INTRODUCTION

The placenta provides functions such as transport and secretion even during its development, thus all developmental changes need to be in accordance with its function. Human placenta has a characteristic vascular arrangement from which the volume and flow of blood through the placenta is kept adequate to perform its function. The growth and health of the fetus is dependent on an increasing supply of blood reaching the intervillous space as pregnancy progresses. Physiological change is restricted to the decidual segment as endovascular trophoblast do not invade the myometrial segment and failure of spiral artery transformation may affect the vascular remodelling required for delivering adequate volumes of maternal blood to the placenta in pre-eclampsia. Several other contestable issues such as the vascular plugging and its relation with oxygen, trophoblast invasion from the outside or the inside of the vessels, the impact of haemodynamics on endovascular migration, early decidua-associated vascular remodelling may be disturbed in complicated pregnancies.

Disturbed remodelling is associated with maintenance of high uteroplacental vascular resistance, pre-eclampsia and intrauterine growth restriction. Pre-eclampsia is a pregnancy-specific disease characterized by development of concurrent hypertension and proteinuria, sometimes progressing into a multiorgan cluster of varying clinical features. An impairment of blood flow through the intervillous space results in hypoxia, placental ischaemia, infarction and reduced fetal growth.

During the first trimester, the chorionic villi are covered by an inner cellular villous cytotrophoblast layer and an outer layer of multinucleated syncytiotrophoblasts. As gestation continues, the cytotrophoblast layer becomes discontinuous and syncytiotrophoblast becomes thinner.

In hypoxia, there is irregular thinning of the syncytiotrophoblast with early proliferation of syncytial nuclei. Reduction in number of endoplasmic reticulum, reduction in size and number of mitochondria in the syncytiotum, marginal clumping of nuclear chromatin, general thinning and degeneration of syncytiotum are

ORIGINAL ARTICLE

Structural Changes in Pre-eclamptic and Eclamptic Placentas – An Ultrastructural Study

Sujatha S. Salgado¹ and M.K.R. Salgado²

ABSTRACT

Objective: To determine the ultrastructural changes of the placenta in women with pre-eclampsia and eclampsia compared to the placenta of normotensive patients.

Study Design: Comparative descriptive study.

Place and Duration of Study: Obstetrics Unit of North Colombo Teaching Hospital, Ragama, Sri Lanka in 2004.

Methodology: Placentae of 10 normotensive women and 10 hypertensive women with pre-eclampsia and eclampsia were studied. Morphological abnormalities in chorionic villi, cytotrophoblastic cells and basement membrane under electron-microscope were detected. Findings were recorded and compared.

Results: Microvillous surface of many chorionic villi of hypertensive placentae showed a complex appearance with many distorted microvilli and frequent cytotrophoblastic cells compared to normotensive placentae. The basement membrane of chorionic villi was more thickened in hypertensive placentae. Patchy necrosis with loss of microvilli and gross thinning of the syncytiotum with distorted microvilli were seen in terminal villi of placentae of women with eclampsia. In areas where the syncytiotum was absent, the cytotrophoblastic cells showed numerous vacuolated mitochondria with loss of cristae, and few rough endoplasmic reticulum, lysosomes and glycogen deposits. An accumulation of electron dense amorphous substance and number of vacuolated mitochondria were concentrated in the cytoplasm of endothelial cells of fetal capillaries.

Conclusion: Ultrastructural villous changes were found in the placentae of women with pre-eclampsia and eclampsia which are likely to influence adversely on placental function.

Key words: Pre-eclampsia. Eclampsia. Villous changes. Fetal capillaries. Placenta ultrastructure change.

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In hypoxia, there is irregular thinning of the syncytiotrophoblast with early proliferation of syncytial nuclei. Reduction in number of endoplasmic reticulum, reduction in size and number of mitochondria in the syncytiotum, marginal clumping of nuclear chromatin, general thinning and degeneration of syncytiotum are
shown in pre-eclampsia. Obvious degeneration and significant ultrastructural changes placenta in gestational hypertension and pre-eclampsia has been demonstrated when compared to normal placenta. The prevalence of placental abruption (8.3%) and the prevalence of perinatal deaths (28.7%) is significantly higher in early-onset pre-eclampsia and fetal growth retardation. Ten percent of women have high blood pressure during pregnancy, and pre-eclampsia complicates 2% to 8% of pregnancies. Overall, 10% to 15% of direct maternal deaths are associated with pre-eclampsia and eclampsia. Perinatal mortality is high following pre-eclampsia, and even higher following eclampsia.

