6 (20.00%)	1 (1.67%)	**0.0022**

Similarly, Fetal Vascular Malperfusion (FVM) was also observed more frequently in LBW infants. Key findings such as focal Avascular Villi (AV), Thrombosis in fetal vessels (T), Vascular Intramural Fibrin Deposition (VIFD), Vascular Ectasia (VE) and Fibromuscular Sclerosis (FS) were more common in LBW cases. These findings were overlapping for most of the cases. However, Villous Stromal Vascular Karyorrhexis (VSVK) was not found in both cases and controls. The statistical significance of these findings further supports the critical role of FVM in the occurrence of LBW in infants.

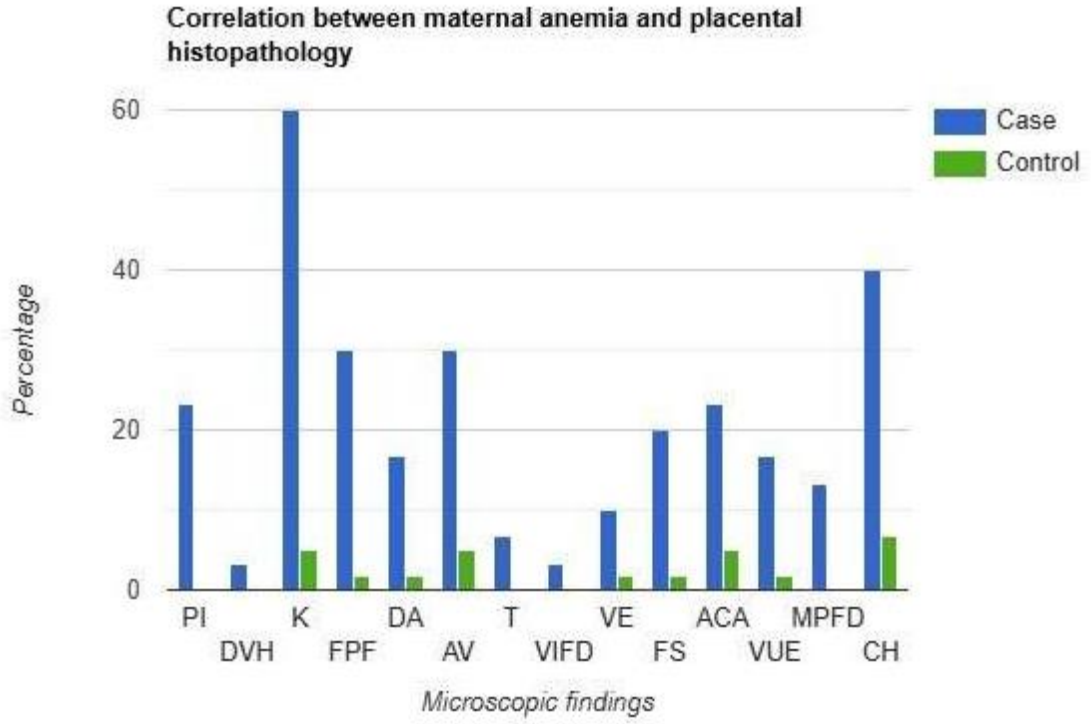
TABLE 15. Comparison of other microscopic findings

Microscopic Findings	Case (Count, %)	Control (Count, %)	p-value
ACA	11 (36.67%)	10 (16.67%)	**0.0007**
VUE	5 (16.67%)	1 (1.67%)	**0.0072**
CHI	0 (0.00%)	0 (0.00%)	0.62
MPFD	6 (20.00%)	2 (3.33%)	**0.0152**
CH	18 (60.00%)	14 (23.33%)	**0.0000003**
DVM	0 (0.00%)	0 (0.00%)	0.62

Acute Chorioamnionitis (ACA), Villitis of Unknown Etiology (VUE), Massive perivillous fibrin deposition (MPFD) and Chorangiosis (CH) showed a higher occurrence in LBW cases as compared to controls with p-value less than 0.05, making them statistically significant.

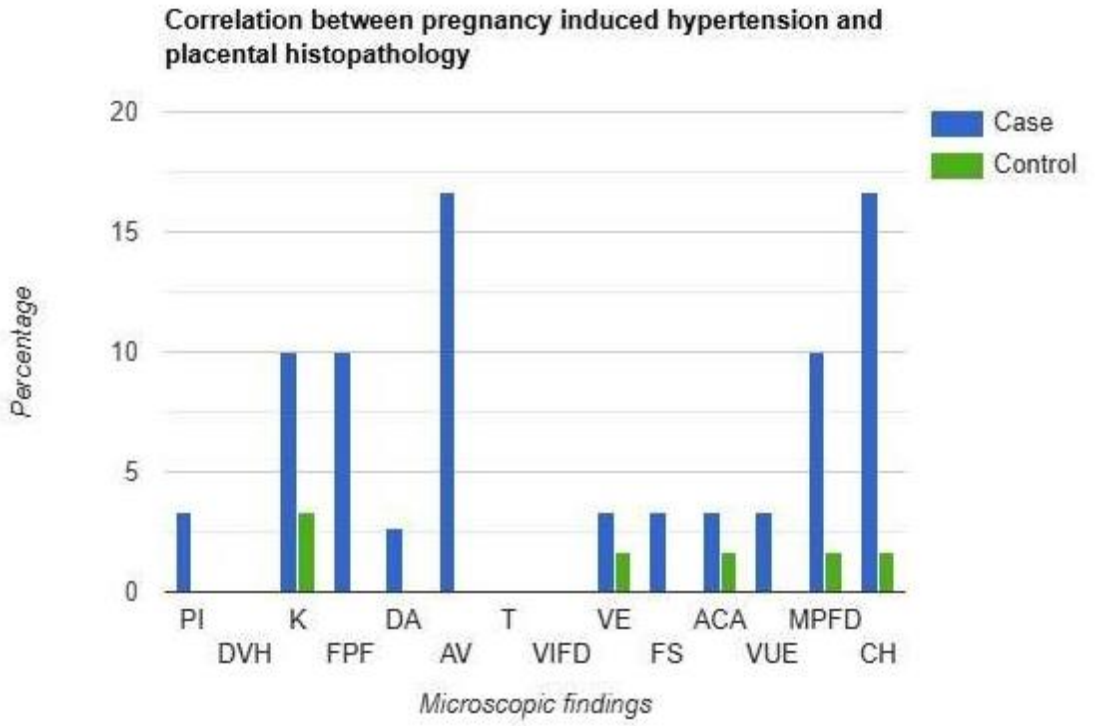
However, Chronic Histiocytic Intervillositis (CHI) and Delayed villous maturation (DVM) did not show statistically significant differences in the study, suggesting that they may not have a direct correlation with low birth weight cases.

GRAPH 2. Correlation between maternal anemia and placental histopathology



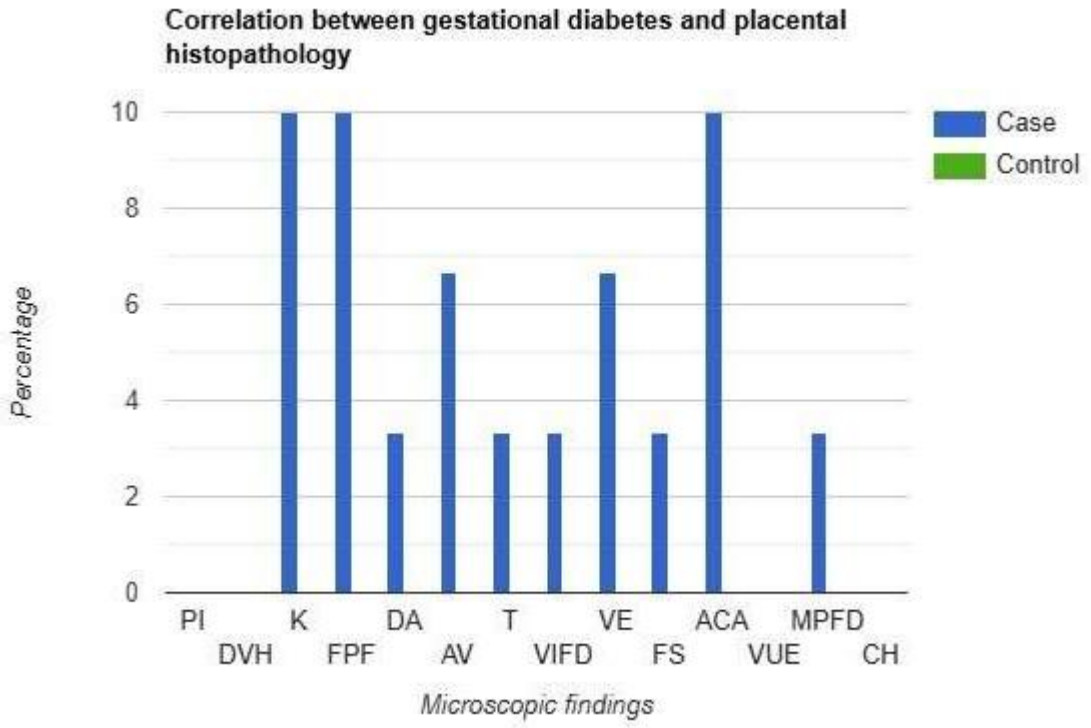
The histopathological features like Placental infarction, increase in syncytial knots (K), presence of focal perivillous fibrin (FPF), decidual arteriopathy (DA), presence of focal avascular villi (AV), fibromuscular sclerosis (FS), acute chorioamnionitis (ACA), villitis of unknown etiology (VUE), presence of massive perivillous fibrin deposition (MPFD) and chorangiosis (CH) were found more in LBW cases associated with maternal anemia as compared to NBW controls and showed statistical significance with a p value of less than 0.05.

GRAPH 3. Correlation between pregnancy induced hypertension and placental histopathology



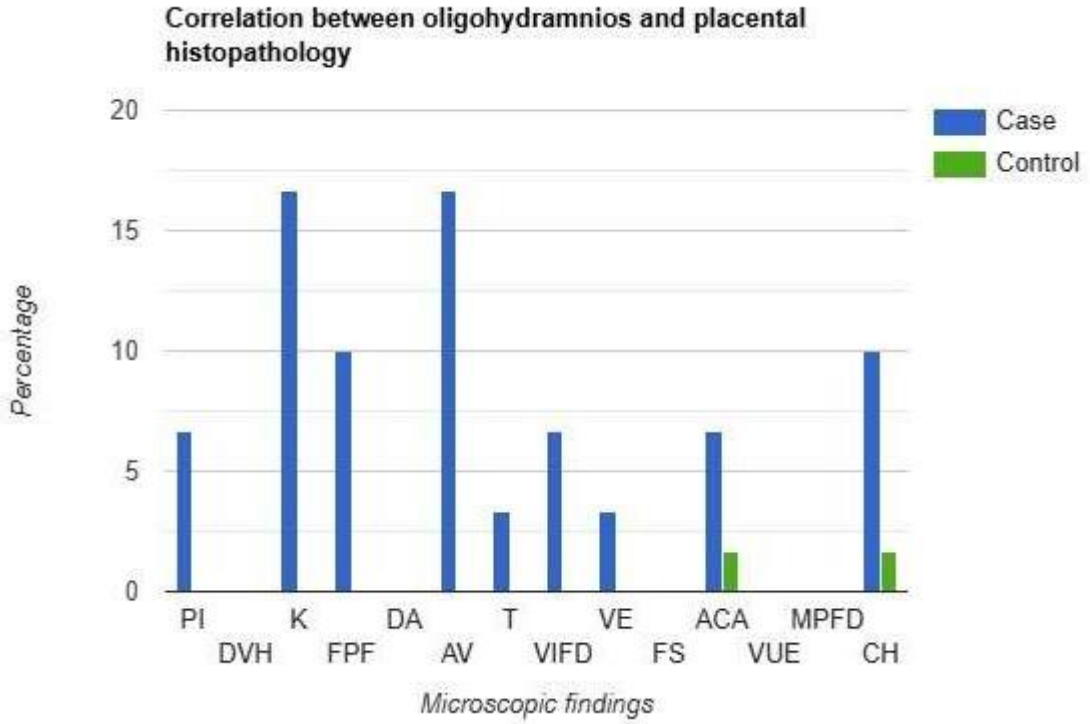
The histopathological features like presence of focal perivillous fibrin (FPF), presence of focal avascular villi (AV) and chorangiosis were found more in LBW cases associated with pregnancy induced hypertension as compared to NBW controls and showed statistical significance with a p value of less than 0.05.

GRAPH 4. Correlation between gestational diabetes and placental histopathology



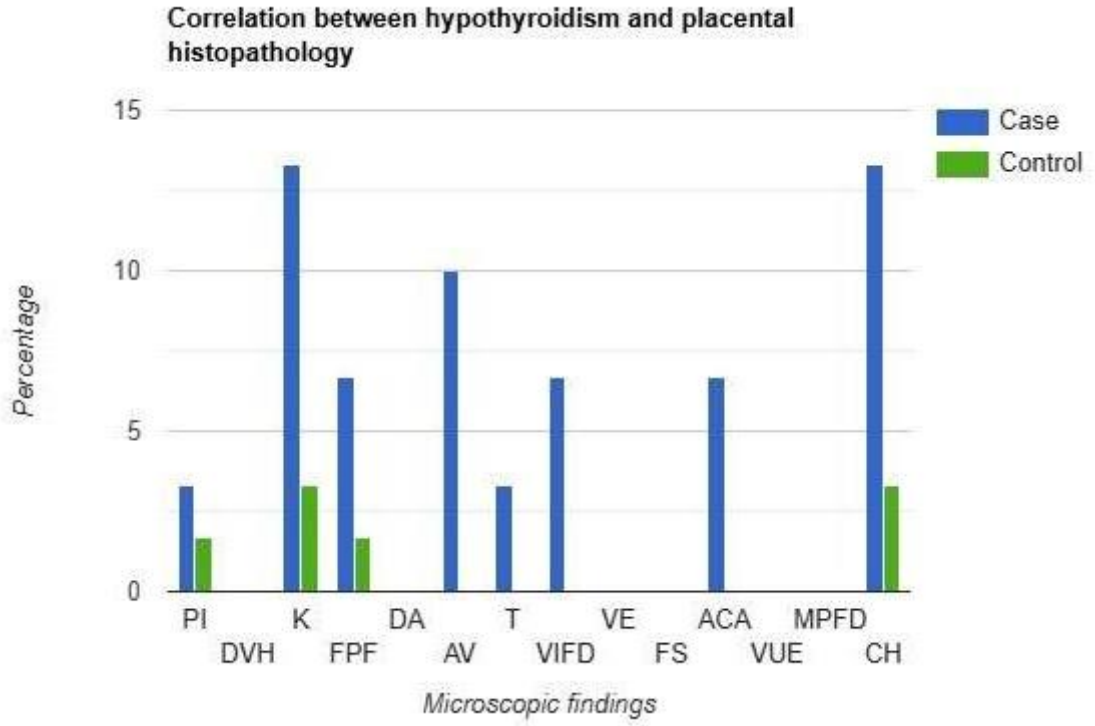
The histopathological features like increase in syncytial knots (K), presence of focal perivillous fibrin (FPF) and acute chorioamnionitis (ACA) were found more in LBW cases associated with gestational diabetes as compared to NBW controls and showed statistical significance with a p value of less than 0.05.

GRAPH 5. Correlation between oligohydramnios and placental histopathology



The histopathological features like increase in syncytial knots (K), presence of focal perivillous fibrin (FPF) and focal avascular villi (AV) were found more in LBW cases associated with oligohydramnios as compared to NBW controls and showed statistical significance with a p value of less than 0.05.

GRAPH 6. Correlation between hypothyroidism and placental histopathology



The presence of focal avascular villi (AV) was the only histopathological feature which was found more in LBW cases associated with hypothyroidism as compared to NBW controls that showed statistical significance with a p value of less than 0.05.

