5. REVIEW OF LITERATURE

Further observations on distribution of phosphatases in mammalian placentae was a study conducted by Dempsey et al in the year 1947. They observed increased amount of alkaline phosphatase activity in human placentae at term. Preeclamptic placentae showed premature increase in alkaline phosphatase activity.\(^{28}\)

The metabolism of human placenta in vitro was a study conducted by Claude Villi in the year 1953. They observed that there was marked decrease in glycogen content of normotensive placenta at term. Placental glycogen begins to decrease at ten to twelve weeks of gestation and decreases steadily throughout gestation.\(^{29}\)

In the year 1963 Jeacock et al studied the activity of alkaline and acid phosphatase in the human placenta. They observed increased activity of placental alkaline phosphatase in preeclamptic placentae as compared to normotensive placentae.\(^{30}\)

Variations in enzymatic histochemistry of the placenta was a study conducted by Curzen P in the year 1964. They reported increased activity of placental alkaline phosphatase in preeclamptic placentae as compared to normotensive placentae.\(^{31}\)

Placental pathology in eclampsia and preeclampsia was a study conducted by Moqueo et al in the year 1964. Their results showed histological changes like extensive area of fibrosis, crowded villi, marked congestion of all vessels, disappearance of large areas of trophoblast, thinning of syncytium and narrowing of decidual arteriolar lumen with marked atheromatosis in preeclamptic placentae.\(^{32}\)

Comparative histochemical distribution of glycogen and alkaline phosphatase in the placenta was a study conducted by George Christie in the year 1967. They observed small concentration of glycogen in the stroma of normotensive human placenta. Rabbit placenta showed reduced amount of glycogen at term. Cat, dog and ferret placentae showed positive glycogen activity around blood vessels at term. Human placenta showed patchy distribution of alkaline phosphatase activity at term while rabbit placenta showed negative placental alkaline phosphatase activity at term.\(^{33}\)

Curzen et al in their study on enzyme assays in the management of pregnancy in the year 1970 reported that there is increase in alkaline phosphatase enzyme in normal pregnancy...
and it can increase further or decrease in abnormal pregnancies. According to them abnormally high serum heat stable alkaline phosphatase levels represent placental damage and abnormally low levels indicate poor placental development.\(^{34}\)

Dempsey et al conducted a study on regional specializations in the syncytiotrophoblast of early human placentae in the year 1971. They observed that trophoblast exhibits a well-marked layering of structure during first trimester. The apical surface of syncytiotrophoblast characteristically showed microvilli between which there were canals leading to small and large coated vesicles. They called this as the zone of absorption. Beneath this they observed a region predominantly occupied by cisternae lined by rough endoplasmic reticulum. This was termed as zone of secretion. Still deeper was a region containing organelles similar to those of cytotrophoblastic cells of Langhans. This was termed as zone of accrual. Under these layers were the cytotrophoblastic cells of Langhans resting on thick basal lamina.

It was observed that the basal zone of syncytiotrophoblast resembled the cytotrophoblast in three features. I: Presence of glycogen was seen as individual granules or clumps in both the regions. II: A characteristic relationship was seen in both sites between dilated cisternae and mitochondria. III: Cytotrophoblast cells were attached by numerous desmosomes to the syncytiotrophoblast. Mitochondria of syncytiotrophoblast are small in the middle and outer zones and slightly more smaller in basal zone. Those in the Langhans cells are larger and more numerous than that of syncytiotrophoblast. Certain regions showed syncytiotrophoblastic masses containing several nuclei but were lacking both Langhans cells and connective tissue cores. These masses were attached to terminal villi and were termed as syncytiotrophoblastic sprouts. There were few structures protruding into the intervillous space forming an extended base of microvilli. These were termed as syncytiotrophoblastic protrusions. Occasionally well-defined clots were also observed in the intervillous space.\(^{35}\)

Studies conducted by Brosens et al in the year 1972 showed that in preeclampsia acute atherosis developed in muscular arteries of placental bed including spiral arteries. The whole thickness of vessel wall was affected cause of fibrinoid necrosis, there was accumulation of lipophages in the wall and mononuclear infiltrate around the damaged vessel. Atherosclerosis was seen in spiral arteries in preexisting hypertension and later developed acute atherosis when preeclampsia supervenes hypertension.\(^{36}\)
A study on quantity and distribution of placental glycogen was conducted by Robb et al in the year 1976. They reported that in first trimester the glycogen levels were high, but from about 12 weeks to term the levels were within a narrow range. There was no appreciable deviation in the glycogen levels of normal and a range of other clinical conditions.\(^\text{37}\)

Histopathology of placental insufficiency was a study conducted by Fox et al in the year 1976. They observed necrotic changes in villi, perivascular fibrin deposition, avascular villi and increased cytotrophoblast proliferation in preeclamptic placentae.\(^\text{38}\)

Uteroplacental arterial changes related to interstitial trophoblast migration in early human pregnancy was a study conducted by Pijnenborg et al in the year 1983. They found significant morphological alterations in spiral arteries such as swelling of endothelium, oedema and disruption of architecture of vessel wall and hypertrophy of individual smooth muscle cells. They concluded that these findings indicated that interstitial cytotrophoblasts may have a role to play in the preparation of myometrial segments of uteroplacental arteries for the second wave of endovascular trophoblast migration.\(^\text{39}\)

Francis et al in the year 1984 conducted a study in which they measured the total alkaline phosphatase in maternal plasma and placental extracts in normal and preeclamptic pregnancies. They concluded that total alkaline phosphatase concentration in placental tissue was higher in normotensive pregnancies as compared to preeclamptic pregnancies. However total plasma alkaline phosphatase was elevated during the last trimester in both normal as well as preeclamptic pregnancies.\(^\text{40}\)

Isemura M et al in the year 1985 investigated human placentae for distribution of glycosaminoglycans, collagens and fibronectin in which they showed presence of fibronectin and type IV collagen around fetal blood vessels and in stroma of placental villi. Glycosaminoglycans were indicated by alcian blue staining.\(^\text{41}\)