In Sri Lanka, pre-eclampsia is one of the commonest complications of pregnancy with an incidence of about 5%. Placental pathology is important in clarification of the causes of many adverse pregnancy outcomes, improvement of risk assessment for future pregnancies. Therefore, the objective of this study was to find out ultrastructural changes in chorionic villi of placentae in pre-eclampsia and eclampsia compared to the placentae delivered in normotensive women.

**METHODOLOGY**

It was a comparative descriptive study and was performed at the Obstetrics Unit of North Colombo Teaching Hospital, Ragama, Sri Lanka in 2004. The study sample consisted of 10 pregnant women with hypertension complicating pregnancy as cases and 10 normotensive pregnant women as controls. A pregnant woman with a blood pressure of less than 140/90 mmHg, throughout the pregnancy was considered as normotensive. Those women were recruited using a systematic sampling method. All had an uncomplicated period of gestation of 37-42 completed weeks.

Pregnant women with an absolute rise in blood pressure of atleast 140/90 mmHg, if the previous blood pressure is not known or rise in systolic pressure of at least 30 mmHg or a rise in diastolic pressure of atleast 15 mmHg over previously known blood pressure was considered as hypertension complicating pregnancy. Pre-eclampsia was classified as hypertension after 20th week of gestation having 100-300 mg/dl proteins in urine and eclampsia was defined in women with blood pressure of 116/110 mmHg and above, severe proteinuria of 1000 mg/dl with fits. Urine protein estimation was performed by human test combine 9SG dipstick method. Those with any other illness other than hypertension were excluded from the study. Maternal demographics including age, parity, height, weight, period of gestation were noted.

Women were informed about the study and written consent was obtained at the time of recruitment. Ethical clearance was obtained from the Research, Higher Degrees and Ethics Committee of Faculty of Medicine, University of Colombo.

About 2 mm sized placental tissues were fixed in two percent (v/v) gluteraldehyde overnight and post-fixed in one percent osmium-tetroxide for one hour at 4°C. Tissues were dehydrated and cleared with propylene oxide and embedded in Epon resin. Ultrathin sections (70 nm) were stained with uranyl-acetate and lead citrate and examined with a Joel 1200 electron microscope.

**RESULTS**

Out of ten hypertensive placentae examined eight placentae were from women with pre-eclamptic toxaemia. Two placentae were from women with eclampsia. Ages of these women varied from 21 to 32 years. The period of gestation varied from 36 to 40 weeks. Ten placentae from normotensive women whose gestational age varying from 37 to 40 weeks were also processed as a control, attempting to match for gestational age.

In normotensive placentae, all the chorionic villi were immersed in maternal blood and covered with well developed syncytium, thickness of which varied in different areas. Most of the villi showed thinning of the syncytium in areas where the villous capillaries have reached the trophoblast. In most of the chorionic villi, the syncytium was covered with long regular microvilli but few small promontories with short microvilli with distended bulbous tips were also seen. Numerous rough endoplasmic reticulum with few dilated cisternae and few vesicles were present in the cytoplasm. Occasional cytotrophoblast cells were seen in some of the terminal chorionic villi. The basal surface of the syncytiotrophoblast cells were lying on either the basement membrane or an occasional cytotrophoblast cell. The connective tissue core contained bundles of collagen fibres, variety of connective tissue cells and fetal capillaries.

In the placental chorionic villi from women with pre-eclamptic toxaemia, the thickness of the syncytium varied considerably in different areas. In some of the chorionic villi, the syncytial surface showed small protrusions and irregularly placed short microvilli, frequently with distended tips. The microvillous surface of many chorionic villi showed a very complex appearance having large number of distorted microvilli. Some cytoplasmic areas were detached from the syncitial surface especially in areas related to fibrin deposition in the intervillous space. The entire syncytiotrophoblast cytoplasm was overcrowded with vesicles of varying sizes in most of the chorionic villi of hypertensive placentae. Some of these were dilated rough endoplasmic reticulum as there were ribonucleo-
protein particles attached to their outer membranes. There were occasional mitochondria with ill defined membranes and altered architectural pattern, but lipid granules, and Golgi bodies were not present. Ribonucleoprotein particles were scattered and few glycogen deposits were seen in the cytoplasm (Figure 1).

Syncytial cytoplasm contained about 8-10 nuclei in aggregate, with condensed chromatin arranged at the periphery. Double nuclear membrane and perinuclear space were prominent and nuclear pores were frequent. Nucleoli were present in few nuclei.