GROSS IMAGES

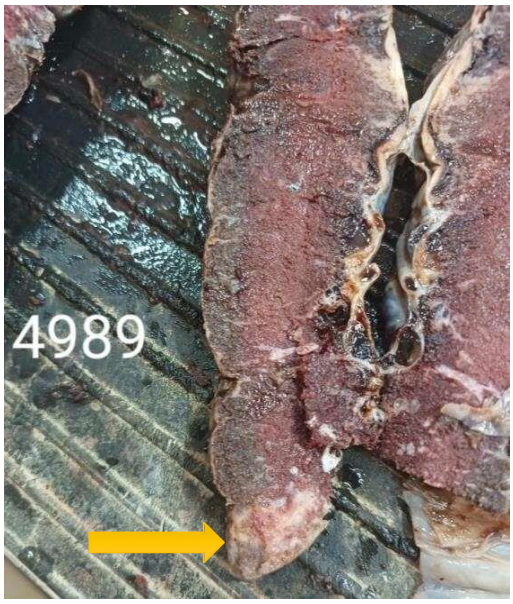


Fig. 30- Placental parenchyma white, firm area of infarct

Fig. 31- Maternal surface of placenta showing showing pale area of infarct

Fig. 32- Marginal insertion of umbilical cord

Fig. 33- Circumvallate placenta

MICROSCOPIC IMAGES

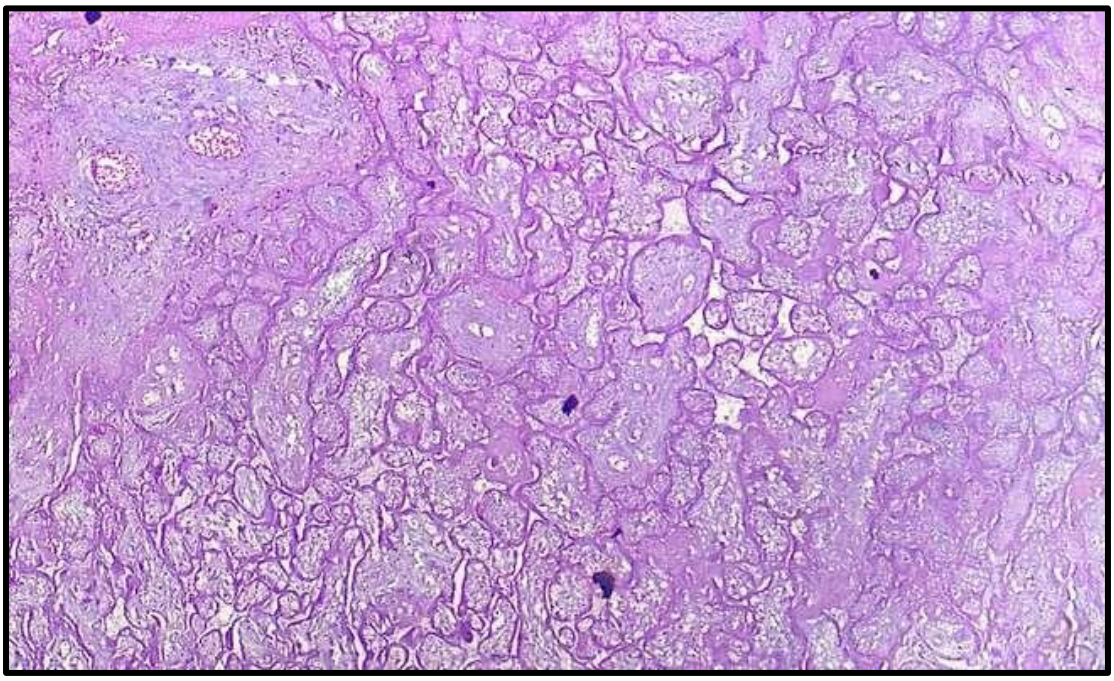


Fig. 34- Placenta showing areas of Infarction (H & E, 200X)

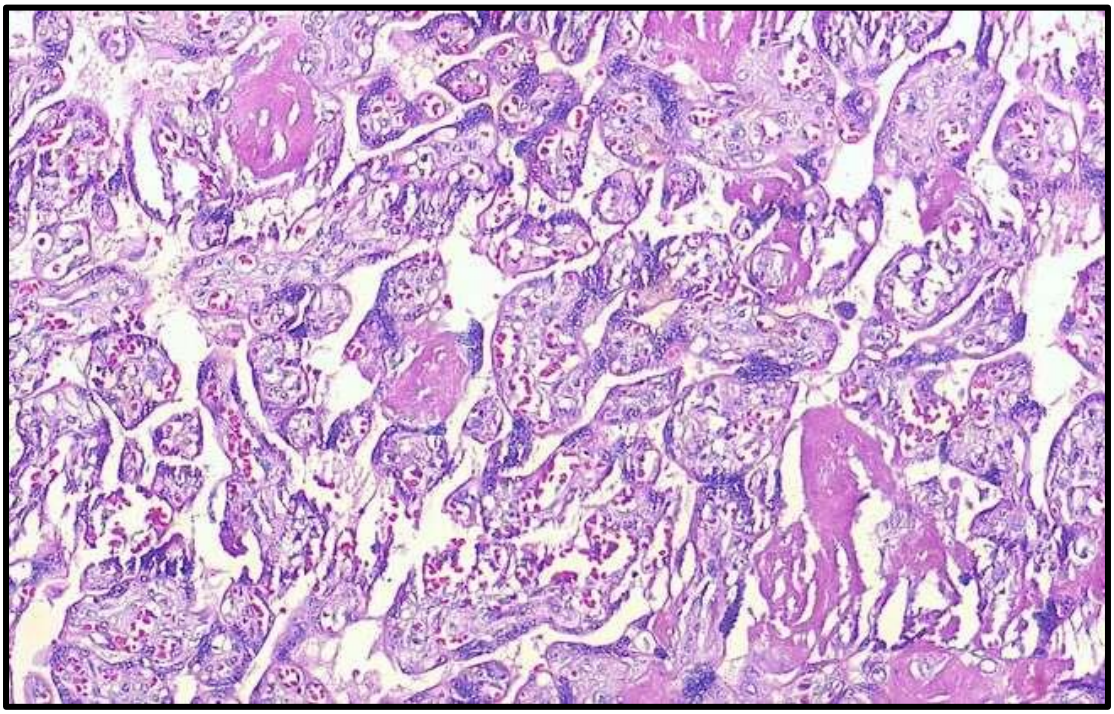


Fig. 35- Placenta showing Increased syncytial knots (H & E, 200X)

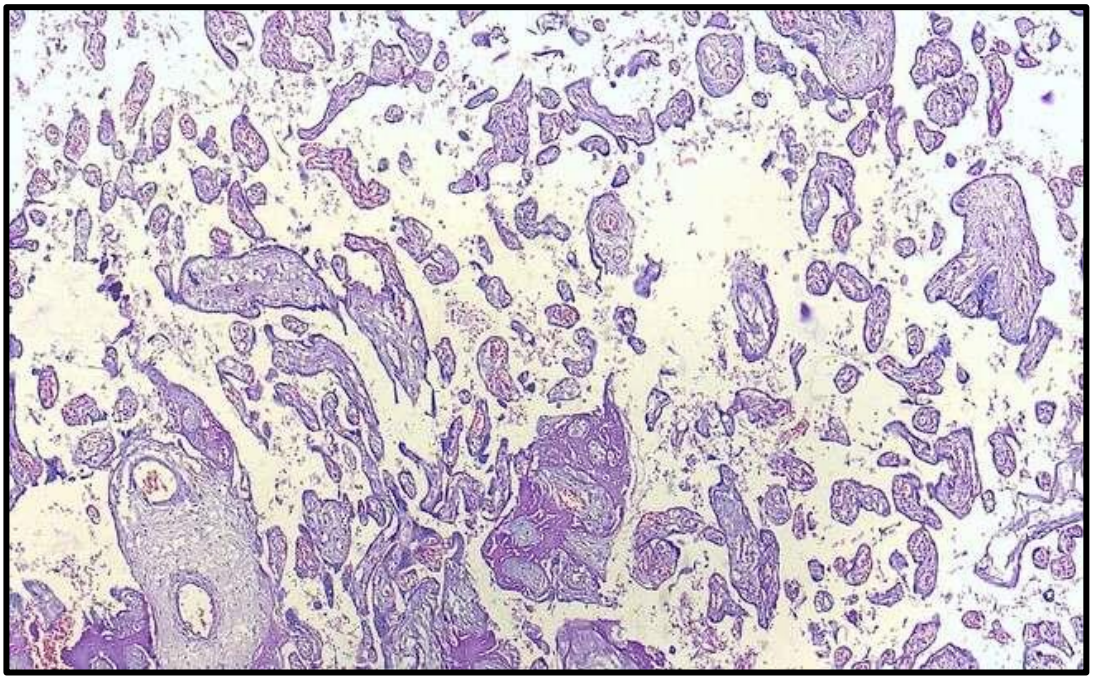


Fig. 36- Placenta showing Distal villous hypoplasia (H & E, 200X)

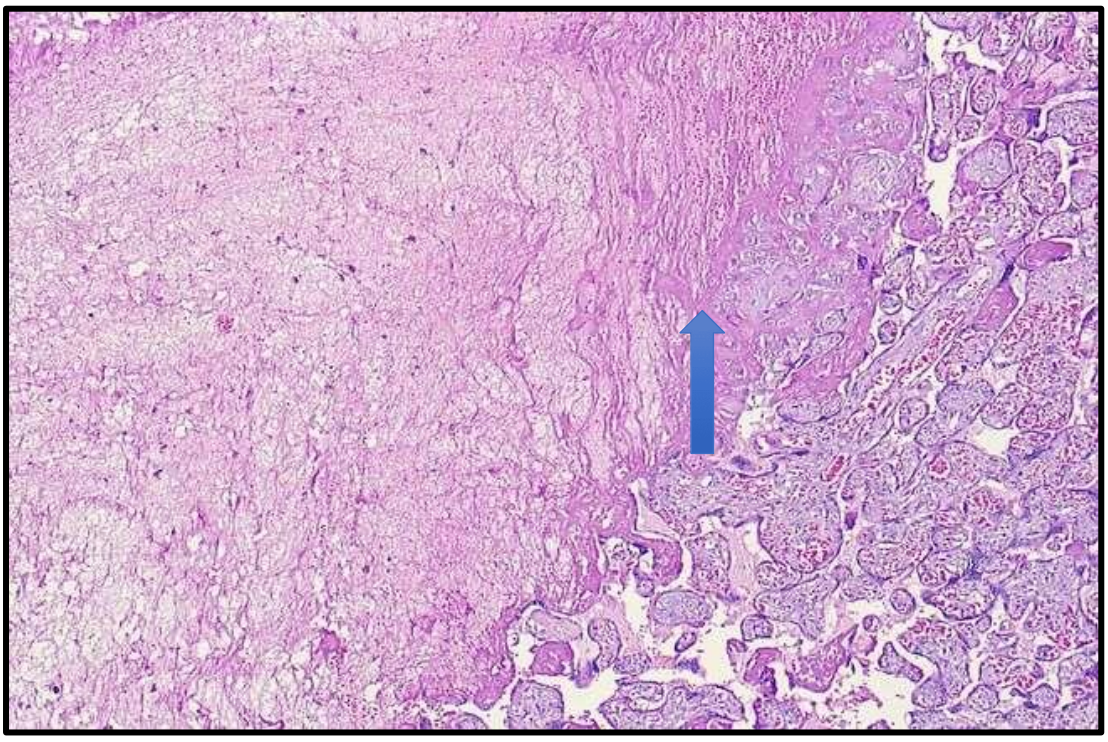


Fig. 37- Placenta showing Laminar decidual necrosis (H & E, 200X)

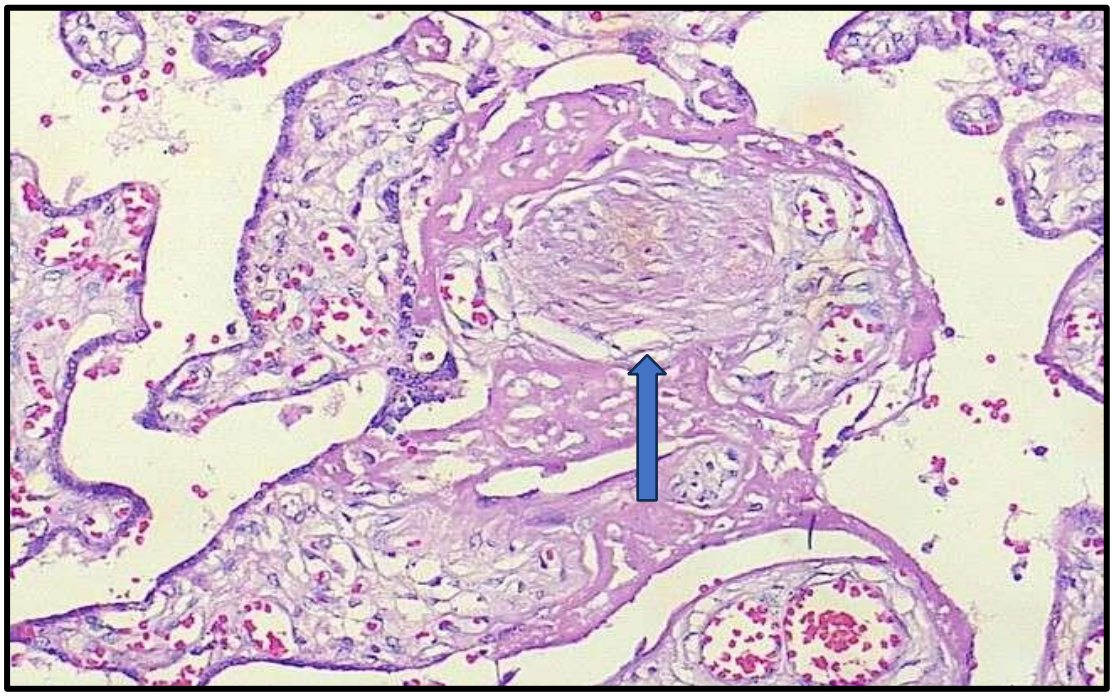


Fig. 38- Placenta showing Avascular villi (H & E, 400X)

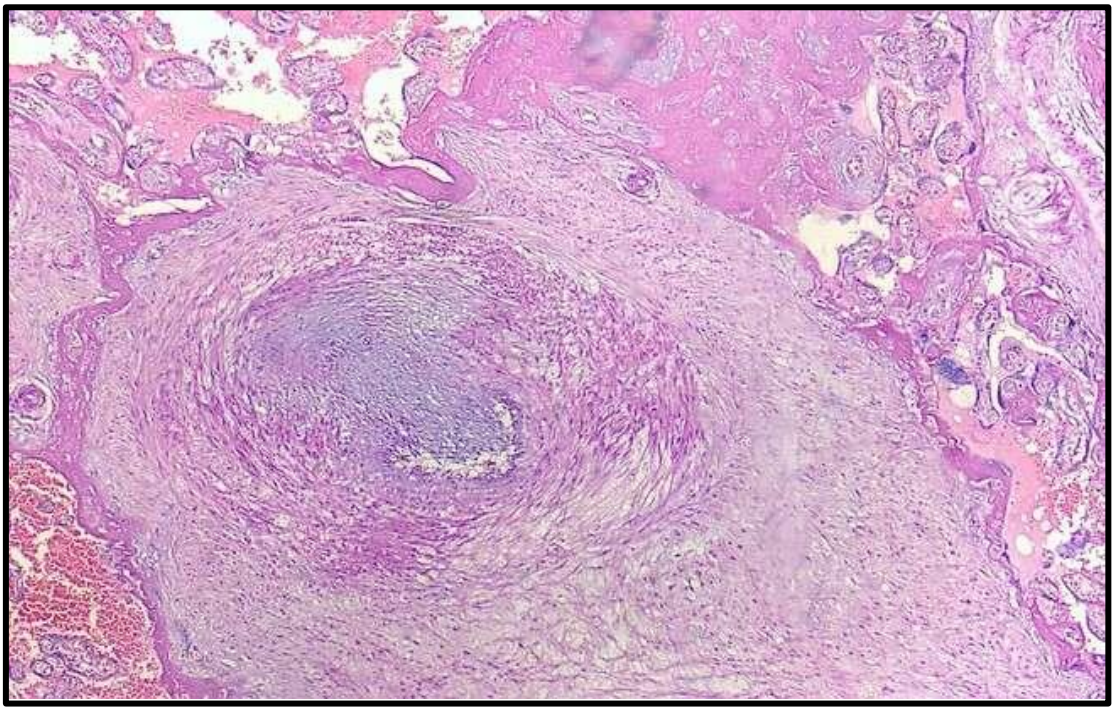


Fig. 39- Placental stem vessel showing a Thrombus (H & E, 400X)

