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ORIGINAL RESEARCH

The Ultrastructure of Placental Syncytial Knots in Normotensive, Preeclamptic and HELLP Syndrome Patients

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Abstract

Background: *Preeclampsia is one of the main causes of perinatal deaths and disabilities and is a multisystemic disorder that is characterized by maternal hypertension, proteinuria, and increased permeability of blood vessel damage.*
Methods: *In our study, increased syncytial nodes examined at ultrastructural level, and the effect of the increase in syncytial node will be revealed by putting forward the possible changes in the mentioned nodes both in women with preeclampsia and HELLP cases. We used the electron microscope techniques to observe morphological and ultrastructural changes in the placenta and placental deposits. Tissue samples were taken from 10 preeclamptic, 10 pregnant with HELLP and 10 healthy pregnant women from the control group. Through electron microscopy methods, the results of the patients with preeclampsia, control group of pregnant women and patients with HELLP were evaluated.*
Results: *As a result of electron microscopy studies, in placental tissues: in preeclampsia group, while in fetal peripheral sections; we observed cytoplasmic common vacuolisations in syncytiotrophoblasts and dilatation in endoplasmic reticulum cisterns, thinning in capillar endothelial cells and necrotic appearance in syncytiotrophoblasts in contact with capillaries were found to be the dominant view. In this group, reduction in the number of microvilli of syncytiotrophoblasts as well as the connective tissue edema was one of the most remarkable findings. When HELLP maternal peripheral and central cross-sections were analyzed, intracytoplasmic edema and degenerative vacuollar were observed in syncytiotrophoblasts, both structures and villous edema seemed to be obvious. In HELLP fetal peripheral sections, the presence of diffuse cellular debris in intervillous space was the most important result.*
Conclusion: *Compared with the control group, increase was observed in the number of syncytial nodes and histological changes in ultrastructural structure in placentas with preeclampsia and HELLP.*
Keywords: *Preeclampsia, HELLP, Syncytial knot, Ultrastructure.*

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Introduction

Pregnancy is a factor, which causes changes in the entire body of the mother. Hypertension is the most frequent medical problem in pregnancy, which is of the first three reasons for maternal mortality while it ranks first in perinatal mortality (1). Preeclampsia is a systemic disease specific to pregnancy, characterized with vasospasm and secondary organ perfusion decrease. It accompanies many organ involvement and dysfunction: preeclampsia is observed in about 5-8% of all pregnancies and is still one of the leading reasons for maternal and fetal morbidity and mortality (2-3). A severe form of preeclampsia, HELLP syndrome (Hemolysis-Elevated Liver enzymes-Low Platelets), is a condition, observed in about 4-20% of preeclamptic patients, characterized with hemolysis, increased liver enzymes and decrease in thrombocytes, and associated with high maternal and perinatal morbidity and mortality (4-5). It was addressed for the first time in 1954 by Prichard and described in 1982 by Weinstein (6). While it is observed with preeclampsia generally in the third trimester, it can also be seen rarely in earlier weeks of pregnancy or in the postpartum period and without hypertension (4). In patients with HELLP syndrome, such complications as acute respiratory distress syndrome, intracerebral bleeding, acute kidney failure, hepatic rupture, widespread intravascular coagulation and septic shock may develop and a need for intensive care may emerge (7). The most stressed point in preeclampsia is insufficient throphoblastic invasion. In normal placentation, extra villous throphoblasts invade elastic lamina and middle smooth muscle coats of maternal spiral arteries. This is completed until the 20^{th} week of pregnancy. Thus, spiral arterial diameters of the uterus increase, their vasoconstructive abilities diminish and they turn into high flow low resistance veins. These morphologic changes occur to increase perfusion of the placental bed. The syncytial knot on the outer surface of the placental villus in the third trimester is focal aggregation or clustering of the syncytial nucleus. About 10-30% terminal villi is present in the term, which is also available in the immature placenta increasing gradually throughout pregnancy. The syncytial knot is thought to function as an internal support system to protect villous capillaries from sudden shifts in the intervillous area pressure during delivery by creating intervillous bridges (8). It was reported that the number of microvilli on the syncytiotrophoblast surface decreased, some of the areas did not have any microvillus at all and the present microvilli were not healthy, lost their specific shapes and were shorter than normal in preeclampsia (9). The aim of this study is to make a comparison by reviewing syncytial knots in placentas of cases with preeclampsia and HELLP at the level of electron microscope.