Although cytotrophoblast cells were few and rather inconspicuous in chorionic villi of normotensive placentae, basal surface of the syncytiotrophoblast was lying on the frequently occurring cytotrophoblast cells in most of the chorionic villi of hypertensive placentae, forming almost a layer. Although the contact between syncytiotrophoblast and cytotrophoblast cells was preserved by desmosomes, there were numerous dilated spaces between them (Figure 2).

Most prominent component of cytotrophoblast cells were the elongated mitochondria with tubular cristae which were larger than the syncytial mitochondria. Rough endoplasmic reticulum were also prominent, occurred more in the form of tubules. Well developed Golgi membranes were present. Numerous glycogen deposits and ribonucleoprotein granules were seen in considerable quantities than in the syncytiotrophoblast. Nuclei were large and irregular in shape and a prominent nucleoli were shown (Figure 3).

The basement membrane was much thickened, constituted by an amorphous granular substance of moderate electron density in which filaments work felt could be identified. Numerous bundles of fine fibrils were incorporated into the basement membrane (Figure 4).

Few capillaries in the stroma were in close proximity to the trophoblast, but there was no thinning of

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**Figure 1:** Electron-micrograph of a terminal chorionic villous of a placenta from a woman with pre-eclamptic toxaemia showing the syncytiotrophoblast with promontories (P), complexed microvilli (MV), dilated endoplasmic reticulum (ER), mitochondria (M), glycogen (G), nucleus (N) magnification x 7500 Bar - 1µ.

**Figure 2:** Electron-micrograph of a terminal chorionic villous of a placenta from a woman with pre-eclamptic toxaemia showing syncytiotrophoblast (Sy), promontory (P), microvilli (MV), rough endoplasmic reticulum (ER), pinocytotic vesicles (P), mitochondria (m), desmosomes (D), subsyncytial space with microvilli (SP), cytotrophoblast (Cy), cytotrophoblast mitochondria (Cm), Golgi body (go), cytotrophoblast nucleus (N) magnification x 1000 Bar - 500 nm.

**Figure 3:** Electron-micrograph of a terminal chorionic villous of a placenta from a woman with pre-eclampsia showing several cytotrophoblasts (CY), syncytiotrophoblast (SY), irregular short microvilli (MV), numerous dilated rough endoplasmic reticulum (ER), nucleus (N), nucleous (NU), capillary (CAP), endothelium (E) magnification 5000 Bar - 1µ.

**Figure 4:** Electron-micrograph of a terminal chorionic villous of a placenta from a woman with pre-eclampsia showing unduly thickened subtrophoblastic basement membrane (BM), syncytiotrophoblast (Sy), microvilli (MV), subsyncytial space (SP), glycogen deposits (g) magnification x 25000 Bar - 200 nm.

**Figure 5:** Electron-micrograph of a terminal chorionic villous of a placenta from a woman with pre-eclampsia showing endothelial pericytic interaction. Foetal capillary (CAP), pericytic processes (P), endothelium (E), endothelial process (EP), magnification x 12000, Bar - 500 nm.

**Figure 6:** Electron-micrograph of a terminal chorionic villous of a placenta from a woman with eclampsia showing remnants of necrotic syncytiotrophoblast (SV), exposed cytotrophoblast (CY), swollen vacuolated mitochondria (M), desmosomal junctions (D), subtrophoblastic basement membrane (BM), capillary (CAP), and endothelium (E), collagen (C), magnification x 12000 Bar - 500 nm.
Structural changes of the placenta in pre-eclampsia and eclampsia

the overlying syncytium. Cytotrophoblast cells were intervened between syncytium and the capillary. Most of the capillaries were small and deeply situated and lined with 6-7 endothelial cells. Large mitochondria, oval or elongated, with tubular cristae, rough endoplasmic reticulum and smooth endoplasmic reticulum were present in the endothelial cells with clusters of ribonucleoprotein particles dispersed throughout the cytoplasm Golgi were infrequent. The mitochondria were swollen, having ill defined membranes, and normal architectural pattern was lost. Large number of ribonucleoprotein particles and glycogen deposits, were present. The vascular basement membrane was thickened having a unilaminar or multi lamellar appearance. Endothelial cells were frequently surrounded by pericytes. Endothelial cell processes extended towards the pericytic processes and made very close contact with them. In some regions, pericytic processes were enclosed within the capillary basement membrane and endothelial cell and the pericytic process were closely in contact with each other (Figure 5).