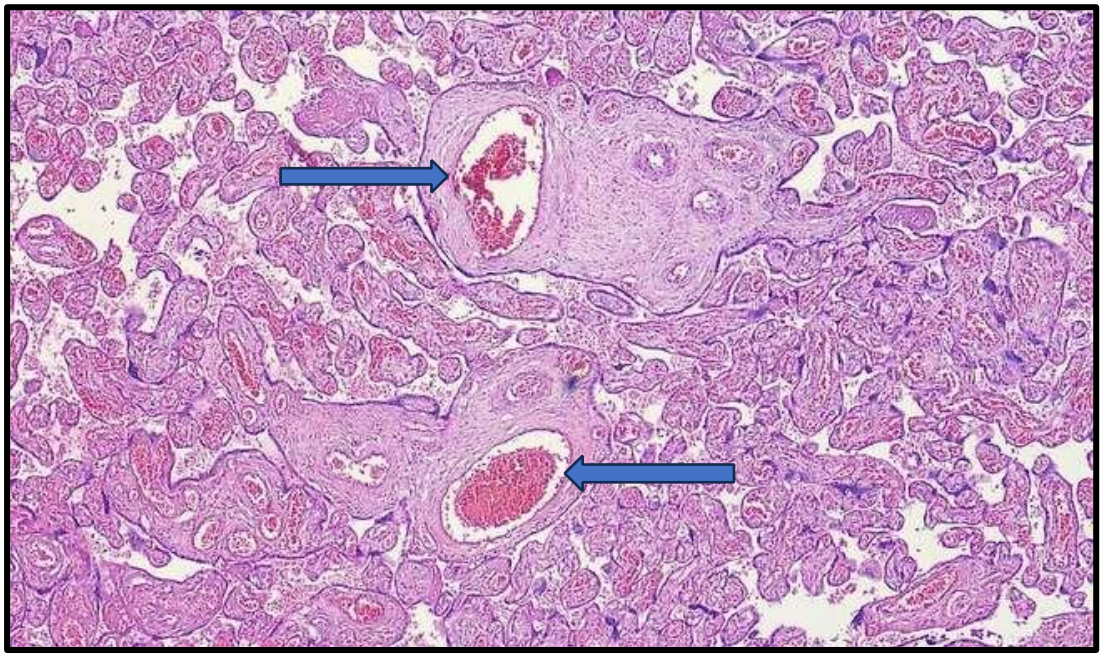


Fig. 40- Placental stem vessels showing Vascular ectasia (H & E, 200X)

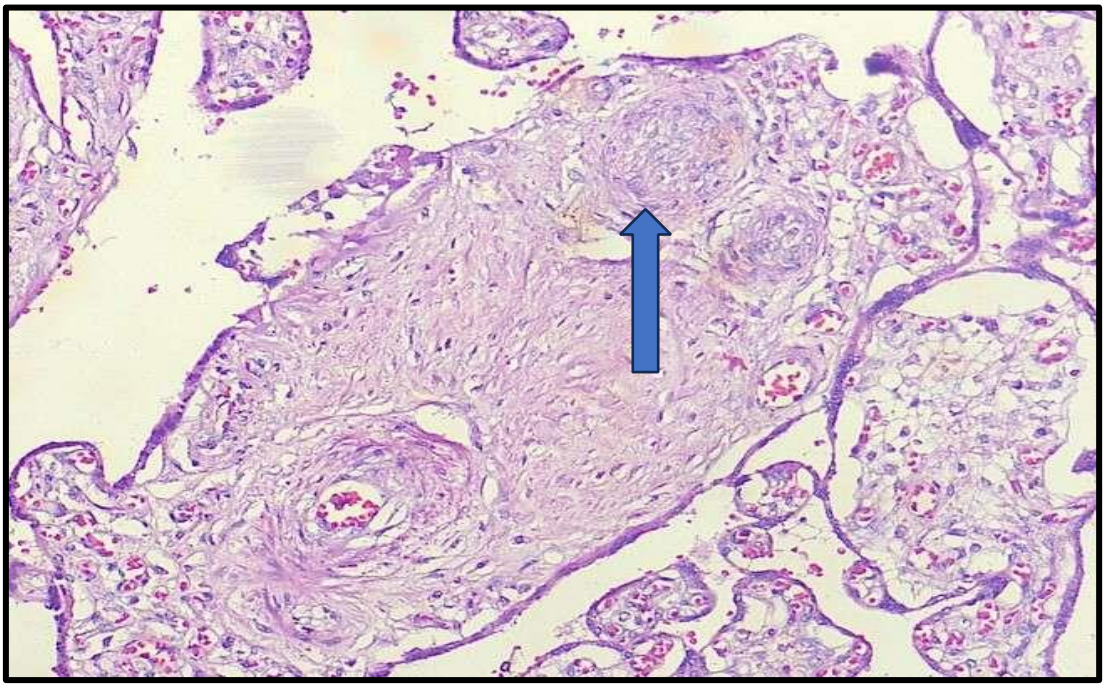


Fig. 41- Placenta showing Fibromuscular sclerosis (H & E, 200X)

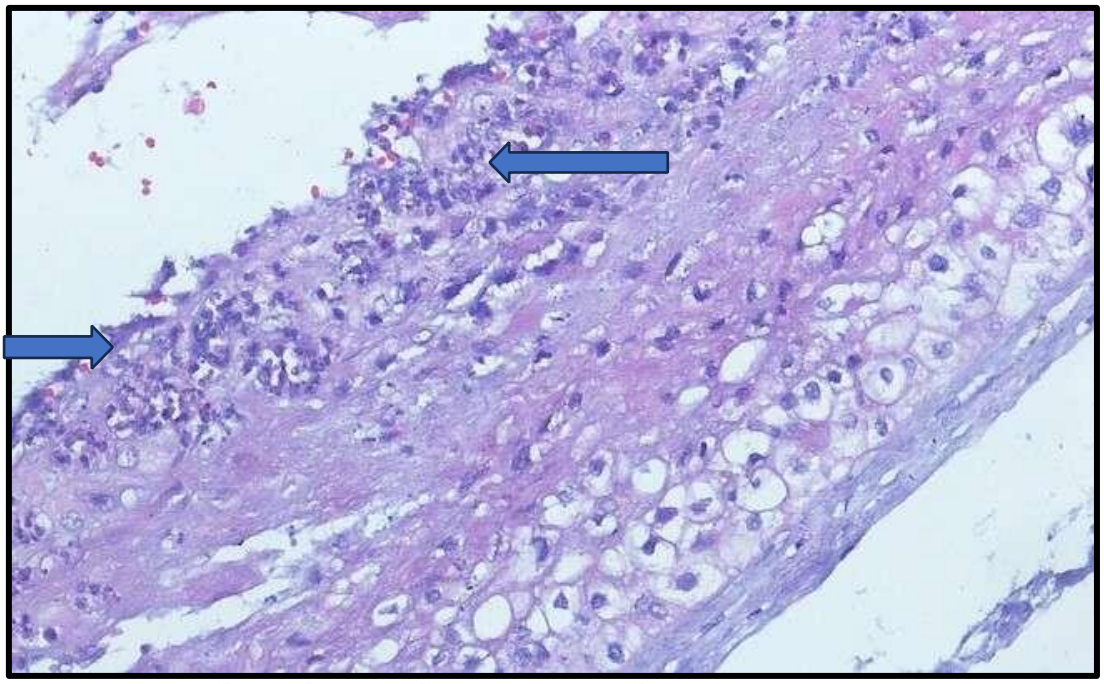


Fig. 42- Fetal membranes showing Acute Chorioamnionitis (H & E, 200X)

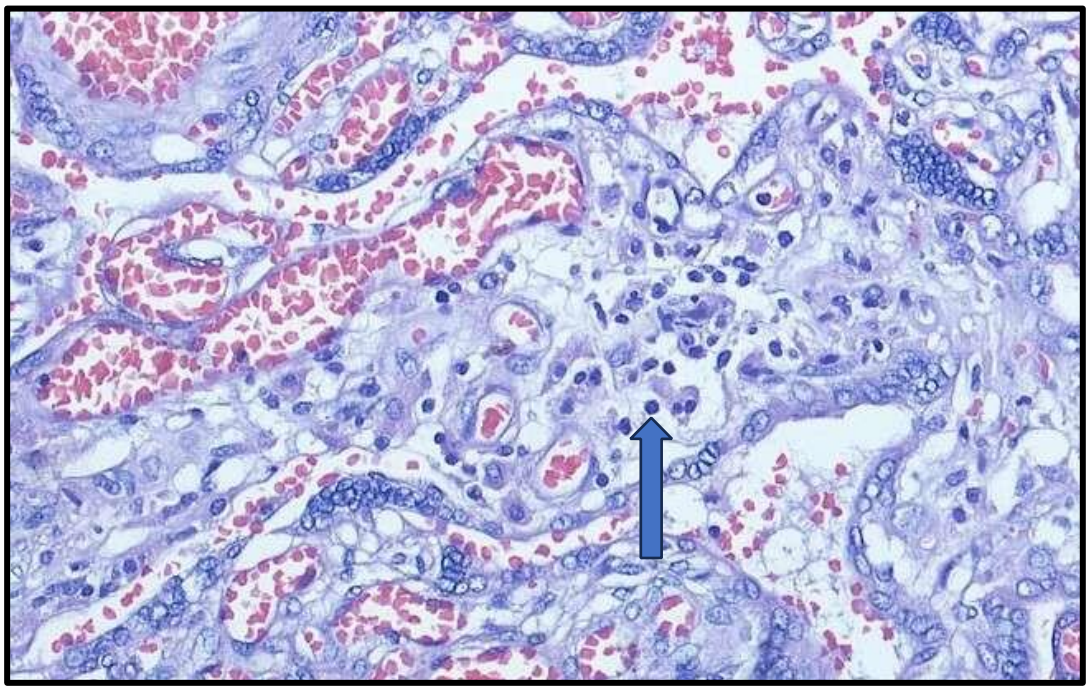


Fig. 43- Placenta showing Villitis of unknown etiology (H & E, 200X)

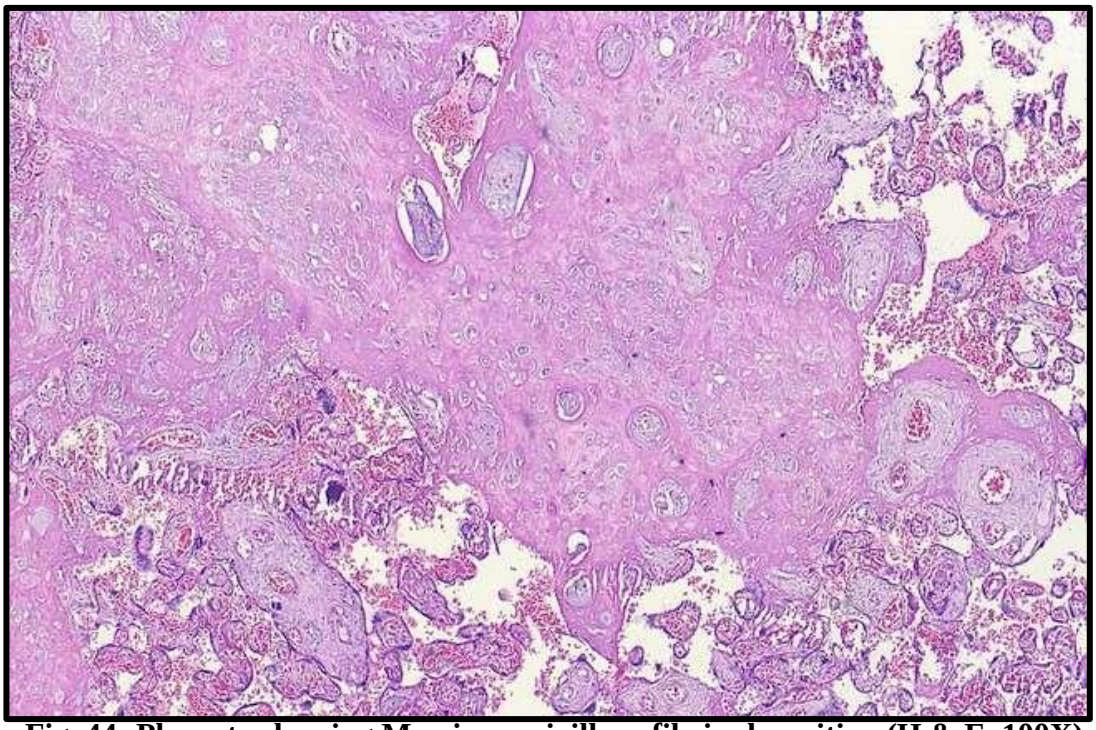


Fig. 44- Placenta showing Massive perivillous fibrin deposition (H & E, 100X)

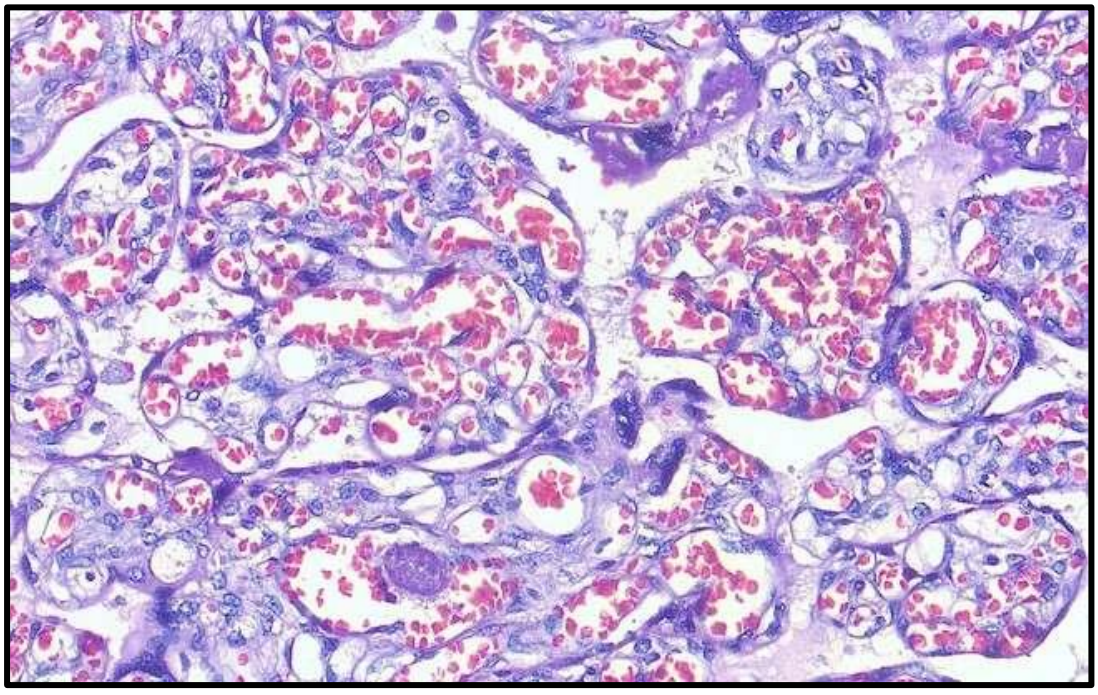


Fig. 45- Placenta showing Chorangiosis (H & E, 200X)

DISCUSSION

This study intended to evaluate placental morphology and assess its clinical correlation in term LBW infants in comparison with term NBW infants by using Amsterdam classification system for placental pathology. We studied several variables like maternal risk factors including maternal diseases, placental morphometry and histopathological changes in the placenta.

In the present study, maternal age was divided into four categories. The commonest maternal age group was between 18 to 25 years which were seen in 15 (50%) of the LBW cases and 26 (43.33%) of NBW controls. This is similar to the observations by Govindarajan et al.[107] where 44 (62.9%) of cases and 37 (52.8%) of controls were in the age group of 18 to 25. Similarly, study by Jadhav et al.[3] found 18 to 25 age group in 32 (64%) of the cases. In contrast, Magesh et al.[9] found higher proportion of cases, 39 (78%) in the same age group. These findings suggest that maternal age is one of the independent risk factors for LBW. Eiríksdóttir et al.[108] further studied relationship between socioeconomic position, maternal age and its association with LBW. It was found that odd's ratio (1.85) was statistically significant in this age group and was associated with stressful economic crisis.[108] Hence, further studies are recommended to study correlation of socioeconomic position with the occurrence of LBW.

In the present study, primiparity was seen in 14 (46.67%) of the cases, 24 (40%) of controls and multiparity was seen in 16 (53.33%) cases, 36 (60%) controls. Similar observations were noted in a study by Jadhav et al.[3] where primiparity was seen in 26 (52%) cases and multiparity was seen in 24 (48%) of the cases. In contrast,

Magesh et al.[9] noted primiparity in 37 (74%) cases and multiparity in 13 (26%) of the cases.