Placental morphology and clinical correlations in pregnancies complicated by hypertension is a study conducted by Bartl et al in the year 1985. Their result showed increased number of trophoblastic sprouts, trophoblastic hyperplasia, fibrinoid degeneration and necrosis in hypertensive pregnancies which increased even more with severity. These changes were rare in term placentae of healthy women. They concluded
that these changes may lead to retardation of placenta and immature placental perfusion which seems to be responsible for decreased fetal birth weight in case of hypertensive pregnancies.\textsuperscript{42}

Studies by Khong et al in the year 1986 document partial or complete lack of physiological changes that is, only a part of the vessel wall is affected and physiological changes are seen only in decidua in pregnancies complicated by preeclampsia.\textsuperscript{43}

Bloxam et al in their study on placental glycolysis and energy metabolism in preeclampsia in the year 1987 documented that there is significant metabolic abnormality in placentae of mothers with severe preeclampsia. Glycogen and glucose concentrations were high in preeclamptic placentae which supports the evidence of inhibited glycolysis.\textsuperscript{44}

Histomorphometry of the human placenta in preeclampsia, associated with severe intrauterine growth retardation was a study conducted by Teasdale et al 1987. They observed that preeclamptic placentae were comparatively smaller than control placentae. There was reduction in transverse diameter of preeclamptic placentae.\textsuperscript{45}

MS Thakur et al conducted a study in in the year 1988 in which they used sudan black stain to microscopically observe and monitor lipid production by microbes.\textsuperscript{46}

Preeclampsia an endothelial cell disorder was a study by Roberts et al in the year 1989. They proposed that poorly perfused placental tissue release certain factors into the systemic circulation that leads to endothelial cell injury which in turn set a motion of dysfunctional cascade of vasoconstriction, coagulation and intravascular fluid redistribution that results in clinical syndrome of preeclampsia.\textsuperscript{47}

In the year 1990 sudan black stain was used for staining lipids by Subramaniam et al in their study on evaluation of intracellular lipids by standardized staining with sudan black B fraction.\textsuperscript{48}

In the year 1992 Suster S et al conducted studies using alcian blue to stain mucosubstances and found hydrophic degeneration of villi which indicates intravillous accumulation of sulphated mucosubstances. Thus connective tissue of placenta shows non specific stromal reaction to variety of noxious stimuli.\textsuperscript{49}
Studies conducted by Arkwrith et al in the year 1993 showed presence of more glycogen in villi of preeclamptic placentae as compared to control placentae. Glycogen phosphorylase and glycogen synthase activity was much higher in cases with preeclampsia. Glycogen phosphorylase activity was higher in preeclamptic placentae but to smaller extent as compared to control placentae.\(^{50}\)

A study of placental bed spiral arteries and trophoblastic invasion in normal and preeclamptic placentae was conducted by Meekins et al in the year 1994. They reported that in preeclamptic placentae trophoblastic invasion was seen more in decidual than myometrial segments. Variation in morphological features was seen not only in different spiral arteries but also in different segment of same spiral artery. Endovascular trophoblastic invasion was complete, partial or isolated. Hyperplasia in the myometrial arteries and acute atherosis in decidual arteries was commonly seen in preeclampsia. Vascular changes seen in normal pregnancy were physiological.\(^{51}\)

Trophoblast and placental villous core production of lipid peroxides, thromboxane and prostacyclin in preeclampsia was a study conducted by Walsh et al in the year 1995. They concluded that increased production of lipid peroxides by placenta originates from both trophoblast and villous core compartments. Placenta secretes lipid peroxide and hence it could be a source of increased lipid peroxides in maternal circulation of women with preeclampsia. Increased placental vasoconstriction could be as a result of increased ratio of thromboxane to prostacyclin in the villous core.\(^{52}\)

In the year 1995 Salafia et al in their study on placental pathologic features of preterm preeclampsia found that chronic uteroplacental vasculitis, avascular villi, chronic villitis and hemorrhagic endovasculitis was more frequent in preeclampsia. They concluded that immunopathologic processes and coagulation may be involved in pathophysiologic mechanisms of preterm preeclampsia.\(^{53}\)

Lyall et al in the year 1996 suggested that hyperlipidaemia may be enhanced in preeclampsia, thus abnormal lipid metabolism may have a role in this disorder. Preeclamptic women have increased lipid peroxides products in their serum. Decidual vessels show fibrinoid necrosis of the vessel wall and focal accumulation of lipid laden macrophages similar to that seen in atherosclerosis.\(^{54}\)
Increased mitochondrial damage by lipid peroxidation in trophoblast cells of preeclamptic placentae was a study conducted by Morikawa et al in the year 1997. They suggested that lipid peroxidation byproducts damage the mitochondrial proteins, thus causing dysfunction of trophoblasts that contribute to the pathophysiology of preeclampsia.

Bax et al conducted a study on energy metabolism and glycolysis of human placental trophoblast during differentiation in the year 1997. Their results showed that energy metabolism in cytotrophoblast is different from that in syncytiotrophoblast.

In the year 1997 Zhou et al conducted a study on defective endovascular invasion in preeclampsia. They reported that in control pregnancy cytotrophoblasts had two types of interactions with maternal arterioles. In first type of interaction large aggregates of cells were found inside the vessel lumen. These aggregates either lied adjacent to apical surface of endothelium or replaced it in such a way that they appeared to be attached to the vessel wall directly. Thus cytotrophoblasts achieved endovascular invasion. In case of preeclampsia, cytotrophoblast interaction with spiral arteries was very different. Endovascular cytotrophoblastic invasion was limited to vessels that span the superficial decidua. Even if cytotrophoblasts gained access to the lumen they failed to form tight aggregates and remained as individual rounded cells suggesting that they poorly anchored the vessel wall. Thus in preeclampsia cytotrophoblasts displayed altered morphology in their interaction with maternal arterioles and had a limited capacity of endovascular invasion.

