Study Of Placental Histopathology In Hypertensive Disorders Of Pregnancy And Its Correlation With Maternal And Fetal Outcome

by

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LIST OF ABBREVIATIONS

APGAR – Appearance Pulse Grimace Activity Respiration

ARF – Acute renal Failure

DIC – Disseminated Intravascular Coagulation

FGR – Fetal Growth Restriction

GDM -Gestational Diabetes Mellitus

GHTN – Gestational Hypertension

H & E – Haematoxylin and eosin

HELLP – Haemolysis Elevated Liver Enzymes Low Platelet

IUD – Intrauterine Death

NICU- Neonatal Intensive Care Unit

OBG – Obstetrics & Gynaecology

PIH – Pregnancy Induced Hypertension

STMB - Syncytiotrophoblast microparticles

USG – Ultrasonography

ABSTRACT

BACKGROUND:

Placenta, being the filter bed and gateway for the exchange of nutrients and metabolic waste products between mother and foetus is a vascular organ. As the hypertensive changes affect the cardiovascular system in adults, it also has its effect on the foetus through various changes predominantly in the vasculature of placenta. These changes have a significant impact in terms of growth and development of the embryo during gestation and gets extended to postpartum in both mother and the new-born complications.

OBJECTIVE:

To study placental histopathology in patients with hypertensive disorders of pregnancy and correlate with maternal and fetal outcome.

MATERIALS AND METHODS:

The placenta with attached membranes and umbilical cord received in histopathology section of Department of Pathology from clinically diagnosed Hypertensive disorders of pregnancy would be considered for this study. Clinical details were obtained, and the cases were categorized as: Gestational Hypertension (GHTN), Mild Preeclampsia, Severe Preeclampsia, Eclampsia.

The shape, size and weight of the specimen was noted. All relevant gross findings were documented. The specimens were processed according to routine histopathology protocols, 3-4□m thick sections were obtained which were subjected to Haematoxylin & Eosin staining procedure. These slides were evaluated under bright field microscopy. Presence of increased syncytial knots, villous stromal fibrosis, fibrinoid necrosis, intervillous haemorrhages and calcification were analysed in 100x and 400x magnification.

APGAR score and birth weight of the infant was noted. Fetoplacental weight ratio was calculated in all the cases. Maternal outcome was documented by observing for the complications.

RESULTS:

A total of 128 cases were included in the study, majority (n=100) of the cases were in 18 - 25 years of age group and rest 28 cases were in 26 – 30 and >30years. Among the hypertensive disorders 41.4% (n=53) were GHTN, 13.3%(n=17) were mild preeclampsia, 22.7%(n=29) were severe preeclampsia and another 22.7% (n=29) were of eclampsia.

The shape of the placentae was irregular in majority of severe preeclampsia and eclampsia cases. The average placental weight was 422 gm. The average diameter was 15.1cm and mean thickness was 2.8cm. Microscopic findings like fibrinoid necrosis, intervillous haemorrhages, villous stromal fibrosis, syncytial knots and calcification were seen in 54.7 %, 43%, 41.4 %, 35.2 % and 39.1 % of cases respectively.

Eight cases had IUDs and a single case of still birth which were seen predominantly in severe preeclampsia and eclampsia group. Among live births i.e. 93%, lower APGAR score (<7) was seen in 38.7% of cases. A reduced fetoplacental weight ratio (mean - 5.8) was noted. Maternal complications like DIC, HELLP syndrome and ARF was seen in 10.2% of cases.

CONCLUSION:

Histomorphological features of placenta like weight and diameter were considerably reduced in preeclampsia / eclampsia. Microscopic features like increased syncytial knots, fibrinoid necrosis, intervillous hemorrhages, villous stromal fibrosis and calcification were found more in severe preeclampsia / eclampsia as against GHTN/ mild preeclampsia placenta. Fetal outcome observed as low birth weight and IUDs in cases of eclampsia and preeclampsia

group had a statistically significant p-value. New-born babies with APGAR score <7 were more in cases of eclampsia and severe preeclampsia groups.

KEYWORDS: Hypertensive disorders of pregnancy, Fetal outcome, Maternal complications.

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Introduction

Placenta defined as the "apposition of foetal membranes to the uterine mucosa for physiological exchange" by Mossman.[1] It is a highly specialised organ which provides the nutrients and gaseous exchange in the form of a filter for the developing foetus. Along with the gestational age the requirements of the foetus increase, which are fully supported by the maternal circulation through the placenta. These demanding needs make the placenta go through structural changes dynamically over time. Any deviations from these normal developmental changes because of various reasons can affect the foetus. [2,3]

Placenta being such an important organ in the developmental phenomenon of the foetus not only provides the nutrients, also helps in avoidance of unnecessary or hazardous substances entry and aids in clearing of the metabolic waste products from the fetus. It is comprised of the sinusoids/collection spaces where in the exchange happens between feto-maternal circulation. Placenta increases in size all throughout the gestation in accordance with the age of the foetus. However, multiple maternal related factors like Gestational Diabetes Mellitus, Gestational Hypertension and other conditions influence placental course structurally. These factors will have a direct influence on the fetal growth and health as well as indirect effects. Pivotal among these indirect effects is through the alteration in both the structural and functional parameters of the placenta.

Amongst the various factors affecting the feto-maternal outcome hypertension is known to have a significant effect in terms of permanent alteration of the vascular structure and size of the placenta. This altered vascular structures have a deciding role and influences the maternal and neonatal outcome, like the placental weight, fetal weight, placental microscopic changes in terms of alterations in the trophoblasts, villous density, syncytial knots and calcifications.

These changes were known to be associated in accordance with the severity of the hypertensive disorder of pregnancy like the preeclampsia, eclampsia and chronic hypertension.

Hence having a better understanding of these structural changes in the spectrum of hypertensive disorders of pregnancy will aid in overall management of the mother as well as the foetus.

Objective of the study:

To study placental histopathology in patients with hypertensive disorders of pregnancy and correlate with maternal and fetal outcome.

Review of Literature

History:

As early as 1559, in his work titled "*De re anatomica"* Realdo Colombo (Columbus) coined the term Placenta. However, the presence of this organ and its function has been described even much earlier during the times of Egyptian and Hebrew scriptures and various drawings thereafter. It was known by many names during these periods in terms of "Alter ego", "External Soul", "Bundle of Life", & "Flat cake".[1]

Aristotle studied extensively about the membranes and established that the foetus receives its nutrition from the umbilical vessels joining the uterus similar to the plants gaining the nutrients from the soil through the roots. Thereby establishing the function and early foundations of the concept of foetal development which was further expanded in detail by Galen in his treatises dividing it into four stages. The dogmatic understanding and theorisation of the blood supply was put to rest in the early seventeenth century once circulation of blood was described.[1]

In the early half of the 18th century, Alexander Monro primus dissected the placentae of five women to state that the uterine vessels are not in continuation with the fetal vessels and end in sinuses. He concluded that the tips of the fetal vessels extend beyond placenta and reach the uterine vessels. Wilhelm Noortwyck, who pioneered the injected preparations of organs was the first to inject placenta. However, he wrongly documented that some of the fetal vessels were in continuity with the maternal vessels.[1]

Carnegie institute of Washington, Harvard Medical school to name a few, have played a significant role in creating a better understanding of the placental structure, circulation and function through various investigators working in the field with primate animal models as well as using advanced techniques. This opened a new era of information and brought clarity and

substance to the theories prevailing till that time wherein some are proved to be right and the others being disproved.[1]

Physiological aspects of Placenta

Multiple authors studied the approach to illustrating, explaining the physiological aspects by studying the animals and humans, timing the pregnancy in Rhesus monkeys and this work was carried out in in the late nineteenth and early twentieth century. Majority of the understanding at this level brought to fore the processes like endocytosis, diffusion mechanisms and transport of various substances.

Louis Barkhouse Flexner, pioneer in using radioactive isotopes helped in answering the quantification of the substances needed for supporting the fetal growth. This utilization of radioactive isotopes for understanding biological phenomena was a first and Flexner successfully quantified the exchange of sodium and water all throughout the term in terms of grams of placental tissue.[1]

Histological studies of Mossman helped in understanding the circulation of the placenta wherein he demonstrated using the rodent placenta that the fetal and maternal circulation happens in the opposite direction.[2] However, the uterine circulation in the intervillous space was yet to be explored and not fully chartered territory. This was given a serious look into by the Carnegie investigators who used “Cine-angio-radiography” to better understand this process. This group of investigators set out to explore and authenticate the work of Mossman and whether it is same in the humans and is it a counter current mechanism of exchange in the humans as well.

The diffusing capacity of the placenta was estimated by measuring the carbon dioxide levels and the partial pressure of oxygen levels wherein it was that there is an equilibrium achieved between the fetal and maternal levels thus disproving the theory that the placenta was a barrier

to the diffusion. The uneven perfusion is similar to the lung and the distribution of the unequal oxygenation thereby exposing the blood from the foetus to different levels of oxygen. In the recent past the metabolic functions and hormone synthesis of placenta was identified which led to the concept of maternal placental fetal unit due to its interactions with the maternal endocrine system and the fetal adrenal glands and other organs.[3] As a part of the unit, placenta exerts its effects on the maternal blood volume and initiation of labour.

Development:

Along with the understanding of the function and anatomical aspects of placenta, there was an increase in the knowledge of the microscopic anatomy as well due to the advances in the techniques and the evolving instruments which aided this. The studies panned across the histology, gross anatomy [4] and histochemistry. Stages of placenta according the development and time interval are as follows Preimplantation stage, Prelacunar, Lacunar and villous stages.

The earliest stage referred as preimplantation begins as early as 7 days post conception where the hatched blastocyst attaches to the uterine epithelium. This is the beginning of the placental formation, which is followed by prelacunar stage. The important step in this stage is the localisation of the trophoblasts overlying the inner cell mass. The trophoblasts exactly opposite to these inner cell mass cells are vital in the implantation. This is of paramount importance as any rotation of the blastocyst will lead to the improper contact of polar trophoblasts and failure of implantation.[5]

The next important step in this stage being the development of syncytiotrophoblast of the oligonucleated variety. This has an invasive phenotype which enables the strengthening of the implantation by penetrating the uterine epithelium. The rest of the trophoblastic cells are referred to as the cytotrophoblasts underneath the syncytiotrophoblast with mononucleated cells and have no contact with the maternal tissues. The cytoptrophoblasts fuses with the syncytiotrophoblasts and the growth of the embryo follows. The presence of contact between

the syncytiotrophoblast and the maternal epithelium and fluids which is limited just to this layer leads to the minimal rejection of the embryo. [5]

The lacunar stage which starts chronologically as early as from 8th day onwards, with the development of lacunae in the syncytiotrophoblastic layer leads to the formation of three zones in the placenta namely early chorionic plate towards the embryo, intervillous space and the villi inbetween. The third, primitive basal plate lies towards the maternal endometrium. [5]

Close to two weeks post conception, nearly 12 days, the implantation is considered to be complete and during this period the invasion of the maternal vessels in the endometrium leads to the entry of these vessels in the syncytiotrophoblastic layer and the presence of the maternal RBCs is seen. Embryo is completely surrounded in the maternal tissues during this period and the thickness of the syncytial layer is more on the implantation side than the abembryonic side where it is thinner having comparatively smaller lacunae and trabeculae. Chorion, comprising of the cells derived from primitive streak positioning themselves on the top of cytotrophoblastic cells is formed.[5]

Further expansion of the placental tissues starts and the cytotrophoblasts for the very first time reaches the maternal tissue at around day fifteen marking the only second cells which reach the maternal side other than the syncytiotrphoblasts and these migrated cells form extravillous cytotrophoblasts. This is followed by the invasion of stroma and blood vessels in the endometrium by the endovascular trophoblast. This is the initial stage of reepithelialisation by the invading trophoblast and destruction of the muscle wall of the spiral arterioles, a physiological transformation.[5]

Day 13 marks the development of **primary villi**, which are comprised of trophoblastic cells with cytotrophoblasts in the middle, in the form of sprouts. The extraembryonic mesodermal cells follow the cytotrophoblasts shortly after this stopping short of the terminal

portion towards the maternal side. This migration of the mesodermal cells gives a core to the villi leading to the transformation of primary villi to the **secondary villi**. In the mesoderm of these secondary villi, development and differentiation of the hematopoietic stem cells by day 20 (post conception) forming the first placental blood cells and vessels apart from embryonal vessels. This development of placental vessels in the secondary villi gives rise to the **tertiary villi**.[5]

Gross morphology of placenta:

The gross morphology of the placenta is highly variable and is dependent on the factors like the type of delivery, where the placenta has been clamped and the when it was clamped. This is due to the change in the volume due to the loss of both maternal and fetal blood. The average dimensions of placenta are as follows – diameter of about 22cm with a central thickness of about 2.5cm and an average weight of about 470gm. [5]

Placenta has two surfaces named as fetal and maternal surface. Amnion covered chorionic plate forms the fetal placental surface comprised of avascular connective tissue, mesenchyme and unilayered epithelium which attaches loosely to the chorion thereby gets separated from the chorion easily in the delivered placenta. The chorionic mesenchyme has the vessels in continuity with the umbilical cord arteries which branch centrifugally and connecting the villous trees. The veins of the chorion, which are direct continuation of the villous tree veins cross underneath the arteries and forms the single umbilical vein. [5]

Maternal surface, comprised of the basal plate, is due to the separation of the placenta from uterine wall at the time of delivery. It is comprised of varying amounts of extracellular matrix, blood clots, trophoblasts, decidual cells and immune component comprised of natural killer cells as well as macrophages.

With the advancing technologies and the development of various tools for human anatomy at the microscopic level has delivered immense knowledge and enhances the basic understanding by the pioneering work of many scientists. To name a few the initiation of this was done Antony Van Leewenhoek and Robert hook who contributed immensely by establishing the techniques. The microscopic anatomy of the placenta has gone through the tectonic shift like any other organ with the introduction of the complex, informative techniques like electron microscopy, scanning EM and immunohistochemistry which aided the light microscopy.

The chorionic plate was the base from which the fetal lobules arise and branch further out into the intervillous space as free floating villi. A few of these branches reach out till the basal plate which are called as the anchoring villi containing the trophoblastic cell columns. These villi are classified into five types based on the stromal characteristics, vessel calibre, appearance and structure namely Mesenchymal villi, Immature intermediate villi, Stem villi, Mature intermediate villi and Terminal villi.

The foremost appearing villi till the six weeks period post menstruation are the mesenchymal villi containing a weak mesenchymal core with missing vessel lumen at times and the villous diameter are found to be in the range of 100 to 250 micrometer.[6,7] These villi persist till later part of pregnancy and most of these transforms into the intermediate type bringing down their number near term.[8] The intermediate villi, with a diameter of 100 to 400 micrometer present predominantly during the 8^{th} week till the 22^{nd} week of gestation. These villi transform into the stem villi due to the fibrosis from the center of the villi to the periphery. This brings a characteristic arrangement of the villous core with the parallel arrangement of these strands of matrix free structures parallel to the long axis of the villi.[9] Like the mesenchymal villi these villi too are found be decreased towards the term and if persisting caution to be practiced in wrongly labelling them as oedematous villi. The characteristic pattern

of the stroma along with the small arterioles and placental macrophages helps in their identification.

Third in line to appear and the largest villi are the stem villi with diameters ranging upto 3000 micrometers are derived from the immature intermediate villi.[9] These villi primarily provide the much needed mechanical support to the villous tree for which they are equipped with a strong core formed by the dense fibrous stroma.[10,11] Their physiological role is limited due to their fibrous stroma and offers more of a mechanical strength and helps in the myofibroelastic perivascular contractility of the vessels.

Mature intermediate villi, in the range of 80 to 120 micrometer in diameter are seen to appear in the mid pregnancy. They have a loose stroma with few peripheral vessels. A characteristic feature of the villous stroma in these villi is that the vessels of the stroma occupy nearly half of the cross-sectional area. Arising from these mature intermediate villi are the terminal villi which are aptly named as they are found on the terminal branches of the villous structures. They have lengths upto 100 micrometer and a diameter of upto 80 micrometer. The stroma in these villi has a higher degree of the presence of capillaries with the more than half of the cross-sectional area comprised of the vessels. These structures are the most important structures in the villous tree due to their partly thin placental barrier ranging upto 2 microns and also few vessels terminating as sinusoids lined by the vasculo-syncytial membranes called the placental barrier. This is comprised of joint basement membrane anchoring syncytiotrophoblast on the one side and capillary endothelium on the other.

Placental microstructure:

The basic villous structure is made up of the basement membrane separating the epithelial layer – trophoblast from the stromal core. The villous trophoblast has two layers and the cytotrophoblast is always in contact with the basement membrane and the apical surface of

these cytotrophoblasts are in contact with the syncytiotrophoblasts. These villous cytotrophoblasts become extravillous trophoblasts in any of the following events, losing contact with the basement membrane or syncytiotrophoblast. If the superficial layer is damaged, the maternal clots forms the deposits of fibrin on these cytotrophoblasts thereby minimising the contact with the maternal epithelium and thus leading to the formation of extravillous trophoblast in the villous tissue.[12,13.]

With the progression of pregnancy, the initial complete coverage by the cytotrophoblast in the first trimester is reduced to upto a 15% contribution to the total villous trophoblast. With the help of stereological studies, it has been quantified that the cytotrophoblastic nuclei rise by six times from one billion nuclei during the early (13-16 weeks) gestation to six billion nuclei during the term (37-41 weeks) gestation.[14,15] The expansion in the villous surface explains the apparent reduction of the cytotrophoblast.

Morphologically, the undifferentiated cytotrophoblast has a cuboidal shape with very few organelles which differentiates and acquires the appearance of intermediate cells with features in between that of the syncytiotrophoblast and the undifferentiated cells with many ribosomes, mitochondria, rough endoplasmic reticulum and mRNA. The highly differentiated cytotrophoblasts with higher organelle content than the intermediate cell type will finally fuse with the syncytial layer.

Syncytiotrophoblast is a multinucleate polar layer with the cells with the basal membrane adherent to the basement membrane or to the cytotrophoblast. The apical side of the cells contain the microvilli which enhance the surface area of the syncytiotrophoblasts as they are in direct communication with the maternal blood. The absence of proliferative activity of these cells makes them dependent on the cytotrophoblasts for the entire period of gestation. The nuclei which enter the syncytial layer from the cytotrphoblast layer undergo a series of morphological changes from large ovoid nuclei initially containing rich euchromatin to small

dense nuclei and finally with annular chromatin in a span of 3-4weeks. The final annular chromatin aggregation in the form of packed pyknotic nuclei marks the apoptotic changes in some of the syncytiotrophoblasts, these are called the **syncytial knots** which are shed into the maternal circulation. These syncytial knots due to their sheer size are not seen in the peripheral blood of mother even though they are seen in the maternal uterine vein and pulmonary vessels.[14]

Supportive matrix of the villi is formed by the free cells like macrophages called as Hofbauer cells and blood vessels and the fixed connective tissue. The fixed tissue is comprised of cells with capability to differentiate into many cell types ranging from blood cells myofibroblasts, smooth muscle cells and fibroblasts. Hofbauer cells in the stroma has varied origin, from progenitor cells of the mesenchyme, penetration of the marrow derived cells of fetus into the stroma of villi. They appear as early as 35 days post menstruation.[14]

Fetal vessels form the junctional complexes linking the adjacent cells and also reduce paracellular transport through their non- fenestrated endothelium. Sinusoids along with the capillaries are arranged on a basement membrane with no supporting cells. However, the arterioles and arterioles are having a media with smooth muscle cells barring the elastic lamina. The luminal diameter of these vessels is controlled by the autocrine and paracrine factors as the placenta is not having neural innervation.[15,16]

The other part of the matrix material is Fibrinoid which is present throughout the gestation in all stages. This is classified into two types - fibrin type and matrix type. The earlier one contains the fibrin, fibrinogen and fibrin fibres meshwork. As it is derived from the maternal blood due to the clotting, it is devoid of any cells including the trophoblasts. Thus, it is always seen in relation to the intervillous space and the maternal blood. Whereas the matrix type is found much deeper and never in association with the maternal blood. It also contains all sorts

of proteins like “tenascin, fibronectin, collagen and laminin among many others like heparan sulphate, vitronectin, fibrillin and merosin”.[17,18]

Placenta and Hypertension:

With the evolving knowledge and having a better understanding of the normal phenomena in the placental growth and histology, focus has shifted towards the pathological conditions, its effects on the placenta, fetal and maternal outcome. This has been tackled from various viewpoints like anatomical changes like altered implantation site like placenta previa[19] and hypertension,[20] morphometric analysis of placenta.[21]

To better understand the changes in the placenta due to the changes related to pathological conditions, it is only possible if the variations due to normal aberrations and ranges are known. In this regard, a lot of analysis, comparative studies and morphometric analysis happened in the subject spanning across full term and low birth weight. There is a glaring disparity between the reference ranges of the placental weight is reduced in small for gestational age (SFA) pregnancy which is logical too. The mean weight of placenta normal term babies in the Indian population is found to be 388gm whereas the SFA placenta had a mean weight of 321gm. This decrease was also noted in the number of cotyledons, placental volume and placental surface area. However, the presence of calcified areas, abnormal insertion of cord and infarcted areas were more in the SFA placentae as per the prior studies.[22]

Hypertension has been known as “hard pulse disease” from the ages, as early as 2600B.C.[23] Various treatment modalities and misconceptions were persistent till the late 17th and early 18th centuries which were cleared and established to be false in the early part of the 20th century with the help of pioneering work of many illustrious physicians, scientists and landmark studies. Measurement of the blood pressure was demonstrated as early as 17th century, coining of the term “hypertonie essential” and “hypertensive vascular disease” by

Frank and Janeway respectively in the beginning of the 20th century. Till the year 1957, an effective way of handling this non-communicable burden during the period became a boon to many in the form of diuretics. The phased-out treatment modalities prior to these diuretics ranged from venesection, salt restriction and sympathectomy to mention a few.[23]

Hypertension has a significant effect on the pregnancy like many other conditions. Elevated blood pressure has its effects both on the mother and the fetus. The normal uncomplicated gestation is a physiologic roller coaster event for the circulatory system wherein the pressures fall and rise over time from the pre-pregnancy levels. This is a significant factor in the management of the pregnancy. The systolic and diastolic levels of blood pressure fall from the luteal phase and this fall in levels is maintained till the 20th week of gestation if the conception happens. This fall is quantified to the level of upto 10% than the levels prior to pregnancy with the decrease more in the diastolic than that of systolic.[24]

From the 20th week till 40th week, the uptick happens slowly and reaches the pre-pregnancy levels of mean arterial pressures. This knowledge of normal changes in the levels during various stages of pregnancy forms the core information in better assessing the pathological spectrum of changes like gestational hypertension, preeclamspia, eclampsia and preeclampsia in a woman affected with chronic hypertension. The term chronic hypertension in pregnancy is defines as either increase in the pressures before the 20th week or already a known case of hypertension prior to pregnancy and the raised pressure last beyond 12weeks post pregnancy or confinement.[24]

Definitions:

Gestational hypertension: New onset hypertension occurs after 20 weeks' gestation (in a woman who had normal blood pressure before 20 weeks' gestation) and

• diastolic blood pressure is ≥90 mmHg or systolic blood pressure is ≥140 mmHg 99

• the woman has none of the abnormalities that define pre-eclampsia

• her blood pressure returns to normal within three months after giving birth.[25]

Mild Preeclampsia: The new onset of hypertension occurs after 20 weeks' gestation (in a woman who had normal blood pressure before 20 weeks' gestation) or superimposed on pre-existing hypertension and one or more of the following also develop as new conditions:

proteinuria – spot urine protein:creatinine ratio ≥30 mg/mmol or ≥2+ on dipstick testing confirmed by a protein:creatinine ratio test.[25]

Severe Preeclampsia: Severe hypertension (dBP ≥110 mmHg or sBP ≥160 mmHg) – thrombocytopenia (platelet count less than 100 × 109/L) – impaired liver function-cerebral symptoms- pulmonary edema- new onset of headaches and visual disturbances – HELLP syndrome – eclampsia.[25]

Eclampsia: New onset of seizures occurs in association with preeclampsia. It is a severe manifestation of pre-eclampsia and can occur before, during or after birth. It can be the presenting feature of pre-eclampsia in some women.[25]

To bring uniformity in identification of the condition and better management over the year's several guidelines have been made.[26-30] American Society of Hypertension, NICE guidelines UK, Canadian hypertension society consensus conference and guidelines from New Zealand Australia demarcated the gestational hypertension, pre-eclampsia and eclampsia. Focus was also present on defining the stages, complications and treatments. Many authors studied the effectiveness and implementation of these guidelines in the pregnancy outcome.[31,32]

Hypertension in pregnancy is a significant condition causing complications upto 1 in every 10 mothers in the United States.[33] It is also one among the leading causes of death and has a significant effect on the fetal outcome. However, its pathophysiology is not fully

elucidated. In the gestational period, hypertension is defined with a cut off of 140 and 90 mm Hg for the systolic and diastolic respectively.[33]

It affects the placenta histomorphologically and morphometrically. The effects of hypertension on pregnancy and the pathophysiology of the condition is not fully understood and the area is being investigated actively.[34] Multiple studies were conducted to find out the association between these disorders and the dietary factors like energy, dietary patterns and supplements. The meta-analysis and systematic review of these studies totalling to 23 cohort studies and 15 case control studies led to the observations with respect to the calorie intake, magnesium intake had a relation with the incidence of these disorders. However, the authors concluded that the number of studies were limited and need additional evidence as these observations were not statistically significant.[35]

Gestational weight Gain (GWG) was also evaluated in 56,101 pregnant females in Norway spanning over a decade as per the American Institute of Medicine and found that the weight gain has a significant effect on the hypertensive disorders. If the weight gain was more than that of the recommended, there was an increased risk of hypertensive disorders in both nulliparous and multiparous normal weight and overweight mothers.[36]

Authors also studied the relationship between the work, physical activity and the hypertensive disorders. The findings were that the regular physical activity had a protective effect and there was no relation with the type of work. [37] The other factors that were studied include obstructive sleep apnea[38], calcium supplementation[39] ambient air pollution[40] maternal obesity[41] and the seasonal variation with the hypothesis that prevalence is more during the winter months.[42]

Placenta is the main source of pathology in hypertensive disorders as the disease state reverts at the earliest as soon as placenta is out. Further adding to this, the disease manifestations are seen even in the case if no fetus is present but with the presence of instigating factor like trophoblast tissue in abundance comparatively.[43] Theories have been put forth to explain the same, the two stage model emphasises about the substances which are released due to the first stage of reduced placental perfusion.