The present study included data of NBW controls and LBW cases at term gestation. Despite both groups achieving term births, the LBW cases were associated with a lower mean gestational age (38.16 ± 0.59 weeks) than the NBW controls (38.76 ± 0.99 weeks), with a statistically significant p-value of 0.001. This finding suggests that even minor reduction in gestational age, could affect the birth weight which may possibly be resulting from placental insufficiency. Liu et al.[109] documented similar change of decrease in gestational age among LBW newborns. In another study by Leyto et al.[110], it was concluded that gestational age has a significant influence on the occurrence of low birth weight.

In this study, the mean maternal weight gain during gestation was significantly lower in LBW cases (8.88 ± 0.76 kg) as compared to NBW controls (10.54 ± 0.70 kg), with a highly significant difference ($p < 0.0001$). Balasubramanian et al.[14] in their study observed that the mean of pre-pregnancy weight ($p=0.003$) and weight at delivery ($p=0.0024$) were significantly lower in the LBW cases in comparison with NBW controls. The reason for LBW in infant of women with low pre-pregnancy weight may be that the fetus did not receive adequate nutrient supply from mother due to malnourishment which lead to reduced intrauterine development of the fetus.[5]

In our study maternal diseases were present in 29 (96.66 %) of the cases and 26 (43.33%) of the controls. Amongst the diseases, maternal anemia was highest with 21(70.00%) in LBW cases and 19 (31.67%) in NBW controls, followed by pregnancy induced hypertension which was 6 (20.00%) in cases and 3 (5.00%) in controls. This was followed by oligohydramnios which was 6 (20.00%) in cases, 3 (5.00%) in

controls and gestational diabetes which was 3 (10.00%) in cases, absent in controls. These results coincide with the study conducted by

Govindarajan et al.[107], who observed that maternal anemia was highest occurring disease with 25 (35.7%) in LBW cases and 11 (15.7%) in NBW controls. Similarly, they found that pregnancy induced hypertension was second highest occurring disease with 12 (17.1%) in cases and 4(5.7%) in controls.[107] Maternal anemia limits maternal oxygen uptake and decreased oxygen delivery to the fetus consequently resulting in fetal growth restriction.[111] Likewise, study by Liu et al.[109] found that LBW highly correlated with presence of hypertensive disorders of pregnancy with odds ratio being 1.77. Hypertension may affect the development of placental villous tree leading to decline in placental function which may result in reduced fetal growth and LBW.[109] Pre-eclampsia and eclampsia are known to cause maternal vascular changes which reduces uteroplacental flow.[112] Decreased uteroplacental function is the most common pathophysiological mechanism of LBW. Hence the management of elevated blood pressure in gestation is essential in the prevention of LBW.[109] Another study conducted by Jarmuzek et al.[113] recognized gestational diabetes as a factor leading to modified placental architecture, which diminishes the efficacy of nutrient exchange resulting in LBW.

In our study, eccentric cord insertion was seen in 24 (80%) of LBW cases and 47 (78.33%) of NBW controls whereas marginal cord insertion was seen in 6 (20%) of LBW cases and only 1 (1.67%) of NBW controls. This is similar to the research done by Balasubramanian et al.[14] where 18 (60%) cases, 34 (56.67%) controls had eccentric cord insertion and 4(13.33%) cases, 6(10%) controls had marginal cord insertion. Similarly, in the study by Nigam et al.[8],

eccentric cord insertion was seen in 40(66.67%) of the LBW cases. Similar findings were found in the study by Sharma et al.[7] in which eccentric cord insertion was present in 61.8% of LBW cases and 32.3% of NBW controls.[7] In a study by Jadhav et al.[3], marginal and eccentric insertion of umbilical cord was found in 58% of LBW cases. These results imply that aberrant cord attachments like marginal and eccentric lead to increased placental thrombi in fetal vessels, impairing the placental perfusion, further aggravating constraints on embryonic growth ultimately leading to LBW.[3]

Placental weight and dimensions were notably lower in LBW cases than in NBW controls, according to our study. This finding is consistent with research done by Balasubramanian et al.[14], Govindarajan et al.[107] and Senapati et al.[114], Nkwabong et al.[112], Sharma et al.[7], Nigam et al.[8] and Singh et al.[5] (Table 16). Reiterating the link between placental insufficiency and fetal undernutrition, Sanchita et al.[11] discovered that placental weight and diameter were much lower in term LBW cases than in NBW controls. Study by Leyto et al.[110] concluded that the occurrence of LBW were more than six times more in infants with a placental weight below the normal range as compared to those having normal placental weight. It can be explained saying that lower placental size restricts the transfer of nutrients to the intrauterine fetus which in turn limits fetal development causing poor neonatal outcomes like LBW. The study also revealed that the incidence of LBW was more than five times with a lower placental thickness compared to infants having normal thickness of the placental. This could be due to reduced vascularization and abnormal structural organization of the thin placenta which leads to decreased oxygen supply and nutrient supply thus restricting the growth of the intrauterine fetus.[110]

These results imply that LBW in infants follow directly from a decrease in placental size and weight corresponding with a lower fetal nutrition supply.[110]

TABLE 16- Studies comparing placental weight in LBW infants (cases) and NBW infants (controls)

	Placental weight in Cases (in gm), Mean ± S.D.	Placental weight in Controls (in gm), Mean ± S.D.
Present Study	370.00 ± 55.48	447.33 ± 91.58
Study by Balasubramanian et al.[14]	420 ± 70	560 ± 100
Study by Govindarajan et al.[107]	353.04 ± 81.207	530.39 ± 35.062
Study by Senapati et al.[114]	404.79 ± 19.37	547.83 ± 29.09
Study by Sanchita et al.[11]	370.14	464.59
Study by Nkwabong et al.[112]	468.3 ± 87.9	655.6 ± 133.5
Study by Sharma et al.[7]	325.9 ± 82	432.6 ± 73.3
Study by Nigam et al.[8]	266.94	399.31
Study by Singh et al.[5]	407 ± 114	529 ± 150

In comparison with NBW controls, the LBW cases had statistically significant microscopic findings of MVM which included presence of placental infarction, increased syncytial knots, focal perivillous fibrin deposition and decidual arteriopathy. Significant findings of FVM include focal Avascular villi, thrombosis in fetal vessels, vascular intramural fibrin deposition, vascular ectasia and fibromuscular sclerosis. Findings of acute chorioamnionitis, villitis of unknown etiology, massive

perivillous fibrin deposition and chorangiosis were also found more in cases as compared to controls.

In the present study, placental infarction was seen in 8(26.66%) of the cases, 2(3.33%) of controls which is similar to the study by Balasubramanian et al.[14], where it was seen in 6(20%) cases and 4(6.67%) controls. However, these findings were lower as compared to the study by Nkwabong et al.[112] where it was seen in 20 (66.7%) of cases, 6 (20%) controls and the study by Jadhav et al.[3] where placental infarction was seen in 32 (64%) of the cases. Placental infarction reduces the surface area for exchange of nutrients which leads to reduced nutrient and oxygen transfer to fetus resulting in LBW.[112]

In the present study, increase in syncytial knots were seen in 24 (80%) of cases and 13 (43.33%) of controls which correlated with the study by Balasubramanian et al.[14] where it was found in 22 (73.33%) cases and 18 (30%) controls. Similarly study by Govindarajan et al.[107] found increased syncytial knots in 57 (81.4%) cases, 15 (21.4%) controls and Magesh et al.[9] found it to be present in 38 (76%) of the cases. Study by Jadhav et al.[3] found increased syncytial knots in 100% of the cases. Syncytial knots occur due to chronic utero-placental insufficiency which leads to reduced perfusion of villi.[3] This is associated with an increase in oxidative stress which results in hypoxia[115], reduced placental perfusion and nutrient supply in turn leading to LBW.[11]

Focal perivillous fibrin deposition was found in 16 (53.33%) of the cases and 9 (15.00%) controls in the present study which correlated with the study by Jadhav et al.[3] where it was noted in 28 (56%) of the cases. However, study by Govindarajan et al.[107] found it in 55 (78.6%) cases and 13 (18.5%) controls. Perivillous fibrin

deposition leads to entrapment of villi which make them incapable of participating in the nutrient transfer to the fetus, ultimately resulting in LBW.[115]

Decidual arteriopathy, characterized by atherosis and fibrinoid necrosis of the decidual artery[112] was found in 6 (20.00%) of the cases and 2 (3.33%) of controls in the present study. In similarity, study by Sharma et al.[7] found atherosis to be present in 20.6% of the cases, 2.9% of controls and fibrinoid necrosis in 23% of the cases. In consistence with our study, Balasubramanian et al.[14] found fibrinoid necrosis in 6 (20%) of the cases, 4 (6.67%) of the controls and Jadhav et al.[3] found it in 8 (16%) of the cases. Similarly, Nkwabong et al.[112] found decidual arteriopathy in 9 (30%) of the cases. In contrast, Magesh et al.[9] found fibrinoid necrosis in 32 (64%) of the cases.

Focal Avascular villi which include loss of villous capillaries and stromal fibrosis[116] was seen in 19 (63.33%) of the cases and 9 (15.00%) ocontrols in present study. In resemblance, the study by Sharma et al.[7] found stromal fibrosis in 58.8% of the cases and 32.3% of controls. Similarly, study by Balasubramanian et al.[14] found focal avascular villi in 15 (50%) cases and 10 (16.67%) controls. Furthermore, study by Jadhav et al.[3] found stromal fibrosis in 24 (48%) of the cases. In contrast, Govindarajan et al.[107] found stromal fibrosis in 58 (82.9%) cases and 13 (18.5%) controls. Jadhav et al.[3] noted that in stromal fibrosis, increased villous fibrin leads to reduced functioning of the villi thus causing placental insufficiency which impairs nutrient transfer and leads to LBW.[3]

Fibromuscular sclerosis was seen in 6 (20.00%) of the LBW cases and 1 (1.67%) of NBW controls in our study. This resembles the study by Balasubramanian et al.[14] where it was seen in 3 (10%) cases and study by Jadhav et al.[3] where it was found in 5 (10%) of cases.

Acute chorioamnionitis was observed in 11 (36.67%) of cases and 10 (16.67%) of controls in the present study as compared to that observed by Govindarajan et al.[107] who found it in 45 (64.3%) cases and 26 (37.1%) controls. Acute chorioamnionitis as an indicator of intrauterine infection, impairs placental function via inflammation, potentially jeopardizing fetal health and in turn leading to LBW.[117]

Chronic villitis is currently classified as villitis of unknown etiology (VUE).[35] In the present study, Villitis of unknown etiology was seen in 5 (16.67%) of the cases and 1 (1.67%) of controls as compared to the study by Jadhav et al.[3] where chronic villitis was found to be present in only 2 (4%) of the cases. Similarly, study by Nkwabong et al.[112] found presence of chronic villitis in 6 (20%) of cases and 1 (3.3%) of controls. In chronic villitis, there is alteration of the diffusion of substrates from the intervillous space into the fetal circulation because of the presence of inflammatory infiltrate in the villi. This leads to reduced nutrient supply to the fetus and LBW.[112]

Massive Perivillous Fibrin Deposition was seen in 6 (20.00%) of the cases and 2 (3.33%) of controls in the present study which is similar to study by Nkwabong et al.[112] where it was found in 6 (20%) of the cases and 2 (6.7%) of controls. However, in the study by Sharma et al.[7], 50% of cases and 17.7% controls showed massive perivillous fibrin deposition. The chorionic villi are embedded in fibrin in massive perivillous fibrin deposition which leads to impairment of nutrient exchange between villi and intervillous space, ultimately resulting in LBW.[115]

Chorangiosis was found in 18 (60.00%) of LBW cases and 14 (23.33%) of NBW controls in our study which was similar to the study by Sharma et al.[7] who found it in 58.8% of cases and 26.5% of controls. In contrast, study by Nkwabong et

al.[112] found 9 (30%) cases, 4 (13.3%) controls with chorangiosis and study by Magesh et al.[9] found it in 10 (20%) cases. Chorangiosis is an outcome of low grade placental hypoxia which is associated with poor pregnancy outcome namely LBW.[7]

We further tried to see if there is any correlation between maternal disease and placental histopathology. The LBW cases which were associated with presence of maternal anemia showed statistically significant presence of increased syncytial knots which was similar to the study by Govindarajan et al.[107] Similarly, the presence of focal avascular villi LBW cases associated with pregnancy induced hypertension in our study, correlated with the findings of above study. Our findings of placental changes in association with gestational diabetes contrasted with the study by Jarmuzek et al.[113] where villous immaturity, villous fibrinoid necrosis, chorangiosis and increased angiogenesis were seen more frequently. We suggest the conduct of more studies which are focussed on specific maternal diseases and its correlation with occurrence of specific histopathological finding to validate the findings of our study.

CONCLUSION

Histopathological study of placenta with help of Amsterdam classification system is a simple technique and easy to perform which helps in studying the pathological findings contributing to low birth weight in full term deliveries along with clinical examination.

Our findings substantially support recognized connections between LBW and various kinds of placental pathology. The consistency of our results with previously published material lends legitimacy to these connections and offers a more comprehensive knowledge of the processes by which placental malfunction affects fetal development.

All the major macroscopic and microscopic placental findings in the present study ultimately pointed towards decreased blood flow to the placenta ultimately resulting in chronic placental insufficiency.

The end result of these events is the occurrence of LBW in neonates.

Furthermore, maternal risk factors causing placental abnormalities show that these diseases can reduce placental function by altering maternal blood flow, thereby affecting nutrient and oxygen delivery to the fetus and compromising its function. This underlines the need to control maternal health issues throughout pregnancy to avoid placental malfunction and related consequences on fetal development.

The results provide critical new insights into the pathophysiology of LBW. They could guide prenatal health care plans, including the monitoring and management of maternal risk factors thereby reducing placental dysfunction and enhancing fetal outcomes.

SUMMARY

Mothers with LBW infants presented with more often maternal problems including maternal anemia, hypertension abnormalities, oligohydramnios and gestational diabetes. Furthermore, term LBW infants had less maternal weight gain during gestation than normal birth weight infants. Fetal distress and fetal growth restriction was noted more in LBW cases than NBW controls.

In comparison to NBW infants, gross placental findings in term LBW infants revealed an increased incidence of eccentric and marginal umbilical cord insertion, green color of fetal membranes, circumvallate attachment of fetal membranes, maternal surface with missing cotyledons and presence of areas of infarction in placental parenchyma. LBW cases had decreased placental weight, length, breadth, and thickness in comparison with NBW controls.

The microscopic findings in placenta of LBW cases following Amsterdam classification system which were significant were MVM which include maximum cases with increased syncytial knots followed by focal perivillous fibrin deposition, placental infarction and decidual arteriopathy. Among FVM category, maximum cases were of focal avascular villi followed by vascular ectasia, fibromuscular sclerosis, thrombosis in fetal vessels and vascular intramural fibrin deposition. Acute chorioamnionitis, villitis of unknown etiology, massive perivillous fibrin deposition and chorangiosis were also more in cases in comparison with controls.

These results together draw attention to the notable clinical findings, morphological and histological variations in placentas connected to LBW cases. The information supports the need for maternal health, prenatal care, and placental evaluation in comprehending and maybe reducing the occurrence of LBW.

LIMITATIONS

Although this study provides critical new insights into the relationship between LBW and placental anomalies, several limitations should be considered when interpreting the results.

There were only 30 LBW cases and 60 NBW controls in the study. A greater sample size may improve the statistical analysis's resilience and help identify minor variations among groups. The small sample size can reduce the study's power and make it difficult to detect notable links within a larger population.

The study also excluded other possible confounding elements, such as maternal diet, environmental exposures, and genetic factors affecting fetal weight and development. Although not measured in this investigation, these elements may help explain the noted variations in placental size and histological findings. Including these aspects in a more thorough research might help to clarify the elements affecting LBW.

FUTURE PROSPECTS

The findings of this study present various opportunities for further research on placental malfunction and its influence on LBW. Building on the present, future research should address the noted shortcomings, including expanding the sample size and investigating additional factors that affect fetal development. Future studies in this crucial field will focus on the pharmacological and genetic mechanisms of placental failure. Although the molecular bases of placental abnormalities—including gene expression and protein markers— remain largely unknown, this work concentrated on macroscopic and microscopic placental findings. Understanding how placental malperfusion occurs and its role in limiting fetal growth requires investigating these molecular mechanisms. This would enable more tailored prenatal treatment by helping to identify signs for early diagnosis of placental malfunction.

Furthermore, a more comprehensive understanding of the relationship between LBW and placental insufficiency would emerge from longitudinal studies that follow maternal health, placental alterations, and fetal outcomes over time. Early identification of placental malfunction made possible by this strategy may enable early therapies during pregnancy and potentially reduce the prevalence of LBW. Future research could offer a fascinating route in creating pharmacological treatments to enhance placental performance. Research could investigate, for instance, the potential benefits of dietary supplements, pharmaceutical medications, or lifestyle modifications on maternal vascular health. Clinical investigations could assess whether these treatments reduce the frequency of placental malfunctions and improve delivery outcomes.