Materials and Methods

Placental Samples Collection

The Institutional Ethics Committee of University of Dicle approved the study according to the principles of the Declaration of Helsinki. Placental samples were collected immediately after caesarean (24 elective and 4 emergency) delivery at 38–40 weeks of gestation, after the mothers had provided informed consent. Our exclusion criteria in this study were especially diabetes, intrauterine growth restriction as well as any complication of pregnancy in women and babies. To determine and compare ultrastructural of the syncytial knot electron microscopy levels, women with normal pregnancies and HELLP pregnancies those with pregnancies complicated by preeclampsia placentas were collected from 10 normal pregnant (elective caesarean) and 10 patients with preeclampsia (8 elective and 2 emergency caesarean) and 10 patients with HELLP (8 elective and 2 emergency caesarean).

Diagnostic criteria for preeclampsia in this study were as follows: onset of hypertension with blood pressure of or greater than 140/90 mmHg in formerly normotensive women, along with proteinuria of or more than 3g/24h developing after 20 weeks of gestation.

Diagnostic criteria for HELLP: The diagnosis is established by the presence of preeclampsia and the following criteria:

- Microangiopathic hemolytic anemia with characteristic schistocytes on blood smear
- Platelet count <100,000 cells/μL
- Serum lactate dehydrogenase >600 IU/L or total bilirubin >1.2 mg/dL
- Serum aspartate aminotransferase (AST) >70 IU/

After the whole placentas were carefully and quickly washed in physiologic saline solution, placental tissue samples were obtained from peripheral and central part of both maternal and fetal sides, in total four pieces of tissue obtained from each placenta.

Preparation of placental samples for electron microscopic examination

Placental samples were taken from four different areas (maternal central, maternal peripheral, fetal central, fetal peripheral) from 10 healthy full term placentas in the first group, from 10 patients diagnosed with preeclampsia based on the World Health Organization criteria in the second group and from 10 pregnant women with HELLP in the third group and were started to be monitored to be reviewed in TEM. All tissue samples were fixed in 2.5% glutaraldehyde for 4 hours and postfixation 1% osmium tetroxide were kept in buffer solution for 10 minutes. Semi-thin sections were taken on the slide and stained with toluidine blue. Ultrathin sections were cut into (Leica ultracut R ultramicrotome) and were taken on copper grids. Ultra-thin sections stained and were examined under electron microscope (Carl Zeiss Libra 120) as well as photographed.

This study was conducted by retrospective investigation of the files of 370 patients who have admitted to Dicle University Medical Faculty Emergency Department between January 2010 and September 2014 due to electrical injuries. First intervention to the patients was carried out at the time of presentation by emergency department. All the patients received fluid therapy, monitorization, burn care, analgesia, tetanus prophylaxis, escharotomy and faciotomy depending on the indication and were resuscitated according to the ATLS (Advanced Trauma Life Support) program. Patients in a good condition after the firts 12-hour follow-up were discharged. The other patients were hospitalized in burn unit clinic or intensive care for treatment and follow-up. Patients with missing data and those having lightning strike were excluded from the study.
Data in this study included age, gender, cause of electric shock, type of electric shock, electric voltage, falling down from height, burn degree, total burn surface area (TBSA), length of stay in hospital, organ injuries, Glasgow Coma Score (GCS), serum enzymes (alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), blood creatine kinase (CK), creatine kinase-myocardial band (CK-MB), troponin T), developing complications and cardiac arrhythmias. These parameters were compared in terms of low/high voltage electrical injuries and mortality.

Results

Preeclampsia group

While cytoplasmic diffuse vacuolizations were observed in syncytiotrophoblasts and dilatation in endoplasmic reticulum cisternae, it was also noticed that capillary endothelium cells became thinner, and that necrotic view was prevailing in syncytiotrophoblasts in contact with capillaries. While it visually drew attention that the number of microvilli decreased in syncytiotrophoblasts in this group, degenerations were observed in the cell membrane of the syncytiotrophoblast cell (Figure 1). Similar findings were observed in fetal central sections. In addition to these findings, presence of edema in cyto-syncytiothrophoblast junction in fetal central sections significantly attracted attention (Figure 2).