In the year 1998 Knight et al in their study on shedding of syncytiotrophoblast microvilli into the maternal circulation in preeclamptic pregnancies found that higher levels of syncytiotrophoblast microvilli were found in plasma of preeclamptic women. Higher concentrations were found in uterine venous plasma as compared to peripheral venous plasma which confirmed their placental origin. They concluded that high levels of syncytiotrophoblast microvilli shed into maternal circulation may contribute to endothelial dysfunction underlying the maternal syndrome in preeclampsia.

In the year 1999 Staff et al reported increased total cholesterol, phospholipids and lipid peroxides in decidua basalis of preeclamptic samples as compared to samples from normotensive controls.
Evidence for peroxynitrite formation in vasculature of women with preeclampsia is a study conducted by Roggensack et al in the year 1999 in which they noted that gestational age at delivery and fetal birth weights was significantly lower in case of preeclamptic group as compared to control group.\(^{60}\)

In the year 1999 Dfederico et al in their study on association of preeclampsia with apoptosis of placental cytotrophoblasts found that there was no evidence of apoptotic nuclei in trophoblast cells of floating villi in preeclamptic placentae. Also there was very little apoptosis seen in cytotrophoblast population of control samples. A tissue sample of severe preeclampsia obtained at 26 weeks of gestation showed numerous cytokeratin positive cytotrophoblasts in anchoring villi. Widespread apoptosis of cells that did not express cytokeratin was observed in a sample obtained at 28 weeks of gestation.\(^{61}\)

Pathophysiology of hypertension during preeclampsia linking placental ischaemia with endothelial dysfunction is a study by Granger et al in the year 2001 in which they documented that placental ischaemia is an important initiating event in preeclampsia. During early human pregnancy spiral arteries are invaded by cytotrophoblasts, replacing endothelial layer of these vessels by destruction of elastic and muscular tissue. Uterine spiral arteries are exclusively lined by cytotrophoblasts and endothelial cell layer is no longer present by the end of second trimester. This remodelling leads to formation of low resistance arteriolar system with increased blood supply to the fetus. In preeclampsia spiral arteries of placental bed escape endovascular trophoblast remodelling and invasion of spiral arteries is limited. Myometrial segments of these arteries remains anatomically intact. Mean external diameter of uterine spiral arteries in preeclamptic women is less than one half of the diameters of similar vessels from uncomplicated pregnancies. Reduced uteroplacental perfusion and increased ischaemic changes in placenta occur in preeclampsia as a result of failure of trophoblastic invasion. Also increased placental infarcts and increased syncytial knots as a result of abnormal cytotrophoblast proliferation have been found in preeclamptic placentae.\(^{62}\)

Studies conducted by Young et al in the year 2002 found lower birth weights and placental weights in hypertensive IUGR cases as compared to normotensive cases. They also found higher incidence of villous infarcts, multifocal lesions, syncytial knots and decidual vasculopathy in hypertensive IUGR cases.\(^{63}\)
Serdar et al in their study on lipid peroxidation in preeclampsia in the year 2002 reported that lipid peroxidation was enhanced in preeclamptic group.\textsuperscript{64}

In the year 2002 Hirano et al found in their study that spiral arteries in preeclampsia had thicker wall and narrow lumen as compared to normal pregnancy. Spiral arteries in preeclampsia also showed remnants of elastic fiber at 31 weeks of gestation while normal pregnancy showed hardly any elastic musculature. Observations in their study showed that thin walls had trophoblasts which were not present in thick walls. Thus trophoblastic invasion was related to thinning of walls and decreased elasticity of spiral artery.\textsuperscript{65}

In the year 2003 Mehew et al in their study to quantify placental morphology in pregnancies complicated by preeclampsia gave particular attention to dimensions and compositions of peripheral villi. In their study they found that fetal weights were reduced in all complicated pregnancies and preeclampsia. Intrauterine growth restriction was associated with placentae having reduced volumes of intervillous space and all types of villi.\textsuperscript{66}

A non-invasive study on evidence of impaired microvascular function in preeclampsia was conducted by Nyame et al in the year 2003. They suggested that in preeclampsia microvascular dysfunction occurs which is related to alterations in endothelial cell and neutrophil activation. They also noted that fetal birth weight was similar in both normal and preeclamptic groups, however women with preeclampsia had higher systolic and diastolic blood pressures, low platelet counts and higher serum uric acid levels as compared to control group. Also plasma albumin concentrations were lower in preeclampsia as compared to normal pregnancy.\textsuperscript{67}

In the year 2003 Moldenhauer JS et al in their study on placental lesions with preeclampsia found decidual arteriolopathy, intervillous thrombi and hyper maturity of villi.\textsuperscript{68}

Endovascular trophoblast invasion was a study conducted by Kaufmann et al in the year 2003 in which they reviewed the routes, mechanism and control of endovascular trophoblastic invasion. They suggested that endovascular trophoblastic invasion involves a side route of interstitial invasion. Impaired interstitial trophoblastic invasion is followed by failure of vascular invasion.\textsuperscript{69}
Duley et al in the year 2003 conducted a study on preeclampsia and the hypertensive disorders. They reported that preeclampsia is commonly seen among women who have conditions associated with large placenta and in women who have microvascular disease. In preeclampsia there is abnormal trophoblastic invasion with reduced placental perfusion. Endothelial dysfunction occurs due to unknown factors that are released into the maternal circulation and act on endothelial cells. This results in vasospasm.  

Udaina et al in the year 2004 conducted a study on relation between placental surface area, infarction and fetal distress in pregnancy induced hypertension with its clinical relevance. They reported that the mean surface area in placentae affected by pregnancy induced hypertension (PIH) decreases with increase in severity of PIH, also cases showing fetal distress have lesser surface area as compared to cases not having fetal distress.  