Later research should, all things considered, provide a growing sample size, give molecular and genetic analysis high priority, prioritize longitudinal investigations, and explore prospective therapeutic approaches. These studies will enable the development of more effective strategies for low-birth-weight care and help us better understand its pathogenesis.

BIBLIOGRAPHY

1. United Nations Children's Fund (UNICEF), World Health Organization (WHO). UNICEF-WHO Low birthweight estimates: Levels and trends 2000–2015. Geneva: World Health Organization; 2019. [Internet]. [cited 2023 Feb 16]. Available from: https://www.unicef.org/reports/UNICEF-WHO-low-birthweight-estimates-2019

2. Dutta DC, Konar H. DC Dutta's textbook of Obstetrics: Including Perinatology and contraception. 8th ed. New Delhi: Jaypee Brothers Medical Publishers; 2015. p. 527-40.

3. Jadhav CR, Srinivasamurthy BC, Bhat RV, Agrawal V, Kumar H. Placental pathology in low birth weight babies a prospective observational study. Indian J Pathol Oncol. 2018 Apr;5(2):178-83.

4. Pusdekar YV, Patel AB, Kurhe KG, Bhargav SR, Thorsten V, Garces A, et al. Rates and risk factors for preterm birth and low birthweight in the global network sites in six low-and low middle-income countries. Reproductive health. 2020 Dec;17(3):1-6.

5. Singh G, Chouhan R, Sidhu K, Maternal Factors for Low Birth Weight Babies. Med J Armed Forces India. 2009 Jan; 65(1): 10-2

6. Kleebkaow P, Limdumrongchit W, Ratanasiri T, Komwilaisak R, Seejorn K. Prevalence of placental pathology in low birthweight infants. Journal-Medical Association of Thailand. 2006 May 1;89(5):594.

7. Sharma M, Bhatia JK, Malik A. A clinicopathologic study of placentae of low birth weight and normal birth weight babies born at a tertiary care center in western India. Medical Journal of Dr. DY Patil University. 2021 Mar 1;14(2):166-71.

8. Nigam J, Misra V, Singh P, Singh P, Chauhan S, Thakur B. Histopathological study of placentae in low birth weight babies in India. Ann Med Health Sci Res 2014;4:S79-83.

9. Magesh P, Sheeba D, Ravi S, Subashini S, Varghese D. Placental histopathology in full term low birth weight new born babies in a tertiary care centre. [Internet]. [cited 2023 Feb 18]. Available from: https://jmscr.igmpublication.org/v7-i2/47%20jmscr.pdf

10. Singh K, Cohen MC. Anatomy & histology-placenta & umbilical cord. PathologyOutlines.com website. Available from: https://www.pathologyoutlines.com/topic/placentanormalhistology.html. Accessed November 2nd, 2024.

11. Sanchita P, Binoy BK, Amilee G. Evaluation of Placental Pathology in Term Low Birth Weight Babies. Journal of Maternal and Child Health. 2022 Sep 16;7(5):572-9

12. Redline RW. Placental pathology: a systematic approach with clinical correlations. Placenta. 2008 Mar 1;29:86-91.

13. Turco MY, Moffett A. Development of the human placenta. Development. 2019 Nov 15;146(22):dev163428

14. Balasubramanian R, Baliga SS, Kangle R, et al. Association of Placental Risk Factors and Birth Weight of Newborn: A Case–Control Study. J South Asian Feder Obst Gynae 2022;14(5):519–26.

15. Kr D, Parashuram R. Study of variations in human placental attachment of umbilical cord and its clinical significance. Int J Anat Res. 2020;8(1.2):7333-37.

16. Silver RM, Landon MB, Rouse DJ, Leveno KJ, Spong CY, et al. Maternal morbidity associated with multiple repeat cesarean deliveries. Obstetrics & Gynecology. 2006 Jun 1;107(6):1226-32.

17. Baergen RN. Manual of pathology of the human placenta. Springer Science & Business Media; 2011

18. Singh I. Human embryology. J P Medical Ltd; 2014 Sep 30.

19. Huppertz B. The anatomy of the normal placenta. Journal of clinical pathology. 2008 Dec 1;61(12):1296-302.

20. Luckett WP. Origin and differentiation of the yolk sac and extraembryonic mesoderm in presomite human and rhesus monkey embryos. Am J Anat 1978;152:59–97.

21. Enders AC, King BF. Formation and differentiation of extraembryonic mesoderm in the rhesus monkey. Am J Anat 1988;118:327–40.

22. Dempsey EW. The development of capillaries in the villi of early human placentas. Am J Anat 1972;134:221–38.

23. Demir R, Kaufmann P, Castellucci M, et al. Fetal vasculogenesis and angiogenesis in human placental villi. Acta Anat 1989;136:190–203.

24. Jackson MR, Mayhew TM, Boyd PA. Quantitative description of the elaboration and maturation of villi from 10 weeks of gestation to term. Placenta 1992;13:357–70.

25. O'Dowd G, Bell S, Wright S. Wheater's Functional Histology, E-Book: A Text and Colour Atlas. Elsevier Health Sciences; 2023 Apr 11.

26. Kapila V, Chaudhry K. Physiology, placenta. InStatPearls [Internet] 2023 Jul 24. StatPearls Publishing.

27. Cross JC. Placental function in development and disease. Reprod Fertil Dev. 2006;18(1-2):71-6.

28. Theofanakis C, Drakakis P, Besharat A, Loutradis D. Human Chorionic Gonadotropin: The Pregnancy Hormone and More. Int J Mol Sci. 2017 May 14;18(5)

29. Sengupta A, Biswas P, Jayaraman G, Guha SK. Understanding utero-placental blood flow in normal and hypertensive pregnancy through a mathematical model. Med Biol Eng Comput. 1997 May;35(3):223-30.

30. Schmiedl UP, Komarniski K, Winter TC, Luna JA, Cyr DR, Ruppenthal G, Schlief R. Assessment of fetal and placental blood flow in primates using contrast enhanced ultrasonography. J Ultrasound Med. 1998 Feb;17(2):75-80; discussion 81-2.

31. Gude NM, Roberts CT, Kalionis B, King RG. Growth and function of the normal human placenta. Thromb Res. 2004;114(5-6):397-407.

32. Robbins JR, Bakardjiev AI. Pathogens and the placental fortress. Curr Opin Microbiol. 2012 Feb;15(1):36-43.

33. Aasa KL, Zavan B, Luna RL, Wong PG, Ventura NM, Tse MY, Carmeliet P, Adams MA, Pang SC, Croy BA. Placental growth factor influences maternal cardiovascular adaptation to pregnancy in mice. Biol Reprod. 2015 Feb;92(2):44.

34. Sadler TW. Langman's medical embryology. Lippincott Williams & Wilkins; 2022 Dec 29.

35. Folkins AK, Roberts DJ. Placenta. In: Longacre TA, Greenson JK, Hornick JL, Reuter VE, editors. Mills and Sternberg's Diagnostic Surgical Pathology. 7th ed. Vol. 2. Philadelphia: Wolters Kluwer; 2022. p. 2545-79.

36. Boyd JD, Hamilton WJ. The human placenta. Cambridge: Heffer and Sons, 1970.

37. Kaufmann P. Basic morphology of the fetal and maternal circuits in the human placenta. Contrib Gynecol Obstet 1985;13:5–17.

38. Eroschenko VP, Di Fiore MS. DiFiore's atlas of histology with functional correlations. Lippincott Williams & Wilkins; 2013.

39. Redline RW, Ravishankar S, Bagby CM, Saab ST, Zarei S. Four major patterns of placental injury: a stepwise guide for understanding and

implementing the 2016 Amsterdam consensus. Modern Pathology. 2021 Jun 1;34(6):1074-92.

40. Redline RW, Boyd T, Campbell V, et al. Maternal vascular underperfusion: nosology and reproducibility of placental reaction patterns. Pediatr Dev Pathol. 2004;7(3):237-249.

41. Burton GJ, Jauniaux E. Placental oxidative stress: from miscarriage to preeclampsia. J Soc Gynecol Investig. 2004;11(6):342-352.

42. Burton GJ, Jones CJ. Syncytial knots, sprouts, apoptosis, and trophoblast deportation from the human placenta. Taiwan J Obstet Gynecol. 2009;48(1):28-37.

43. Brosens I, Puttemans P, Benagiano G. Placental bed research: I. The placental bed: from spiral arteries remodeling to the great obstetrical syndromes. Am J Obstet Gynecol. 2019;221:437–56.

44. Harris LK, Benagiano M, D'Elios MM, Brosens I, Benagiano G. Placental bed research: II. Functional and immunological investigations of the placental bed. Am J Obstet Gynecol. 2019;221:457–69.

45. Cindrova-Davies T, Fogarty NME, Jones CJP, Kingdom J, Burton GJ. Evidence of oxidative stress-induced senescence in mature, post-mature and pathological human placentas. Placenta. 2018;68:15–22.

46. Burke SD, Zsengeller ZK, Khankin EV, Lo AS, Rajakumar A, DuPont JJ, et al. Soluble fms-like tyrosine kinase 1 promotes angiotensin II sensitivity in preeclampsia. J Clin Invest. 2016;126:2561–74.

47. Levine RJ, Lam C, Qian C, Yu KF, Maynard SE, Sachs BP, et al. Soluble endoglin and other circulating antiangiogenic factors in preeclampsia. N. Engl J Med. 2006;355:992–1005.

48. Maynard SE, Min JY, Merchan J, Lim KH, Li J, Mondal S, et al. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. J Clin Invest. 2003;111:649–58.

49. Brosens I, Pijnenborg R, Vercruysse L, Romero R. The "Great Obstetrical Syndromes" are associated with disorders of deep placentation. Am J Obstet Gynecol. 2010;204:193–201.

50. Smith GC, Stenhouse EJ, Crossley JA, Aitken DA, Cameron AD, Connor JM. Early pregnancy levels of pregnancy-associated plasma protein a and the risk of intrauterine growth restriction, premature birth, preeclampsia, and stillbirth. J Clin Endocrinol Metab. 2002;87:1762–7.

51. Krebs C, Macara LM, Leiser R, Bowman AW, Greer IA, Kingdom JC. Intrauterine growth restriction with absent enddiastolic flow velocity in the umbilical artery is associated with maldevelopment of the placental terminal villous tree. Am J Obstet Gynecol. 1996;175:1534–42.

52. Lausman A, Kingdom J, Maternal Fetal Medicine C, Gagnon R, Basso M, Bos H, et al. Intrauterine growth restriction: screening, diagnosis, and management. J Obstet Gynaecol Can. 2013;35: 741–57.

53. Miremberg H, Grinstein E, Herman HG, Marelly C, Barber E, Schreiber L, et al. The association between isolated oligohydramnios at term and placental pathology in correlation with pregnancy outcomes. Placenta. 2020;90:37–41.

54. Arias F, Victorio A, Cho K, Kraus FT. Placental histology and clinical characteristics of patients with preterm premature rupture of membranes. Obstet Gynecol. 1997;89:265–71.

55. Gibbins KJ, Silver RM, Pinar H, Reddy UM, Parker CB, Thorsten V, et al. Stillbirth, hypertensive disorders of pregnancy, and placental pathology. Placenta. 2016;43:61–68.

56. Naeye RL, Harkness WL, Utls J. Abruptio placentae and perinatal death. A prospective study. Am J Obstet Gynecol. 1977;128:740–8.

57. Ray JG, Vermeulen MJ, Schull MJ, Redelmeier DA. Cardiovascular health after maternal placental syndromes (CHAMPS): population-based retrospective cohort study. Lancet. 2005;366:1797–803.

58. Wen X, Triche EW, Hogan JW, Shenassa ED, Buka SL. Association between placental morphology and childhood systolic blood pressure. Hypertension. 2010;57:48–55.

59. Pinar H, Sung CJ, Oyer CE, et al. Reference values for singleton and twin placental weights. Pediatr Pathol Lab Med 1996;16(6):901–7.

60. Proctor LK, Fitzgerald B, Whittle WL, et al. Umbilical cord diameter percentile curves and their correlation to birth weight and placental pathology. Placenta 2013;34(1):62–6.

61. Slack JC, Parra-Herran C. Life after Amsterdam: placental pathology consensus recommendations and beyond. Surgical Pathology Clinics. 2022 Jun 1;15(2):175-96.

62. Fitzgerald B, Shannon P, Kingdom J, Keating S. Rounded intraplacental haematomas due to decidual vasculopathy have a distinctive morphology. J Clin Pathol. 2011;64:729–32.

63. Loukeris K, Sela R, Baergen RN. Syncytial knots as a reflection of placental maturity: reference values for 20 to 40 weeks' gestational age. Pediatr Dev Pathol 2010;13(4):305–9.

64. Khong TY, Mooney EE, Ariel I, et al. Sampling and definitions of placental lesions: amsterdam placental workshop group consensus statement. Arch Pathol Lab Med 2016;140(7):698–713.

65. Zhang P. Decidual vasculopathy in preeclampsia and spiral artery remodeling revisited: shallow invasion versus failure of involution. AJP Rep 2018;8(4): e241–6.

66. Stanek J. Hypoxic patterns of placental injury, a review. Arch Pathol Lab Med. 2013;137:706-720.

67. Stanek J. Utility of diagnosing various histological patterns of diffuse chronic hypoxic placental injury. Pediatr Dev Pathol. 2012;15(1):13-23.

68. Redline RW, Ariel I, Baergen RN, DeSa DJ, Kraus FT, Roberts DJ, et al. Fetal vascular obstructive lesions: nosology and reproducibility of placental reaction patterns. Pedia Devel Pathol. 2004;7:443–52.

69. Redline RW, Ravishankar S. Fetal vascular malperfusion, an update. APMIS 2018;126(7):561–9.

70. Parast MM, Crum CP, Boyd TK. Placental histologic criteria for umbilical blood flow restriction in unexplained stillbirth. Hum Pathol. 2008;39(6):948953.

71. Redline RW. Placental inflammation. Semin Neonatol. 2004;9: 265–74.

72. PrabhuDas M, Bonney E, Caron K, Dey S, Erlebacher A, Fazleabas A, et al. Immune mechanisms at the maternal-fetal interface: perspectives and challenges. Nat Immunol. 2015;16: 328–34.

73. Redline RW, Faye-Petersen O, Heller D, Qureshi F, Savell V, Vogler C. Amniotic infection syndrome: nosology and reproducibility of placental reaction patterns. Pediatr Dev Pathol. 2003;6:435–48.

74. Lau J, Magee F, Qiu Z, Hoube J, Von Dadelszen P, Lee SK. Chorioamnionitis with a fetal inflammatory response is associated with higher neonatal mortality, morbidity, and resource use than chorioamnionitis displaying a maternal inflammatory response only. Am J Obstet Gynecol. 2005;193:708–13.

75. Laborada G, Nesin M. Interleukin-6 and interleukin-8 are elevated in the cerebrospinal fluid of infants exposed to chorioamnionitis. Biol Neonate. 2005;88:136–44.

76. Leviton A, Paneth N, Reuss ML, Susser M, Allred EN, Dammann O, et al. Maternal infection, fetal inflammatory response, and brain damage in very low birth weight infants. Developmental Epidemiology Network Investigators. Pediatr Res. 1999;46:566–75.

77. Van Marter LJ, Dammann O, Allred EN, Leviton A, Pagano M, Moore M, et al. Chorioamnionitis, mechanical ventilation, and postnatal sepsis as modulators of chronic lung disease in preterm infants. J Pediatr. 2002;140:171–6.

78. Redline RW, Wilson-Costello D, Borawski E, Fanaroff AA, Hack M. The relationship between placental and other perinatal risk factors for neurologic impairment in very low birth weight children. Pediatr Res. 2000;47(6):721726.

79. Gibbs RS, Blanco JD, St Clair PJ, Castaneda YS. Quantitative bacteriology of amniotic fluid from women with clinical intraamniotic infection at term. J Infect Dis. 1982;145(1):1-8.

80. Zhou YY, Ravishankar S, Luo G, Redline RW. Predictors of high grade and other clinically significant placental findings by indication for submission in singleton placentas from term births. Pediatr Dev Pathol. 2020;23:274–84.