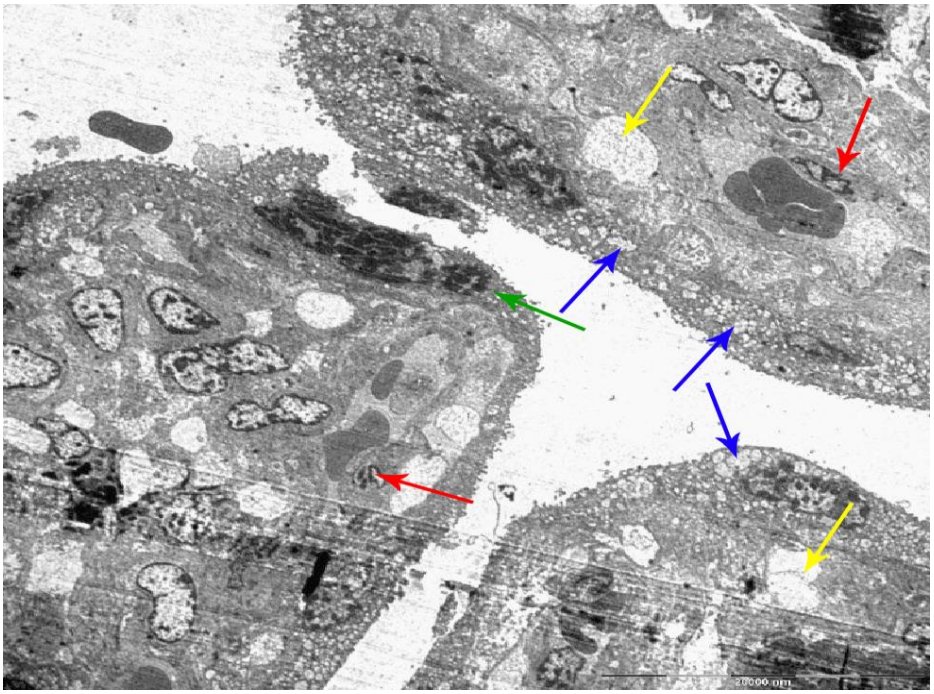

Figure 1. In preeclampsia group fetal peripheral sections, cytoplasmic diffuse vacuolizations, dilatation (blue arrow) in endoplasmic reticulum cisternae, capillary endothelium cells became thinner (red arrow) and necrotic view in syncytiotrophoblasts (green arrow) in contact with capillaries. Note at junction sito-syncytiotrophoblast edema (yellow arrow) (uranyl acetate-lead nitrate, Bar: 20.000 nm).

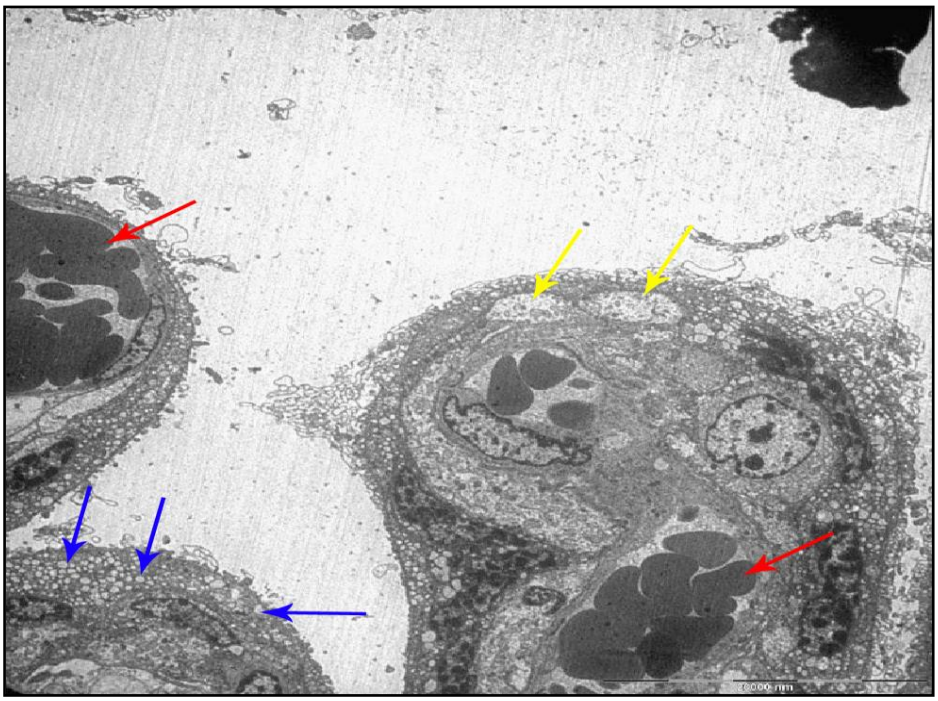

Figure 2. In preeclampsia group fetal central section, intrastoplasmic vacuolizations in syncytiotrophoblasts and dilatation in endoplasmic reticulum cisternae (blue arrows). Note at junction sito-syncytiotrophoblast edema (yellow arrows) and diffuse intravascular coagolation (red arrows), (uranyl acetate-lead citrate, Bar: 20.000 nm).

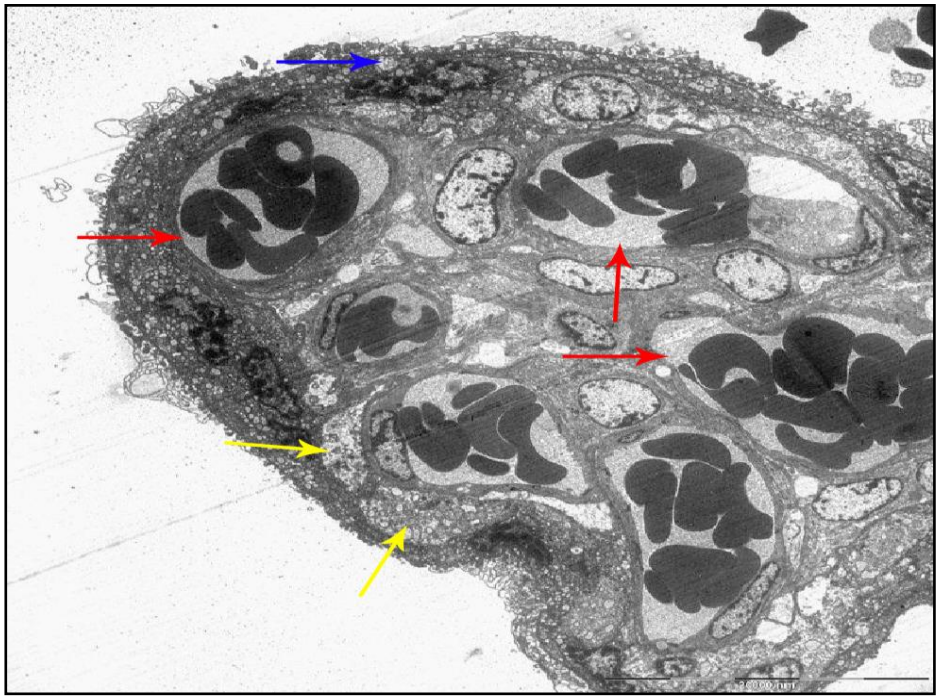

Figure 3. In preeclamptic maternal peripheral section, diffuse intravascular coagulation (red arrows), edema (yellow arrows) in sito-syncytiotrophoblast junction. Note intrasitplasmic vacuolization and dilatation in endoplasmic reticulum cisternae (blue arrows) in syncytiotrophoblasts, (uranyl acetate-lead citrate, Bar: 20.000 nm).

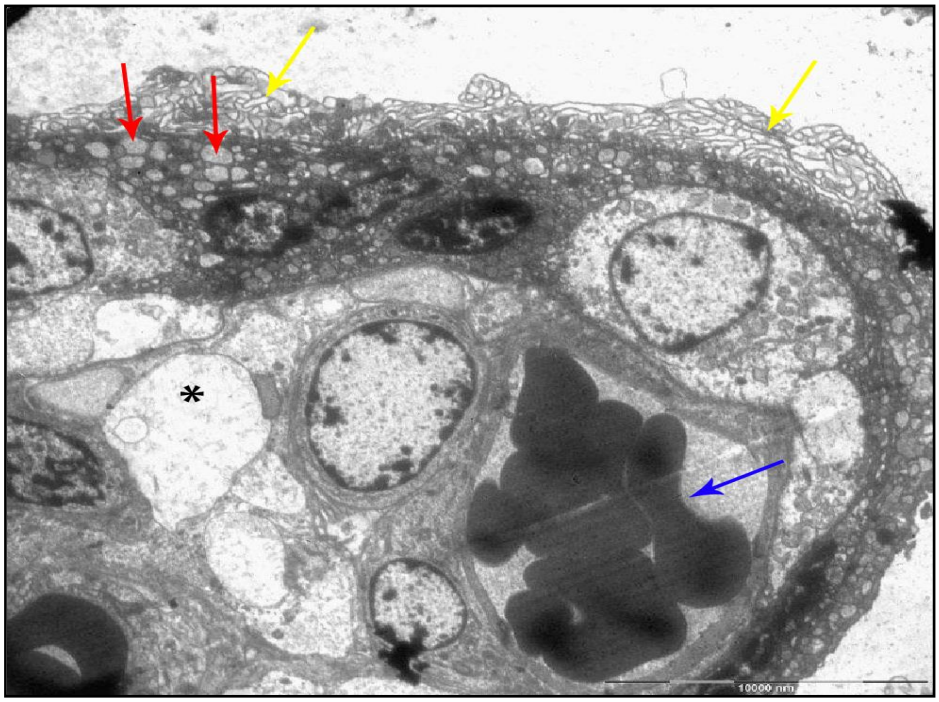

Figure 4. In preeclampsia group maternal central section, a structural view similar to intensively dilated cisternae on the surface of syncytiotrophoblasts, diffuse intrastoplasmic vacuolizations (red arrows) and intravascular coagolation (blue arrow), (uranyl acetate-lead citrate, Bar: 20.000 nm).

In preeclamptic maternal peripheral sections, edema was present in cyto-syncythiothrophoblast junction in addition to intracytoplasmic vacuolization in syncytiotrophoblasts and dilatation in endoplasmic reticulum cisternae. Furthermore, while a significant thinning was observed in capillary endothelium cells in this group, intensive intravascular coagulation was one of the interesting findings (Figure 3). When maternal central sections from the same group were examined, a structural view similar to intensively dilated cisternae was observed on the surface of syncytiotrophoblasts. Cytoplasms of these cells exhibited widespread vacuolizations. Moreover, connective tissue edema was one of the interesting results in this group, and intravascular coagulation was observed in the sections (Figure 4).

HELLP group

In HELLP fetal peripheral sections, presence of intensive cellular debris in intervillous area was the most important finding. While degenerative modifications were observed in surface membranes of syncytiotrophoblasts, the presence of red blood cells was determined in extravascular areas dues to endothelial degeneration besides intravascular coagulation (Figure 5).
While the presence of intravascular coagulation in fetal central sections was similar to peripheral sections, the presence of extravascular red blood cells was not noticed. Furthermore, it was observed in this group that surface membranes of syncytiotrophoblasts were relatively healthier and in a complete structure. However, edema in the subsyncytial area was one of the significant findings (Figure 6).
Considering HELLP maternal peripheral and central sections, while intracytoplasmic edema and degenerative vacuoles were observed in syncytiotrophoblasts in both structures, degenerative findings were determined in cell surface membranes. Moreover, villous edema drew attention significantly (Figure 7). Same findings were observed in HELLP maternal central placenta sections (Figure 8).

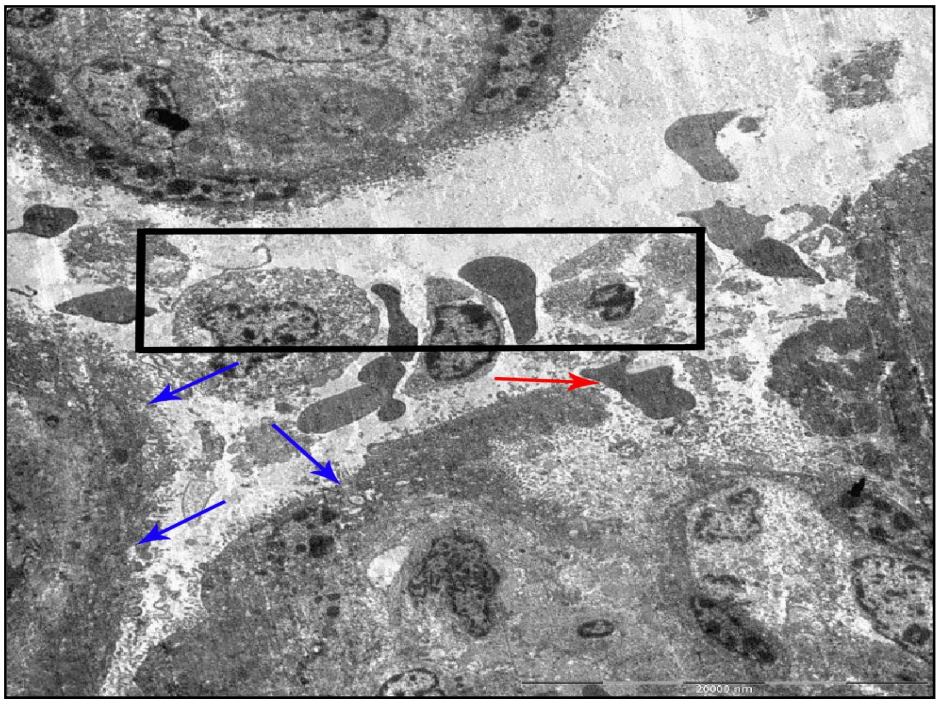

Figure 5. In HELLP fetal peripheral section. Note the presence of intensive cellular debris in intervillous area (□), red blood cells (red arrow) in extravascular areas and degenerative modifications (blue arrow) in surface membranes of syncytiotrophoblasts, (uranyl acetate-lead citrate, Bar: 20.000 nm).

Discussion

Macroscopic and microscopic alterations were observed in the placenta structure in preeclampsia and intrauterine growth retardation. Infarct areas, fibrosis and calcifications were detected in the placenta at macroscopic level (10). At microscopic level, increase in syncytial knots was defined for the first time by Tenney and Parker, syncytial knots having shown an increase in 10-50% of normal terminal villuses and almost all terminal villuses with preeclampsia. It is known that there is a correlation between the frequency of syncytial knots and the severity of preeclampsia (11). Jones et al. (12) reported advanced degenerative modifications such as pyknosis, peripheral chromatin condensation and incorporation of nuclear membranes in ultrastructural analysis of cell nuclei in syncytial knots.
These morphological changes exhibit similarity to findings in apoptosis known as programmed cell death (13). Similar studies drew attention to increase in the number of apoptotic nuclei in trophoblasts of cases with preeclampsia (14-16).

Rath et al. (17) reported that significant trophoblastic basal membrane thickening is connected to pathologic conditions such as preeclampsia.

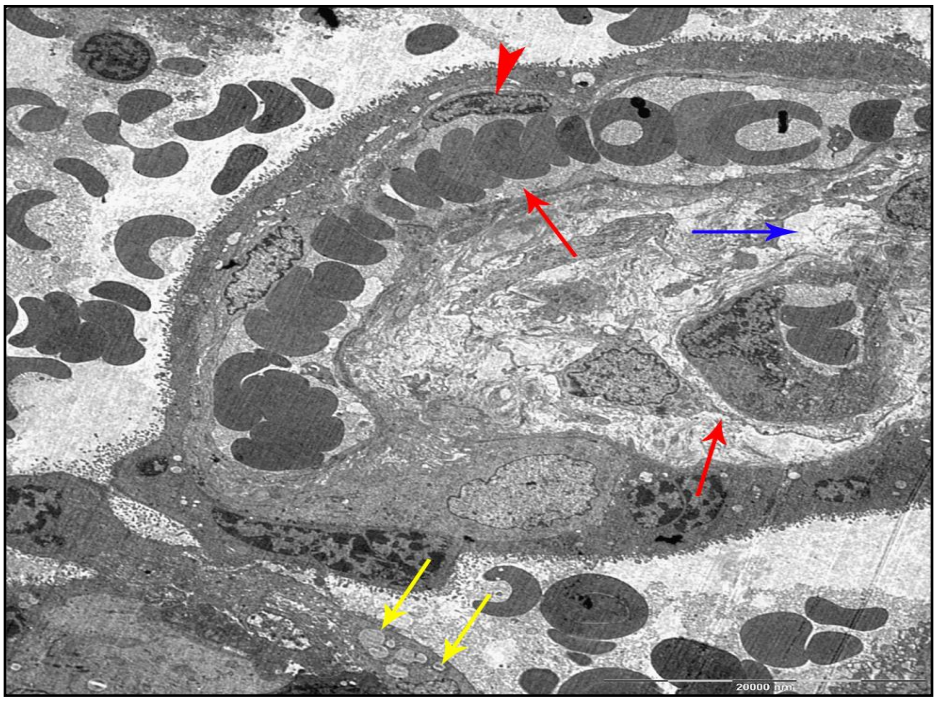

Figure 6. In HELLP fetal central section, intravascular coagulation (red arrow), thinner of capillary endothelium cells (arrowhead), in villous edema (blue arrow) and degenerative vacuoles (yellow arrows), (uranyl acetate-lead nitrate, Bar:20.000 nm).

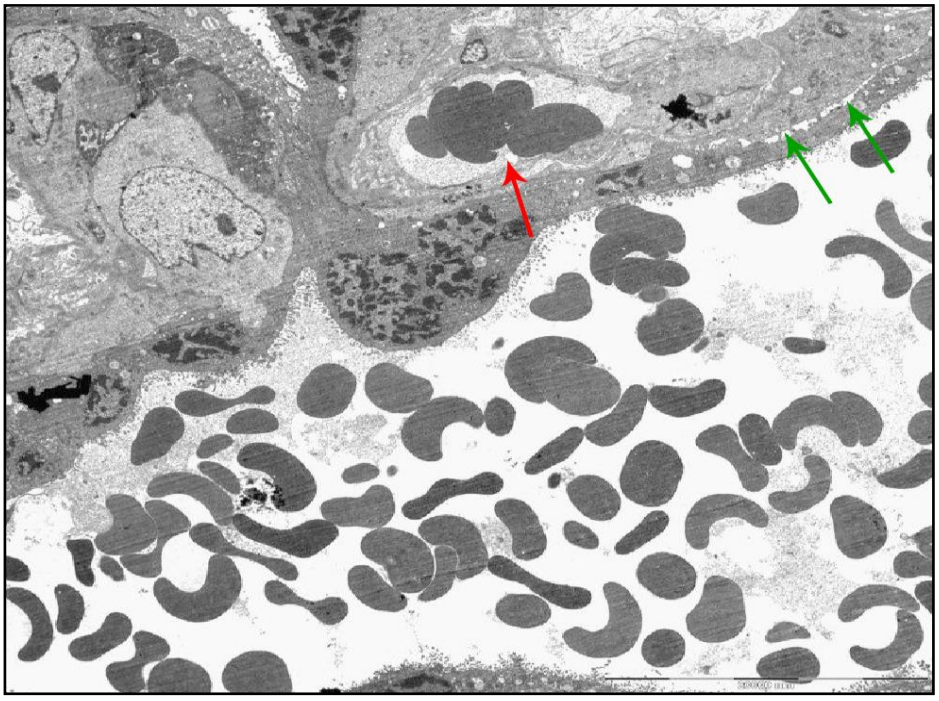

Figure 7. In HELLP maternal peripheral section, intravascular coagulation (red arrow) ,in the subsyncytial area edema (green arrows) and lost microvilli (arrowhead) in cell surface membranes (uranyl acetate-lead nitrate,Bar:20.000 nm).

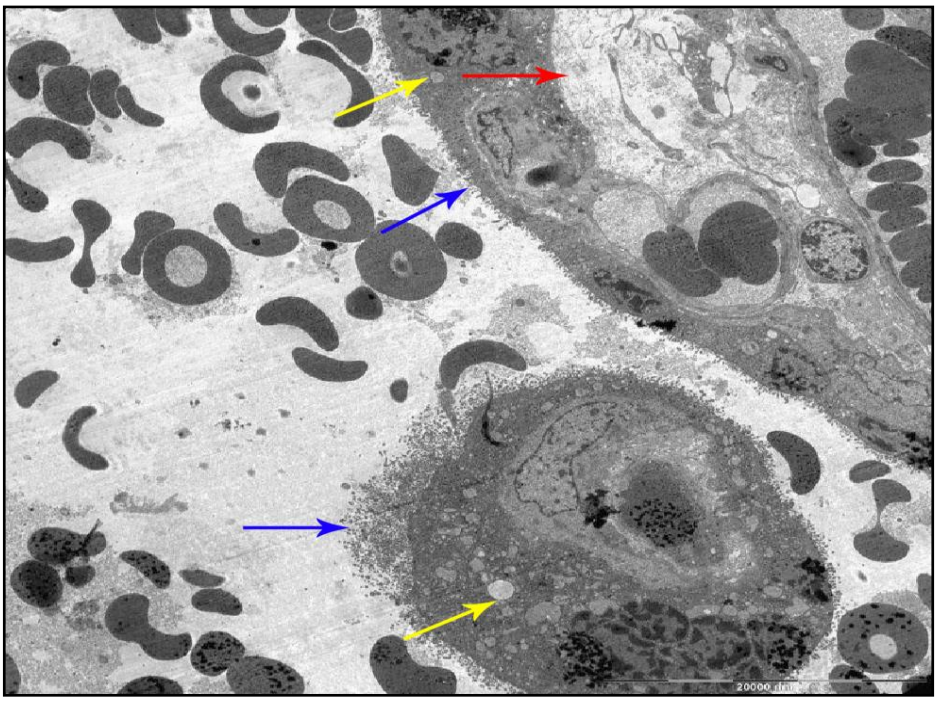

Figure 8. In HELLP maternal central section, in villous edema (red arrow) and degenerative modifications (blue arrows) in cell surface membranes: Intrasitoplasmic edema and degenerative vacuoles (yellow arrows) in the syncytiotrophoblasts are seen, (uranyl acetate-lead nitrate, Bar: 20.000 nm).

Morphologic differences which are associated with these conditions and a gradual increase were observed in preeclampsia and HELLP groups graded according to clinical tables such as hypertension proteinuira observed in preeclampsia. Gradual increase in syncytiotrophoblasts and significant microvilli loss in pregnant women with preeclampsia and HELLP are thought to cause less absorption from maternal blood and thus, insufficient feeding of the fetus. Observation of gradually increasing large vacuoles and decreasing pinocytic vesicles in cystoplasms of syncytiotrophoblast cells in the group with preeclampsia leads us to think that transport character of syncytiotrophoblasts gradually decrease. Frequently observed expansions in GER cisternae and low electron condensed matter accumulation in them are thought to be responsible for creation of highly thickened basal membrane especially in HELLP cases and to create a diminishing effect in placental barrier function in thickened basal membranes.

SER and GER cisternae were reported highly expanded in many syncytiotrophoblast cells in another study in a way to support our findings (18).

Weakness of placental barrier in preeclampsia cases is among significant differences. Undersized delivery of babies of mothers with preeclampsia is related to their insufficient nutrition. Under syncytiotrophoblasts, higher number of cytotrophoblast cells compared to physiologic placental villus entered directly between cell bodies or cell extensions and the placental barrier and created a less functional barrier. Excessive cytotrophoblast proliferation observed in certain chorion villi of HELLP cases, their invasion into the stroma as a common epithelial mass and the views which thus cause accumulation of the stroma in a highly narrow central region make us think about the placental barrier function which has extremely diminished and even vanished completely in these villi. It was thought that certain placental villous stromae with preeclampsia including intensive collagen bundles might be associated with insufficient gas and nutrition exchange between the baby and the mother and this intensive collagen content might locate itself in areas that cause placental barriers and might cause decrease in placental barrier function.Altough collagen tissue is observed very widespread and thin, thus fetus nutrition is easier in healthy placental villuses. It was thought that placental villus collagen

amount might require a more important study. A study suggested that TGF- β3, besides its various roles, is chemoattractant for collagen producing fibroblasts and might induce collagen synthesis, and thus collagen increase might be related to TGF- β3 in the preeclampsia group (19).

We also observed fibroblasts with expanded GER cisternea, which were highly activated in the preeclampsia and the HELLP groups, carry collagen fiber content in the vesicles and secrete them into the interstitial tissue at certain points, in an increasing way in the chorion villus stroma. Therefore, it was emphasized that invasion of the placental bed of the uterus and spiral artery by extrvillous trophoblasts result in loss of arterial muscular elastic membrane and replacement with ,which is necessary for a successful pregnancy (20). Expected physiologic changes were observed in spiral arteries in placental beds with preeclampsia. Trophoblast cells were observed farther outside the spiral artery wall than from inside it, in an increasing way in preeclampsia and HELLP cases. Therefore, it was observed that spiral arteries with preeclampsia had more muscular structure and thicker walls due to trophoblast prevention and replacement with smooth muscles. This decreases blood flow to the placenta (21-24). Changes in endothelium cells induced by maternal blood decline were discussed in electron microscopic studies on placental tissue lesions in preeclampsia (25-26). Dokras et al. (27) pointed out mitochondrial changes in hepatocytes, epidermal and dermal cells, blood leukocytes, smooth muscle cells of the myometrium, interstitial cells of the myometrium and veins of women with preeclampsia.

Similar structural changes, cerebral edema brain ischemia and anoxia were also reported (28). It was reported that utero placental blood flow diminished in severe hypertension preeclampsia cases (29). Histological changes such as decrease in syncytial microvilluses, cytotrophoblast cell proliferation, focal syncytial necrosis, trophoblast basal membrane thickening and fetal capillary contraction were determined in these cases. It was reported that increase in the number of syncytial knots is correlated with the severity of preeclampsia and duration of hypertension in pregnancy (30-31).
Increase in the number of syncytial knots we observed in central placenta areas in cases with preeclampsia in our study makes us think that central area of the placenta is sensitive to hypoxia that may occur in perfusion by maternal veins. Hypoxia was reported to be an important factor for the increase of the number of syncytial knots (30). The number of syncytial knots in placenta sections can increase in maternal anemia, post mature placentas in extended pregnancies of women living at high altitude, placental malaria infection, placentas of women with antiphospholipid syndrome and some preterm deliveries, apart from preeclampsia (32).

More intensive perivillous and intervillous fibrin accumulation was observed in placenta sections in preeclampsia cases compared to control cases in this study. Diffuse increase in perivillous fibrin amount is thought to be related with perfusion problems in chorionic villuses. This increased fibrin amount might be associated with intrauterine growth retardation observed in preeclampsia cases (33).
Thickenings were observed in the trophoblast basal membrane in preeclampsia cases in our study. The placental membrane (placenta barrier), which allows transfer of nutrients, carbon dioxide, oxygen and other metabolic substances and acts as an immunologic barrier between the mother and the fetus is comprised of trophoblast cells, trophoblast and villous capillary endothelium basal membrane and terminal villus capillary endothelium cells. These vasculosyncytial membranes gradually get thinner as pregnancy progresses and reach a thickness less than 2μm at term. This thickness is a little more than the pulmonary alveolar blood-air barrier. Brunori et al. (33) reported in their electron microscope study that variations are available at different degrees in thickness of the trophoblast basal membrane at preeclampsia. Battistelli et al. (34) detected thickness in the cyncytiorophoblast basal membrane in intrauterine growth retardancy in their electron microscope study issued in 2004. There was intrauterine growth retardation at the preeclampsia case in which thickening was detected in the basal

membrane presented in this study. Thickening is observed in the trophoblast basal membrane in maternal diabetes and intrauterine growth retardation cases in which end diastolic umbilical blood flow stops, apart from preeclampsia. Building blocks of basal membranes are synthesized, emitted and demolished when expired by villous trophoblasts and endothelium cells; therefore, the reason for thickening in basal membranes observed in preeclampsia is thought to depend on an imbalance between the endothelium and trophoblasts metabolism (32). In conclusion, In comparison of the preeclampsia and the HELLP group placentas with the control group placentas at light microscope and electron microscope level, following changes were observed: relative increase in the number of syncytial knots and trophoblast basal membrane thickness in the preeclampsia group placentas, common vacuolizations in syncytiotrophoblast cytoplasms and dilatation in endoplasmic reticulum cisternae in the preeclampsia and HELLP groups, decrease in microvilli in syncytiotrophoblasts. The above declared electron microscopic histological changes were observed more significantly in the HELLP group than the preeclampsia group.

Conflicts of interest

There is no conflict of interest

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