Going in detail into the pathophysiology starts at the very beginning during the early period of gestation during the time of implantation, the first ten weeks of gestation where the embryo is surrounded by a low oxygen tension environment and the nutrients are provided by the glands in the endometrial tissue. After the ten-week period, vessels of maternal origin starts perfusing the embryonic tissue and thus starting the vascularisation of the intervillous space. During this period of initial low oxygen tension, the placental tissue responds accordingly as well, proliferation in the initial period followed by reduction once the oxygen tension increases.

The invasion of the trophoblastic cells into the maternal vessels microscopically leads to the replacement of the endothelial cells and acquiring a lining of the trophoblastic cells on the decidual side. These spiral arterioles on the decidual side being dilated to a striking extent, lose the smooth muscle and even the inner elastic lamina thereby becoming the dilated tubes which are unresponsive to hormonal stimulus. This change extends into the inner thirds of the myometrium which is not seen in the preelampsia where this remodelling does not occur and these changes are not seen upto the myometrium even if it occurs in very few vessels.[43]

Extensive research on this topic focused on the failure of the dilation of the tip of the vessels, understanding that the flow will not increase to the fourth power of the radius due to the failure in the dilatation of the vessels as noted in the Poiseuille's law. However, the importance of the absence of vascular changes into the depth of the myometrium also plays a significant role as explained by Burton.[43] He also stated that the retained smooth muscle in the

vessels in the inner third of the myometrium enabling the stoppage of blood flow in the non-pregnant uterus will fail in these situations to reduce the increased flow of blood to the gravid uterus, the main premise of the dilation of the vessels. These changes are accompanied by the acute atherosis which is not pathognomonic to preeclampsia. These changes also lead to Fetal Growth Restriction (FGR).[43]

Histopathological changes in placenta in Hypertensive disorders:

Gross morphological features are pronounced in the placenta of pregnant women suffered from preeclampsia. These changes range from shape to weight, as found in a study where thousands of placentae were studied (6410) over a decade time, an oblong shape. The weight of the placenta stratified into centiles, shown that the infants were towards the lower side weight wise in case of placenta weighing less than the 30th centile and were larger in the placentae weighing more than the 90th centile.[43]

The change in the shape into oblong form was explained due to the ineffective invasion of the vessels by the trophoblast. In a normal placentation the invasion is maximum in the centre of the placenta and the trophoblastic invasion allows enough time, whereas on the periphery along with the reduced invasion and plugging of the vessels leads to insufficient oxygen supply and excessive oxidative stress leading to necrosis and thereby a circular shape. Whereas in a case of placenta affected by the hypertensive disorders, the inefficient implantation leads to a haphazard regression unlike the circumferential regression in normal pregnancy. This hypothesis also explains the prevalence of thicker placentas in preeclampsia due to the villi and the cells due to the high rate of flow of blood in the blood vessels which were not transformed.[43,44]

Histological changes in these pregnancies include many syncytial knots, branching villi and sclerosed smaller villi. As expressed by Burton, hypoxia might be the major reason for the

generation of reactive oxygen species which in turn causes the morphological changes These changes include increased syncytial knots, fibrinoid necrosis, intervillous haemorrhages, villous stromal fibrosis, calcification and vessel changes due to atherosis. The extent of these changes histologically depends on the severity of the disease process. [44]

The exaggerated morphological appearances in the placenta like syncytial knots were found to be due to Reactive Oxygen Species (ROS), hypoxia and hyperoxia [45] The placental cells were cultured in vitro and found to have increased knots in hypoxia, hyperoxia as well as ROS. These syncytial knots were described as the aggregation of nuclei over the surface of terminal villi. In case of term placenta, the apparent appearance of syncytial knots was thought to be of artefactual origin and only rarely due to sprouts or apoptosis. These help in assessing the maturity of villi and ranges upto 30% in normal term placenta.[46] Excessive formation of these syncytial knots called as "**Tenney-Parker change**" is associated in cases of placental pathology due to malperfusion. [45,47]

The need for differentiation of the tenny parker change from the true knots and syncytial sprouts which increase with the gestational age and indicate trophoblast proliferation respectively thereby leading to the better characterisation of these changes as follows. The nuclei of true knots have a chromatin which is highly condensed and aged[47] Knotting index can be used for severity however the confounding factors due to tangential sectioning resulting in false knotting reduced the utility of this. Serial sectioning and IHC markers helps in differentiating the true from false knotting.[47] The nuclei in the false knots and sprouts were found to be transcriptionally active whereas the nuclei in true knots were found to be inactive thereby negative for transcriptional markers. These true knots can also be differentiated with their positivity for 8-oxo-deoxyguanosine.[47]

The features like fibrinoid necrosis, stromal fibrosis and cytotrophoblastic hyperplasia are also thought to be due to the insufficient vascular supply in the preeclampsia placentae and

which were found to be increased in comparison to the normal pregnancy.[48] Vascular changes like atherosis and thrombosis were also in the cases of gestational hypertensive disorders. Atheorsis characterised by lipid laden macrophages located sub-endothelially along with lymphocyte infiltration adjacent to the vessels and fibrinoid necrosis was characteristically seen along the spiral arterioles which were not transformed in cases of preeclamspia. Kim et al studied the presence of atherosis in 16,345 placentas[49], found that the placenta in preeclampsia had increased incidence in comparison to the normal pregnancies to the tune of 10% to 0.4% respectively and also noted that the atherosis was found to be more common in cases of preeclampsia rather than any other causes.[49] Anjali et al in their analysis of preeclampsia and quantitative analysis of placental villi histopathologically found that the syncytial knots, cytotrophoblastic proliferation and fibrinoid necrosis were more in the study group.

Similar results were also noted by Bhawana Sahay *et al* who studied 30 placentae in correlation with normal pregnancy with a special focus on cytotrophoblastic cell hyperplasia fibrinoid necrosis and stromal fibrosis which were found to be increased in the study group with a statistically significant results and concluded that these observations might be due to the insufficient vascular supply. Cytotrophoblastic cell hyperplasia and fibrinoid necrosis were much more frequent than the stromal fibrosis nearly to the tune being almost double the occurrence of hyperplasia and fibrinoid necrosis.[48]

Madhusmita Jena et al, studied the syncytial knots, vasculosyncytial membrane basement membrane thickening along with the stromal fibrosis and fibrinoid necrosis by counting 400 villi. With a p- value of <0.05 to be significant results, authors found that theses abnormal observation were statistically significant in the pregnancy induced hypertension group in comparison to the normal group particularly full-term placenta. Amongst these parameters fibrinoid necrosis, stromal fibrosis and vascular syncytial membrane paucity were found to be more common with occurrence of over 80%.[50]

Ratnamala S et al has done a clinical correlation and medical disorders in pregnancy by studying 50 placentae. Disorders studied ranged from hypertensive disorders, anaemia, diabetes mellitus and heart disease. Hypertension associated pregnancy disorders had a significant calcification along with infarction in gross observations of the placenta. Further they also noted that extensive infarction was associated with low APGAR score and perinatal deaths in 82% and 66.7% of the cases respectively. Authors noted that there was no significant microscopic change noted in heart disease. However, anaemia had stromal fibrosis and increased syncytial knots, diabetes had villous edema as the most significant finding.[51]

Rodica Ilie et al studied the structural modifications in 68 placentae in pregnancy induced hypertension. Using three different stains focused approach was followed in studying the lumen and the intimal layer changes.[52]

Complications:

Hypertensive disorders of pregnancy complicate the outcome in both mother and the fetus. The milder side of the spectrum in which pathology and its effects are transient and have nil/minor effects on the maternal and fetal outcome if managed well during the course.[53]

Osman et al studied over 219 pregnancies affected by eclampsia and HELLP syndrome. They have studied the presence or absence of the HELLP syndrome and the occurrence of seizure in the mother. Pregnancies affected by HELLP syndrome had a significantly shorter duration from the seizure to the delivery. Perinatal mortality rates were nearly double in the case of pregnancy with HELLP syndrome.[53]

Targeted approach towards the HELLP syndrome by Simone Onrust et al in Netherlands documented that nearly half of the cases of maternal mortality were affected by it and suggested that diagnosing the condition early and managing the disease with timely measures.[54]

Pradeep sharma in his observational study correlated fetal and maternal outcome in eclampsia as per the gestational age stating that it is associated with preterm delivery. He noted that the complications observed in his study group ranged from aspiration pneumonia, pleural effusion and pulmonary edema.[55] The incidence of eclampsia was more in the 31-35 years age group. Antenatal care visits lesser than the recommendations were attributed to these complications and noted the relation between the duration of the seizure and delivery which affected the incidence of complications.[55]

Habib et al studied the relation between first seizure and various features like the prodromal symptoms, imaging studies and treatment given in cases of late postpartum eclampsia. A total of 178 patients were included in the study among which only 22% had prior history of preeclampsia. The complications observed included aspiration pneumonia, pulmonary edema, pleural effusion and DIC in the decreasing order of frequency.[56]

Melissa et al focussed their study on the intensive care issues found in these gestational hypertensive disorders were DIC, ARDS, acute renal failure and rare complications like hepatic rupture, hematoma and sepsis. They concluded that a multidisciplinary team involved in the expectant management with close maternal and fetal monitoring reduces the complications.[57]

There was keen interest in the topic in the Indian subcontinent region as well. Narasimha et al studied the histopathological changes of placenta in mild preeclampsia, severe preeclampsia and eclampsia in 63 placentae post 28 weeks gestation. Gross morphological lesions were noted by the authors with respect to shape, size and thickness. Histological changes like increased syncytial knots, fibrinoid necrosis and stromal fibrosis were analysed by these authors.

Pasricha et al also stratified the cases into mild severe preeclampsia and eclampsia. They studied a total of 30 placentae in their study group with a focus on the fetal outcome along

with correlation of the microscopic features like cytotrophoblastic proliferation, syncytial knots stromal knots and fibrinoid necrosis.

With time, the interest in understanding the placental pathology in terms of the microscopic changes and comparatively very few authors studied the relationship between the placental histopathology and fetal outcome. One such study done by Marie Therese[58] documented that the mothers suffering from preeclampsia deliver prematurely and the new born was also growth restricted. The symptoms correlated with the pathology affecting the placenta.

Correlation of placental pathology along with the severity of the disease and the maternal and fetal outcome provides intricate details into the understanding of the disease process as well as helping in the better management of the case in the future by attributing the reasons for the pathophysiological processes. Hence this study was undertaken in a tertiary care center which caters to the rural population. This analysis also helps in designing the programs for targeting the mothers and educating them about the disease and the care that must be taken during and after the pregnancy in cases of the present as well as future pregnancies. How the diseases process can be handled in a better manner and how well the gestation can be managed with minimal complications.

Materials and methods

Source of data:

A prospective cross-sectional study was carried out at Department of Pathology from 1st December, 2017 to 30th June, 2019.

Inclusion criteria:

All placental specimens received in the histopathology section of Department of Pathology with a clinical diagnosis of hypertensive disorders of pregnancy.

Exclusion criteria:

- Congenital fetal anomaly
- Fetus incompatible with survival
- Patients who were diagnosed with other causes of convulsions in pregnancy like cerebral malaria and epilepsy
- Pregnancies complicated with diabetes mellitus, primary renal disease and collagen vascular diseases.

Methods of collection of data:

The placenta with attached membranes and umbilical cord received in histopathology section of Department of Pathology from clinically diagnosed Hypertensive disorders of pregnancy in Department of Obstetrics and Gynaecology (OBG) were included in the study. Clinical details were obtained and categorized as:

- Gestational Hypertension
- Mild Preeclampsia
- Severe Preeclampsia
- Eclampsia

The size, shape and weight of placental specimens were documented as per the standard protocols followed in the department of Pathology. The initial observations were done in the fresh state as soon as received from the Department of OBG and any other relevant

findings were noted down. The placenta was fixed in 10% formalin after following bread loafing technique for a duration of 24hours.

The fixed specimens were processed according to routine histopathology protocol as follows, thin slices of the placenta with a thickness of around 3 to 5 millimeter which were then placed into a tissue processor and cycled through a 16hour formalin, graded alcohol and xylene containers. Paraffin embedded blocks were prepared and 3-4μm thick sections were obtained which were stained with Haematoxylin & Eosin technique. Bright field microscopy was used for the analysis at different magnifications. Syncytial knots, villous stromal fibrosis, fibrinoid necrosis intervillous haemorrhages and calcifications were analysed using 10x and 40x magnification.

The new-born babies were inspected for congenital anomalies during the course of the study and if present, those cases were excluded from the study. APGAR score and birth weight of the infants along with the fetoplacental weight ratio was calculated in all the cases.

Maternal outcome was observed for the complications during the intrahospital stay for 6 days in case of LSCS and 3 days in case of normal vaginal delivery.

Sample Size:

As in the study done by Narasimha A. *et al*. Spectrum of changes in placenta in toxemia of pregnancy, with 95% confidence level and margin of error of ±10%, a minimum sample size of 105 of hypertensive disorder of pregnancy subjects were allowed the study to determine the morphological study of placentae in hypertensive disorder of pregnancy and fetal outcome with finite population correction (N=2500).

Statistical formula:

$$n=\frac{Z^2 x\ p\ x\ (1-p)}{d^2}$$

n= sample size

Z=statistic for 95% level of confidence

p=expected prevalence or proportion.

d=margin of error

Hence, a minimum of 105 cases were to be included in the study. However, during the course of study 128 cases were included in the study.

Statistical analysis:

All characteristics were summarized descriptively. For continuous variables, the summary statistics of mean± standard deviation (SD) were used. For categorical data, the number and percentage were used in the data summaries and diagrammatic presentation. Chi-square (χ^2) test was used for association between two categorical variables.

The difference of the means of analysis variables between two independent groups was tested by unpaired t test. The difference of the means of analysis variables between more than two independent groups was tested by ANOVA and F test of testing of equality of Variance.

If the p-value was < 0.05, then the results were considered to be statistically significant otherwise it was considered as not statistically significant. Data were analysed using SPSS software v.23.0. and Microsoft excel 2019.

Results

During the study period, 128 females were diagnosed to be suffering from hypertensive disorders in pregnancy and were included in the present study. Among these 128 cases, over 78% of the cases were under the age of 25 or less followed by 10.9% each in the 26-30 years and in more than 30 years age group. The details of which are mentioned in the Table 1.

Table 1 Distribution of cases according to maternal age

AGE (yr)	N	%
≤25	100	78.2
26-30	14	10.9
>30	14	10.9
Total	128	100

Cases were further classified into the groups as gestational hypertension, mild preeclampsia, severe preeclampsia and eclampsia based on the severity of the disease process which was diagnosed clinically. As per the stratification, highest mean age of 24.7 years was found in the severe preeclampsia group and the mean age of incidence of the hypertensive disorders in the pregnant females was 23.7 years (**Table 2** & **Figure 1**).

Table 2: Mean age according to gestational hypertensive disorders

Parameters	Gestation Hypertension		Mild Preeclampsia		Severe Preeclampsia		Eclampsia		Total		p value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Age(yr)	23.9	4.1	22.6	3.0	24.7	4.4	23.1	4.3	23.7	4.1	0.305

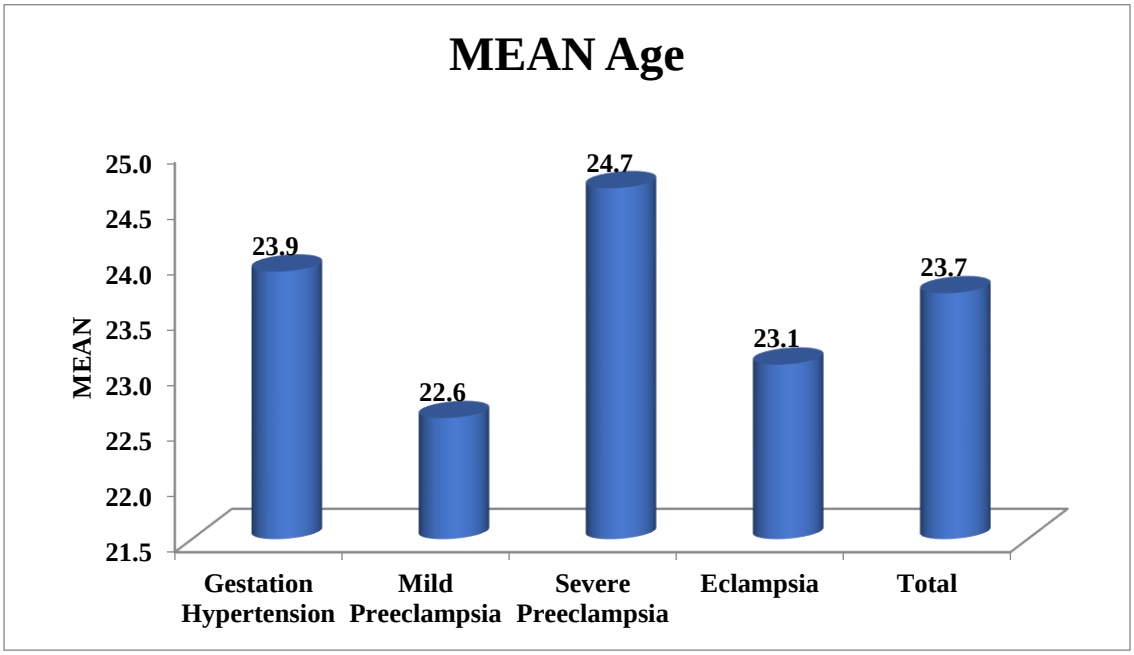


Figure 1: Mean age according to gestational hypertensive disorders

Cases were further distributed into two groups based on the maternal parity, with 60.2% of the cases being primigravida in the study group, the rest 39.8% comprised of the multigravida females. Among the 128 cases, Singleton gestations were 95.3% (n=122) and there were 4.7% (n=6) twin gestations.

Table 3: Distribution according to maternal parity

PARITY	N	%
MULTI	51	39.8
PRIMI	77	60.2
Total	128	100

Table 4: Parity according to hypertensive disorders of pregnancy									
Parity	**Gestation Hypertension**		**Mild Preeclampsia**		**Severe Preeclampsia**		**Eclampsia**		**p value**
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
MULTI	30	56.6%	4	23.5%	10	34.5%	7	24.1%	0.010*
PRIMI	23	43.4%	13	76.5%	19	65.5%	22	75.9%	
Total	**53**	**100.0%**	**17**	**100.0%**	**29**	**100.0%**	**29**	**100.0%**	

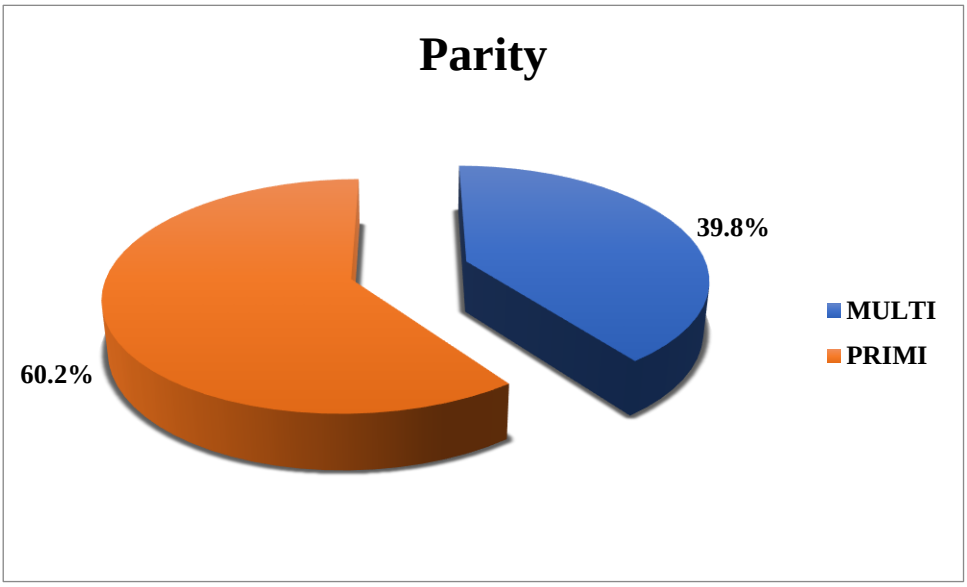


Figure 2 Distribution according to maternal parity

Preeclampsia and eclampsia were more in the case of primigravida, whereas the gestational hypertension was more in case of multiparous mothers. With 53 cases, gestation hypertension was the most common among the study group as well as among both the primipara and multiparous groups. With 29 each in the severe preeclampsia and eclampsia group and finally, 17 cases were falling under the group of mild preeclampsia. The graphical representation of the same was depicted in **Figure 3**.