81. Hood IC, DeSa DJ, Whyte RK. The inflammatory response in candidal chorioamnionitis. Hum Pathol. 1983;14:984–90.

82. Qureshi F, Jacques SM, Benson RW, Peterson OM, Heifetz SA, Redline RW, et al. Candida funisitis: a clinicopathologic study of 32 cases. Pedia Devel Pathol. 1998;1:118–24.

83. Ohyama M, Itani Y, Yamanaka M, Goto A, Kato K, Ijiri R, et al. Re-evaluation of chorioamnionitis and funisitis with a special reference to subacute chorioamnionitis. Hum Pathol. 2002;33: 183–90.

84. Redline RW. Villitis of unknown etiology: noninfectious chronic villitis in the placenta. Hum Pathol. 2007;38:1439–46.

85. Redline RW, Patterson P. Villitis of unknown etiology is associated with major infiltration of fetal tissue by maternal inflammatory cells. Am J Pathol. 1993;143:473–9.

86. Myerson D, Parkin RK, Benirschke K, Tschetter CN, Hyde SR. The pathogenesis of villitis of unknown etiology: analysis with a new conjoint immunohistochemistry-in situ hybridization procedure to identify specific maternal and fetal cells. Pediatr Dev Pathol. 2006;9:257–65.

87. Becroft DM, Thompson JM, Mitchell EA. Placental villitis of unknown origin: epidemiologic associations. Am J Obstet Gynecol 2005;192(1):264–71.

88. Styer AK, Parker HJ, Roberts DJ, et al. Placental villitis of unclear etiology during ovum donor in vitro fertilization pregnancy. Am J Obstet Gynecol 2003;189(4):1184–6.

89. Redline RW. Classification of placental lesions. Am J Obstet Gynecol 2015;213(4, Supplement):S21–8.

90. Kim CJ, Romero R, Chaemsaithong P, et al. Chronic inflammation of the placenta: definition, classification, pathogenesis, and clinical significance. Am J Obstet Gynecol 2015;213(4, Supplement):S53–69.

91. Ernst LM, Bockoven C, Freedman A, et al. Chronic villitis of unknown etiology: Investigations into viral pathogenesis. Placenta 2021;107:24–30.

92. Freedman AA, Goldstein JA, Miller GE, et al. Seasonal variation of chronic villitis of unknown etiology. Pediatr Dev Pathol 2020;23(4):253–9.

93. Baergen RN, Heller DS. Placental pathology in Covid-19 positive mothers: preliminary findings. Pediatr Dev Pathol 2020;23(3):177–80.

94. Benirschke K, Coen R, Patterson B, et al. Villitis of known origin: varicella and toxoplasma. Placenta 1999;20(5):395–9.

95. Ravishankar S. 4 main categories. PathologyOutlines.com website. https://www.pathologyoutlines.com/topic/placenta4categories.html. Accessed March 17th, 2025.

96. Boyd TK, Redline RW. Chronic histiocytic intervillositis: a placental lesion associated with recurrent reproductive loss. Hum Pathol. 2000;31(11):1389-96.

97. Doss BJ, Greene MF, Hill J, Heffner LJ, Bieber FR, Genest DR. Massive chronic intervillositis associated with recurrent abortions. Hum Pathol. 1995;26(11):1245-51.

98. Chen A, Roberts DJ. Placental pathologic lesions with a significant recurrence risk - what not to miss! APMIS. 2018;126(7):589-601.

99. Koby L, Keating S, Malinowski AK, D'Souza R. Chronic histiocytic intervillositis—clinical, biochemical and radiological findings: an observational study. Placenta. 2018;64:1-6.

100. Mekinian A, Costedoat-Chalumeau N, Masseau A, et al. Chronic histiocytic intervillositis: outcome, associated diseases and treatment in a multicenter prospective study. Autoimmunity. 2015;48(1):40-45

101. Bane AL, Gillan JE. Massive perivillous fibrinoid deposit causing recurrent placental failure. International J Obstet Gynecol 2003;100:292-295.

102. Naeye RL. Maternal floor infarction. Hum Pathol. 1985;16(8):823-828.

103. Heller DS, Tellier R, Pabbaraju K, et al. Placental massive perivillous fibrinoid deposition associated with coxsackievirus A16-report of a case, and review of the literature. Pediatr Dev Pathol. 2016;19(5):421-423.

104. Yu W, Tellier R, Wright JR Jr. Coxsackie virus A16 infection of placenta with massive perivillous fibrin deposition leading to intrauterine fetal demise at 36 weeks gestation. Pediatr Dev Pathol. 2015;18(4):331-334.

105. Katzman PJ, Genest DR. Maternal floor infarction and massive perivillous fibrin deposition: histological definitions, association with intrauterine fetal growth restriction, and risk of recurrence. Pediatr Dev Pathol. 2002;5(2):159-164

106. Boyraz B, Roberts D. Chorangioma. PathologyOutlines.com website. https://www.pathologyoutlines.com/topic/placentachorangioma.html. Accessed December 29th, 2024.

107. GovIndarajan G, GanaPathy S, SudalaIMuthu M. Histological Study of Placental Changes in Low Birth Weight Neonates in a Tertiary Care Hospital. Journal of Clinical & Diagnostic Research. 2020 Nov 1;14(11).

108. Eiríksdóttir VH, Asgeirsdottir TL, Bjarnadóttir RI, Kaestner R, Cnattingius S, Valdimarsdottir UA. Low birth weight, small for gestational age and preterm births before and after the economic collapse in Iceland: a population based cohort study. PloS one. 2013 Dec 4;8(12):e80499.

109. Liu Y, Li N, An H, Li Z, Zhang L, Li H, Zhang Y, Ye R. Impact of gestational hypertension and preeclampsia on low birthweight and small-for-gestational-age infants in China: A large prospective cohort study. The Journal of Clinical Hypertension. 2021 Apr;23(4):835-42.

110. Leyto SM, Mare KU. Association of placental parameters with low birth weight among neonates born in the Public Hospitals of Hadiya Zone, Southern Ethiopia: an Institution-Based Cross-Sectional Study. International Journal of General Medicine. 2022 May 16:5005-14.

111. Kumar M, Verma R, Khanna P, Bhalla K, Kumar R, Dhaka R, et al. Prevalence and associate factors of low birth weight in North Indian babies: A rural based study. Int J Community Med Public Heal 2017;4:3212-17.

112. Nkwabong E, Nounemi NK, Sando Z, Mbu RE, Mbede J. Risk factors and placental histopathological findings of term born low birth weight neonates. Placenta. 2015 Feb 1;36(2):138-41.

113. Jarmuzek P, Wielgos M, Bomba-Opon D. Placental pathologic changes in gestational diabetes mellitus. Neuroendocrinol Lett. 2015 Jan 1;36(2):101-5.

114. Senapati S, Nayak L, Behera SS, Chinara PK. Morphometric study of placenta of full term new born & its relation to fetal weight: a study in Tertiary Care Hospital of Odisha. Journal of Evolution of Medical and Dental Sciences-Jemds. 2015 Jan 15;4(5):742-7.

115. Barwari SS, Mohammed SS. Histological Evaluation of Placentas in Idiopathic Intrauterine Growth Restriction. Cureus. 2024 Oct 31;16(10): e72789

116. Heider A. Fetal vascular malperfusion. Archives of Pathology & Laboratory Medicine. 2017 Nov 1;141(11):1484-9.

117. Daskalakis G, Psarris A, Koutras A, Fasoulakis Z, Prokopakis I, Varthaliti A, Karasmani C, Ntounis T, Domali E, Theodora M, Antsaklis P. Maternal infection and preterm birth: from molecular basis to clinical implications. Children. 2023 May 22;10(5):907.

ANNEXURES

ANNEXURE – I - INFORMED CONSENT FORM

"CLINICOPATHOLOGICAL ANALYSIS OF PLACENTA IN TERM LOW BIRTH WEIGHT INFANTS IN COMPARISON WITH TERM NORMAL BIRTH WEIGHT INFANTS - A CASE CONTROL STUDY AT TERTIARY CARE HOSPITAL, BELAGAVI"

Name of Student/Principal Investigator: _____

Name of Guide/Co Investigator: _____

Name of Co-Guide/Co Investigators: _____

Introduction: Low birth weight is a major public health problem that affects nearly a third of the Indian population. The placenta is a vital organ that connects the mother and the fetus during the gestational period and is delivered after childbirth.

Objective: This study aims at assessing the placenta and understanding its clinical correlation in infants with term low birth weight as compared to term normal birth weight infants.

Explanation of procedure: Your clinical case details about present and previous pregnancy will be taken and your placenta which is sent for histopathological investigation will be evaluated.

Withdrawal from participation in the study: Participation in this study is voluntary. You will be free to decide whether to participate in this study or continue

participation once enrolled. In case you decide to withdraw your participation, you are free to do so. However, please convey the decision to the principal investigator.

Possible benefits from participating in the study: You will not get any benefits by participating in this study. The data gathered will help the population at large.

Possible risks from participating in the study: There are no risks involved in participating in this study.

Privacy and confidentiality: The information collected from you will be coded, to prevent any person from identifying you. Your identity will never be revealed. The data collected from you will be kept confidential and only processed or aggregated data will be used for publication.

Financial incentives: You will not receive any payment for participating in this study.

Authorization for publication of aggregated data: Results obtained after processing of the aggregated data will be published for scientific purposes and or presented to scientific groups. However, your identity will never be revealed.

Questions:

If you have any question or complaints with regard to your right as a study participant you may contact Dr Harsha Hegde, Chairperson, Ethical committee of JNMC, 0831-2473777 Extension 4052.

Legal rights: By signing this consent form, we are not waving any of your legal rights

ANNEXURE - II -PROFORMA

Name of the participant	
Screening Id of the patient (Case / Control)	
IP number of the participant	
Birth weight of the infant	
Gestational age at delivery	
Sex of the infant	
Maternal Age	
FTVD/LSCS/Forceps or Vacuum assisted delivery	
Gravida, parity, live births, Any previous abortion/ IUFD/ Stillbirth	
Maternal anemia	
Pregnancy-induced hypertension	
Gestational diabetes	
Maternal infection during present gestation	
HIV, HBsAg, HCV, Syphilis status	
Oligo/Polyhydramnios	
Placenta previa	
Placental abruption	
Maternal chronic health conditions like diabetes, heart disease, kidney disease, hypertension, infectious disease, autoimmune disease	
Weight gain during present gestation	
USG findings	
Double marker test (Beta hCG, PAPP-A)	
Any other findings	

Gross description

HP no -_____, Fresh/ fixed specimen, IP number_____

UMBILICAL CORD

1. Dimensions - _____(length) × _____(diameter)
2. Attachment - To placental disc/ placental membranes
3. Color - white tan/ green yellow/ green brown/ brown red/ with white spots
4. Insertion - centrally/ eccentrically/ marginally/ velamentously _____cm from the disc margin
5. Coils -____in ____cm of cord, cord coil index - ____
6. Any True knots/ edema/ other focal lesions
7. Periarterial wharton's jelly - Normal presence / Not present
8. Appearance & consistency of sectioned surface- Sectioning reveals white tan cut surface displaying _____ (number) blood vessels._____

FETAL MEMBRANES

1. Complete/ Incomplete
2. Membrane rupture _____ cm from nearest placental edge
3. Translucent/ opaque
4. Tan/ green/ brown
5. Attachment - normally at the disc margin/ circummarginate/ circumvallate
6. Velamentous vessels - Yes/ no
7. Any other significant findings (any local or generalized lesions)_____

PLACENTAL DISC

1. Trimmed weight - _____ g
2. Measurement _____x_____x____cm
3. Shape - Discoid/ oval/ Triangular/ Irregular
4. Bilobed/ Multilobed/ Accessory lobe - present / no
5. Appearance of fetal surface - pale blue/pink, smooth and glistening or _____
6. Any thrombi in the chorionic plate vessels/ Any subchorionic lesion
7. Appearance of maternal surface - grey brown/_____, cotyledons appears intact/ disrupted
8. Any lesions, if yes measure, color, _____ cm from disc margin, single/ multiple, focal/ diffuse _____
9. Appearance & consistency of sectioned surface (on serial sectioning at 5 mm intervals) - placental parenchyma is spongy, dark red
10. Any lesion (occupying _____% of placental volume) measurement, color, _____ cm from disc margin, single/ multiple, focal/ diffuse_____

Microscopic findings

	PI	AVM	DVH	K	FPV	IH	DA	AV	T	VIFD	VE	VSVK	FS	ACA	VUE	CHI	MPFD	CH	DVM
Case	P /NP	P /NP	P /NP	P /NP	P /NP	P /NP	P /NP	P /NP	P /NP	P /NP	P /NP	P /NP	P /NP	P /NP	P /NP	P /NP	P /NP	P /NP	P /NP
Control	P /NP	P /NP	P /NP	P /NP	P /NP	P /NP	P /NP	P /NP	P /NP	P /NP	P /NP	P /NP	P /NP	P /NP	P /NP	P /NP	P /NP	P /NP	P /NP

ANNEXURE - III - HEMATOXYLIN AND EOSIN STAIN

REAGENTS

1. Erhlich's Hematoxylin solution
2. Eosin Y solution 1%
3. 1% acid alcohol solution

STAINING PROCEDURE

1. Deparaffinise the tissue sections in Xylene (Xylene 1 for 5 minutes + Xylene 2 for 5 minutes).
2. Subject the tissue section to water through reducing grades of alcohol (90% alcohol for 5 minutes + 70% alcohol for 5 minutes).
3. Keep it in Hematoxylin for 8 to 10 minutes.
4. Rinse it in tap water for 2 minutes.
5. Differentiate with 1% acid alcohol for 10 seconds.
6. For bluing - place in tap water for about 10 minutes.
7. Counter stain with Eosin for 1 to 2 minutes.
8. Rinse in tap water.
9. Dehydrate using increasing grades of alcohol (70% alcohol for 30 seconds + 90% alcohol for 30 seconds).
10. Do clearing with Xylene (Xylene 1 for 5 minutes + Xylene 2 for 5 minutes).
11. Mount the slide with Dibutylphthalate Polystyrene Xylene (DPX).

ANNEXURE - IV - KEY TO MASTERCHART

1.	ACA	Acute chorioamnionitis
2.	A-FM	Appearance of fetal membranes
3.	A-FS	Appearance of fetal surface
4.	A-MS	Appearance of maternal surface
5.	At-FM	Attachment of fetal membranes
6.	A-UC	Appearance of sectioned surface of umbilical cord
7.	AV	Avascular villi
8.	AVM	Accelerated villous maturation
9.	B	Breadth of placental disc
10.	Br	Brown
11.	BWI	Birth weight of Infant
12.	C	Complete
13.	CCI	Cord coil index
14.	Ce	Central
15.	C-FM	Color of fetal membranes
16.	C-FS	Color of fetal surface
17.	CH	Chorangiosis
18.	CHI	Chronic histiocytic intervillositis
19.	CKD	Chronic kidney disease
20.	CM	Circummarginate

21.	C-SS	Color of sectioned surface of placental disc
22.	Cs-SS	Consistency of sectioned surface of placental disc
23.	CV	Circumvallate
24.	CVD	Cerebrovascular disease
25.	D	Discoid
26.	DA	Decidual arteriopathy
27.	Da Re	Dark red
28.	DM	Diabetes mellitus
29.	DMr	Disc margin
30.	DVH	Distal villous hypoplasia
31.	DVM	Delayed villous maturation
32.	EC	Eccentric
33.	FD	Fetal distress
34.	FGR	Fetal growth restriction
35.	FPF	Focal perivillous fibrin
36.	FS	Fibromuscular sclerosis
37.	FTND	Full term normal delivery
38.	FTVD	Full term ventouse delivery
39.	FVM	Fetal vascular malperfusion
40.	G	Gender
41.	Ga	Gestational age

42.	GD	Gestational diabetes
43.	GPLA	Gravida, parity, live births, any previous abortion
44.	Gr	Green
45.	Gy-Br	Grey brown
46.	Hb	Hemoglobin
47.	HM	Hypothyroidism
48.	HTN	Hypertension
49.	I	Incomplete
50.	IH	Intravillous hemorrhage
51.	Ir	Irregular
52.	K	Syncytial knots
53.	L	Length of placental disc
54.	LSCS	Lower segment caesarean section
55.	MA	Maternal anemia
56.	MCD	Maternal chronic diseases
57.	MDPP	Maternal diseases in present pregnancy
58.	MI	Maternal infection during present gestation.
59.	MOD	Mode of delivery
60.	MPDPP	Maternal placental diseases in present pregnancy
61.	MPFD	Massive perivillous fibrin deposition
62.	Mr	Marginal