In majority of the terminal chorionic villi of placenta of women with eclampsia patchy necrosis and gross thinning of the syncytium with distorted microvilli were seen. In certain areas microvilli on the surface were lost. Cytotrophoblast cells formed almost a layer, but it was also thinned out, with few ribonucleoprotein particles, and glycogen deposits. In areas where the syncytium was absent, the cytrophoblast showed numerous mitochondria which were vacuolated with loss of cristae, and few rough endoplasmic reticulum, lysosomes and glycogen deposits (Figure 6).

The villous stroma contained numerous collagen fibres and fibroblast cells. Numerous of vacuoles concentrated in the cytoplasm of the endothelial cells of some of the capillaries were most probably vacuolated mitochondria. Some electron dense, amorphous substance collected in the cytoplasm and large number of pinocytotic vesicles were present (Figure 7).

DISCUSSION

Thinning of the syncytiotrophoblast and progressive increase in syncytial knots in conjunction with the increasing severity of the pre-eclampsia were noted by some authors.17 When placental villi were maintained in hypoxic conditions and well oxygenated organ culture, gradual increase in vacuolation and progressive thinning of the syncytium, increase in sub-trophoblastic space and increase in intravillous collagen were seen in placental villi exposed to hypoxia. The similarities of the structural changes seen in chorionic villi of pre-eclampsia and the in vitro changes of hypoxia, suggest that the placental abnormalities seen in pre-eclampsia are a result of hypoxia rather than the cause of the disease.18 Marked thinning and vacuolation of the syncytiotrophoblast in spontaneous and induced hypoxia, changes in the syncytiotrophoblast in spontaneous and induced hypoxia, changes in the syncytium having large projections of the cytoplasm with clubbing of the microvilli were seen. Large promontories with irregular microvilli frequently with distended tips were shown in placentae from women with pre-eclampsia in the present study. This complex surface with branching microvilli, provides a considerable area for absorption, and globular terminal expansions of many of these villi have been thought to be associated with active absorption.

Presence of numerous dense lipoid droplets throughout the syncytium, and in greater frequency in basement membrane of normotensive human placentae have been thought to be associated with steroid hormone production.20 In the present study, lipoid droplets were almost absent in the syncytiotrophoblast of hypertensive placentae which would have affected this function.

In functional terms, mitochondrial activity is the first function of the trophoblast to suffer the effect of oxygen deficiency.10 Reduction in number and size of the mitochondria in toxemic placentae in this study may reflect the diminished function, both in transport across the syncytiotrophoblast and its metabolic activity. Thickening of the sub-trophoblastic basement membrane and increase in number of dilated spaces separating the syncytiotrophoblast from underlying structures were shown in an ultrastructural study of the placenta in maternal eclampsia.21 It was confirmed by the present study and found that these spaces were filled with microvilli from the syncytial surface. In some of the chorionic villi, fibrillar component of the basement membrane was increased, having a lamellated appearance and incorporating that into the surrounding...
profiles of collagen. Thickening of villous subtrophoblastic basement membrane beyond its normal width 1000 - 3000 angstrom is commonly seen in toxemic placentae. Thus it seemed certain that thickening of the basement membrane can be a consequence of utero-placental ischaemia. But this change was seen in other conditions in which there was no suggestion of a reduced maternal blood flow through the placenta and is therefore a non-specific change. Increased intravillous collagen and marked proliferation of stromal cells were observed in a previous study carried out to detect the ultrastructural changes of normal human trophoblast maintained in an organ culture with 6% and 26% oxygen. In the present study, all placental sections examined from hypertensive women, the amount of collagen in the stroma of terminal chorionic villi varied in different villi, often being increased, when compared with chorionic villi of normotensive placentae. When normal placentae examined the vascular basement membrane was thin and the endothelium appeared to be devoid of one. In hypertensive placentae vascular basement membrane was thickened, which may be as a consequence of utero-placental ischaemia. The increased number of pericytic processes associated with endothelial cells and highly complexed interaction between these two types of cells were seen in terminal villous capillaries of hypertensive placentae when compared with normotensive placentae.

CONCLUSION

In pregnancies complicated by pre-eclampsia and eclampsia, the placenta can have marked morphological changes characterized by an abnormal maturation and necrosis of terminal villi probably due to uteroplacental ischaemia. These changes are likely to influence adversely on placental function by decrease in the transfer and synthetic activity of the trophoblast.

Disclosure: The research work reported in this article was presented as poster at the World FIGO Conference, 2006 Malaysia and its abstract was published in the abstract book of the same.

REFERENCES