Davidson et al in the year 2004 reported that during normal placental development there is cytotrophoblast invasion into the spiral arterioles. These cytotrophoblasts completely remodel the spiral arterioles into low resistance large capacitance vessels. This endovascular invasion involves replacement of endothelium as well as highly muscular tunica media. The pathogenesis of preeclampsia may involve abnormal cytotrophoblast invasion of spiral arteries, increased oxidative stress, endothelial dysfunction and decreased uteroplacental perfusion.  

Angiogenic imbalance in pathophysiology of preeclampsia was a study conducted by Bdolah et al in the year 2004. They noted that normal pregnancy requires balance between pro and anti angiogenic proteins that are made by placenta. They hypothesized that normal physiological increase in anti angiogenic factors at the end of pregnancy occurs too soon or there is excess production of anti angiogenic proteins which results in preeclampsia. They used Periodic acid schiff’s (PAS) stain for histopathologic analysis.  

Preeclampsia and the systemic inflammatory response was a study conducted by Redman et al in the year 2004. They stated that the inflammatory response in preeclampsia is exaggerated and increased to the point of decomposition. Some women have placental preeclampsia in which pregnancy is normal but there is ischaemic placenta. In placental preeclampsia there is a stage when the uteroplacental circulation fails to develop fully.
Levy et al in the year 2005 conducted a study on the role of apoptosis in preeclampsia. They reported that excess apoptotic activity in preeclamptic women increases trophoblast apoptosis and inhibits trophoblast invasion into the spiral arteries, thus affecting each step in pathogenesis of preeclampsia.\textsuperscript{75}

In the year 2005 Mangal et al conducted a study which showed bilaminar localisation of placental alkaline phosphatase in syncytiotrophoblast of preeclamptic placentae. They showed that increased activity of placental alkaline phosphatase was directly proportional to maternal blood pressure.\textsuperscript{76}

In the year 2005 Mujumdar S et al conducted a study and found significant number of syncytial knots, fibrinoid necrosis, calcified villous spots, endothelial proliferation, cytotrophoblast cellular proliferation in hypertensive group as compared to control group. Stromal and villous histopathological changes like proliferation of tunica media of medium sized blood vessel, stromal fibrosis and calcified areas were significant in hypertensive pregnancies as compared to control group.\textsuperscript{77}

According to study conducted by Kos et al in the year 2005 physiological changes were seen in the first and second trimester of pregnancy where spiral arteries of the placenta were converted into the uteroplacental arteries. These changes lead to losing of muscular elements in the vessel walls and make them unable to respond to vasomotor effects. There was infiltration and replacement of spiral arteries by intermediate trophoblastic cells. These cells which infiltrated the walls of spiral arteries are called migratory, non-villous cells. These cells also penetrated the lumen of the vessels and formed endovascular plugs. Changes were also noticed in basal plate and amniochorionic membranes. Changes like chorionic villitis, intervillous thrombosis, and subchorial thrombosis were found.\textsuperscript{78}

Histomorphometric study of placental villi vascular volume in toxemia and diabetes is a study by Maly et al in the year 2005 in which they observed ischaemic changes, branching angiogenesis, prominent syncytial knots, presence of increased immature intermediate villi and decreased number of terminal villi in cases of preeclamptic placentae.\textsuperscript{79}
In the year 2005 Boronkai et al found a case of extremely high maternal alkaline phosphatase serum concentration. Histochemical examination of index and control placentae were done and they reported that compared to controls the index placenta showed minimal positivity of alkaline phosphatase enzyme in spite of patient having extremely high serum alkaline phosphatase. They suggested that loss of syncytial membranes in immature villi lead to increased alkaline phosphatase concentrations in maternal circulation.

In the year 2006 Gupta et al reported that increased lipid peroxidation in preeclampsia leads to formation of lipid hydro peroxides which bind to lipoproteins. These hydro peroxides are then carried to distant sites where they cause ongoing lipid peroxidation and result in systemic oxidative stress which in turn leads to increased super oxide production by placenta. Increased production of lipid peroxides and thromboxane was demonstrated from both villous core components and trophoblast in placentae of preeclamptic patients.

Goswami et al in the year 2006 conducted a study on syncytiotrophoblast shedding and they concluded that in preeclampsia higher amounts of syncytiotrophoblast microparticles are shed into the maternal circulation as compared to normal pregnancy. These microparticles are believed to be the stimulus for the systemic inflammatory response and endothelial cell damage which characterizes the maternal syndrome.

In the year 2006 Zhang et al conducted a study on evaluation of frequency and maternal vasculopathy and usefulness of placental examination in pregnancy induced hypertension. They reported that vascular changes such as maternal atherosis, fibrinoid medial necrosis and intervillous thrombosis were observed in preeclampsia.

In the year 2006 Dokras et al studied feto-placental abnormalities in preeclampsia in mice. They found diminished fetal weights and placental masses in preeclampsia as compared to controls. They reported 40 to 50 percent reduction in placental masses at early and mid-gestational age. Also throughout pregnancy fetuses were significantly smaller. Abnormalities in all placental zones such as proportional depth of placental disc relative to the decidua was markedly diminished in hypertensive strain as compared to that in controls. There was significant reduction in amount of space occupied by the placenta as compared to the decidua in hypertensive mice which suggested restricted
expansion of placenta at early gestational age. Further morphometric analyses showed reduction in placental depth in hypertensive mice. This was largely due to decrease in fractional area occupied by junctional zone in these mice. Histological examination showed PAS positive vacuolated glycogen cells, non-vacuolated eosinophilic cells and trophoblast giant cells in both hypertensive as well as control placentae which indicates that total loss of specific cell type does not contribute to reduction in the size. The labyrinth zone of control placentae showed trophoblast cells that undergo branching morphogenesis and result in large surface area for nutrient and gas exchange between mother and fetus. This labyrinth zone had uniformly elongated fetal vessels with elaborate branching morphogenesis. In contrast to this the labyrinth zone of hypertensive placentae showed attenuated and irregular branching and the extent of expansion of labyrinth towards the junctional zone was reduced. PAS staining showed that fetal vessels of control placentae advanced uniformly towards the trophoblasts with increasing gestational age. In contrast to this in preeclampsia PAS positive broad trabecular columns were seen between the fetal vessels at early gestational age and smaller clusters of trophoblast cells persisted through middle and late gestation. PAS positive fibrinoid deposits that lacked trophoblasts were also prominently observed in fetal labyrinthine blood spaces in hypertensive strain. These fibrinoid deposits were rarely seen in control placentae. Morphological changes were prominent in control placentae and the spiral arteries were dilated and thin walled while hypertensive placentae had narrow lumen and onion skin appearance which indicated thickening of arterial wall. Areas of linear necrosis and PAS positive fibrinoid deposits were observed within decidual layers of hypertensive mice. These deposits were rarely seen in control placentae. Also compromised maternal placental circulation was observed in hypertensive mice.\textsuperscript{84}

In the year 2006 Coelho et al studied the microvessel density in placental bed among preeclampsia patients. They observed that mean fetal birth weight and microvascular density of decidual segment and myometrial segment was lower in preeclamptic cases as compared to normal controls. They concluded that poor microvascular densities in preeclampsia worsened with increasing hypertension and proteinuria.\textsuperscript{85}

In the year 2007 Hung et al in their study on oxidative stress and antioxidants in preeclampsia reported that there has been increased evidence that oxidative stress in
Preeclampsia cause endothelial cell dysfunction. It was hypothesized that deficient trophoblast invasion of endometrial arteries cause intermittent placental perfusion and ischaemia which results in release of free radicles. These free radicles attack fatty acids in cell membranes and form lipid peroxides. Lipid peroxides further cause endothelial cell dysfunction. In the year 2006 histochemical techniques such as alcian blue and PAS was used in study conducted by Prieto et al on placental lactogen.

In the year 2008 Huppertz et al conducted a study on placental origins of preeclampsia and concluded that there is aberrant development of villous syncitiotrophoblast which causes impaired maintenance in placental barrier. This leads to necrotic and aponecrotic trophoblast fragments and overall inflammatory response by the mother.

In the year 2008 Peng M et al in their study concluded that there was more superficial depth of invasion of trophoblasts in preeclampsia than normal pregnancy. Superficial myometrial segment showed pathological changes of spiral arteries in placental bed and changes in invasion of trophoblasts which was related to severity of illness. They showed that there is impairment of microvascular development in placental bed in preeclampsia.

In the year 2008 Saleh et al found that nuclei in syncitiotrophoblasts had a tendency of cluster formation in preeclampsia, there was bridging of long syncitial strands in intervillous space which gave the villous tree a pseudolabyrinthine appearance, there was absence of villous core in sectioned syncitial strands, fetal capillaries mostly dissappeared few were recognizable, capillaries which were still preserved showed red blood corpuscles in the lumen, in terminal villi there was proliferation of connective tissue which completely replaced fetal blood sinusoids. Fibrosis and endothelial degeneration was seen in basal decidual arterioles, fewer terminal villi and large plaques of fibrin like material between villi was also found.

In the year 2008 Correa et al in their study on placental morphometrical and histopathological changes in different clinical presentations of hypertensive pregnancy observed histological changes such as syncytial knots and fibrin deposits in hypertensive
placentae. They concluded that there could be different types of hypertension but the final pathway leads to microscopic lesions in the placenta which are the same.\(^90\)

In the year 2008 Guller et al in their study found that some syncytial products are released into maternal blood which negatively impact the function of maternal endothelium and promote manifestations of preeclampsia. They also suggested that placental damage and placental infarction associated with preeclampsia reduces placental transport leading to IUGR.\(^91\)

Hypertension in pregnancy, abnormal placentation is a hallmark of preeclampsia is a study conducted by Lindheimer et al in the year 2008. They reported that there is failure of normal trophoblastic invasion of the spiral arteries and failing of these vessels to remodel and dilate. This underlies the theory that restriction of placental blood flow leads to hypoxic utero-placental environment which leads to release of factors that enter the mother’s circulation and initiate the maternal syndrome.\(^92\)

Study of proportional and absolute volume of placental parenchyma and non parenchyma between normal pregnant women and preeclamptic women was conducted by Kishwara et al in the year 2008. They reported reduction in both proportional and absolute volume in preeclamptic placentae as compared to normotensive placentae.\(^93\)

Is human placenta proteoglycan remodelling involved in preeclampsia was a study conducted by Warda et al in the year 2008. They used alcian blue stain to find the content of glycosaminoglycans in placental tissue. Their results showed that the content of glycosaminoglycans was markedly less in preeclamptic placentae as compared to normotensive placentae.\(^94\)

According to study conducted by Kishwara et al in the year 2009 transverse diameter, volume, number of cityledons and size of placentae in preeclampsia were significantly reduced as compared to control placentae.\(^95\)

A potential role of free fatty acids in the pathogenesis of preeclampsia was a study conducted by Robinson et al in the year 2009. They reported that lipid droplet accumulation was significantly increased in the maternal plasma from pregnancies complicated with preeclampsia as compared to normal uncomplicated controls.\(^96\)
A study on role of angiogenic factors in pathogenesis of preeclampsia was conducted by Wang et al in the year 2009. They reported that severe preeclampsia is associated with placental hypoperfusion and ischaemia. Acute atherosis, diffuse vascular obstruction, fibrin deposition, intimal thickening, necrosis, endothelial damage and atherosclerosis are findings of preeclampsia. Occlusion of spiral arteries resulting in placental infarcts is also common. In normal placental development uterine spiral arteries of decidua and myometrium are invaded by cytotrophoblasts of fetal origin. These cytotrophoblasts replace the endothelial layer of maternal spiral arteries and transform them from high resistance vessels to high caliber capacitance vessels. In preeclampsia cytotrophoblast invasion is limited to superficial decidua and transformation of spiral arteries is incomplete, thus myometrial segments remain narrow.\(^{97}\)

Uteroplacental hemodynamics in the pathogenesis of preeclampsia was a study by Hutchinson et al in the year 2009. They observed that in preeclampsia there were increased perfusion rates on maternal side while the fetal side flow rates remained constant. They reported that these elevated flow rates resulted in morphological damage, vacuolation and shedding of cytotrophoblasts and other features which were previously defined in preeclampsia. Biochemical markers of syncytial damage such as alkaline phosphatase was found in maternal perfusates recovered under high flow conditions. They concluded that alterations in intervillous blood flow have the potential to influence the integrity of syncytiotrophoblast as well as the liberation of potentially pathogenic soluble factors.\(^{98}\)

Studies conducted by Sammak et al in the year 2009 showed that there was diminished activity of alkaline phosphatase enzyme in syncitiotrophoblast and villous stroma in preeclamptic placentae as compared to control group which showed a very strong reaction to alkaline phosphatase activity. They showed that in preeclamptic placentae alkaline phosphatase activity gradually decreased until it disappeared. This could be as a result of reduced uteroplacental perfusion, endothelial cell damage and placental ischaemia.\(^{99}\)

Early onset preeclampsia is characterized by altered placental lipid metabolism is a study by Han et al in the year 2010. They examined total placental fatty acids and reported that fatty acids were significantly decreased preeclamptic placentae as compared to normal
controls. There was no significant difference found between preeclamptic and control placentae after 28 weeks of gestation.\textsuperscript{100}

As documented by Eskild et al in the year 2010 in their study on placental weight and preeclampsia, preeclamptic pregnancies were in the highest decile of placental weights as compared to normotensive pregnancies. They concluded that placental weight is linked to the fetal birthweight, but is not associated with risk of preeclampsia. Thus placental weight is not a useful indicator of placental dysfunction in preeclampsia.\textsuperscript{101}

Lipid peroxidation and antioxidant status in preeclampsia is a study by Kashinakunti et al in the year 2010. They reported that lipid peroxidation product and uric acid level is significantly increased in preeclamptic group as compared to normal.\textsuperscript{102}

Marini et al in the year 2010 conducted a study on distribution of sugar residues in human placentae from pregnancies complicated by hypertensive disorder in the year 2010. They observed that glucose oxidase reactivity was weaker in preeclamptic placentae.\textsuperscript{103}

A study was conducted on histo morphometry of umbilical cord blood vessels in preeclampsia by Blanco et al in the year 2011. Their results showed reduction in mean birth weight and significantly shortened gestation period for preeclamptic group as compared to control group.\textsuperscript{104}

Vinnars et al in the year 2011 carried out a study in which their objective was to correlate the ischaemic changes in placentae with clinical severity of preeclampsia. The placental histopathological changes showed that the amount of infarction increased with severity of preeclampsia.\textsuperscript{27}

Spectrum of changes in placenta in toxemia of pregnancy is a study by Narasimha et al in the year 2011 in which they concluded that striking villous abnormalities such as cytotrophoblast proliferation, thickening of villous basement membrane, fibrinoid necrosis, increase in syncytiatal knots, villous stromal fibrosis, endarteritis obliterans, paucity of vasculosyncytial membranes and decreased villous vascularity was observed in preeclamptic placentae.\textsuperscript{105}
In the year 2011 Salgado et al in their study on structural changes in preeclamptic placentae observed that chorionic villi of hypertensive placentae showed a complex appearance with many distorted microvilli and frequent cytotrophoblast cells as compared to normal placentae. Chorionic villi showed thickening of basement membrane. Terminal villi of preeclamptic placentae showed patchy necrosis with loss of microvilli and gross thinning of syncytium. Numerous vacuolated mitochondria with loss of cristae, lysosomes, few rough endoplasmic reticulum and glycogen deposits were seen in cytotrophoblast cells where syncytium was absent.\textsuperscript{106}

It was observed that there was absence of vasculosyncytial membrane in villi of hypertensive placentae as compared to normal placentae in a study conducted by Ansari et al in the year 2011 on vasculosyncytial membrane in placental villi of normotensive and hypertensive pregnancies.\textsuperscript{107}

In the year 2011 Londhe et al conducted a morphometric study on placenta and its correlation in normal and hypertensive pregnancy. They reported that mean placental weight, number of cotyledons, mean placental volume and fetal birth weight was lower in hypertensive group as compared to the control group. While mean number of infarcted areas, calcified areas and marginal insertion of cord was higher in case of hypertensive placentae as compared to control placentae.\textsuperscript{108}

In the year 2011 Powe et al in their study on preeclampsia a disease of maternal endothelium reported that there is abnormal placentation in preeclampsia. Cytotrophoblasts of fetal origin invade the maternal spiral arteries in normal placental development and transform them from small caliber resistance vessels to high caliber capacitance vessels. These vessels are then capable of providing adequate placental perfusion to sustain the growing fetus. During this process of vascular invasion the cytotrophoblasts differentiate from epithelial phenotype to endothelial phenotype. This process is referred to as pseudo vasculogenesis. Cytotrophoblasts fail to adopt invasive endothelial phenotype in case of preeclampsia. Instead there is shallow invasion of spiral arteries and they remain small caliber resistance vessels.\textsuperscript{14}

Kishwara et al conducted a study on effects of preeclampsia on perinatal outcome in the year 2011. They reported reduced mean birth weight and mean APGAR score in babies born to preeclamptic mothers as compared to those of controls.\textsuperscript{109}
In the year 2011 Sun Y et al conducted a study which aimed to minimize autofluorescence of renal tissue and demonstrate efficient method to reduce it using sudan black stain.\textsuperscript{110}

Use of PAS and sudan black stain was used in study conducted by Tewari on histological study on placentae of diabetic women in the year 2011.\textsuperscript{111}

In the year 2011 Lima et al studied the serum lipid levels in pregnancies complicated by preeclampsia. Their results showed that very low density lipoproteins and triglyceride values of preeclamptic women were higher than those of healthy women. However there was no significant difference between serum LDL and HDL levels of preeclamptic and healthy controls.\textsuperscript{112}

Lipid peroxidation and antioxidant status was studies by Begum R in the year 2011. They concluded that increased lipid peroxidation may be the important factor in pathogenesis of preeclampsia.\textsuperscript{113}

In the year 2011 Ilie et al reported histological changes like enlargement, atrophy and disruption of endothelium, fibrinoid necrosis, hypertrophy of smooth muscles in the wall of spiral arteries, avascular small villi, hyaline fibrosis of villous stroma, and thrombosis of spiral arterioles were noticed in pregnancy induced hypertensive placentae. Also microscopic changes like heterogenous placental maturation, decreased chorionic villi, decreased density of villous cytotrophoblastic cells and disappearance of fetal capillaries in most villi were observed in pregnancy induced hypertensive placentae as compared to normotensive placentae.\textsuperscript{114}

In the year 2012 use of alcian blue and PAS was done for staining sections and find mucins in placental tissue. This study was conducted by Schefer on normally delivered alpacas and lamalas.\textsuperscript{115}

In the year 2012 Lee et al in their study observed for glycogen phosphorylase isoenzyme plasma concentrations in preeclampsia. They reported that cases of preterm severe preeclampsia had higher glycogen phosphorylase isoenzyme concentration as compared to term preeclamptic cases. Also preeclamptic women had higher concentration of plasma glycogen phosphorylase enzyme as compared to women with normal pregnancy outcome.\textsuperscript{116}
Gheorman et al conducted a study on histochemistry of placenta in the year 2012 using alcian blue and PAS and found glycogen deposits in villous interstitium.\textsuperscript{117}

A study on placental pathology and blood pressure level in women with hypertensive disorders in pregnancy was carried out by Krielessi et al in the year 2012. They observed that placental lesions were seen more often in the severe hypertensive group. Villous fibrinoid necrosis and infarction was significantly increased in severe hypertensive group as compared to mild hypertensive group.\textsuperscript{118}

Nafees et al conducted a study on histopathology of preeclamptic placentae in the year 2012. They concluded that there is improper placental development in preeclampsia. Changes in preeclampsia are due to reduction in maternal uteroplacental blood flow which leads to construction of fetal stem arteries and fetal hypoxia is due to maternal vasospasm.\textsuperscript{119}

Sudan black staining method was used in study conducted by Ravikumar et al on biodiesel production from oleaginous fungi in the year 2012.\textsuperscript{120}

In the year 2012 Kalar et al conducted a study on lipid levels in preeclampsia. Enzymatic calorimetric method was used to determine lipid profile. They concluded that preeclamptic women had deranged lipid profile as compared to normal pregnant women.\textsuperscript{121}

Histological changes like accelerated villous maturation, decidual arteriopathy, placental infarction and intervillous thrombosis in preeclamptic placentae was observed by Mehrabian et al in their study on comparison of placental pathology between severe preeclampsia and HELLP syndrome in the year 2012.\textsuperscript{122}

In the year 2012 Akhlaq et al in their study found that preeclamptic placentae were less in size and thickness as compared to normal placentae. Microscopic features found were hypoplasia of distal villi, smooth muscle hypertrophy of spiral arterioles, villous necrosis, perivillous fibrin deposits and syncytial knots in preeclamptic placentae.\textsuperscript{123}

Histological changes in placentae in pregnancies complicated by preeclampsia and eclampsia and correlation with fetal outcome was a study by Navbir et al in the year 2012. They observed histological changes in preeclamptic placentae such as
cytotrophoblast proliferation in significant villi, vasculosyncytial membrane deficiency, basement membrane thickening, excessive syncytial knotting, stromal fibrosis and fibrinoid necrosis.\textsuperscript{124}

In the year 2012 Alladin et al in their study have reported that syncytiotrophoblast cells in placenta which are in direct contact with the mother are involved in preeclampsia. There is an extensive remodelling of maternal spiral arteries in normal placenta. Invasion of trophoblasts into the spiral arteries transform small caliber vessels into large capacity vessels. This arterial network is able to access more and more mother’s blood as per the increased requirement of placenta. When placenta is not able to access more nutrients from the mother because of ill developed maternal spiral arteries it can lead to preeclampsia or fetuses that are small for gestational age. Poor placentation and increased oxidative stress causes hypoxia resulting in lack of oxygen is thought to cause clinical signs of preeclampsia. More demand of nutrients from growing fetus is not met by the mother as a result of early poor placentation. Failure of trophoblasts to invade into the decidua prevents remodelling of spiral arteries which finally leads to insufficient blood flow from mother to placenta.\textsuperscript{125}

Saeed et al studied the histomorphological changes in placentae of preeclamptic mothers in the year 2012. Their results showed that there were increased number of terminal villi, increased number of syncytial knots and increased vasculosyncytial membrane thickness in hypertensive group as compared to normal controls. They concluded that this increase in syncytial knots and vasculosyncytial membrane thickness may be the cause or effect of hypoxia.\textsuperscript{126}

Immuno histochemical study of the syncytial knots in preeclamptic placentae was studied by Sharma et al in the year 2012. They observed increased number of syncytial knots in preeclamptic placentae as compared to normotensive placentae. They also observed increased number of syncytial knots in peripheral section of preeclamptic placentae as compared to central section.\textsuperscript{127}

Placental morphology and its correlation with fetal outcome in pregnancy induced hypertension is a study by Navbir et al in the year 2012. They found that the placental weight and volume were much lower in higher proportion of cases eclampsia and moderate to mild preeclampsia. Feto-placental weight ratio was lower in cases of severe
form of disease than in case of milder form of toxaemia. They concluded that lighter placentae usually accompanied low birth weight fetus. Placental infarcts, retroplacental haematoma and calcification were three main gross lesions that were observed, the incidence of which was higher in placentae of hypertensive pregnancies as compared to those of control group. Study group more commonly showed placental calcification while control group showed this feature to a lesser degree. \(^{128}\)

Huang et al studied placental phospholipids in preeclamptic pregnancies in the year 2013. They found an increase in total phospholipid content as well as changes in individual classes of phospholipids in preeclamptic placental tissue as compared to control placentae. They reported that these alterations could be due to pathological changes in preeclampsia, such as dysregulation of lipid transport across the syncytiotrophoblast or lipid peroxide insult. \(^{129}\)

Role of lipid peroxidation and antioxidant status in pathogenesis of preeclampsia is a study by Phalak et al in the year 2013. They reported that increased level of lipid peroxidation product and decreased levels of antioxidants in preeclamptic women suggested that oxidative role plays a key role in endothelial dysfunction in preeclampsia. \(^{130}\)

Studies conducted by Dubova et al in the year 2013 found irregularity in expression of glucose transporters in preeclamptic placentae and concluded that disturbance in glucose transporters could play a major role in IUGR development in severe cases of preeclampsia. \(^{131}\)

Nag et al in the year 2013 conducted a study on morphological changes in placenta of hypertensive pregnant women. They concluded that there is increased chance of ischaemic to the placental tissue and maldeveloped villi in patients with pregnancy induced hypertension. As a result of this there may be impaired nutrient transfer and low birth weight babies. \(^{132}\)

Effects of pregnancy induced hypertension on placenta was a study conducted by Motwani et al in the year 2013. On gross examination they revealed presence of smaller placentae, calcification foci and infarction in the study group. Microscopic examination showed villous abnormalities, syncytial knots, fibrinoid necrosis, hyalinized villi, stromal
fibrosis, hypo vascularity of villi, cytotrophoblastic cell proliferation and basement membrane thickening. They concluded that pregnancy induced hypertension immensely affected placenta which may be responsible for postnatal outcomes.¹³³

Nahar et al carried out a study on pregnancy induced hypertensive placentae in the year 2013. They observed fibrinoid necrosis, syncytial knots, sclerosis, chorangiosis and calcification were more marked in preeclamptic placentae as compared to control placentae.¹³⁴

Kaur et al conducted a study on placental weight, birth weight and fetal outcome in preeclampsia and normotensive pregnancies in the year 2013. They observed that fetal outcome was significantly poor in preeclampsia as compared to normotensive pregnancies.¹³⁵

Placental changes in idiopathic intrauterine growth restriction was a study conducted by Biswas et al in the year 2013. They used PAS stain to observe the chorionic villi in their study.¹

In the year 2013 Modi et al studied morphological changes in preeclamptic placentae. Their results showed reduction in placental weight, placental volume, placental thickness and diameter in case of preeclamptic placentae as compared to normotensive placentae. They concluded that preeclamptic placenta underwent a lot of morphological changes which seemed to be the responsible for placental insufficiency in pregnancy induced hypertension.¹³⁶

Dhabhai et al studied histology of human placenta in normal and pregnancy induced hypertension. They observed increased syncytial knots, increased hyalanized villi, hypovascular villi, fibrinoid necrosis and stromal fibrosis in preeclamptic placentae as compared to normotensive placenta.¹³⁷

Study of placental changes in pregnancy induced hypertension is a study conducted by Maimoona et al in the year 2013. They reported that the mean placental weight and fetal weight to placental weight ratio reduces as PIH severity increases. They also noted that histological changes like infarction, calcification and syncytial knots were more in severe cases of preeclampsia.¹³⁸
Placental pathology suggesting that preeclampsia is more than one disease is a study by Nelson et al in the year 2014. They observed chorionic villitis, ischaemic villous necrosis and vascular lesions like decidual arteriolopathy, narrow caliber of spiral arterioles and residual medial smooth muscle cells, fibrinoid necrosis, atherosis of decidual arterioles. Accumulation of foamy lipid filled macrophages with mural fibrinoid necrosis of decidual arterioles was seen. They concluded that women with preeclampsia onset before 34 weeks of gestation had significantly different placental findings as compared to those with preeclampsia at term. Hence these different findings support the hypothesis that preeclampsia is a different disease depending on gestational age at diagnosis.\textsuperscript{139}

Stark et al in the year 2014 conducted a study in which they compared the histological differences in placentae of preeclamptic gestations by birth weight, placental weight and time of onset. Their results showed that increased birth weight placentae had increased mural hypertrophy of membrane arterioles and decreased syncytial knots. While decreased birth weight showed increased placenta site giant cells. Increased placental weight had decreased distal villous hypoplasia. Decreased placental weight had increased acute atherosis, increased intervillous fibrin and increased syncytial knots. Early onset disease showed increased syncytial knots, villous agglutination, and infarcts. With all these findings they suggested that preeclampsia is composed of several different processes manifesting a single clinical presentation.\textsuperscript{140}

Singh et al in the year 2014 conducted a cross sectional morphological study on preeclamptic placentae. They reported that mean placental weight in case of preeclampsia was less than that of normal placentae. Various pathological changes like retroplacental hematoma, calcification and infarction were noticed in preeclamptic placentae. Decreased placental weight was associated with reduced fetal birth weight with significant increase in severity of hypertension.\textsuperscript{141}

Study of structural changes in placenta in pregnancy induced hypertension was conducted by Salmani et al in the year 2014. They observed reduction in thickness, weight and number of cotyledons in preeclamptic placentae as compared to normotensive placentae. Increased areas of calcification, fibrinoid necrosis, hyalinization, increased syncytial knots were observed in preeclamptic placentae as compared to normotensive placentae. They also observed increased areas of medial coat proliferation in blood vessels in preeclamptic placentae.\textsuperscript{142}