63.	MVM	Maternal vascular malperfusion
64.	N	No
65.	NP	Not present
66.	NV	Number of blood vessels in umbilical cord
67.	O	Oval
68.	OH	Oligohydramnios
69.	Op	Opaque
70.	P	Present
71.	PA	Placental abruption
72.	PB	Pale Blue
73.	PD	Placental disc
74.	PH	Polyhydramnios
75.	PI	Placental infarction
76.	PIH	Pregnancy induced hypertension
77.	Pk	Pink
78.	PP	Placenta previa
79.	PWJ	Periarterial wharton’s jelly
80.	S	Shape of placental disc
81.	SM-GL	Smooth and glistening
82.	Sr. No.	Serial Number
83.	T	Thrombosis in fetal vessels

84.	Ta	Tan
85.	T-FS	Any thrombi on fetal surface
86.	Th	Thickness of placental disc
87.	Tl	Translucent
88.	Tr	Triangular
89.	TW	Trimmed weight of placental disc
90.	UCA	Umbilical cord attachment
91.	UCC	Umbilical cord color
92.	UCD	Umbilical cord diameter
93.	UCIn	Umbilical cord insertion
94.	UCL	Umbilical cord length
95.	V	Velamentous
96.	VE	Vascular ectasia
97.	VIFD	Vascular intramural fibrin deposition
98.	VSVK	Villous stromal vascular karyorrhexis
99.	VUE	Villitis of unknown etiology
100.	Vv	Velamentous vessels
101.	Wg	Weight gain during pregnancy

ANNEXURE - V - MASTERCHART

Patient_ID	Sr. No.	Ma	G	Ga	BWI (kg)	Wg (kg)	Maternal Hb	Maternal anemia	PIH	GD	OH/PH	MI	PP	PA	CKD	HTN	CVD	HM	DM	FD	GPLA	MOD	Other findings	UCL (cm)	UCD (cm)	UCA	UCC	UCIn	CCI	PWJ	A-UC	NV	Fetal membranes	A-FM	C-FM	At-FM	Vv	TW (gm)	L (cm)	B (cm)	Th (cm)	S	A-FS	C-FS	T-FS	A-MS	Cotyledones	Cs-SS	C-SS	Areas of infarction	PI	AVM	DVH	K	FPF	IH	DA	AV	T	VIFD	VE	VSVK	FS	ACA	VUE	CHI	MPFD	CH	DVM
CASES																																																																							
CA-1	1	28	F	38w,6d	2.4	8	11.2	NP	P	NP	OH	NP	NP	NP	NP	NP	NP	NP	NP	P	G3P1L1A2	LSCS	No	10	1	PD	White tan	EC	0.2	P	White tan	3	C	Tl	Ta	DMr	NP	400	16	15	2.5	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re	NP	NP	NP	NP	NP	P	NP	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	P	NP
CA-2	2	26	M	38W,6d	2	8.5	10.2	P	NP	NP	OH	NP	NP	NP	NP	NP	NP	NP	NP	P	G1P1L1	LSCS	FGR	15	1	PD	White tan	EC	0.2	P	White tan	3	C	Tl	Ta	DMr	NP	250	14	11.5	2.5	O	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re	NP	NP	NP	NP	P	NP	NP	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
CA-3	3	23	F	38w,2d	2.4	9.2	11.3	NP	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G3P3L3	FTND	No	10	1	PD	White tan	EC	0.1	P	White tan	3	C	Tl	Ta	DMr	NP	350	13	13	2.2	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re	NP	NP	NP	NP	P	P	NP	NP	P	NP	P	NP	NP	NP	P	NP	NP	NP	NP	NP
CA-4	4	23	M	39w	2.4	8.5	10.5	P	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G2P2L2	FTND	No	15	0.8	PD	White tan	Mr	0.2	P	White tan	3	C	Tl	Ta	DMr	NP	400	15	14.5	2	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re	P	P	NP	NP	P	P	NP	P	NP	NP	NP	NP	NP	P	NP	NP	NP	NP	NP	NP
CA-5	5	23	M	37w,2d	2.3	8.4	10.6	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	P	NP	NP	G1P1L1	FTND	No	15	0.7	PD	White tan	EC	0.2	P	White tan	3	C	Tl	Gr	DMr	NP	450	15	14	2	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re	NP	NP	NP	NP	P	P	NP	NP	P	P	NP	NP	NP	NP	P	NP	NP	NP	P	NP
CA-6	6	23	M	37w, 2d	2.3	9	10.6	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G3P3L3	LSCS	No	19	0.8	PD	White tan	EC	0.1	P	White tan	3	C	Tl	Ta	DMr	NP	425	16.5	13.5	2.5	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re	NP	NP	NP	P	P	NP	NP	NP	P	NP	NP	NP	NP	NP	P	P	NP	P	P	NP
CA-7	7	24	M	38w	2.3	8	14.1	NP	NP	NP	OH	NP	NP	NP	NP	NP	NP	P	NP	P	G1P1L1	LSCS	FGR	5	1	PD	White tan	EC	0.2	P	White tan	3	C	Tl	Ta	DMr	NP	350	13	12	2	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re	NP	NP	NP	NP	P	NP	NP	NP	P	NP	P	NP	NP	NP	NP	NP	NP	NP	P	NP
CA-8	8	25	F	38w	2.3	8	10.5	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G1P1L1	LSCS	No	12	0.7	PD	White tan	Mr	0.1	P	White tan	3	C	Tl	Ta	DMr	NP	350	14	12.5	2	D	SM-GL	PB	NP	Gy-Br	Missing	Spongy	Da Re	P	P	NP	NP	NP	NP	NP	P	NP	NP	NP	P	NP	P	NP	NP	NP	NP	P	NP
CA-9	9	38	M	38w	2.3	8	10.5	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G2P2L2	LSCS	No	12	1	PD	White tan	EC	0.2	P	White tan	3	C	Tl	Ta	CV	NP	325	14	11	1.5	O	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re	NP	NP	NP	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	P	P	NP	NP	NP	NP
CA-10	10	25	M	38w	2.4	7.5	10.6	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G1P1L1	LSCS	No	10	1	PD	White tan	EC	0.1	P	White tan	3	C	Tl	Ta	DMr	NP	400	15	13	2	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re	NP	NP	NP	NP	P	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	P	NP
CA-11	11	28	F	38w,6d	2.4	8	11.2	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	P	G3P1L1A2	LSCS	No	10	1	PD	White tan	EC	0.2	P	White tan	3	C	Tl	Ta	DMr	NP	400	16	15	2.5	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re	NP	NP	NP	NP	NP	P	NP	NP	P	NP	NP	P	NP	NP	NP	NP	NP	NP	P	NP
CA-12	12	26	M	38W,6d	2	8.5	10.2	P	NP	NP	OH	NP	NP	NP	NP	NP	NP	NP	NP	P	G1P1L1	LSCS	FGR	15	1	PD	White tan	EC	0.2	P	White tan	3	C	Tl	Ta	DMr	NP	250	14	11.5	2.5	O	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re	P	P	NP	NP	P	NP	NP	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
CA-13	13	23	F	38w,2d	2.4	9	11.3	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G2P2L2	FTND	No	10	1	PD	White tan	EC	0.1	P	White tan	3	C	Tl	Ta	DMr	NP	350	13	13	2.2	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re	NP	NP	NP	NP	P	P	NP	NP	P	P	NP	NP	NP	NP	P	NP	NP	NP	NP	NP
CA-14	14	23	M	39w	2.4	9	10.5	P	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G3P3L3	FTND	No	15	0.8	PD	White tan	Mr	0.2	P	White tan	3	C	Tl	Ta	DMr	NP	400	15	14.5	2	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re	NP	NP	NP	NP	P	P	NP	P	NP	NP	NP	P	NP	P	P	NP	NP	P	NP	NP
CA-15	15	33	M	37w,2d	2.3	9	10.6	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G2P2L2	FTND	No	15	0.7	PD	White tan	EC	0.2	P	White tan	3	C	Tl	Ta	DMr	NP	450	15	14	2	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re	NP	NP	NP	NP	P	P	NP	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	P	NP
CA-16	16	23	M	37w, 2d	2.3	9.5	10.6	P	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G1P1L1	LSCS	No	19	0.8	PD	White tan	EC	0.1	P	White tan	3	C	Tl	Ta	DMr	NP	425	16.5	13.5	2.5	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re	NP	NP	NP	NP	P	NP	NP	NP	P	NP	NP	NP	NP	NP	P	P	NP	P	P	NP
CA-17	17	24	M	38w	2.3	9	14.1	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	P	NP	NP	G3P3L3	LSCS	No	5	1	PD	White tan	EC	0.2	P	White tan	3	C	Tl	Ta	DMr	NP	350	13	12	2	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re	NP	NP	NP	NP	P	NP	NP	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	P	NP
CA-18	18	25	F	38w	2.3	8.5	10.5	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G1P1L1	LSCS	No	12	0.7	PD	White tan	Mr	0.1	P	White tan	3	C	Tl	Ta	DMr	NP	350	14	12.5	2	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re	P	P	NP	NP	NP	NP	NP	P	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	P	NP
CA-19	19	38	M	38w	2.3	9	10.5	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	P	G2P2L2	LSCS	FGR	12	1	PD	White tan	EC	0.2	P	White tan	3	C	Tl	Ta	DMr	NP	325	14	11	1.5	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re	NP	NP	NP	NP	P	NP	NP	NP	NP	NP	NP	P	NP	NP	NP	NP	NP	NP	NP	NP
CA-20	20	25	M	38w	2.4	9	10.6	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G1P1L1	LSCS	No	10	1	PD	White tan	EC	0.1	P	White tan	3	C	Tl	Ta	DMr	NP	400	15	13	2	D	SM-GL	PB	NP	Gy-Br	Missing	Spongy	Da Re	NP	NP	NP	NP	P	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	P	P	NP
CA-21	21	24	M	38w	2.3	9.2	14.1	NP	NP	NP	OH	NP	NP	NP	NP	NP	NP	P	NP	NP	G1P1L1	LSCS	No	5	1	PD	White tan	EC	0.2	P	White tan	3	C	Tl	Ta	DMr	NP	350	13	12	2	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re	P	P	NP	NP	P	P	NP	NP	NP	NP	P	NP	NP	NP	P	NP	NP	NP	P	NP
CA-22	22	25	F	38w	2.3	10	10.5	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G3P3L3	LSCS	No	12	0.7	PD	White tan	Mr	0.1	P	White tan	3	C	Tl	Ta	DMr	NP	350	14	12.5	2	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re	NP	NP	NP	NP	NP	P	NP	P	NP	NP	NP	NP	NP	P	NP	NP	NP	NP	P	NP
CA-23	23	38	M	38w	2.3	10.3	10.5	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G2P2L2	LSCS	No	12	1	PD	White tan	EC	0.2	P	White tan	3	C	Tl	Ta	CV	NP	325	14	11	1.5	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re	NP	NP	NP	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	P	NP	NP	NP	NP
CA-24	24	35	M	38w	2.4	11	10.6	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G1P1L1	LSCS	No	10	1	PD	White tan	EC	0.1	P	White tan	3	C	Tl	Ta	DMr	NP	400	15	13	2	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re	NP	P	NP	NP	P	P	NP	NP	P	P	NP	NP	NP	NP	NP	NP	NP	NP	P	NP
CA-25	25	28	F	38w,6d	2.4	9.5	11.2	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	P	G3P1L1A2	LSCS	No	10	1	PD	White tan	EC	0.2	P	White tan	3	C	Tl	Ta	DMr	NP	400	16	15	2.5	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re	NP	NP	NP	NP	NP	P	NP	P	P	NP	NP	NP	NP	NP	NP	NP	NP	P	P	NP
CA-26	26	24	M	38W,6d	2	9.2	10.2	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G1P1L1	LSCS	FGR	15	1	PD	White tan	EC	0.2	P	White tan	3	C	Tl	Ta	DMr	NP	250	14	11.5	2.5	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re	NP	NP	NP	NP	P	NP	NP	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
CA-27	27	23	F	38w,2d	2.4	9.5	11.3	NP	NP	P	OH	NP	NP	NP	NP	NP	NP	NP	NP	NP	G1P1L1	FTND	No	10	1	PD	White tan	EC	0.1	P	White tan	3	C	Tl	Ta	DMr	NP	350	13	13	2.2	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re	NP	NP	NP	NP	P	P	NP	NP	P	P	NP	P	NP	NP	P	NP	NP	NP	NP	NP
CA-28	28	22	M	39w	2.4	9	10.5	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G2P2L2	FTND	FGR	15	0.8	PD	White tan	EC	0.2	P	White tan	3	C	Tl	Ta	DMr	NP	400	15	14.5	2	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re	P	P	NP	NP	P	P	NP	NP	NP	NP	P	NP	NP	P	P	NP	NP	NP	NP	NP
CA-29	29	23	M	37w,2d	2.3	8	10.6	P	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	P	G1P1L1	FTND	No	15	0.7	PD	White tan	Mr	0.2	P	White tan	3	C	Tl	Ta	DMr	NP	450	15	14	2	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re	NP	NP	NP	NP	P	NP	NP	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	P	P	NP
CA-30	30	23	M	37w, 2d	2.3	9	10.6	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G2P2L2	LSCS	No	19	0.8	PD	White tan	EC	0.1	P	White tan	3	C	Tl	Gr	DMr	NP	425	16.5	13.5	2.5	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re	NP	P	NP	NP	P	NP	NP	NP	P	NP	NP	NP	NP	P	P	P	NP	NP	P	NP