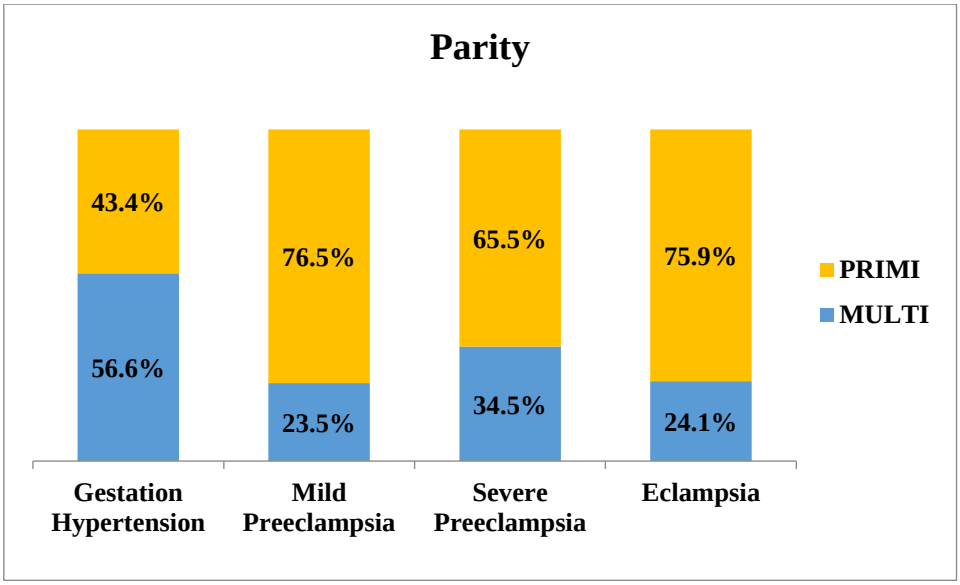


Figure 3 Parity according to gestational hypertensive disorders

As per the gestational age, stratified into weeks in the intervals of 28-32, 33-36 and 37-42 weeks, majority of the cases were in the group of 37-42 weeks followed by 33-36 and 28-32 weeks. The details of this stratification represented in a graphical manner in **Figure 4**

Table 5 Distribution of cases according to gestation age		
Gestation Age (wks)	**N**	**%**
28-32	10	7.8
33-36	35	27.3
37-42	83	64.8
Total	128	100

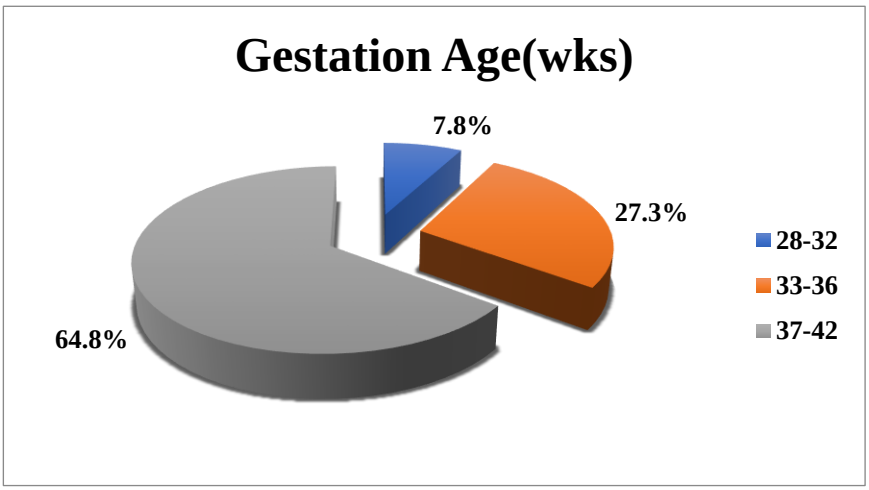


Figure 4: Distribution of cases according to gestation age

Based on clinically diagnosed cases of gestational hypertensive disorders of pregnancy cases were categorised as gestational hypertension 41.4% cases (n=53), mild preeclampsia 13.3% cases (n=17), severe preeclampsia 22.7% of cases (n=29) and eclampsia 22.7% of cases(n=29).

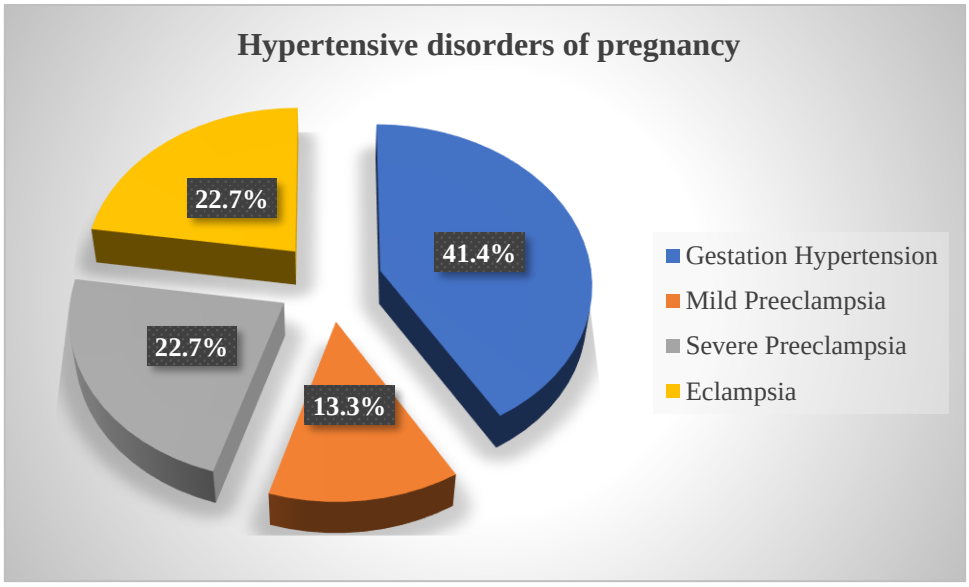


Figure 5: Distribution of cases according to gestational hypertensive disorders

Table 6: Distribution of cases according to gestational hypertensive disorders

HYPERTENSIVE DISORDERS OF PREGNANCY	N	%
Gestational Hypertension	53	41.4
Mild Preeclampsia	17	13.3
Severe Preeclampsia	29	22.7
Eclampsia	29	22.7
Total	128	100

Table 7: Distribution of the hypertensive disorders, parity and gestation age				
Hypertensive disorders of pregnancy	**Parity**	**Gestation Age(wks)**	**N**	**%**
Gestational Hypertension	MULTI	28-32	2	6.7
		33-36	6	20
		37-42	22	73.3
	PRIMI	28-32	0	0
		33-36	4	17.4
		37-42	19	82.6
Mild Preeclampsia	MULTI	28-32	0	0
		33-36	1	25
		37-42	3	75
	PRIMI	28-32	0	0
		33-36	4	30.8
		37-42	9	69.2
Severe Preeclampsia	MULTI	28-32	1	10
		33-36	4	40
		37-42	5	50
	PRIMI	28-32	3	15.8
		33-36	4	21.1
		37-42	12	63.2
Eclampsia	MULTI	28-32	0	0
		33-36	3	42.9
		37-42	4	57.1
	PRIMI	28-32	4	18.2
		33-36	9	40.9
		37-42	9	40.9

Table 7 represents distribution of the hypertensive disorders in correlation with the gestational age in weeks and parity. There was an increased incidence of preeclampsia (65.5%) and eclampsia (75.9%) in primigravida. Whereas in multigravida, gestational hypertension (56.6%) was higher.

Gross morphological examination was done in all the placentae and the twin gestation both the placentae were weighed separately and all the six cases were diamniotic and dichorionic. The parameter of shape evaluated in all the cases included stratification of the placentae into three groups, those with regular shape as oval (55.5%), round (14.8%) and irregular shape amounting to 38 cases close to 30%. Graphical representation of the same was done in the *Figure 6*. The shape of the placenta was further correlated with the hypertensive

Table 8: Distribution of cases according to shape of placenta

SHAPE	**N**	**%**
IRREGULAR	38	29.7
OVAL	71	55.5
ROUND	19	14.8
Total	**128**	**100**

disorders with representation in **Figure 7 & Table 9**. With a significant p-value, the placentae were found to be irregular in the cases of eclampsia to the tune of four in every five whereas the gestation hypertension has close to 90% of them being regular. In case of preeclampsia nearly equal distribution of the regular and irregular placentae were noted.

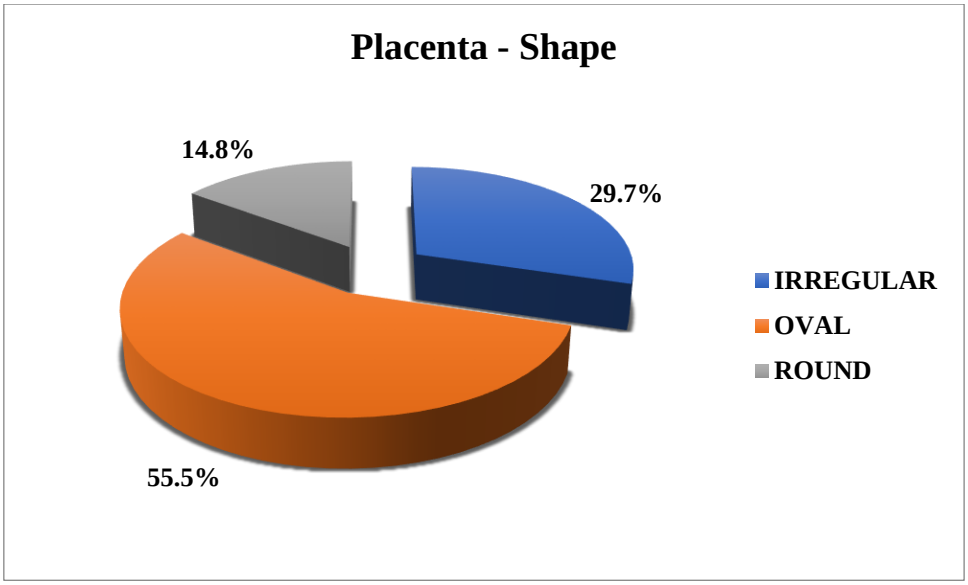


Figure 6 Distribution of cases according to shape of placenta

Table 9: Shape of placentae according to gestational hypertensive disorders									
SHAPE	**Gestation Hypertension**		**Mild Preeclampsia**		**Severe Preeclampsia**		**Eclampsia**		**p value**
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
IRREGULAR	1	1.9%	0	0.0%	14	48.3%	23	79.3%	<0.001*
OVAL	47	88.7%	15	88.2%	5	17.2%	4	13.8%	
ROUND	5	9.4%	2	11.8%	10	34.5%	2	6.9%	
Total	53	100.0%	17	100.0%	29	100.0%	29	100.0%	

Note: * significant at 5% level of significance (p<0.05)

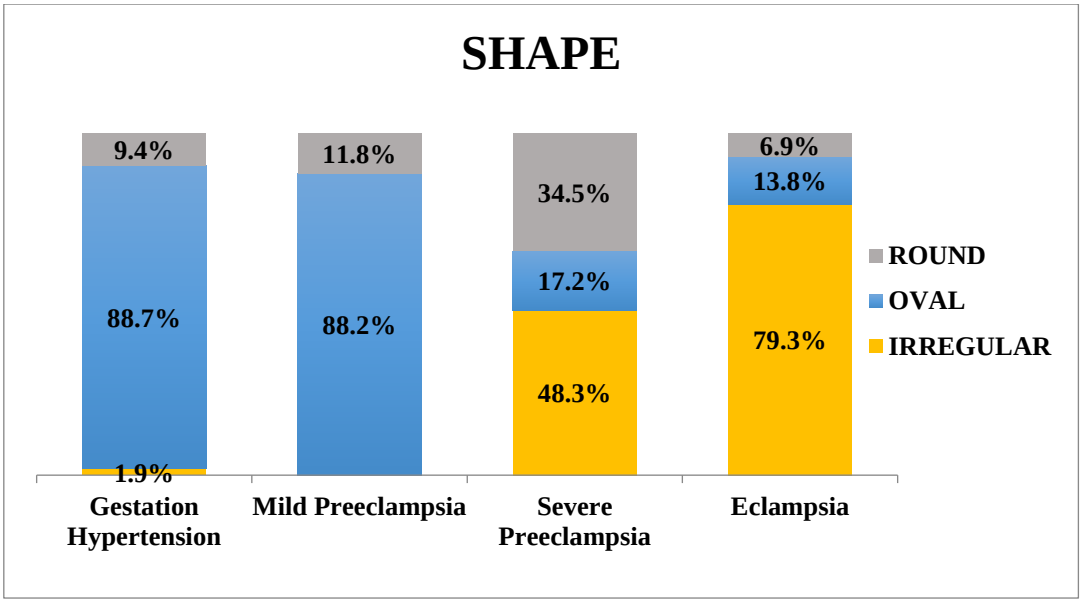


Figure 7: Shape of placentae according to gestational hypertensive disorders

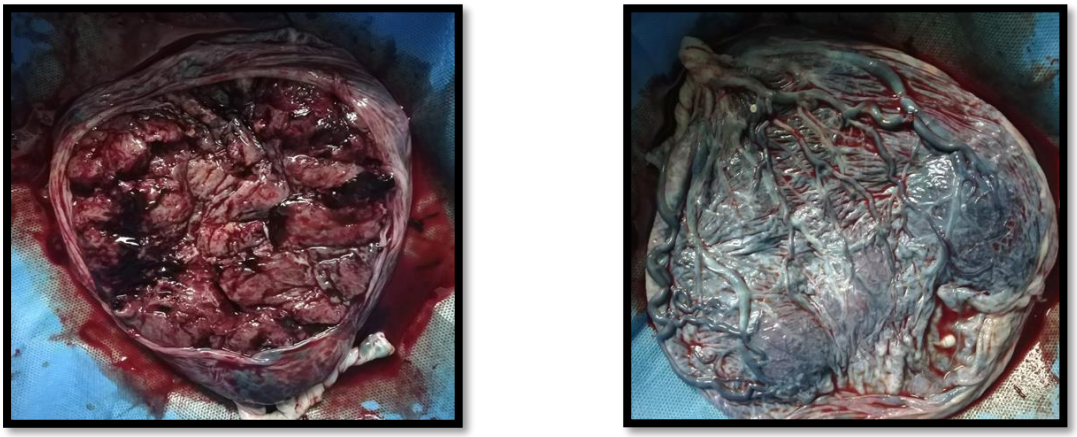


Figure 8 Oval shaped placenta in case of GHTN

(Maternal surface- left side, Fetal surface- right side)

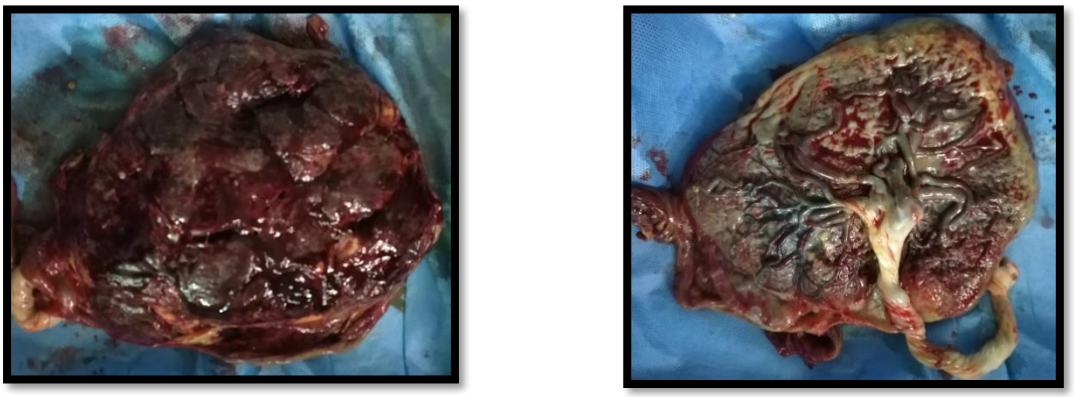


Figure 9 Irregular shaped placenta in case of Severe Preeclampsia

(Maternal surface- left side, Fetal surface- right side)

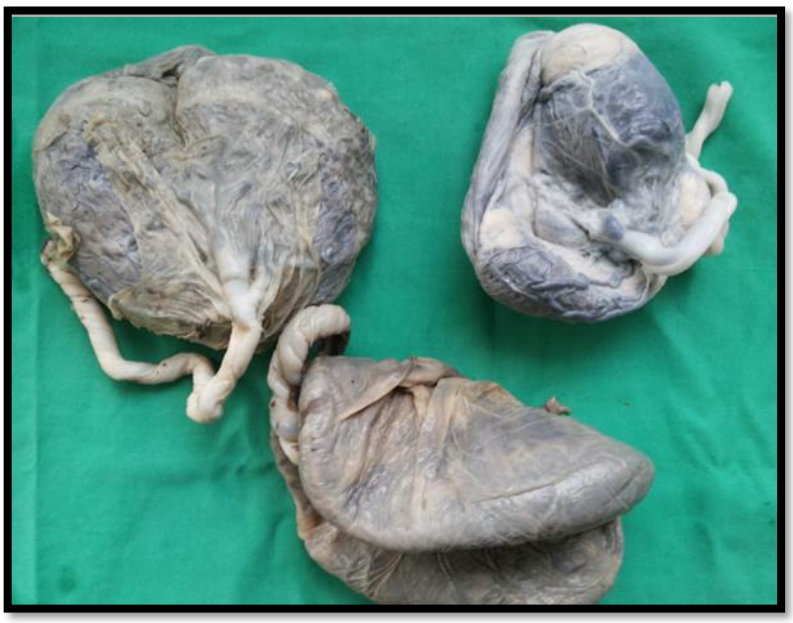


Figure 10 Irregular shaped placenta in cases of Eclampsia

Table 10: Mean placental weight, diameter and thickness according to gestational hypertensive disorders											
Parameters	**Gestation Hypertension**		**Mild Preeclampsia**		**Severe Preeclampsia**		**Eclampsia**		**Total**		**p value**
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Weight	478.8	108.0	461.2	131.8	377.8	114.1	341.7	112.1	422.5	126.8	<0.001*
Diameter	15.9	2.3	15.6	2.5	14.8	2.4	13.6	2.2	15.1	2.5	<0.001*
Thickness	3.1	0.9	3.1	1.0	2.5	0.9	2.2	0.9	2.8	1.0	<0.001*

Note: * significant at 5% level of significance (p<0.05)

Morphological evaluation of placenta included the measurement of the weight, diameter and the thickness at the central portion. The details of these measurements were tabulated and compared amongst the four groups of hypertensive disorders represented in *Table 10*. A decreasing trend was noted in the weight with heaviest in gestational hypertension and least weighing in the eclampsia cases with a difference in the mean to the tune of 137 gm which had a p-value of <0.001. Similar trend was noticed in the case of

diameter as well as thickness. A 0.9cm reduction in the thickness was noted in the eclampsia cases. The graphical representation of the same was done in the **Figure 11**.

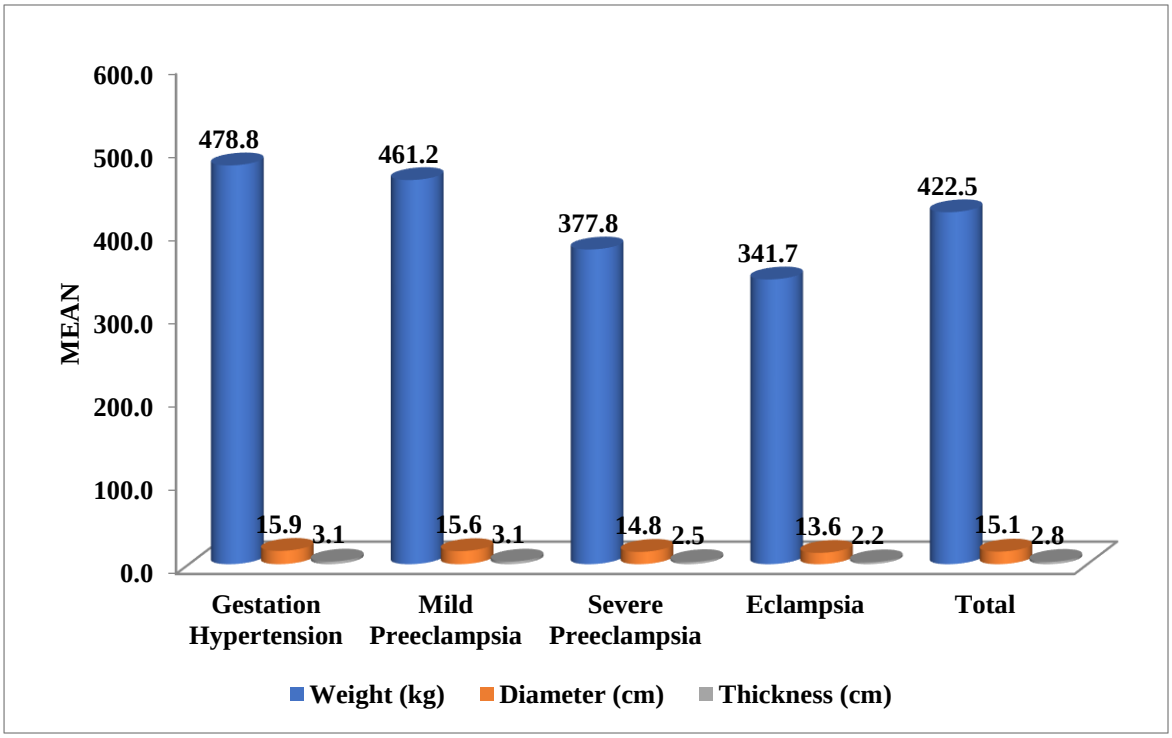


Figure 11: Mean placental weight, diameter and thickness according to gestational hypertensive disorders

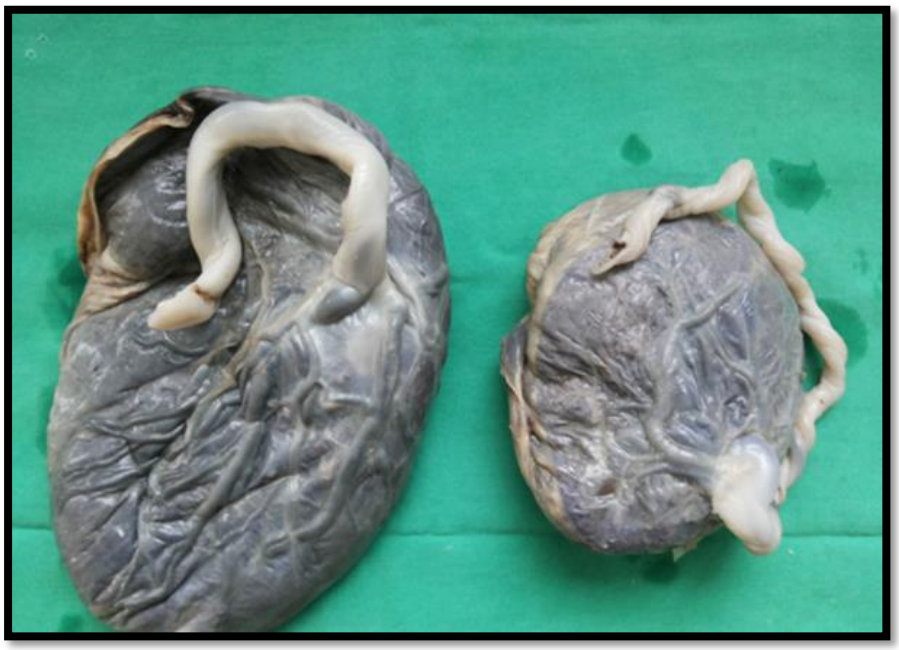


Figure 12 Reduced placental size (right side)

Table 11: Distribution of cases according to microscopic findings		
MICROSCOPIC FINDINGS	**N**	**%**
Increased Syncytial knots	46	35.2
Fibrinoid necrosis	70	54.7
Intervillous haemorrhages	55	43
Villous stromal fibrosis	53	41.4
Calcification	50	39.1
Vessel changes (atherosis/ thrombosis)	58	45.3

During the evaluation of the microscopy the following parameters like Increased Syncytial knots, Fibrinoid necrosis, Intervillous haemorrhages, Villous stromal fibrosis, Calcification and Vessel changes including atherosis and thrombosis were evaluated. With over half of the cases (54.7%) had shown fibrinoid necrosis, followed by vessel changes (45.3%) and intervillous haemorrhage (43%) when the entire study group was considered. However,

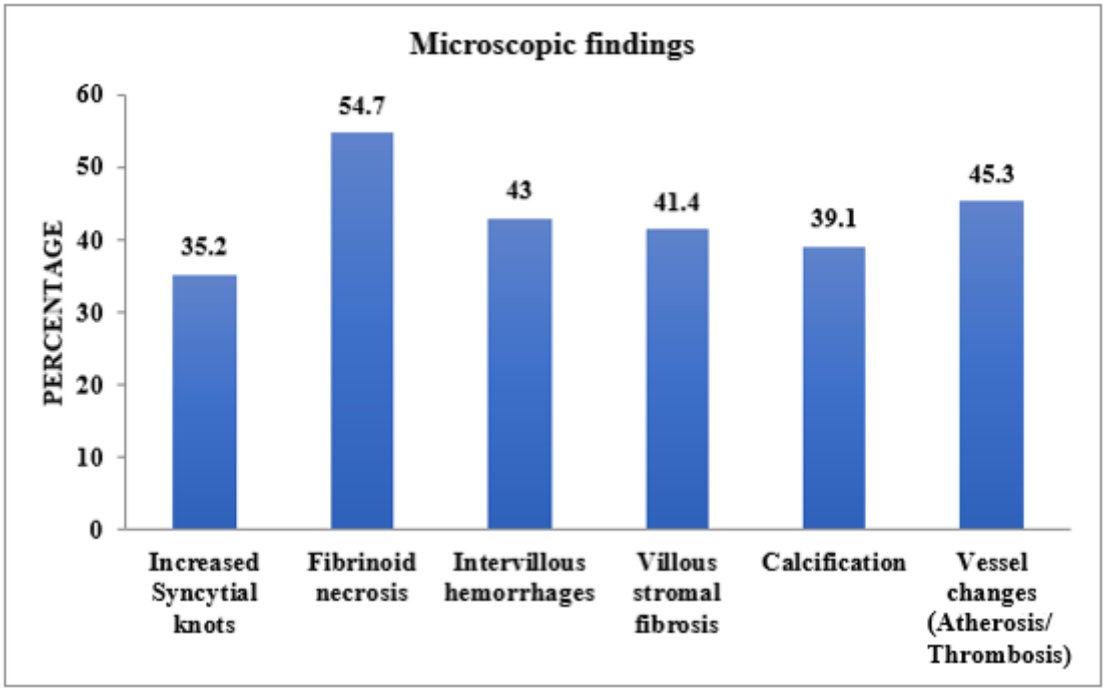


Figure 13: Overall distribution of cases according to microscopic findings

the relative proportion of the cases in consideration as an overall group has given the spuriously low values of these parameters. The graphical representation of the microscopic findings was mentioned in detail in the **Figure 13**.

To correlate this microscopic finding with the severity of the disease and the stratification mentioned earlier, into one of the four categories, was done for each of these parameters. Increased syncytial knots considered based on the criteria that the presence of syncytial knots in over 30% of the villi. This feature was found in 37% of the cases of eclampsia and 32.6% of the cases in preeclampsia. The detailed breakup of this occurrence amongst the cases was done in **Figure 14**.

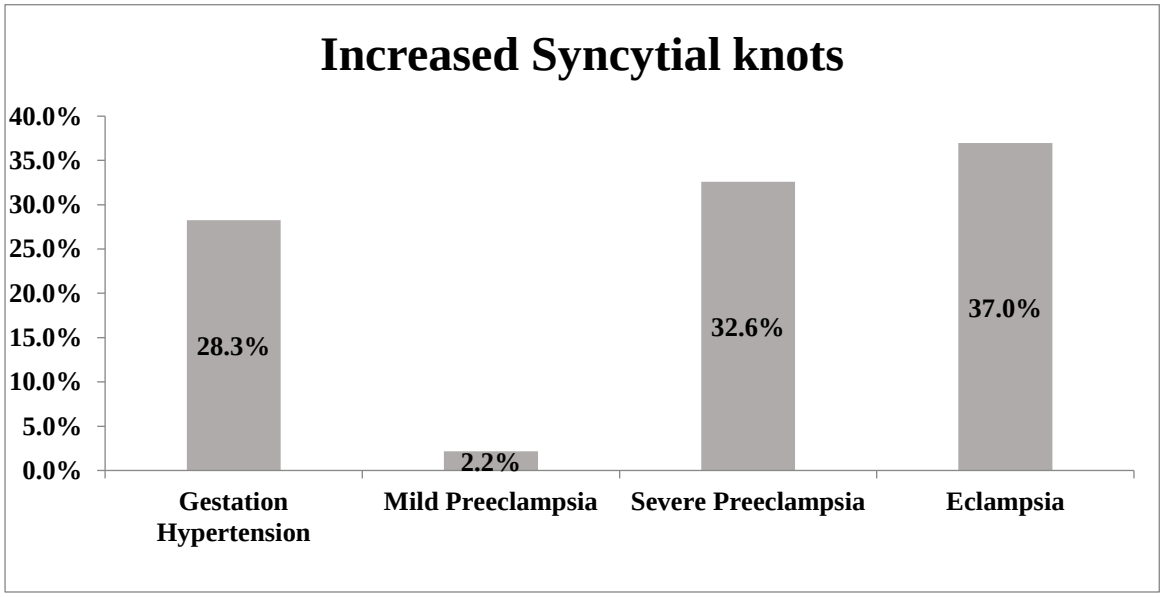


Figure 14: Increased syncytial knots according to gestational hypertensive disorders

The next microscopic feature studied was fibrinoid necrosis which was found in nearly every one in three cases of gestational hypertension, preeclamspia and eclampsia as mentioned in **Figure 15**. The presence of intervillous haemorrhages was noted in 27.3%, 30.9% and 30.9% in cases of gestational hypertension, preeclamspia and eclampsia respectively whereas 7.1% of the cases of mild preeclampsia as represented in **Figure 16**

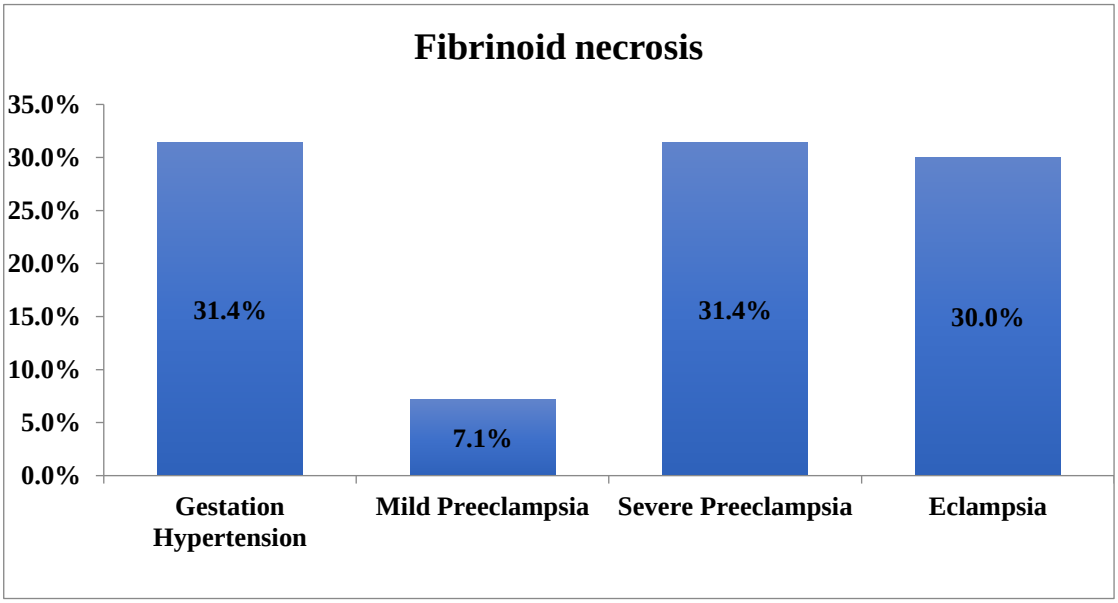


Figure 15: Fibrinoid necrosis according to gestational hypertensive disorders

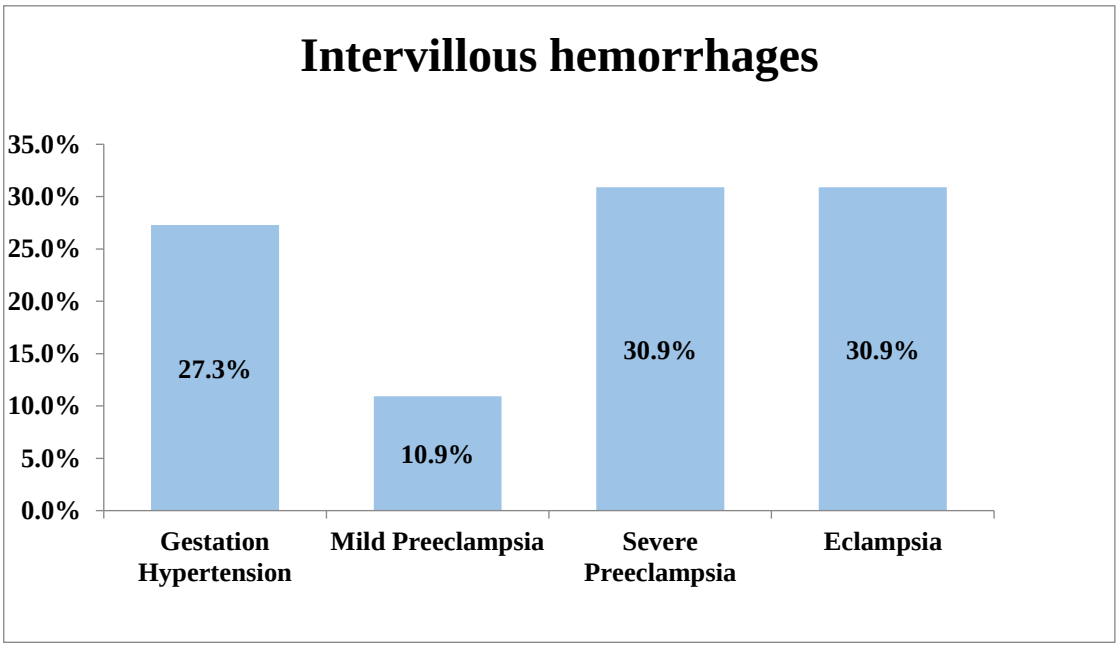


Figure 16: Intervillous haemorrhages according to gestational hypertensive disorders

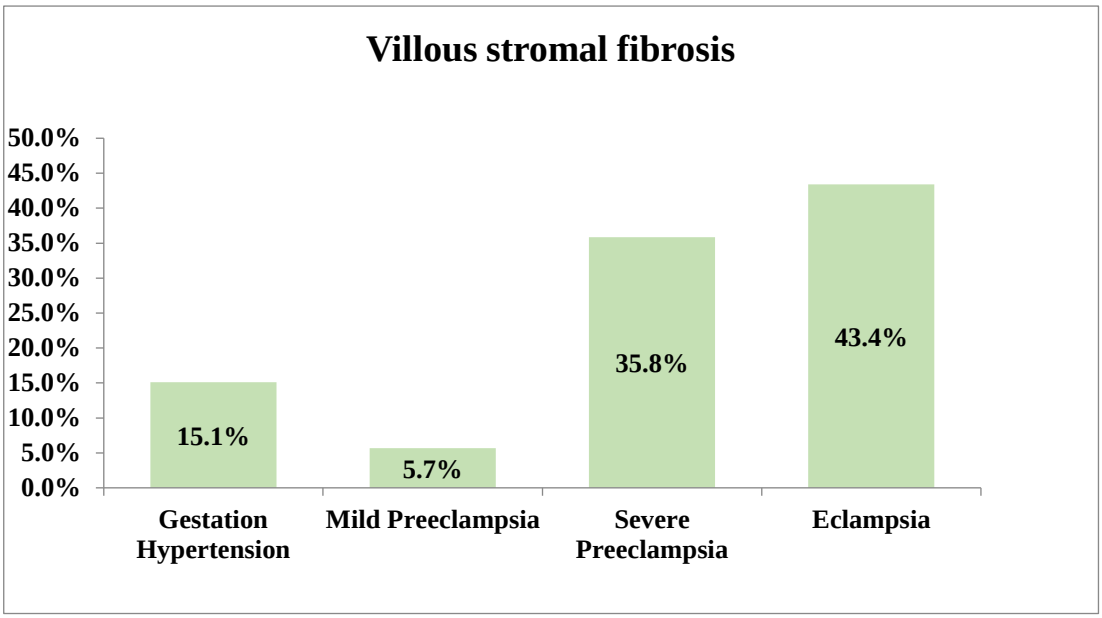


Figure 17*:* Villous stromal fibrosis according to gestational hypertensive disorders

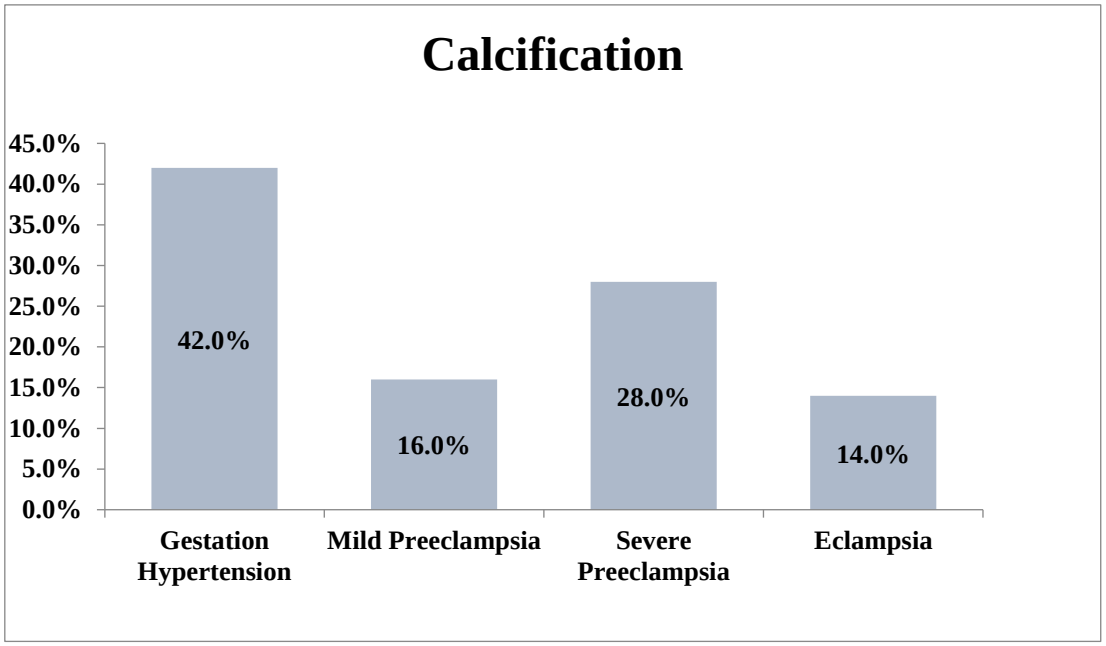


Figure 18: Calcification according to gestational hypertensive disorders

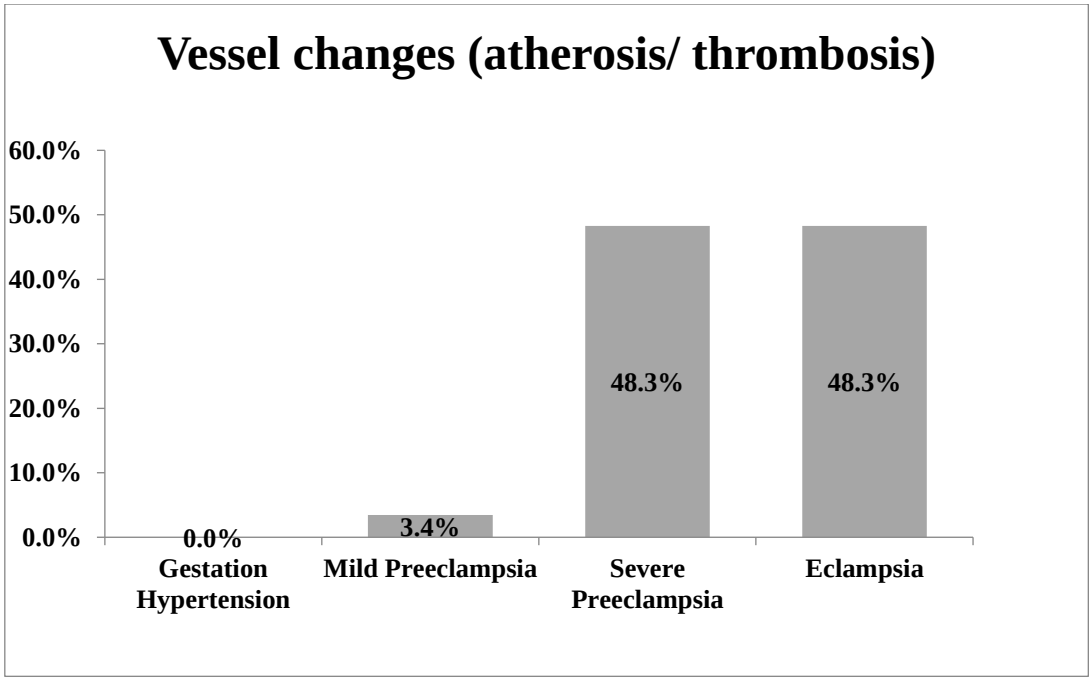


Figure 19: Vessel changes according to gestational hypertensive disorders

The spectrum of microscopic findings correlate with the severity of the disease and the stratification mentioned earlier, into four categories represented in the **Figure 20** **Figure 31**

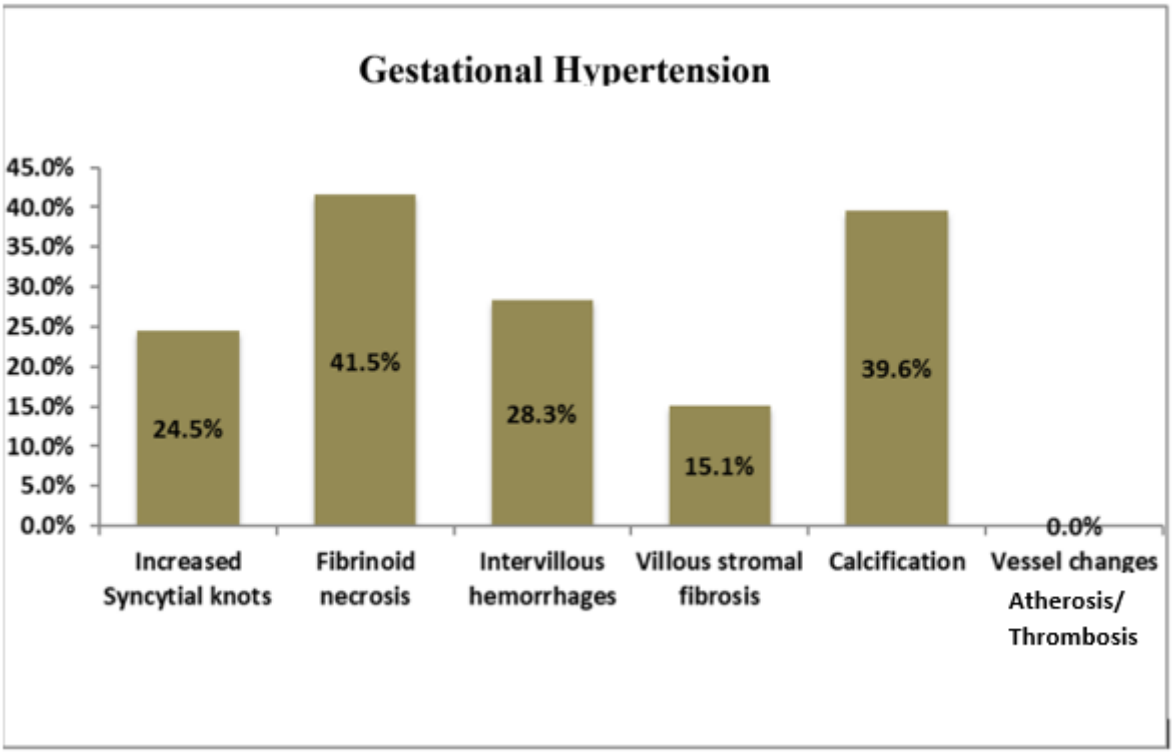


Figure 20 Spectrum of microscopic findings correlated with Gestational Hypertension

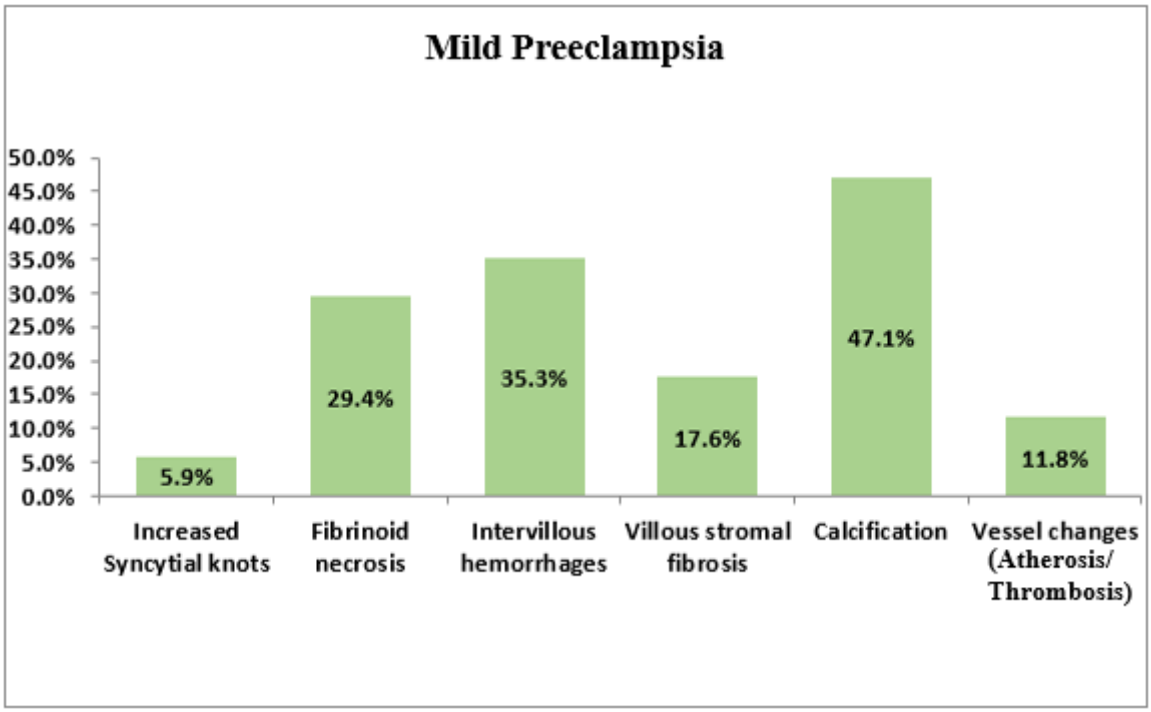


Figure 21 Spectrum of microscopic findings correlated with Mild Preeclampsia

Spectrum of microscopic findings shown from **Figure 22** to **Figure 29** in cases of GHTN and mild preeclampsia

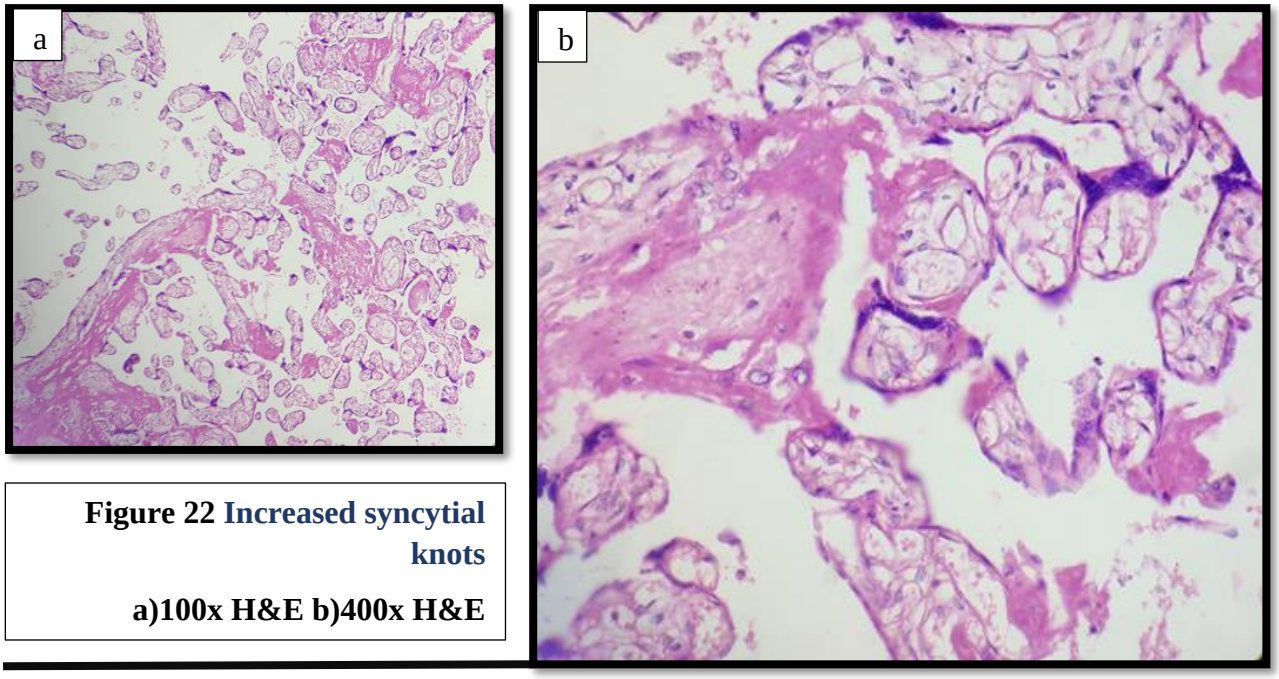


Figure 22 Increased syncytial knots

a)100x H&E b)400x H&E

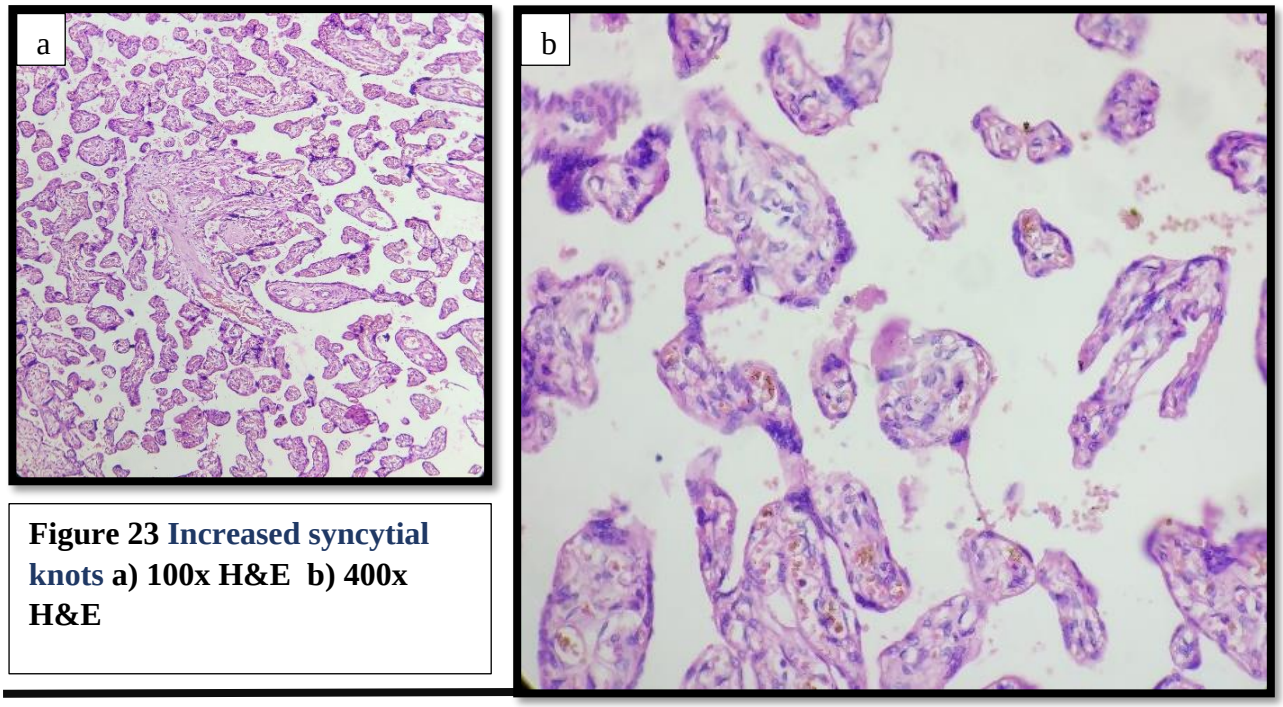


Figure 23 Increased syncytial knots a) 100x H&E b) 400x H&E

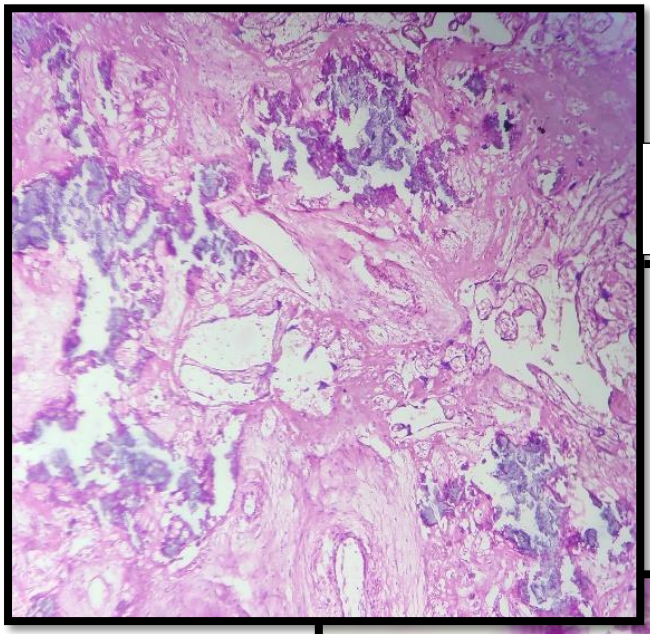


Figure 25 Calcification

100x H&E stain

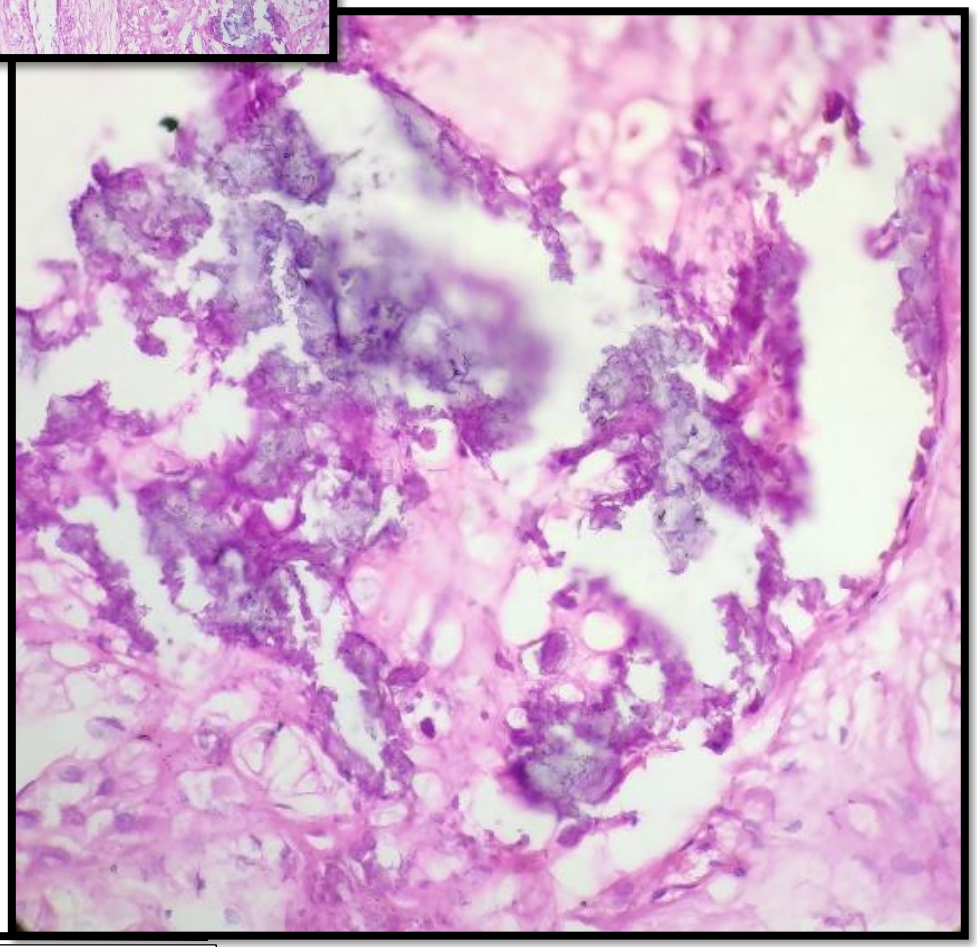


Figure 24 Calcification

400x H&E stain

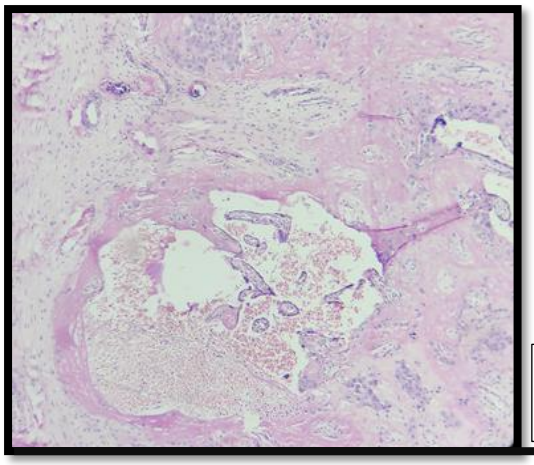


Figure 26 Intervillous haemorrhage
100x H&E stain

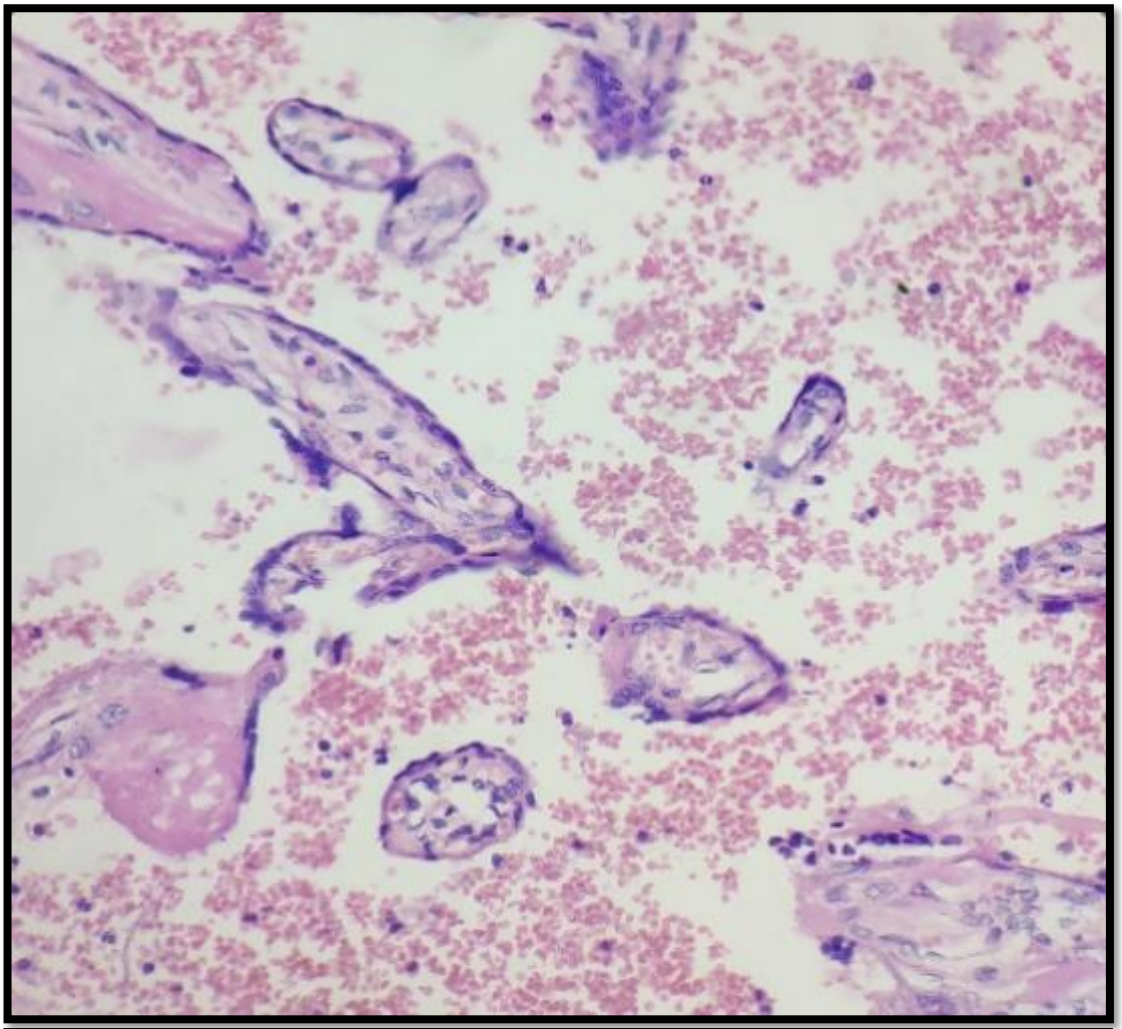


Figure 27 Intervillous haemorrhage

400x H&E stain

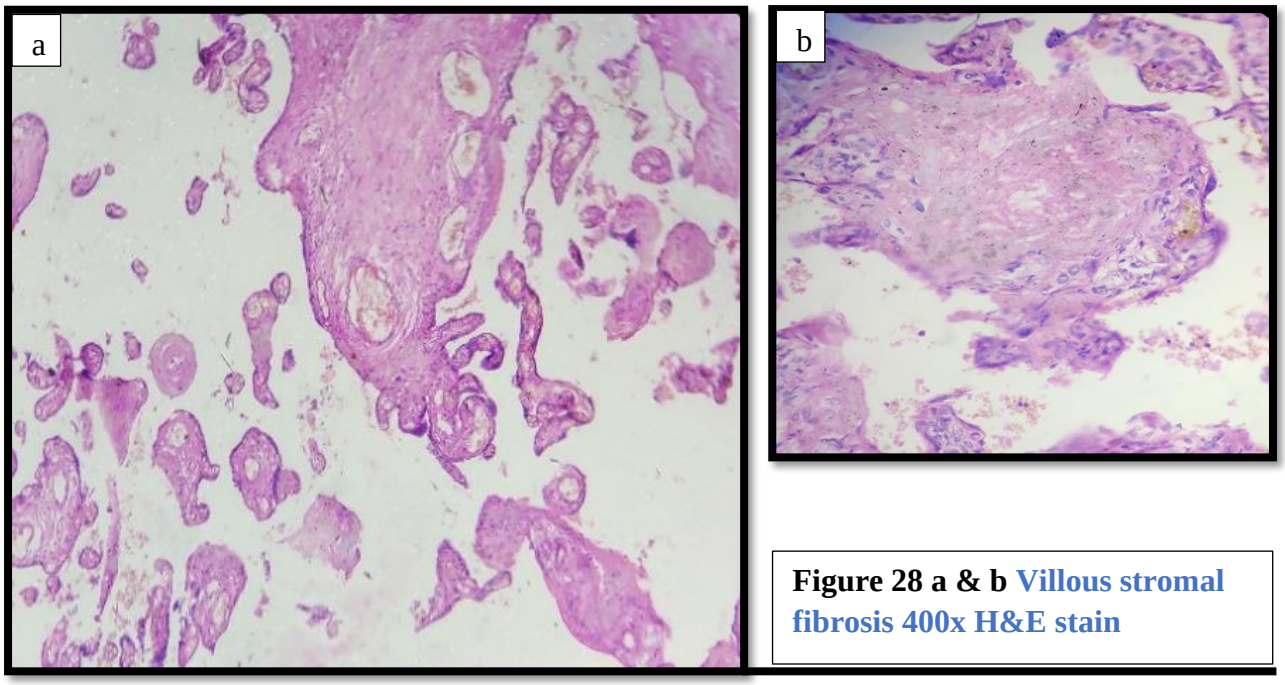


Figure 28 a & b Villous stromal fibrosis 400x H&E stain

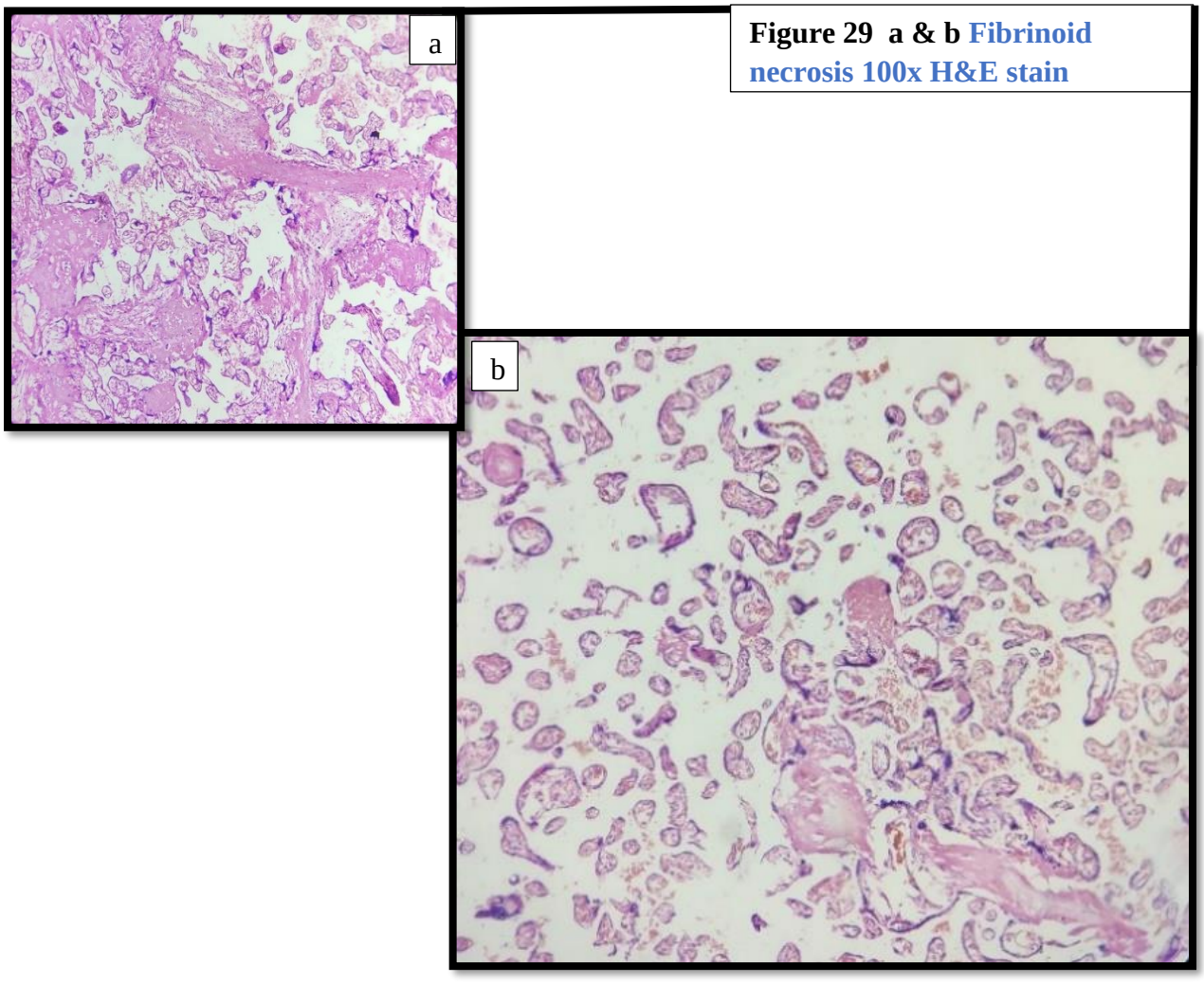


Figure 29 a & b Fibrinoid necrosis 100x H&E stain

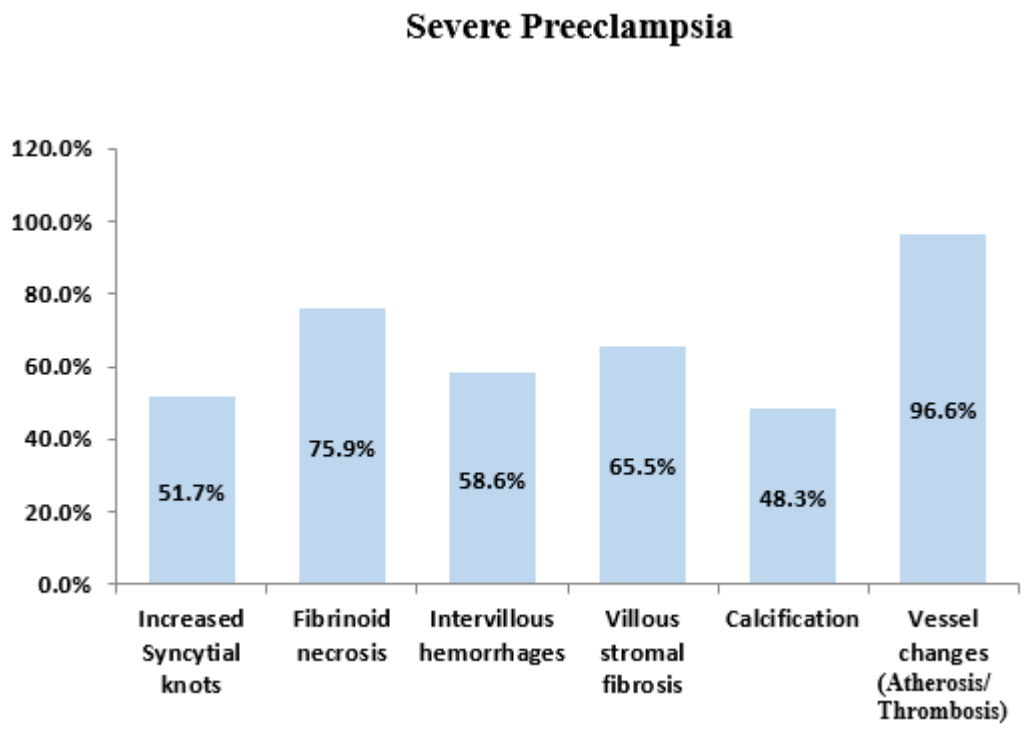


Figure 30 Spectrum of microscopic findings correlated with Severe Preeclampsia

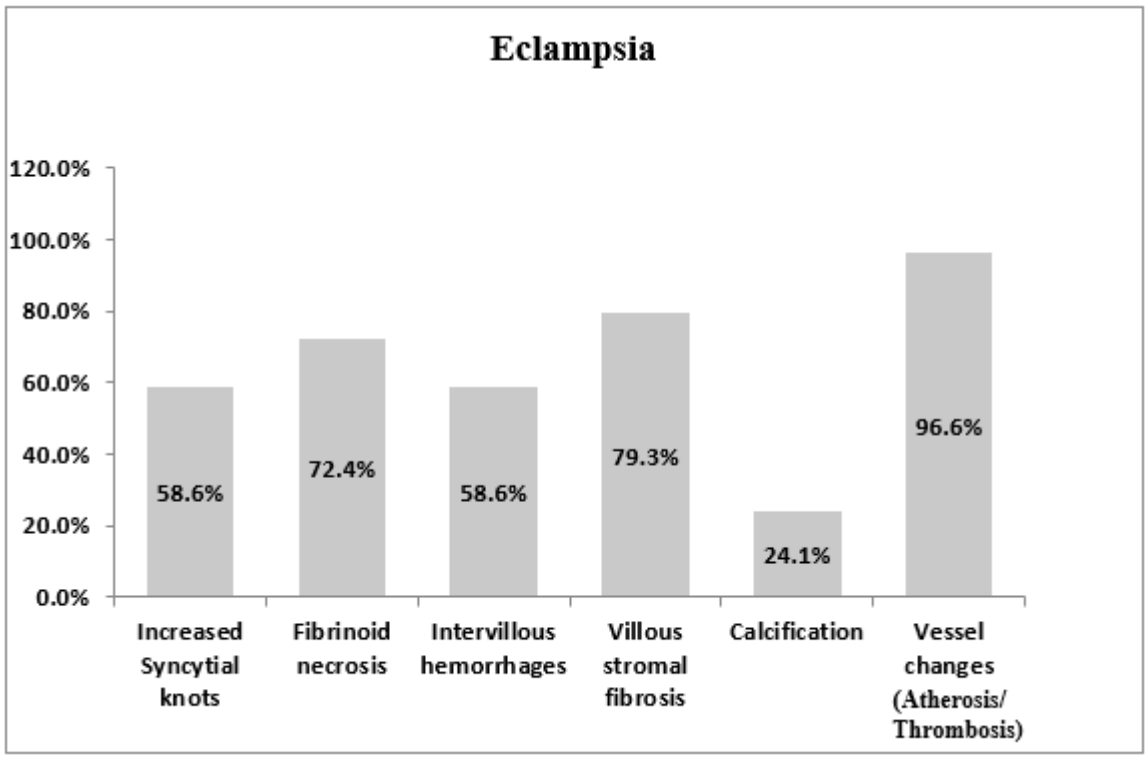


Figure 31 Spectrum of microscopic findings correlated with Eclampsia

Spectrum of microscopic findings are shown from Figure 32 to Figure 45 in cases of severe preeclampsia and eclampsia.

Figure 32 Increased syncytial knots 100x H&E stain

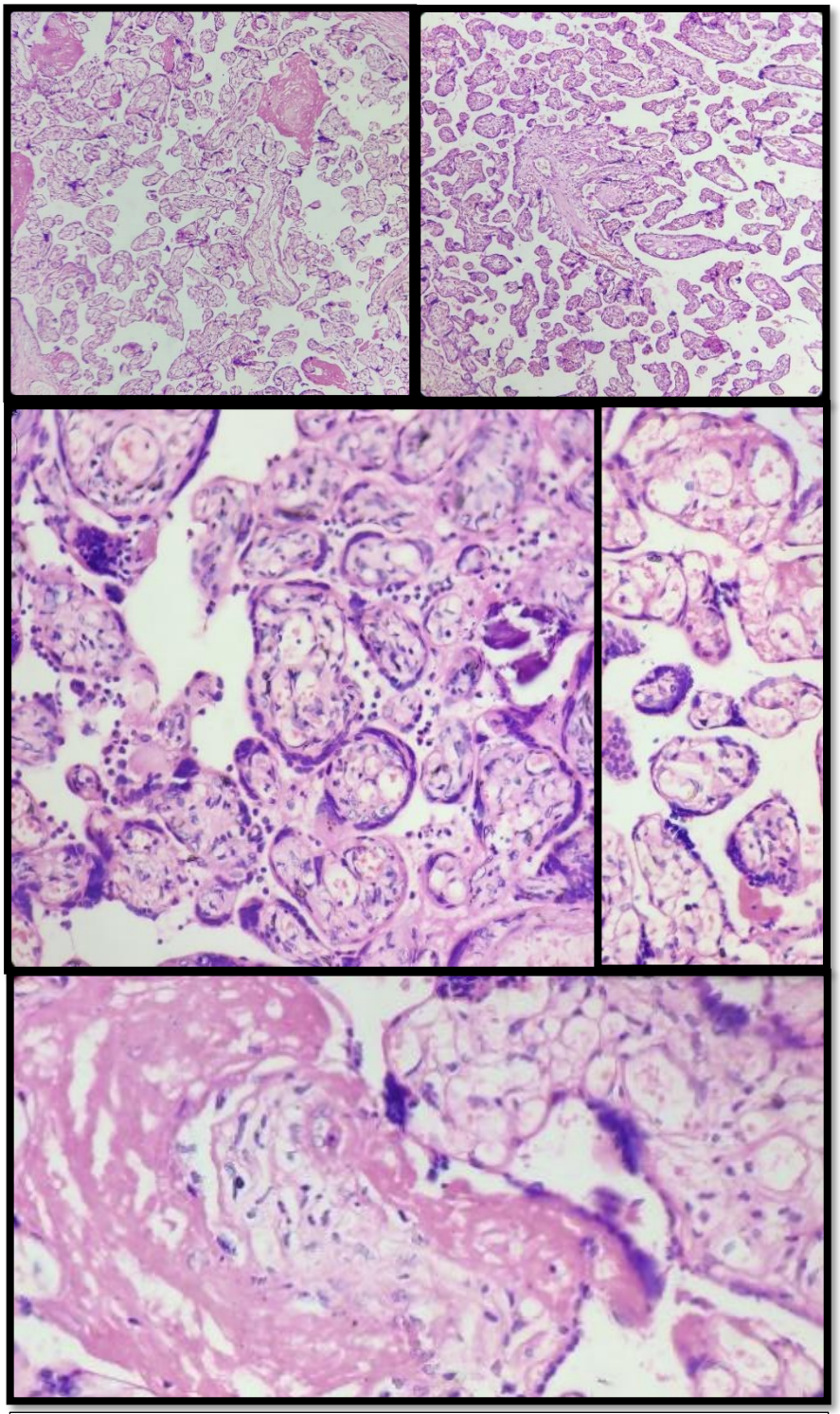
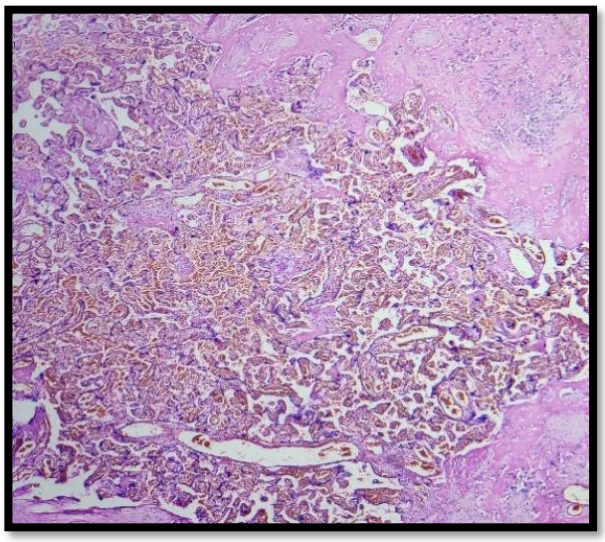


Figure 33 Increased syncytial knots 400x H&E stain

Figure 34 Intervillous haemorrhage 100x H&E stain



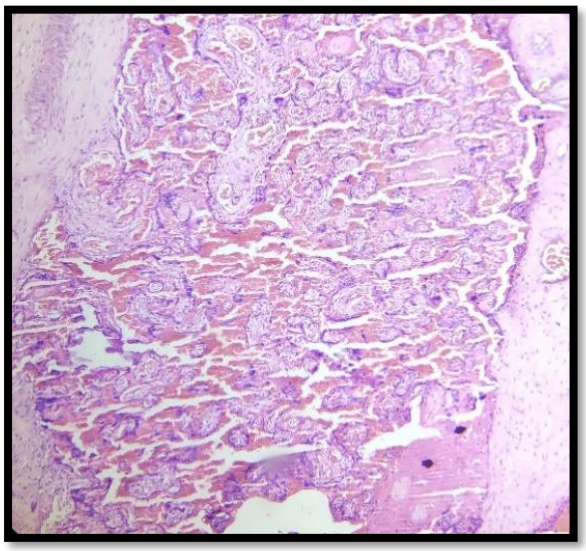
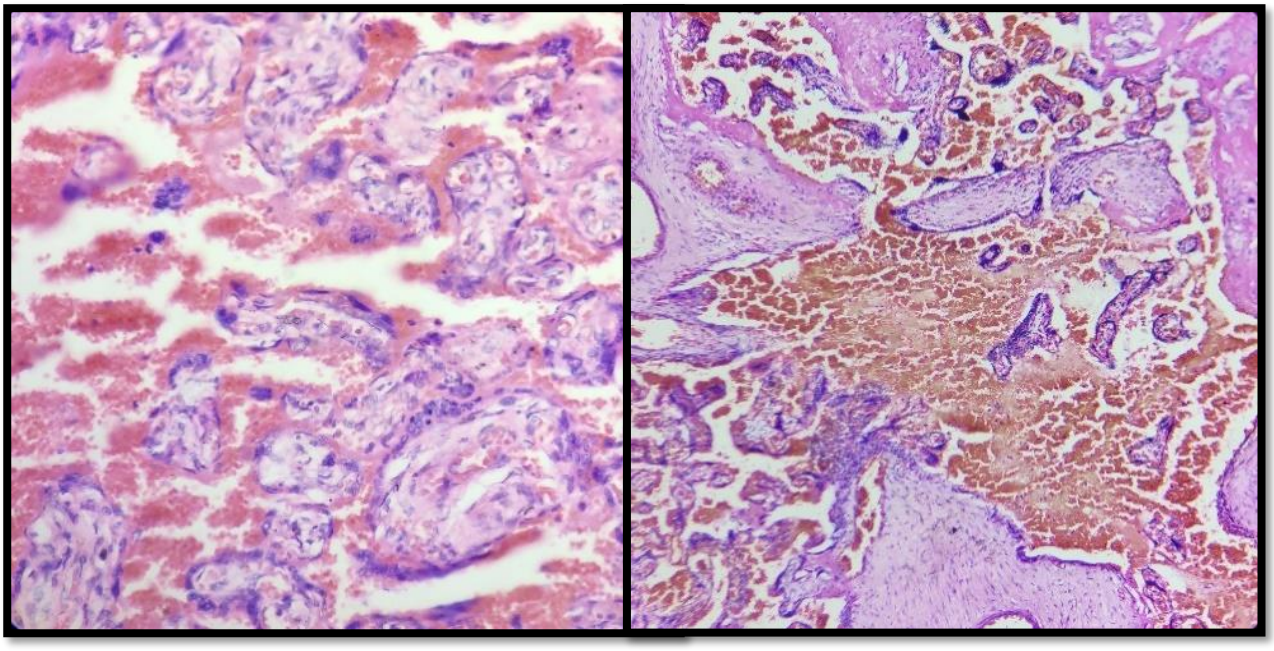


Figure 35 Intervillous Haemorrhage 100x H&E stain

Figure 37 Intervillous haemorrhage 400x H&E stain

Figure 36 Intervillous Haemorrhage 400x H&E stain



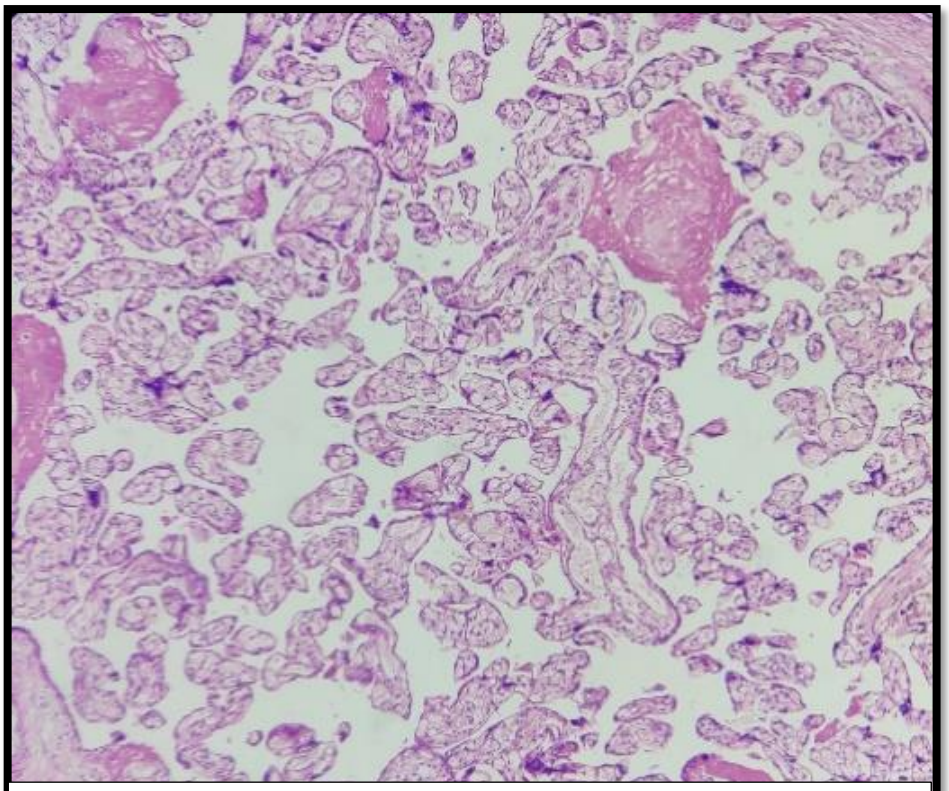


Figure 38 Fibrinoid necrosis 100x H&E stain

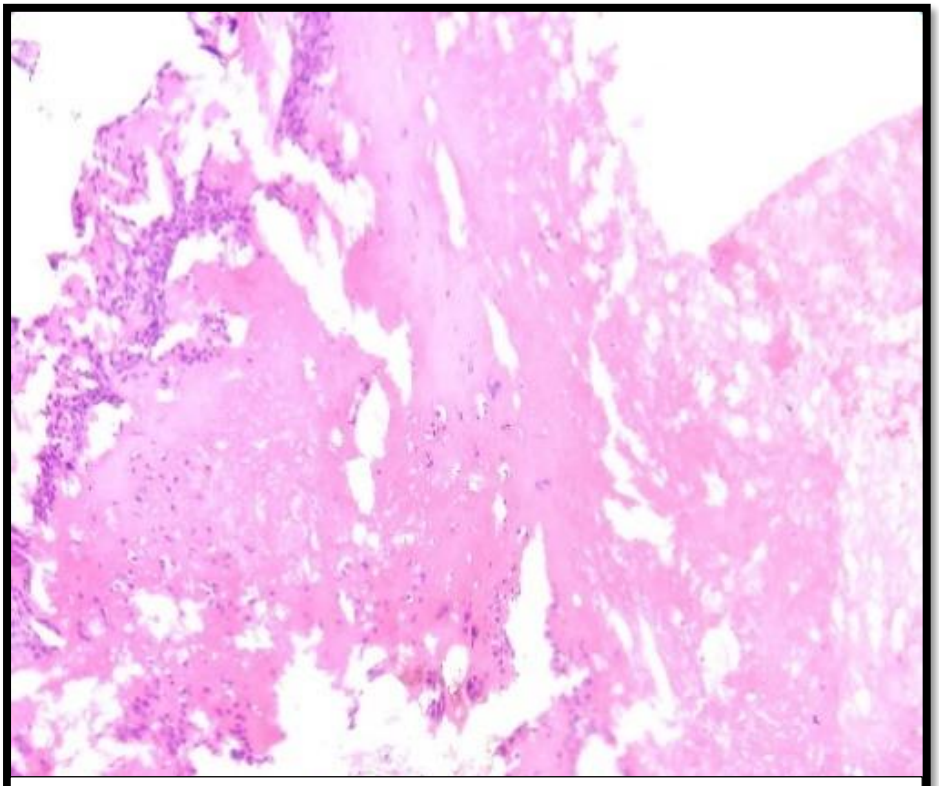
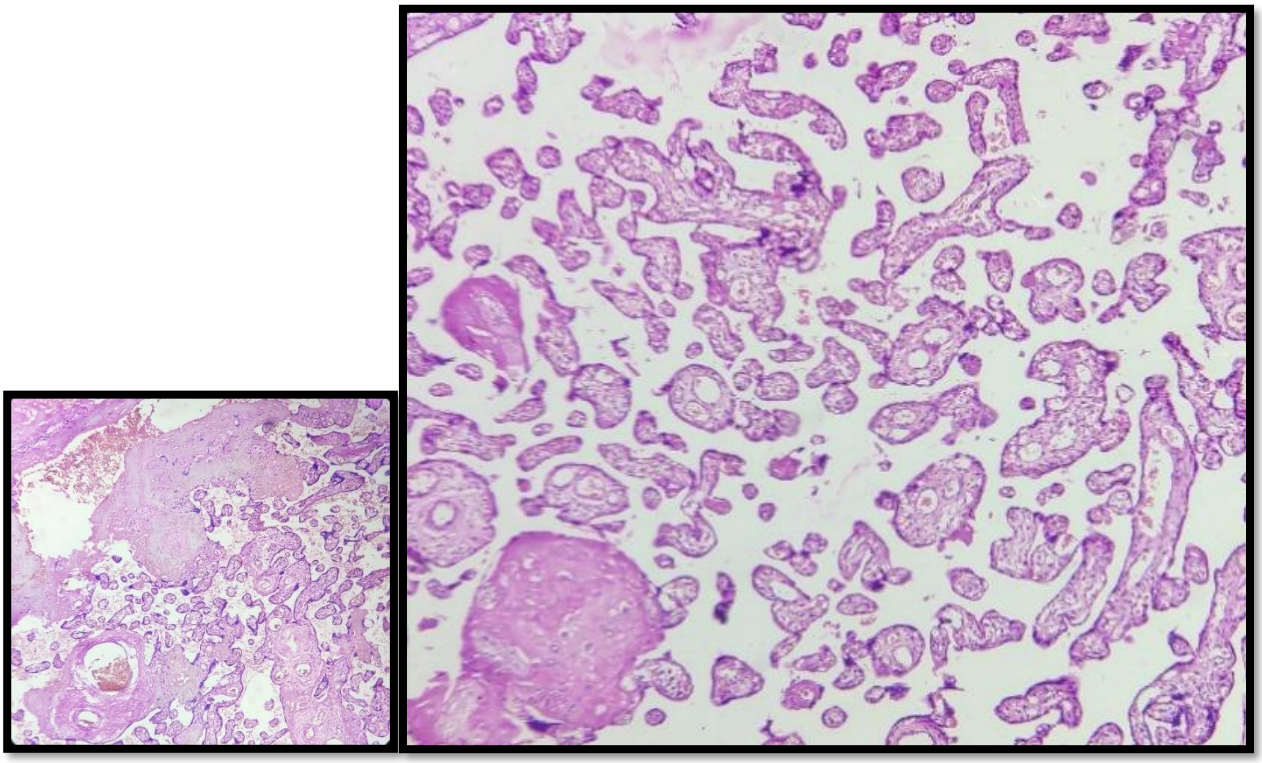


Figure 39 Fibrinoid necrosis 400x H&E stain

Figure 40 Villous stromal fibrosis 100x H&E stain



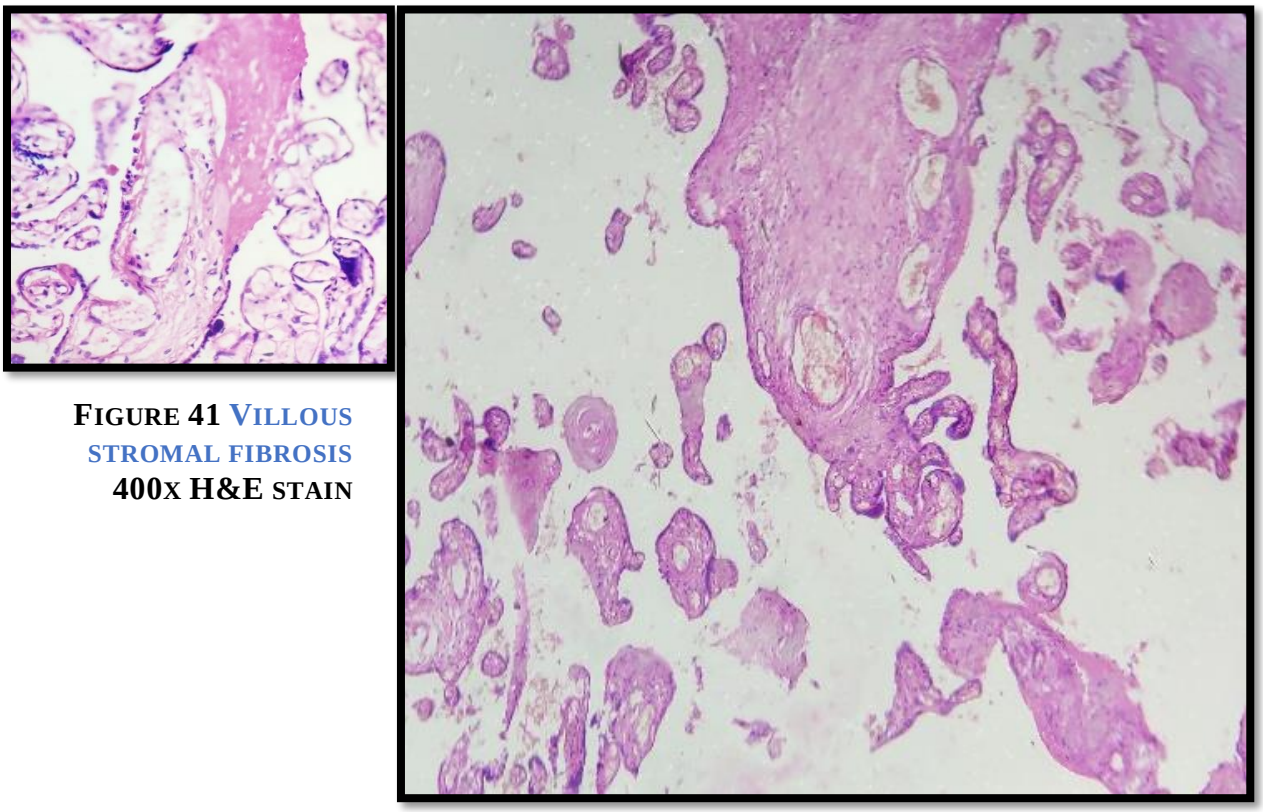


FIGURE 41 VILLOUS STROMAL FIBROSIS 400X H&E STAIN

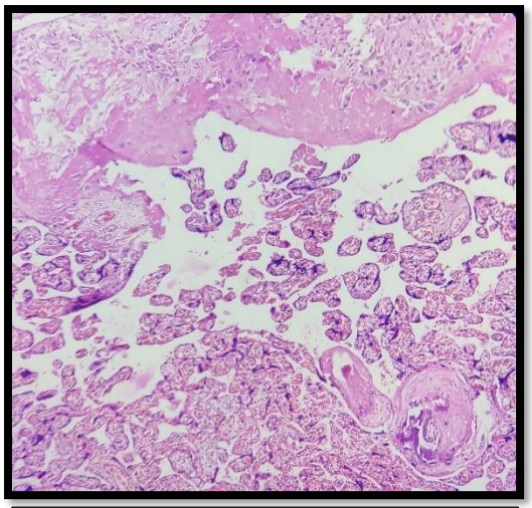


Figure 42 Calcification 100x H&E stain

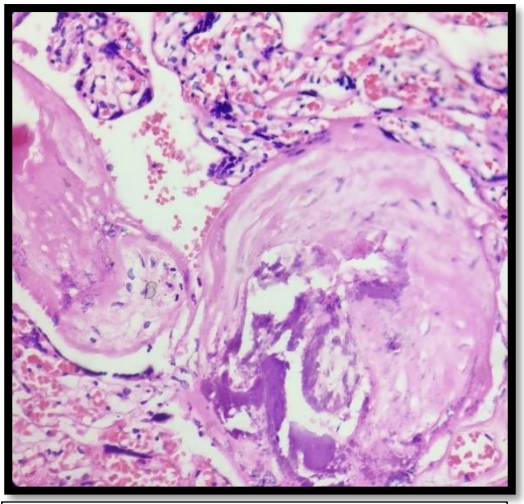


Figure 43 Calcification 400x H & E stain

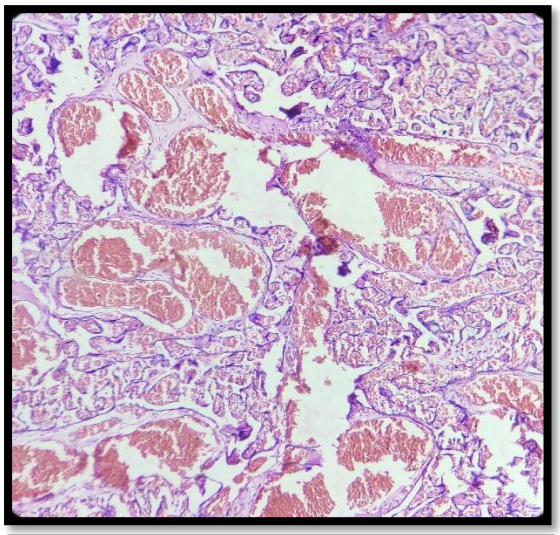


Figure 44 Thrombosis 100x H&E stain

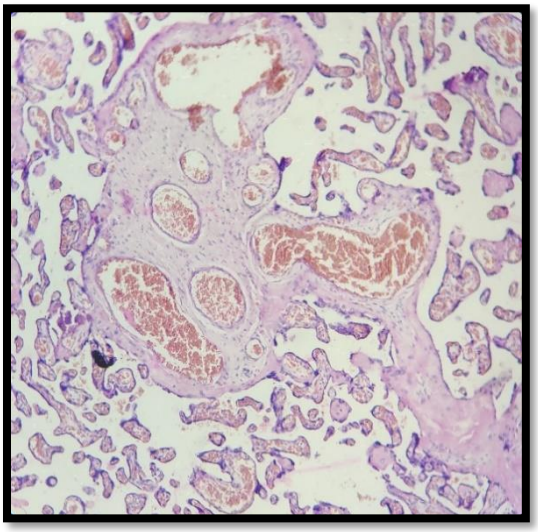


Figure 45 Thrombosis 100x H&E stain

Table 12: Microscopic findings according to hypertensive disorders of pregnancy									
Microscopic findings	**Gestation Hypertension**		**Mild Preeclampsia**		**Severe Preeclampsia**		**Eclampsia**		**p value**
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
Increased Syncytial knots	13	28.3%	1	2.2%	15	32.6%	17	37.0%	0.001*
Fibrinoid necrosis	22	31.4%	5	7.1%	22	31.4%	21	30.0%	0.001*
Intervillous haemorrhages	15	27.3%	6	10.9%	17	30.9%	17	30.9%	0.013*
Villous stromal fibrosis	8	15.1%	3	5.7%	19	35.8%	23	43.4%	<0.001*
Calcification	21	42.0%	8	16.0%	14	28.0%	7	14.0%	0.24
Vessel changes (atherosis/ thrombosis)	0	0.0%	2	3.4%	28	48.3%	28	48.3%	<0.001*

Table 13 Birth according to hypertensive disorders of pregnancy									
BIRTH	**Gestation Hypertension**		**Mild Preeclampsia**		**Severe Preeclampsia**		**Eclampsia**		**p value**
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
LIVE BIRTH	52	98.1%	17	100.0%	25	86.2%	25	86.2%	0.123
IUD	1	1.9%	0	0.0%	4	13.8%	3	10.3%	
STILL BIRTH	0	0.0%	0	0.0%	0	0.0%	1	3.4%	
Total	53	100.0%	17	100.0%	29	100.0%	29	100.0%	

The above table (no 13) presents the detailed analysis of the hypertensive disorders along with the type of birth, whether live, IUD or still birth. A single case of still birth was noted. 98.1%, 100%and 86.2% live births were noted in cases of gestational hypertension, mild preeclampsia and eclampsia respectively. Whereas 10.3% of the mothers had intrauterine death in case of eclampsia. A total of 8 cases of intrauterine death was noted with a case seen in gestational hypertension and four other cases in severe preeclampsia. However, the p-value was not significant. These values were graphically represented in the **Figure 46.**

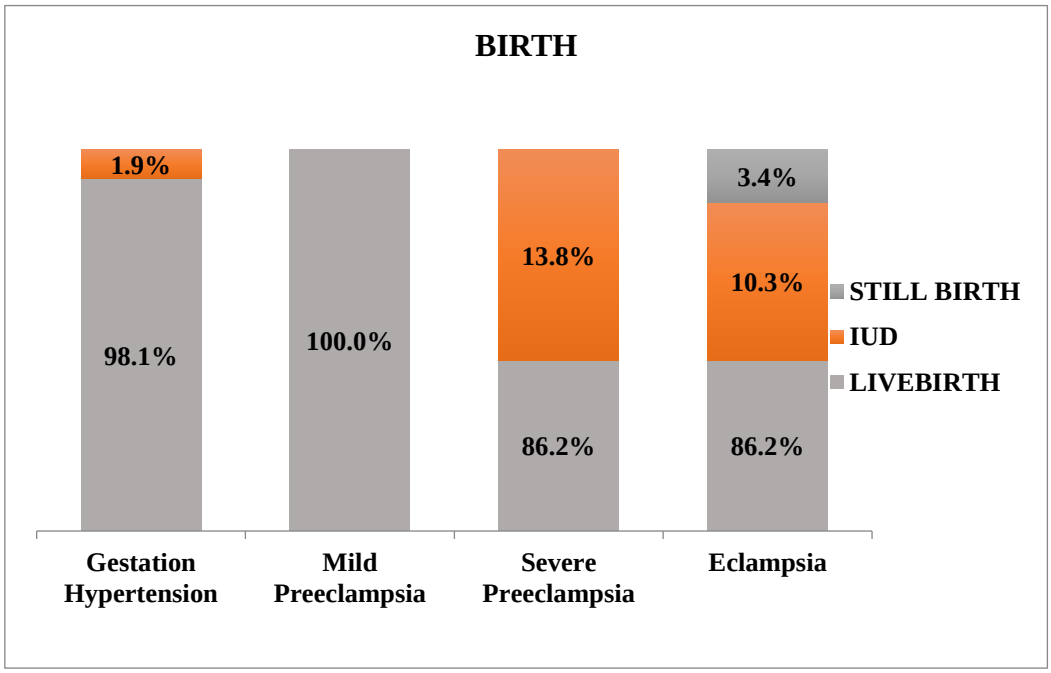


Figure 46: Birth according to gestational hypertensive disorders

As per the standard birth weight for the Indian population, 2.5kgs, the newborn babies were classified into low birth weight and normal birth weight. The birth weight was on the lower side in both severe preeclampsia and eclampsia whereas in gestational hypertension and mild preeclampsia the normal birth weight babies were more which was mentioned in detail in Table 14 and the fetoplacental weight ratios were calculated for all the cases in Table 15. However, these results of fetoplacental weight ratio was not statistically significant.

Table 14: Birth weight according to gestational hypertensive disorders

BIRTHWEIGHT	Gestational Hypertension		Mild Preeclampsia		Severe Preeclampsia		Eclampsia		p value
	N	%	N	%	N	%	N	%	
LOW BIRTH WEIGHT	16	30.8%	9	52.9%	15	60.0%	19	76.0%	0.001*
NORMAL BIRTH WEIGHT	36	69.2%	8	47.1%	10	40.0%	6	24.0%	
Total	52	100.0%	17	100.0%	25	100.0%	25	100.0%	

Note: * significant at 5% level of significance ($p<0.05$)

Table 15 Mean fetoplacental weight ratio according to gestational hypertensive disorders

FETOPLACENTAL WEIGHT RATIO	Gestation Hypertension		Mild Preeclampsia		Severe Preeclampsia		Eclampsia		Total		p value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
	5.8	1.6	5.5	1.4	6.0	2.1	5.9	1.4	5.8	1.7	0.824

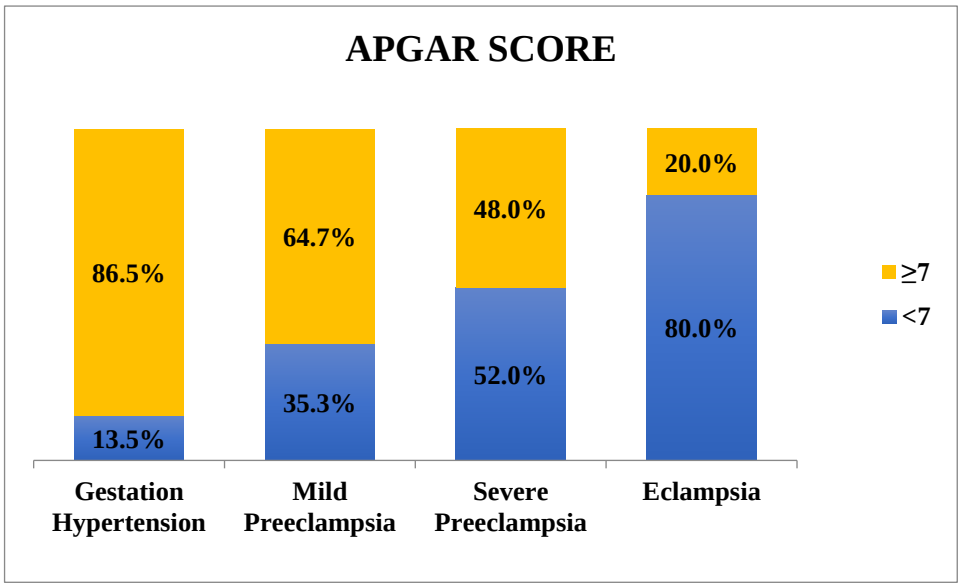


Figure 47: APGAR score according to gestational hypertensive disorders

Among the all four gestational hypertensive disorders of pregnancy, predominantly eclampsia cases i.e. 80%(n=20) showed <7 APGAR score. Others being 52% (n=13), 35.3%(n=6) and 13.5%(n=7) respectively.

Table 16: APGAR score according to gestational hypertensive disorders

APGAR	Gestation Hypertension		Mild Preeclampsia		Severe Preeclampsia		Eclampsia		p value
	N	%	N	%	N	%	N	%	
<7	7	13.5%	6	35.3%	13	52.0%	20	80.0%	<0.001*
≥7	45	86.5%	11	64.7%	12	48.0%	5	20.0%	
Total	52	100.0%	17	100.0%	25	100.0%	25	100.0%	

With the distribution of cases as gestational hypertension 52, mild preeclampsia 17, severe preeclampsia 25 and eclampsia 25 cases 7.7% (n=4), 29.4% (n=5), 48.0% (n=12) and 64.0%(n=16) showed NICU admission of the infants respectively.

Table 17: NICU admission according to gestational hypertensive disorders

NICU Admission	Gestation Hypertension		Mild Preeclampsia		Severe Preeclampsia		Eclampsia		p value
	N	%	N	%	N	%	N	%	
Present	4	7.7%	5	29.4%	12	48.0%	16	64.0%	<0.001*
Absent	48	92.3%	12	70.6%	13	52.0%	9	36.0%	
Total	52	100.0%	17	100.0%	25	100.0%	25	100.0%	

Note: * significant at 5% level of significance (p<0.05)

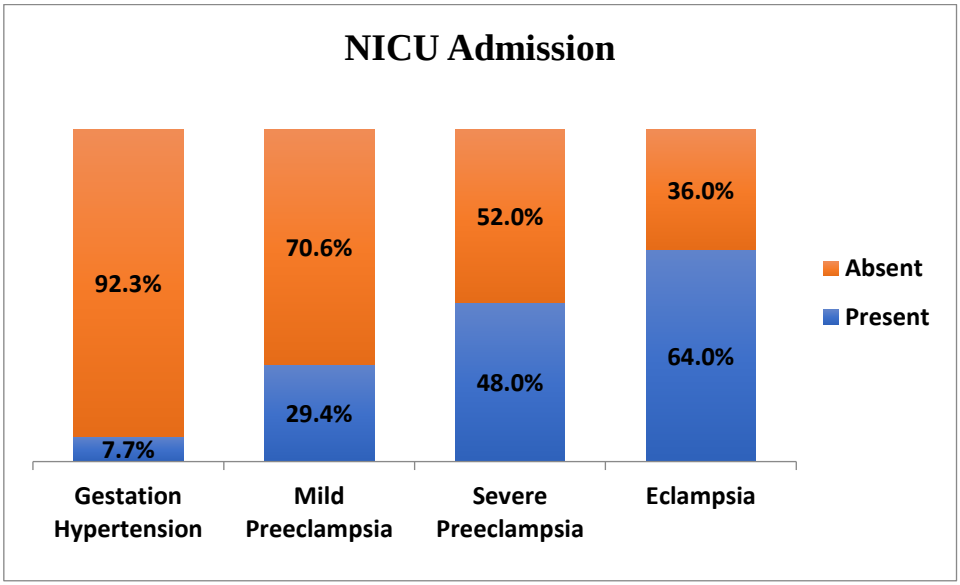


Figure 48: NICU admission according to gestational hypertensive disorders

Tables from 17 to 20 shows the correlation of gross morphological findings of placenta like the weight, diameter and thickness along with the type of birth, birth weight, APGAR score and NICU admission respectively. All these values show a p-value of <0.001 which is statistically significant.

Table 18 Type of Birth Vs Gross findings

GROSS FINDINGS	LIVE BIRTH		IUD/STILL BIRTH		p value
	Mean	SD	Mean	SD	
Weight	436.5	118.2	237.8	88.9	<0.001*
Diameter	15.3	2.4	12.6	1.9	0.001*
Thickness	2.9	0.9	1.4	0.6	<0.001*

Note: * significant at 5% level of significance (p<0.05)

Table 19 Correlation of Gross findings with fetal birth weight

GROSS FINDINGS	<2.5 Kg		>2.5 Kg		p value
	Mean	SD	Mean	SD	
Weight	384.3	104.8	487.8	108.3	<0.001*
Diameter	14.2	2.1	16.4	2.3	<0.001*
Thickness	2.5	0.8	3.2	0.9	<0.001*

Note: * significant at 5% level of significance (p<0.05)

Table 20 Correlation of Gross findings with APGAR Score					
GROSS FINDINGS	**APGAR <7**		**APGAR ≥7**		**p value**
	Mean	**SD**	**Mean**	**SD**	
Weight	357.5	97.4	486.2	102.3	<0.001*
Diameter	13.9	2.0	16.2	2.2	<0.001*
Thickness	2.3	0.7	3.2	0.9	<0.001*

Note: * significant at 5% level of significance (p<0.05)

Table 21 Correlation of Gross findings with NICU Admission					
GROSS FINDINGS	**NICU ADMISSION PRESENT**		**NICU ADMISSION ABSENT**		**p value**
	Mean	**SD**	**Mean**	**SD**	
Weight	363.4	108.2	469.5	107.7	<0.001*
Diameter	13.9	2.2	15.9	2.3	<0.001*
Thickness	2.3	0.8	3.1	0.9	<0.001*

Note: * significant at 5% level of significance (p<0.05)

Tables from 21 to 25 shows the correlation of microscopic morphological findings of placenta like Increased Syncytial knots, Fibrinoid necrosis, Intervillous haemorrhages, Villous stromal fibrosis, Calcification and Vessel changes (atherosis/ thrombosis) along with the type of birth, birth weight, APGAR score and NICU admission respectively.

Table 22 Correlation of microscopic findings with type of birth

Microscopic findings	LIVE BIRTH		IUD/STILL BIRTH		p value
	N	%	N	%	
Increased Syncytial knots	40	33.6%	6	66.7%	0.046*
Fibrinoid necrosis	64	53.8%	6	66.7%	0.454
Intervillous hemorrhages	51	42.9%	4	44.4%	0.926
Villous stromal fibrosis	48	40.3%	5	55.6%	0.371
Calcification	48	40.3%	2	22.2%	0.283
Vessel changes (atherosis/ thrombosis)	52	43.7%	6	66.7%	0.182
Total	119	100.0%	9	100.0%	

Note: * significant at 5% level of significance ($p<0.05$)

Increased syncytial knots were statistically significant in correlation with type of birth. Whereas in correlation with low birth weight and APGAR score cases except calcification and intervillous haemorrhages all the other parameters were significant statistically. In case of NICU admission along with the intervillous haemorrhages and calcification, fibrinoid necrosis was also found to be not statistically significant.

Table 23 Correlation of microscopic findings with Low birth weight					
Microscopic findings	**<2.5 Kg**		**>2.5 Kg**		**p value**
	N	**%**	**N**	**%**	
Increased Syncytial knots	26	44.1%	14	23.3%	0.017*
Fibrinoid necrosis	37	62.7%	27	45.0%	0.049*
Intervillous hemorrhages	29	49.2%	22	36.7%	0.169
Villous stromal fibrosis	33	55.9%	15	25.0%	0.001*
Calcification	22	37.3%	26	43.3%	0.502
Vessel changes (atherosis/ thrombosis)	34	57.6%	18	30.0%	0.002*
Total	46	100.0%	73	100.0%	

Note: * significant at 5% level of significance (p<0.05)

Table 24 Correlation of microscopic findings with APGAR Score					
Microscopic findings	**APGAR <7**		**APGAR ≥7**		**p value**
	N	**%**	**N**	**%**	
Increased Syncytial knots	23	50.0%	17	23.3%	0.003*
Fibrinoid necrosis	30	65.2%	34	46.6%	0.047*
Intervillous hemorrhages	24	52.2%	27	37.0%	0.103
Villous stromal fibrosis	28	60.9%	20	27.4%	<0.001*
Calcification	19	41.3%	29	39.7%	0.864
Vessel changes (atherosis/ thrombosis)	33	71.7%	19	26.0%	<0.001*
Total	59	100.0%	60	100.0%	

Note: * significant at 5% level of significance (p<0.05)

Table 25 Correlation of microscopic findings with NICU Admission					
Microscopic findings	**NICU ADMISSION PRESENT**		**NICU ADMISSION ABSENT**		**p value**
	N	**%**	**N**	**%**	
Increased Syncytial knots	18	48.6%	22	26.8%	0.020*
Fibrinoid necrosis	22	59.5%	42	51.2%	0.404
Intervillous haemorrhages	20	54.1%	31	37.8%	0.097
Villous stromal fibrosis	23	62.2%	25	30.5%	0.001*
Calcification	15	40.5%	33	40.2%	0.976
Vessel changes (atherosis/ thrombosis)	28	75.7%	24	29.3%	<0.001*
Total	37	100.0%	82	100.0%	

Note: * significant at 5% level of significance (p<0.05)

Table 26 Complications according to gestational hypertensive disorders									
Complications	**Gestation Hypertension**		**Mild Preeclampsia**		**Severe Preeclampsia**		**Eclampsia**		**p value**
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
Present	0	0.0%	0	0.0%	5	17.2%	8	27.6%	<0.001*
Absent	53	100.0%	17	100.0%	24	82.8%	21	72.4%	
Total	53	100.0%	17	100.0%	29	100.0%	29	100.0%	

Note: * significant at 5% level of significance (p<0.05)

Coming to maternal complications in hypertensive disorders of pregnancy, severe eclampsia and eclampsia with 17.2% and 27.6% respectively. The complications found in the cases were Disseminated Intravascular Coagulation (DIC), HELLP syndrome and Acute renal Failure

(ARF). 13.8 % of the cases had shown HELLP syndrome and ARF under the eclampsia category and the further details of the complications were mentioned in Table 27.

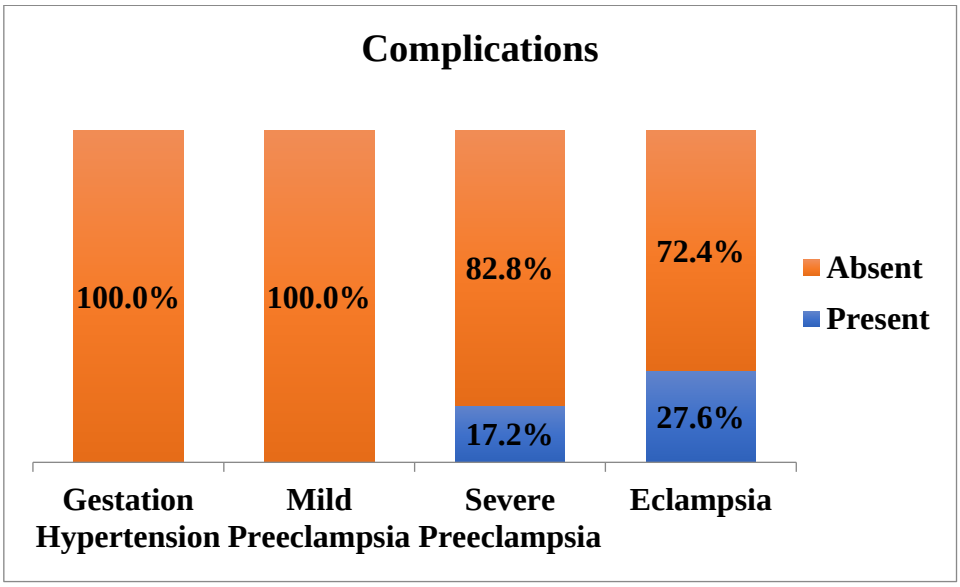


Figure 49 Complications according to gestational hypertensive disorders

Table 27: Details of complications according to gestational hypertensive disorders

Details of complications	Gestation Hypertension		Mild Preeclampsia		Severe Preeclampsia		Eclampsia		p value
	N	%	N	%	N	%	N	%	
DIC	0	0.0%	0	0.0%	1	3.4%	0	0.0%	0.001*
HELLP	0	0.0%	0	0.0%	2	6.9%	4	13.8%	
ARF	0	0.0%	0	0.0%	4	13.8%	4	13.8%	

Note: * significant at 5% level of significance ($p<0.05$)

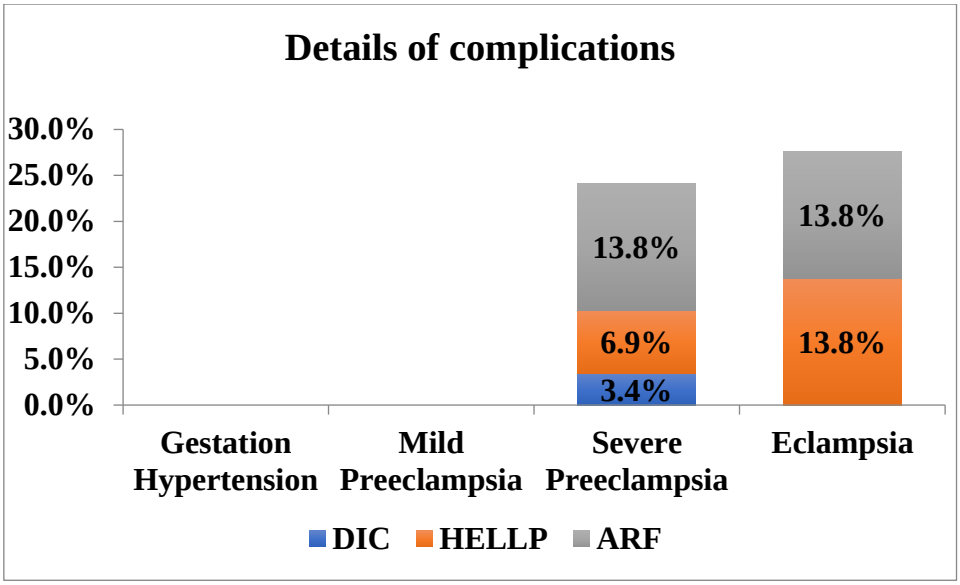


Figure 50: Details of complications according to gestational hypertensive disorders

Finally, the correlation of the gross and microscopic features with the complications was represented in tables 27 & 28 respectively.

Table 28 Correlation of gross morphological findings with maternal complications

GROSS FINDINGS	Complications Present		Complications Absent		p value
	Mean	SD	Mean	SD	
Weight	319.2	129.4	434.2	121.6	0.002*
Diameter	13.5	2.7	15.3	2.4	0.012*
Thickness	2.0	1.0	2.9	1.0	0.002*

Note: * significant at 5% level of significance (p<0.05)

Table 29 Correlation of microscopic findings with maternal complications

Microscopic findings	Complications Present		Complications Absent		p value
	N	%	N	%	
Increased Syncytial knots	8	61.5%	38	33.0%	0.042*
Fibrinoid necrosis	7	53.8%	63	54.8%	0.949

Microscopic findings	Complications Present		Complications Absent		
	N	%	N	%	p value
Intervillous hemorrhages	8	61.5%	47	40.9%	0.154
Villous stromal fibrosis	10	76.9%	43	37.4%	0.006*
Calcification	6	46.2%	44	38.3%	0.58
Vessel changes (atherosis/thrombosis)	12	92.3%	46	40.0%	<0.001*
Total	13	100.0%	115	100.0%	

Note: * significant at 5% level of significance ($p<0.05$)

Discussion

Placenta is one of the most important organs in the entire gestational period for both the mother and fetus. This organ acts as filter for the fetal circulation allowing very few restricted substances to cross over to the fetal side and eliminates most of the toxic and harmful substances for the growing fetus. This level of function and its metabolic activity helps in the overall development, health and outcome of the fetus as well as the mother both directly and indirectly.[4,59]

In cases where there is deviation from normal physiology, pathological processes affect the fetal and pregnancy outcome at times influencing the mothers' overall health. This is more pronounced in case of certain metabolic diseases like gestational diabetes mellitus and gestational hypertensive disorders. Hypertension is a disorder of the vasculature affecting the calibre and elasticity of these vessels. In case of essential systemic hypertension, the changes are happening over time and are not having significant effects on the other systems of the body initially. However, in case of the gestational period, the same infliction of the disorder has paramount effect on the fetal and maternal outcome in a short span of time. The disease alters the placental circulation and fetal growth in a significant way and even is detrimental by causing severe morbidity and mortality in the affected pregnant females and their fetus. This has led to the intense research and study on this topic with various definitions evolving over time and guidelines for the diagnosis and management as well, being updated regularly by various organisations at the national and international level.[60]

Placental pathophysiology is partly understood wherein the aetiology of the disease spectrum namely gestational hypertension, mild preeclampsia, preeclampsia and eclampsia is placed on the hypothesis that the decrease in the calibre of the vessels in the placenta and insufficient trophoblastic transformation leading to the formation of reactive oxygen species, free radicle formation, STMBs and decreased oxygenation.[13,20] This decreased oxygenation is

considered to be the main factor in the pathogenesis by various authors. The clinical correlation of the diagnosis and outcome of the fetus and mother has been done. However, the data is not to this extent and there is a need to correlate the pathological changes and feto maternal outcome. Hence in the present study these parameters were investigated with a specific focus on the pathological changes and the feto maternal outcome along with the requirement of NICU admission of the fetus.

In the present study, 128 cases were included, and the cases represented both the primipara as well as the multipara. The predominant population being rural individuals from the catchment area of the institute serving the rural region, the study gave an insight into the placental weight, birth weight and complications rate in our setup. The age range was 18 years to 40 years. In the study done by Aparna et al[61] the age group ranged from 20 – 35 years and Abdul Hafeez et al[60] study group also comprised of the age range of 18-35 years who had studied 50 and 40 placentae diagnosed clinically as hypertensive disorders of pregnancy. The study done by Nag U et al[62] had an age range of 22-32 years with 50 placentae studied.

Most of the cases in the present study were primipara amounting to 60.2% (n=77) in the study group and the multiparous females were 39.8%. Similar findings were also mentioned by Maham Akhlaq et al wherein primipara were the predominant group.[63] The present study included the gestational age from 28 weeks to 42 weeks similar to the study done by Abdul hafeez et al.[60]

The gross morphological analysis of the parameters like shape, thickness and diameter was done and the analysis led to the observation that irregular placentae were noted in the severe preeclampsia (48.3%) and eclampsia (79.3%) groups. These results were statistically significant. Parth R Goswami[64] had observed the presence of irregular shape in 22% of the cases which was also statistically significant. The results presented by Segupta K et al[65] had

26.7% of the placentae having irregular shape in the cases of preeclampsia. However, these observations in their study was not statistically significant.

A comparison of the number of cases considered in the studies by various authors and the average weight, thickness and mean diameter of the placentae was presented in the Table 30. The average mean weights of the placentae ranged from 307gm to 400 gm in the prior studies.

Table 30 Comparison of number of cases and average weight of placenta

Author	No. of cases	Avg mean wt. in gm	Mean Diameter (cm)	Thickness (cm)
Abdul Hafeez et al[60]	40	307.12	15.82	2.04
Rafah et al[66]	25	400.75	16.0	NA
Kishwara et al[65]	30	311.50	16.08	1.51
Narasimha A et al[61]	63	<500	16.3	2.66
Present study	128	423.2	15.0	2.76

NA – Not mentioned in the study

Table 31 Comparison of Syncytial knots with various studies		
Studies done by authors	**Study group (no. of cases)**	**Increased Syncytial Knots in % of cases**
Parischa et al[67]	30	40.9%
Nag et al[62]	50	40%
Akhlaq et al[63]	100	57%
Rodica et al[52]	34	32.3 %
Present study	128	35.2%

TABLE 32 COMPARISON OF MICROSCOPIC FEATURES WITH OTHER STUDIES		
Eclampsia	Narasimha et al[61]	Present study
Increased Syncytial Knots (%)	66.6%	58.6%
Villous Stromal fibrosis	55.5%	79.3%
Fibrinoid necrosis	66.6%	72.4%
Vessel changes	100%	96.6%
Preeclampsia	Narasimha et al[61]	Present study
Increased Syncytial Knots (%)	55.5%	51.7%
Villous Stromal fibrosis	81.4%	65.5%
Fibrinoid necrosis	92.5%	75.9%
Vessel changes	70.3%	96.6%

The presence of syncytial knots in over 30% of the villi was increased.[67] Rodica et al mentioned that none of the normotensive pregnancies had increased syncytial knots and 32.3% in study group has shown these changes. They concluded that excessive syncytial knot formation as a pathognomic sign in preeclampsia.[52] This was due to decreased foetal perfusion to villi and similar findings were found in the studies done by Pasricha et al[67], Nag et al[62] and Akhlaq et al[63] ranging from 32.3% to 57%.

In the present study frequency of syncytial knots increase in study group was 35.2%. The probable reason for the increased syncytial knots of 57% in Akhlaq et al could be due to the fact that the study population comprised of 50 cases of severe preeclampsia and 50 of eclampsia. The further refinement of the data in terms of severe preeclampsia and eclampsia in the present study yields a percentage of 51.7% and 58.6% in eclampsia cases.[63]

Fibrinoid necrosis was found in 84% and 92% of the severe eclampsia and eclampsia cases in Akhlaq et al study, whereas the Narasimhan et al [61] group found to the extent of 37% in mild preeclampsia, and all the cases of eclampsia of pre-eclampsia.[61,63] Rodica ilie et al had an incidence of 73.5% in toto of the cases considered as the hypertensive disorders of pregnancy.[52] Nag U et al[62], have presented in their paper mean number of areas of fibrinoid necrosis instead of the percentage and mentioned that 8+/-2.4 areas were noted. In the present study percentage of 54.7% has been seen.

Calcification was found in 51% and 34% of cases of preeclampsia and eclampsia in the observations made by Akhlaq et al.[63] The percentages ranged from 26.9% and 22.2% in cases of mild preeclampsia and severe preeclampsia by Narasimha et al.[61] In the present study 48.3% and 24.1% cases of preeclampsia and eclampsia respectively shown calcification in placentae.

Narasimha et al[61] documented the presence of villous stromal fibrosis to the extent of 22.2%, 81.4% and 88.88% in mild preeclampsia, severe preeclampsia and eclampsia.[61] Rodica

Ilie et al noted that 26.47% of the cases of pregnancy induced hypertension have shown villous stromal fibrosis.

Intervillous haemorrhage was found in the present study in mild preeclampsia, severe preeclampsia and eclampsia 35.3%, 58.6% and 58.6% respectively. Narasimha et al presented that the distribution of villous haemorrhage in their study group to be 14.8%, 44.4% and 44.4% in mild preeclampsia, severe preeclampsia and eclampsia respectively.[61]

Atherosis/thrombosis of the vessels was noted in 11.8%, 96.6% and 96.6% of cases in mild preeclampsia, severe preeclampsia and eclampsia respectively. Similar observations were made in the study done by Narasimha et al at 14.8%, 77.7% and 100% for mild preeclampsia, severe preeclampsia and eclampsia respectively.

These microscopic features were also observed in gestational hypertension cases (n=53) in the present study. The details of which are mentioned in the **Figure 20**. Amongst these features, fibrinoid necrosis and calcification were the prominent occurrence with 41.5% and 39.6% respectively.

Maternal complications noted in the present study include predominantly DIC (n=1), HELLP (n=6), and ARF (n=8). The case of DIC was noted in severe preeclampsia, along with 2 cases of HELLP and 4 cases of ARF. Whereas in eclampsia these complications were noted in 4 cases each of HELLP and ARF. There was no incidence of seizures post-delivery in the study group. The present study had a total of 8 cases (6.3%) intrauterine deaths along with a single case (0.8%) of still born baby. Four cases of IUD in mother affected by severe preeclampsia, 3 cases of eclampsia and a single case of IUD in gestational hypertension in the present study. However, these results were found to be not statistically significant.

Low birth weight criteria taken as <2.5kg, was noted in 59 cases (49.6%) among the study group with a mean birth weight of 2.3kg and lowest birth weight being 1.2kg which was

statistically significant with regards to the correlation with the severity of the disease as mentioned in detail in Table 14. Similar results were noted by Nag et al who has presented that the mean birth weight as 2.3 Kg in hypertensive disorders of pregnancy. Abdul Hafeez et al, who also documented the low birth weight noted the occurrence to be statistically significant in the study group similar to the observations in the present study. The vascular insufficiency due to atherosis, thrombotic changes and the intervillous haemorrhages which is more pronounced in the severe preeclampsia and eclampsia supports the fact that these cases lead to the fetal growth restriction, which was also noted by Abdul hafeez et al,[60] Nag et al[62] and Pasricha et al.[67]

The other fetal outcome correlated in the present study, APGAR score stratified into <7 or more than or equal to 7 as noted in **Table 24** shows the of the low APGAR scores were seen in a majority of the cases in the eclampsia group followed by severe preeclampsia to the tune of 80% and 52% respectively. Whereas >7 group has a reverse distribution with highest number of cases aggregated towards the gestational hypertension followed by mild preeclampsia to the order of 86.5% and 64.7% respectively. These similar findings also found by Pasricha et al in their study.[67]

With such statistically significant values with regards to low birth weight, fetal death rate, low APGAR score and also the maternal outcome along with the microscopic observations in the present study, a further analysis in detail along with larger sample size will create the data required for better understanding and even managing the cases in an optimal manner. Inclusion of the imaging analysis from the ultrasonography scans during the gestation period along with the correlation of the histopathological features as well as the feto-maternal outcome gives an insight into the disease process.

Conclusion

With the increasing sophistication in technological advancements and diagnostic modalities disease monitoring and management is reaching new heights in achieving patient safety. However, even in today's era of evidence-based medicine and diagnostic guidelines based patient care, both maternal and fetal outcome in terms of morbidity and mortality is getting affected in patients with hypertensive disorders of pregnancy. They are managed by a multi-disciplinary team involving obstetricians, pathologists, community physicians and at times intensivists.

Towards achieving the goal of making the gestational period complication free and having a better outcome in both maternal and fetal general wellbeing the present study made an attempt to correlate the hypertensive disorders of pregnancy with both the maternal and fetal outcome with a focus on the histopathological changes like the gross morphological appearances and morphometric analysis including the statistically significant measurements like the placental thickness and diameter which were low in the study group.

Histomorphological features of placenta like weight and diameter were considerably reduced in preeclampsia / eclampsia. Microscopic features like increased syncytial knots, fibrinoid necrosis, intervillous hemorrhages, villous stromal fibrosis and calcification were found more in severe preeclampsia / eclampsia as against GHTN/ mild preeclampsia placenta. Fetal outcome observed as low birth weight and IUDs in cases of eclampsia and preeclampsia group had a statistically significant p-value. The microscopic findings like atherosis/ thrombosis and villous stromal fibrosis were seen in majority of cases of severe preeclampsia and eclampsia which showed poor fetal outcome in the form of low birth weight, IUDs, lower APGAR score and NICU admission and had a statistically significant p- value. Maternal complications like DIC, HELLP and ARF were seen in the cases of severe preeclampsia and

eclampsia which also showed statistically significant p- value in microscopic features like vessel changes and villous stromal fibrosis.

Studies focussing on the clinical, radiological as well as histopathological aspects of the disease process along with their correlation helps in creating the data sets and enhancing the understanding of the disease process in a better way.

Summary

Placenta plays a pivotal role in maintenance of the pregnancy and it is not immune to the structural changes caused by the hypertensive disorders of pregnancy. The vascular changes and the pathophysiological effects of these changes are not fully understood and the prominent theory explaining these phenomena is the insufficient vessel calibre, trophoblastic proliferation, impaired oxygenation and free radicals etc in the creation of a milieu which is detrimental to the normal growth and development of the fetus and causes maternal complications as well.

The present study done in a tertiary care centre has included 128 pregnant females diagnosed clinically as hypertensive disorders of pregnancy with the following classification, gestational hypertension, mild preeclampsia, severe preeclampsia and eclampsia. Along with the histopathological examination of the placenta, maternal outcome and fetal outcome was noted in these cases. Using routine techniques of histopathological examination shape, size and weight of placenta were considered along with microscopic findings like increased syncytial knots, fibrinoid necrosis, atherosis, intervillous haemorrhages, villous stromal fibrosis and calcification and correlated with maternal and fetal outcome.

Eight cases of IUD and one case of still birth noted predominantly in the severe preeclampsia and eclampsia cases which also showed higher percentages of presence of the microscopic features in comparison to the gestational hypertension and mild preeclampsia. Low birth weight noted in the eclampsia and preeclampsia group with the cut off taken as 2.5kg. APGAR score was <7 in a majority of these cases of eclampsia and severe preeclampsia groups along with the irregular placentae and higher levels of fibrinoid necrosis (31.4%) and atherosis/thrombosis (48.3%).

Statistically significant findings of microscopic correlation of the parameters like atherosis, intervillous haemorrhages, fibrinoid necrosis was noted in the study group in

correlation with fetal and maternal outcome which further strengthens the concepts of not yet clearly stated pathophysiology of this common pathological condition which is one among the top causes of maternal as well as fetal morbidity and mortality.

The disease spectrum is difficult to manage if not diagnosed in a timely manner and even affects the subsequent pregnancies. Such a disease with huge potential to disrupt the health and strain the resources of the society at large needs to be understood in a better way with targeted approach supported by strong histopathological association. studies with large numbers of placental examination with a focus on early identification and prompt management justifies the time and energy spent in understanding this menace of a disease.

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ANNEXURE-I

B.L.D.E (Deemed to be University),
SHRI B. M. PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTER,
VIJAYAPURA-586103

INFORMED CONSENT FOR PARTICIPATION IN DISSERTATION/RESEARCH

I, the undersigned,_____ ,S/O D/O W/O _____,aged____years, ordinarily resident of _____do hereby state/declare that Dr. _____

of Hospital has examined me thoroughly on _____ at _____ (place) and it has been explained to me in my own language that I am suffering from _____ disease (condition) and this disease/condition mimic following diseases . Further Doctor informed me that he/she is conducting dissertation/research titled _____under the guidance of Dr _____requesting my participation in the study. Apart from routine treatment procedure, the pre-operative, operative, post-operative and follow-up observations will be utilized for the study as reference data.

Further Doctor has informed me that my participation in this study help in evaluation of the results of the study which is useful reference to treatment of other similar cases in near future, and also I may be benefited in getting relieved of suffering or cure of the disease I am suffering.

The Doctor has also informed me that information given by me, observations made/ photographs/ video graphs taken upon me by the investigator will be kept secret and not assessed by the person other than me or my legal hirer except for academic purposes.

The Doctor did inform me that though my participation is purely voluntary, based on information given by me, I can ask any clarification during treatment / study related to diagnosis, procedure of treatment, result of treatment or prognosis. At the same time I have been informed that I can withdraw from my participation in this study at any time if I want or

the investigator can terminate me from the study at any time from the study but not the procedure of treatment and follow-up unless I request to be discharged.

After understanding the nature of dissertation or research, diagnosis made, mode of treatment, I the undersigned Shri/Smt _____ under my full conscious state of mind agree to participate in the said research/dissertation.

Signature of patient:

Signature of doctor:

Witness: 1.

2.

Date:

Place

ANNEXURE-II

PROFORMA FOR STUDY:

NAME	:	OP/IP No.	:
AGE	:		
SEX	:	D.O.A	:
RELIGION	:	D.O.D	:
OCCUPATION	:		
RESIDENCE	:		
Presenting Complaints	:		
Past history	:		
Personal history	:		
Family history	:		
Treatment history	:		

General physical examination:

Pallor	present/absent
Icterus	present/absent
Clubbing	present/absent
Lymphadenopathy	present/absent
Edema	present/absent
Built	poor/average/well

VITALS: PR: RR:

BP: TEMPERATURE: WEIGHT:

SYSTEMIC EXAMINATION:

CLINICAL DIAGNOSIS: GTN/ MILD PE/ SEVERE PE/ ECLAMPSIA

INVESTIGATIONS:

Histopathological examination of placenta:

I Gross

1. Shape
2. Weight
3. Size

II Microscopy

1. Syncytial knots

2. Fibrinoid necrosis

3. Intervillous haemorrhages

4. Villous stromal fibrosis

5. Calcification

Fetal Outcome:

1. Birth weight
2. APGAR Score
3. NICU Admission >24hours for HIE (Hypoxia Induced Encephalopathy)

Maternal Outcome:

1. DIC
2. HELLP
3. Eclampsia
4. ARF
5. Others