CONTROLS

Patient_ID	Sr. No.	Ma	G	Ga	BWI (kg)	Wg (kg)	Maternal Hb	Maternal anemia	PIH	GD	OH/PH	MI	PP	PA	CKD	HTN	CVD	HM	DM	FD	GPLA	MOD	Other findings
CO-1-1	1	20	F	39W,3d	2.5	10	11.8	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G1P1L1	LSCS	No
CO-1-2	2	28	F	39W,4d	2.9	11	13.3	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G3P2L2A1	FTND	No
CO-2-1	3	31	M	38w,6d	3.2	11	12.9	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G5P5L4A1	FTND	No
CO-2-2	4	28	M	38W,5d	3.7	11.2	8.6	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G3P3L3	FTND	No
CO-3-1	5	28	F	37w,4d	2.8	10.7	10.6	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G1P1L1	FTND	No
CO-3-2	6	21	F	40w,1d	3.1	10	10.8	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	P	G1P1L1	LSCS	No
CO-4-1	7	19	M	39w,2d	3	11	12.1	NP	NP	NP	OH	NP	NP	NP	NP	NP	NP	NP	NP	NP	G2P2L2	FTND	No
CO-4-2	8	29	M	39w,4d	2.6	10.8	11.9	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	P	G1P1L1	FTND	FGR
CO-5-1	9	25	M	37w,3d	2.9	11.1	10.8	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G4P3L3A1	LSCS	No
CO-5-2	10	19	M	37w,1d	3.2	11	8.9	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	P	NP	NP	G1P1L1	FTND	No
CO-6-1	11	30	M	39w	3	9	12.3	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G2P1L1A1	FTND	No
CO-6-2	12	33	M	39w,5d	3.8	11.5	12.9	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G2P2L2	LSCS	No
CO-7-1	13	23	M	38w1d	3.2	11	12.8	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G1P1L1	FTND	No
CO-7-2	14	22	M	40w,4d	3	11.2	13.1	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G2P2L2	FTND	No
CO-8-1	15	30	F	37w,6d	2.8	9	9.6	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G2P1L1A1	LSCS	No
CO-8-2	16	26	F	37w,5d	2.6	10	11.2	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G3P3L3	LSCS	No
CO-9-1	17	31	F	38w,5d	3.1	11	12.4	NP	NP	NP	OH	NP	NP	NP	NP	NP	NP	NP	NP	NP	G2P2L2	LSCS	No
CO-9-2	18	23	F	38w,1d	2.8	9	8.5	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G1P1L1	FTND	No
CO-10-1	19	22	M	38w,3d	2.9	10	11.6	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G2P2L1D1	LSCS	No
CO-10-2	20	22	M	37w1d	2.5	10.5	11	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G1P1L1	LSCS	No
CO-11-1	21	29	F	38w1d	2.6	10.5	10.4	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G2P2L2	FTND	No
CO-11-2	22	20	F	39w5d	3	9	11.6	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G1P1L1	FTND	No
CO-12-1	23	25	M	39w1d	2.9	11	11.6	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G2P1L1A1	FTVD	No
CO-12-2	24	22	M	39w2d	2.7	10.5	11.4	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G1P1L1	LSCS	No
CO-13-1	25	25	F	37w3d	2.5	11	11	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G2P2L2	FTND	No
CO-13-2	26	29	F	37w	2.7	10.7	11.2	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G3P2L2A1	LSCS	No
CO-14-1	27	31	M	40w	2.9	11.2	11	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G2P2L2	FTND	No
CO-14-2	28	24	M	39w	3	11	9.7	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G1P1L1	LSCS	No
CO-15-1	29	24	M	39w	3.1	9	9.4	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G1P1L1	LSCS	No
CO-15-2	30	23	M	38w	2.8	11	11.6	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	P	NP	NP	G1P1L1	LSCS	No
CO-16-1	31	25	F	38w	2.8	11.2	11.8	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G2P2L2	LSCS	No
CO-16-2	32	25	M	39w	2.7	10.8	11.9	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G2P2L2	LSCS	No
CO-17-1	33	23	M	38w	2.8	11	7.9	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G3P3L3	LSCS	No
CO-17-2	34	20	F	39W,3d	2.5	10	11.8	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G1P1L1	LSCS	No
CO-18-1	35	28	F	39W,4d	2.9	11	13.3	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G3P2L2A1	FTND	No
CO-18-2	36	31	M	38w,6d	3.2	11	12.9	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G5P5L4A1	FTND	No
CO-19-1	37	28	M	38W,5d	3.7	11.2	8.6	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G3P3L3	FTND	No
CO-19-2	38	28	F	37w,4d	2.8	10.7	10.6	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G1P1L1	FTND	No
CO-20-1	39	21	F	40w,1d	3.1	10	10.8	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	P	G1P1L1	LSCS	No
CO-20-2	40	19	M	39w,2d	3	11.5	12.1	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G1P1L1	FTND	No
CO-21-1	41	29	M	39w,4d	2.6	10.8	11.9	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	P	G1P1L1	FTND	FGR
CO-21-2	42	25	M	37w,3d	2.9	11.1	10.8	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G4P3L3A1	LSCS	No
CO-22-1	43	19	M	37w,1d	3.2	11	8.9	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	P	NP	NP	G1P1L1	FTND	No
CO-22-2	44	30	M	39w	3	10	12.3	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G2P1L1A1	FTND	No
CO-23-1	45	33	M	39w,5d	3.8	11	12.9	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G2P2L2	LSCS	No
CO-23-2	46	23	M	38w1d	3.2	11	12.8	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G1P1L1	FTND	No
CO-24-1	47	22	M	40w,4d	3	10	13.1	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G2P2L2	FTND	No
CO-24-2	48	30	F	37w,6d	2.8	9	9.6	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G2P1L1A1	LSCS	No
CO-25-1	49	26	F	37w,5d	2.6	10	11.2	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G3P3L3	LSCS	No
CO-25-2	50	31	F	38w,5d	3.1	11	12.4	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G2P2L2	LSCS	No
CO-26-1	51	23	F	38w,1d	2.8	9	10.5	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G1P1L1	FTND	No
CO-26-2	52	22	M	38w,3d	2.9	10	11.6	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G2P2L1D1	LSCS	No
CO-27-1	53	22	M	37w1d	2.5	10.5	11	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G1P1L1	LSCS	No
CO-27-2	54	29	F	38w1d	2.6	10.5	10.4	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G2P2L2	FTND	No
CO-28-1	55	20	F	39w5d	3	10	11.6	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G1P1L1	FTND	No
CO-28-2	56	25	M	39w1d	2.9	11	11.6	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G2P1L1A1	FTVD	No
CO-29-1	57	22	M	39w2d	2.7	10.5	11.4	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G1P1L1	LSCS	No
CO-29-2	58	25	F	37w3d	2.5	11	11	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G3P3L3	FTND	No
CO-30-1	59	29	F	37w	2.7	10.7	11.2	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G3P2L2A1	LSCS	No
CO-30-2	60	31	M	40w	2.9	11.2	11	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	G2P2L2	FTND	No

Patient_ID	UCL (cm)	UCD (cm)	UCA	UCC	UCIn	CCI	PWJ	A-UC	NV	Fetal membranes	A-FM	C-FM	At-FM	Vv	TW (gm)	L (cm)	B (cm)	Th (cm)	S	A-FS	C-FS	T-FS	A-MS	Cotyledones	Cs-SS	C-SS
CO-1-1	6.5	1.2	PD	White tan	EC	0.1	P	White tan	3	C	Tl	Ta	DMr	NP	370	14	11.5	3	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-1-2	12	1	PD	White tan	Mr	0.2	P	White tan	3	C	Tl	Ta	DMr	NP	400	15	14	2.5	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-2-1	6	1	PD	White tan	EC	0.2	P	White tan	3	C	Tl	Ta	DMr	NP	350	17	13.5	3	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-2-2	15	1.1	PD	White tan	EC	0.1	P	White tan	3	C	Tl	Ta	DMr	NP	500	18	17	2.5	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-3-1	15	1.1	PD	White tan	Ce	0.2	P	White tan	3	C	Tl	Ta	DMr	NP	350	17	14	2	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-3-2	10	0.7	PD	White tan	EC	0.2	P	White tan	3	C	Tl	Ta	DMr	NP	550	20	17	2.5	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-4-1	20	1	PD	White tan	EC	0.1	P	White tan	3	C	Tl	Ta	DMr	NP	550	17	14	2.5	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-4-2	10	1	PD	White tan	EC	0.2	P	White tan	3	C	Tl	Ta	DMr	NP	400	17	15	3	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-5-1	16	0.8	PD	White tan	EC	0.1	P	WhIte tan	3	C	Tl	Ta	DMr	NP	350	13.5	12	2.5	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-5-2	14	0.8	PD	White tan	EC	0.1	P	White tan	3	C	Tl	Ta	DMr	NP	450	17	15	2.5	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-6-1	19	0.7	PD	White tan	EC	0.2	P	White tan	3	C	Tl	Ta	DMr	NP	425	14	14	2.5	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-6-2	10	1	PD	White tan	Ce	0.1	P	White tan	3	C	Tl	Ta	DMr	NP	650	17	15	3	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-7-1	15	1.2	PD	White tan	EC	0.2	P	White tan	3	C	Tl	Ta	DMr	NP	600	15.5	15	3.5	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-7-2	15	1	PD	White tan	EC	0.1	P	White tan	3	C	Tl	Ta	DMr	NP	525	17.5	15	2.5	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-8-1	6	1	PD	White tan	EC	0.1	P	White tan	3	C	Tl	Ta	DMr	NP	525	16.5	14.5	2.5	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-8-2	10	0.8	PD	White tan	Ce	0.2	P	White tan	3	C	Tl	Ta	DMr	NP	425	15	13	2.5	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-9-1	7	0.7	PD	White tan	EC	0.2	P	White tan	3	C	Tl	Ta	DMr	NP	450	14	14	2.5	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-9-2	7	1	PD	White tan	EC	0.1	P	White tan	3	C	Tl	Ta	DMr	NP	525	13.5	13	3	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-10-1	4	1.2	PD	White tan	EC	0.1	P	White tan	3	C	Tl	Ta	DMr	NP	350	14.5	13.5	2.5	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-10-2	5	1.2	PD	White tan	EC	0.2	P	White tan	3	C	Tl	Ta	DMr	NP	350	13.5	13	2.5	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-11-1	15	1	PD	White tan	Ce	0.2	P	White tan	3	C	Tl	Ta	DMr	NP	350	14.5	14.5	2	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-11-2	15	1.2	PD	White tan	EC	0.1	P	White tan	3	C	Tl	Ta	DMr	NP	625	19	17.5	2.5	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-12-1	15	1.3	PD	White tan	EC	0.2	P	White tan	3	C	Tl	Ta	DMr	NP	475	17.5	13.5	2	O	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-12-2	5	0.8	PD	White tan	Ce	0.2	P	White tan	3	C	Tl	Ta	DMr	NP	300	13.5	11.5	1.5	O	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-13-1	10	1.2	PD	White tan	Ce	0.1	P	White tan	3	C	Tl	Ta	DMr	NP	400	16	10.5	2	O	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-13-2	10	0.8	PD	White tan	EC	0.2	P	White tan	3	C	Tl	Ta	DMr	NP	375	14	13.5	2.5	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-14-1	15	0.8	PD	White tan	EC	0.1	P	White tan	3	C	Tl	Ta	DMr	NP	425	18	14	2	O	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-14-2	10	0.9	PD	White tan	Ce	0.2	P	White tan	3	C	Tl	Ta	DMr	NP	450	16.5	15.5	2.5	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-15-1	10.5	1	PD	White tan	EC	0.1	P	White tan	3	C	Tl	Ta	DMr	NP	475	16	15	2.5	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-15-2	7	0.9	PD	White tan	EC	0.2	P	White tan	3	C	Tl	Ta	DMr	NP	550	17.5	17.5	2	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-16-1	6	1.2	PD	White tan	EC	0.2	P	White tan	3	C	Tl	Ta	DMr	NP	475	14	13.5	2.5	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-16-2	11	1.2	PD	White tan	EC	0.1	P	White tan	3	C	Tl	Ta	DMr	NP	350	13	12.5	1.5	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-17-1	15	0.8	PD	White tan	Ce	0.2	P	White tan	3	C	Tl	Ta	DMr	NP	450	13	12	2.5	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-17-2	6.5	1.2	PD	White tan	EC	0.1	P	White tan	3	C	Tl	Ta	DMr	NP	370	14	11.5	3	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-18-1	12	1	PD	White tan	EC	0.2	P	White tan	3	C	Tl	Ta	DMr	NP	400	15	14	2.5	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-18-2	6	1	PD	White tan	EC	0.2	P	White tan	3	C	Tl	Ta	DMr	NP	350	17	13.5	3	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-19-1	15	1.1	PD	White tan	EC	0.1	P	White tan	3	C	Tl	Ta	DMr	NP	500	18	17	2.5	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-19-2	15	1.1	PD	White tan	Ce	0.2	P	White tan	3	C	Tl	Ta	DMr	NP	350	17	14	2	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-20-1	10	0.7	PD	White tan	EC	0.2	P	White tan	3	C	Tl	Ta	DMr	NP	550	20	17	2.5	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-20-2	20	1	PD	White tan	EC	0.1	P	White tan	3	C	Tl	Ta	DMr	NP	550	17	14	2.5	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-21-1	10	1	PD	White tan	EC	0.2	P	White tan	3	C	Tl	Ta	DMr	NP	400	17	15	2	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-21-2	16	0.8	PD	White tan	EC	0.1	P	WhIte tan	3	C	Tl	Ta	DMr	NP	350	13.5	12	2.5	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-22-1	14	0.8	PD	White tan	EC	0.1	P	White tan	3	C	Tl	Ta	DMr	NP	450	17	15	2.5	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-22-2	19	0.7	PD	White tan	EC	0.2	P	White tan	3	C	Tl	Ta	DMr	NP	425	14	14	2.5	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-23-1	10	1	PD	White tan	EC	0.1	P	White tan	3	C	Tl	Ta	DMr	NP	650	17	15	3	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-23-2	15	1.2	PD	White tan	EC	0.2	P	White tan	3	C	Tl	Ta	DMr	NP	600	15.5	15	3.5	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-24-1	15	1	PD	White tan	EC	0.1	P	White tan	3	C	Tl	Ta	DMr	NP	525	17.5	15	2.5	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-24-2	6	1	PD	White tan	EC	0.1	P	White tan	3	C	Tl	Ta	DMr	NP	525	16.5	14.5	2.5	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-25-1	10	0.8	PD	White tan	Ce	0.2	P	White tan	3	C	Tl	Ta	DMr	NP	425	15	13	2.5	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-25-2	7	0.7	PD	White tan	EC	0.2	P	White tan	3	C	Tl	Ta	DMr	NP	450	14	14	2.5	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-26-1	7	1	PD	White tan	EC	0.1	P	White tan	3	C	Tl	Ta	DMr	NP	525	13.5	13	3	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-26-2	4	1.2	PD	White tan	EC	0.1	P	White tan	3	C	Tl	Ta	DMr	NP	350	14.5	13.5	2.5	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-27-1	5	1.2	PD	White tan	EC	0.2	P	White tan	3	C	Tl	Ta	DMr	NP	350	13.5	13	2	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-27-2	15	1	PD	White tan	EC	0.2	P	White tan	3	C	Tl	Ta	DMr	NP	350	14.5	14.5	3	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-28-1	15	1.2	PD	White tan	EC	0.1	P	White tan	3	C	Tl	Ta	DMr	NP	625	19	17.5	2.5	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-28-2	15	1.3	PD	White tan	Ce	0.2	P	White tan	3	C	Tl	Ta	DMr	NP	475	17.5	13.5	2	O	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-29-1	5	0.8	PD	White tan	EC	0.2	P	White tan	3	C	Tl	Ta	DMr	NP	300	13.5	11.5	1.5	O	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-29-2	10	1.2	PD	White tan	EC	0.1	P	White tan	3	C	Tl	Ta	DMr	NP	400	16	10.5	2.5	O	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-30-1	10	0.8	PD	White tan	Ce	0.2	P	White tan	3	C	Tl	Ta	DMr	NP	375	14	13.5	2	D	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re
CO-30-2	15	0.8	PD	White tan	EC	0.1	P	White tan	3	C	Tl	Ta	DMr	NP	425	18	14	2.5	O	SM-GL	PB	NP	Gy-Br	Intact	Spongy	Da Re

Patient_ID	Areas of infarction	PI	AVM	DVH	K	FPF	IH	DA	AV	T	VIFD	VE	VSVK	FS	ACA	VUE	CHI	MPFD	CH	DVM
CO-1-1	NP	NP	NP	NP	P	NP	NP	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
CO-1-2	NP	NP	NP	NP	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
CO-2-1	NP	NP	NP	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
CO-2-2	NP	NP	NP	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	P	NP	NP	NP	NP	NP
CO-3-1	NP	NP	NP	NP	NP	P	NP	P	NP	NP	NP	NP	NP	P	P	NP	NP	NP	NP	NP
CO-3-2	NP	NP	NP	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	P	NP
CO-4-1	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	P	NP	NP	NP	P	NP
CO-4-2	NP	NP	NP	NP	P	P	NP	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	P	NP
CO-5-1	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
CO-5-2	NP	NP	NP	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	P	NP
CO-6-1	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	P	NP	NP	NP	NP	NP	NP	NP	NP
CO-6-2	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
CO-7-1	NP	NP	NP	NP	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
CO-7-2	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	P	NP	NP	NP	NP	NP
CO-8-1	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
CO-8-2	NP	NP	NP	NP	NP	NP	NP	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
CO-9-1	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
CO-9-2	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	P	NP	NP	NP	NP
CO-10-1	NP	NP	NP	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	P	NP
CO-10-2	NP	NP	NP	NP	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
CO-11-1	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
CO-11-2	NP	NP	NP	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	P	NP	NP	P	P	NP
CO-12-1	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	P	NP
CO-12-2	NP	NP	NP	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	P	NP	NP	NP	NP	NP
CO-13-1	NP	NP	NP	NP	NP	NP	NP	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
CO-13-2	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
CO-14-1	NP	NP	NP	NP	NP	NP	NP	P	NP	NP	NP	P	NP	NP	NP	NP	NP	NP	NP	NP
CO-14-2	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
CO-15-1	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
CO-15-2	P	P	NP	NP	P	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
CO-16-1	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	P	NP
CO-16-2	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	P	NP	NP	NP	NP	NP
CO-17-1	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
CO-17-2	NP	NP	NP	NP	NP	NP	NP	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
CO-18-1	NP	NP	NP	NP	P	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
CO-18-2	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
CO-19-1	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	P	NP	NP	NP	NP	NP
CO-19-2	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
CO-20-1	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	P	NP	NP	NP	NP	NP	NP	P	NP
CO-20-2	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	P	NP
CO-21-1	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	P	NP
CO-21-2	NP	NP	NP	NP	NP	NP	NP	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
CO-22-1	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	P	NP
CO-22-2	NP	NP	NP	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
CO-23-1	P	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
CO-23-2	NP	NP	NP	NP	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	P	NP	NP	NP	NP	NP
CO-24-1	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
CO-24-2	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
CO-25-1	NP	NP	NP	NP	NP	NP	NP	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
CO-25-2	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
CO-26-1	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
CO-26-2	NP	NP	NP	NP	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	P	NP	NP	NP	P	NP
CO-27-1	NP	NP	NP	NP	NP	NP	NP	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
CO-27-2	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
CO-28-1	NP	NP	NP	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	P	P	NP
CO-28-2	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
CO-29-1	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
CO-29-2	NP	NP	NP	NP	NP	NP	NP	NP	P	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
CO-30-1	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
CO-30-2	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP