

The features of placental angiogenesis in early preeclampsia

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Key words: early preeclampsia, placenta, histomorphometria, thrombosis, microcirculation, angiomatosis.

Preeclampsia (PE) - is a disorder in pregnancy, that occurs after 20 weeks of gestation, characterized by blood pressure increase and proteinuria, there are also disorders in vascular, nervous, endocrine and immune systems, hemostasis, renal failure, abnormal liver function, dysfunction of placenta and brain. PE is a reason of high maternity and perinatal morbidity and mortality. Annually from 50,000 to 60,000 women die from preeclampsia worldwide, perinatal mortality vary from 10 to 30 ‰. Also preeclampsia is the reason of a number of complications after the pregnancy in cardiovascular system of child and mother [1, 2].

Nowadays there is no certain opinion about pathogenesis of PE. According to one theory, the trigger of early preeclampsia (develops before 34 weeks) is gestational endotheliopathy, which leads to disorders in spiral arteries remodeling, incomplete invasion of trophoblast into spiral arteries' space, space constriction with undergoing violation of placental perfusion. It develops in hypoxia, which is the reason of secondary endothelial dysfunction and destructive changes in utero-placental system [1,3]. Although substantial heterogeneity, which is observed, cannot be explained only by placental theory. According to this we critically analyze clinical (risk factors, placental bloodstream, biomarkers) and pathological (genetic, molecular, histological) correlates for PE. We should analyze all the evidence, including both placenta and cardiovascular system in early and late (develops after 34 weeks of pregnancy) PE, which show us some main distinctions between this two different signs of the disease [4]. That's why we need to compare morphological specialties of bloodstream in women with early and late preeclampsia more specifically, to find out all pathological criteria.

Purpose: investigation of histomorphometric features in placental bloodstream in women with early preeclampsia.

MATERIALS AND METHODS

To find out morphological changes in bloodstream 20 placenta were taken for histo-

logical examination in women in normal deliveries (reference group) and 20 from women with early preeclampsia - main group, to analyze all the changes between normal and structurally changed within preeclampsia, placenta. Delivery term in both groups was 39 weeks, average from 37 to 41 week.

Pathomorphological investigation was hold in early terms after postpartum, according to the standard technique. Placenta pieces were cut out from the central, paracentral, marginal area, through all thickness of placenta in quantity of 8, sizes 1,0x0,5x0,5 cm., 2 pieces were cut from umbilical cord - 2 cm from the place it's attached to placenta, and on the opposite side.

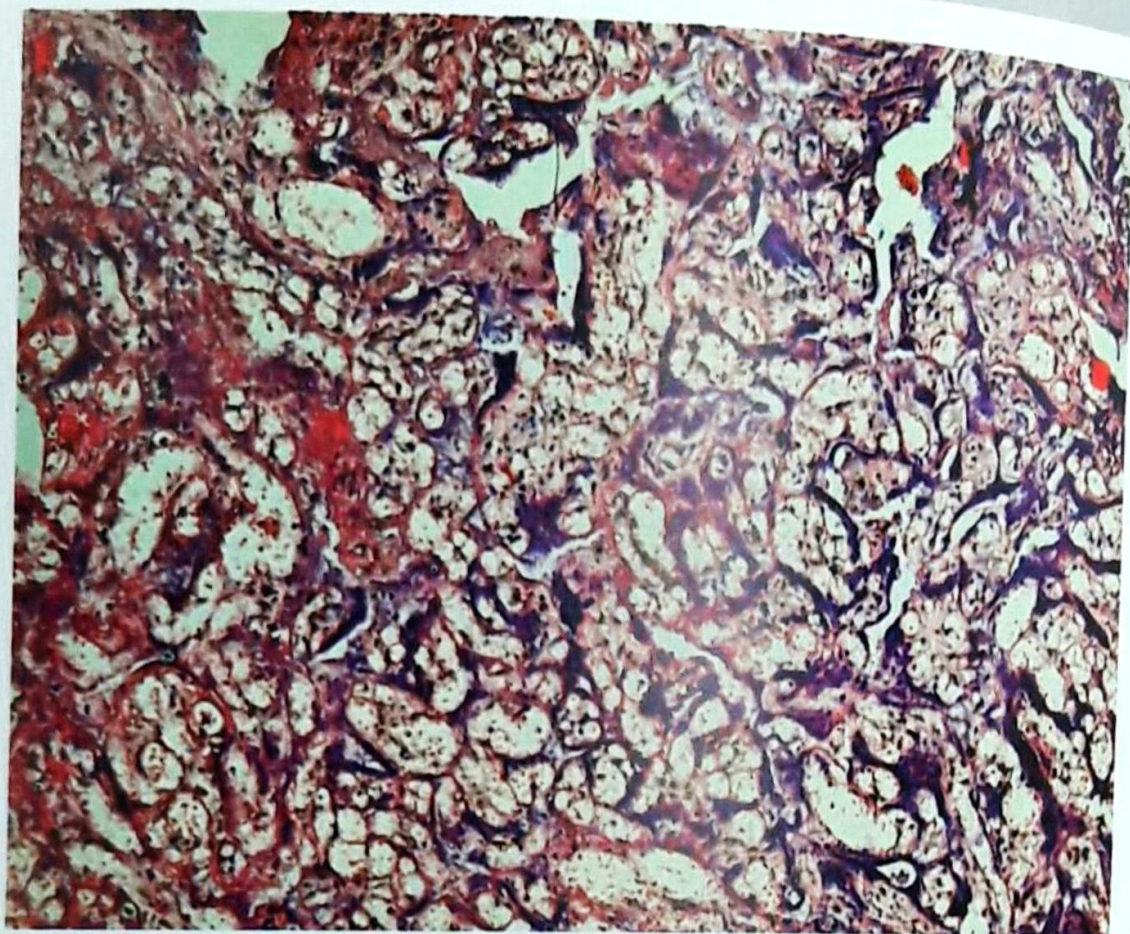
Taken materials were fixed with 10 % neutral formalin solution, not less the 48 hours, then it was washed, and dehydrated in the system of polyhydric alcohols, embedded in paraffin blocks according to standard technique. Half slices, with the thickness of 5-7mkm, were colored with hematoxylin and eosin and according to van Gison technique, followed by light microscopy of histological preparations, with the help of OLIMPUS BX41, with increasing in 100, 200 and 400 times. Determination of morphometric characteristics of bloodstream were conducted with the help of scanning reticle, with 49 squares, each area is $3,45 \times 10^{-4} \text{ mm}^2$ with an increase in 269,2 times, in program «Image Tools 3, 6».

During studying the bloodstream determined outer diameter of arterioles and venules in stem villas of I, II and III order, their inner diameter, wall thickness in arterioles of I, II and III order, elongation factor (the ratio of the larger diameter of the lumen to smaller, which shows vessels' ability to stretch) and vascular obliteration coefficient (the ratio of wall thickness to its lumen).

Evaluation of the statistical probability of the difference of the indicators was performed in Microsoft Excel. For further data processing we used such statistical methods, as average values, quadratic error, Students t-test.

RESULTS OF INVESTIGATION

Figure 1.
Placenta of a woman with severe preeclampsia, delivery on term. X 200. Hematoxylin eosin staining. Extensive focus of dead necrotic villies, surrounded by fibrinoid, angiomas.



According to our morphological investigation, was found domination of round and oval shaped placenta in reference group. The average weight of placenta in the group was 472,45+34,18 g, maternal surface area was 268,72+16,24 cm², volume 433,38+11,3 cm³, the average fetal-placental ratio (FPR) was 0,14+0,04. There were no pathological changes on the fetal surface (roller, circle, focal seals, hematoma etc.). The umbilical cord attachment was mainly central or paracentral. There was no marginal or membranes attachment of the cord during examination of maternal surface cotyledons clearly defined, with no pathological changes (strokes, cysts, calcinates, hematoma). The average length of umbilical cords from the reference group was 53,36+5,18 cm, same thickness all over, with no evident edema, without knots, vein dilation and signs of vascular thrombosis.

According to morphological investigations of placenta in reference group with early PE, round and oval shaped placenta also dominated, but irregular oblong shaped, three-cornered, placenta with extra part were presented. The average weight of placenta in this group was 312,35+34,18 g, maternal surface area was 172,26+13,18 cm², volume 289,78+ 8,4 cm³, the average FPR was 0,1+0,02. Analysis of organometric indicators showed that hypoplasia was found in 46,24 % of cases. Some of them had a roller of different width, other had circles, focal seals,

located in the marginal area, paracentral, and in the central area of fetal surface. Some placenta had hematomas of different sizes and prescription, vein dilation. Unlike in reference group umbilical cord attachment was mostly marginal or membranes. Almost in half of cases took place hyper-tortuosity of the umbilical cord with varicose veins (43,15%), in some cases vessels were located at the edges of the umbilical cord and fell easily. Lateral section had not a round but elongated shape; vessels are not in a shape of a triangle, but in one row and have elongated shape (not round).

While examining maternal surface: it was whole or with defects, with poorly contoured cotyledon, with blood clots of different prescription (signs of partial premature placental abruption); hemorrhagic and ischemic strokes of different location and quantity, numerous calcinates in the decidual plate in the thickness of the placental tissue. There also were cysts, filled with blood.

According to histological investigation of placenta in women with early preeclampsia of different severity, almost all cases (89,25%) had disorders of maternal and fetal bloodstream, in form of acute and chronic hemorrhagic (26,16%), and ischemic (38,18%) strokes, diffuse hemorrhage in the intervillous space (19,12%). Presence of old small hematomas at the edge of the placenta, could be a sign of partial premature pla-

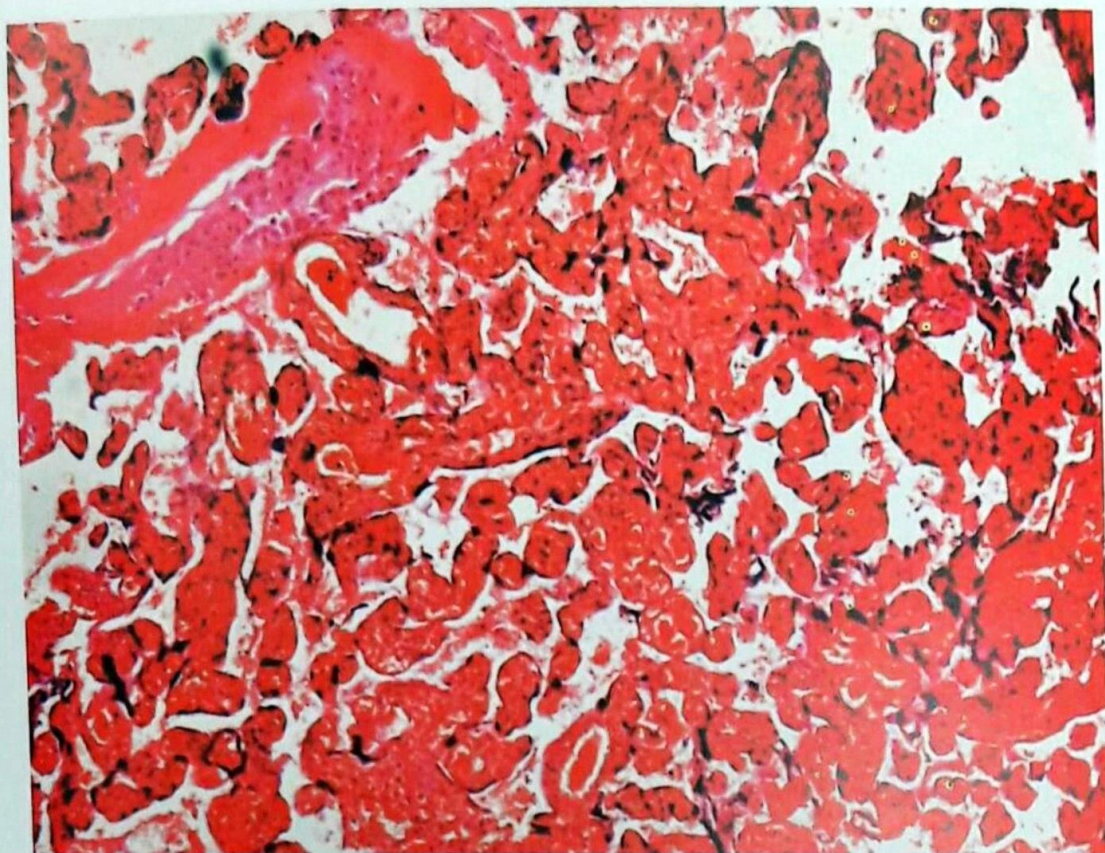


Figure 2. Placenta of a woman with severe preeclampsia, delivery on term. X 100. Hematoxylin eosin staining. Hemorrhagic necrosis of terminal villies, due to congestive plethora and vascular thrombosis. Focal intervillous space collapse.

central abruption (11,26 %). In some cases (7,34%) intervillous thrombosis was determined mainly in the central zones of placenta. Significant deposition of fibrinoid and fibrin particles was noted in the intervillous space and basal plate (Fig. 3), in necrosis areas of villies epithelium (42,14%), with the formation of extended areas of fibrinoid necrosis (Fig. 1). Due to efficient degenerative changes caused by significant disorders in the utero-placental circulation, placenta developed compensatory adaptive mechanisms on the form of focal hyperplasia of terminal villies (Fig. 2) with their budding (14,38 %), focal compensatory angiomasosis (capillary hyperplasia) (Fig. 4) of terminal villies (11,24%), comparing to the reference group compensatory mechanisms expressed not enough (Fig. 5, 6).

Significant changes in vessels of microcirculation were diagnosed in preeclampsia, such as a number of effective vessel crossings were twice lower in PE, then in normal placenta. The weight of avascular villies was in three times bigger in the case of preeclampsia. The general amount of vascular villies in reference group was four times bigger comparing to the main group. In preeclampsia the weight of sclerotic villies and vessels in villies was three bigger then in physiological pregnancy. Significantly increased (in four times) number of fibrinoid altered villies in cases of PE.

Second order villies area significantly de-

creased in PE. Reduction of arterial clearance, decrease in the relative coefficient that shows the weight of the arterial clearance to the total area of the villies, progressed with the development of the pathological process (preeclampsia).

Arteriolospasm with decreasing internal diameter and wall thickening was detected in early preeclampsia moderate severity and progressed under burdened process (the largest values in severe preeclampsia). Pathological vascular remodeling in early medium and severe preeclampsia resulted in a gradual decrease in the elongation factor, at the same time the form of vessels became more and more concentric. Also increased the obliteration of the lumen of arterioles, almost to the complete overlap of the vessel and cessation of blood flow. The lumen of arterioles with a concentric thickening of the vascular wall is significantly narrowed in PE, promotes an increase in vascular resistance in the I and II order stem villies and more and more deepens hypoxia, with the further development of the sclerotic processes in the vascular system of placenta, villies stroma. In severe preeclampsia the shape of arterioles was strictly round (elongation factor is around 1,0). This may indicate a concentric type of remodeling with reduced stretching ability of arterioles.

Vein dilatation with congestive plethora in the stem villies together with the increase in external and internal diameter was noted in early



Figure 3.

Placenta of a woman with severe preeclampsia, delivery on term. X 100. Van Gieson's stain. 1 order stem villies with significant stroma and vascular sclerosis, painted in pink-red. Terminal villies with no signs of sclerosis, with mild compensatory changes, painted in green-brown.

moderate preeclampsia, and progressed with the development of pathological process, reaching the highest values in severe preeclampsia. The values of the elongation factor also increased. At the same time the glimpses of the venules were severely deformed and gained weird shapes.

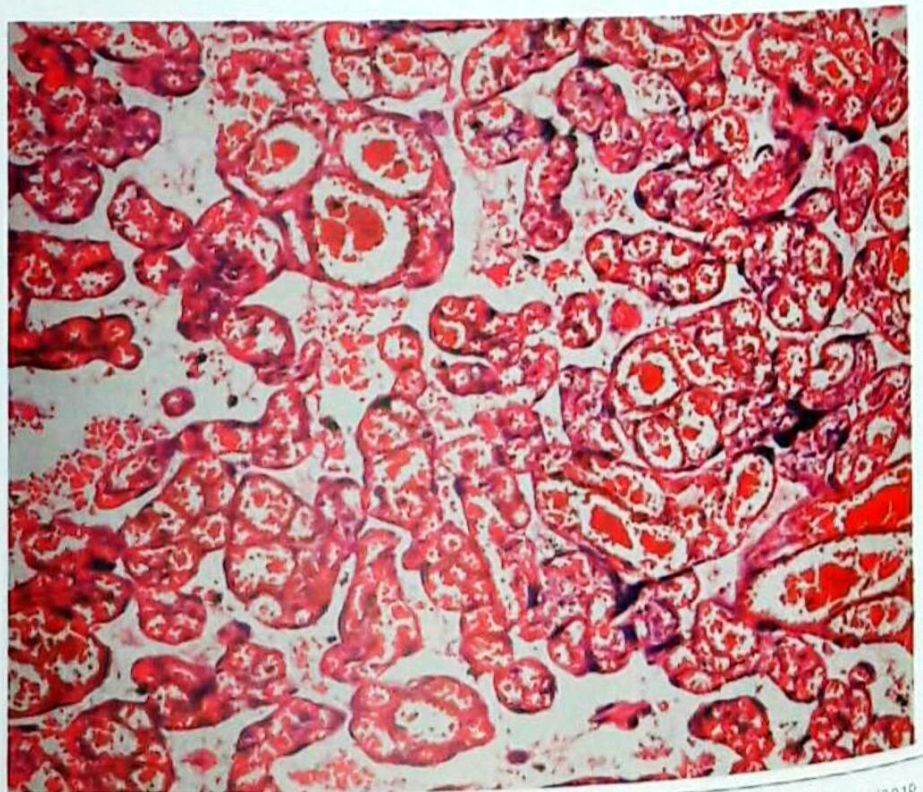
Thus observed disorders in utero-placental bloodstream in placenta in early preeclampsia, in the form of hemorrhagic strokes, focal thrombosis, the formation of extended zones of fibrinoid necrosis and stasis in the intervillous space. Stem villies area significantly decreased in early preeclampsia, comparing to the reference group. The pathological changes described above increased the obliteration of the lumen of arterioles, almost to the complete overlap of the vessel and cessation of blood flow.

PROSPECTS

It is advisable to conduct a comparative study between morpho- and histometric indicators, pathognomonic changes in placenta after early and late preeclampsia. The study will help to develop a personalized algorithm for managing

Figure 4.

Normal placenta, delivery on term. X 200. Hematoxylin eosin staining. Compensatory angiomas of intermediate and terminal villies with full blood vessels in mature placenta.



pregnant women and delivery according to the type of preeclampsia.

CONCLUSION

1. Dystrophic changes with stromal sclerosis of the villies and fibrinoid deposition in stroma of villies and the intervillous space, together with focal fibrinoid necrosis, are common for early preeclampsia.
2. Low levels of surface area and volume of villies are observed in early preeclampsia, as well as the degree of vascularization.

Conflict of interest: None declared.

Ethical approval: The study was approved by the Ethics Committee of the Vinnytsya Pirogov Memorial National Medical University.

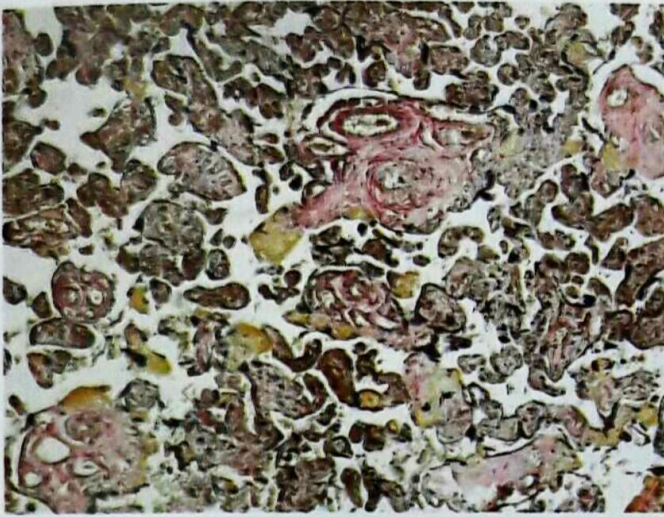


Figure 5. Normal placenta, delivery on term. X 100. Van Gieson's stain. II order stem villies with stroma and vascular sclerosis, painted in pink-red. Terminal villies with no signs of sclerosis, painted in green-brown.

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Erkən preeklampsiya zamanı plasentar angiogenezin xüsusiyyətləri

XÜLASƏ

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Açar sözlər: erkən preeklampsiya, plasenta, histomorfometriya, tromboz, mikrosirkulyasiya, angiomatoz.

Preeklampsiya hamiləlik vaxtı ölümə səbəb olan faktorlar arasında üçüncü yeri, perinatal ölüm faktorları arasında ikinci yeri tutur: hamiləlik və doğuş vaxtı ölüm 15-25% (Ukraynada 12-17%) təşkil edir.

Tədqiqatın məqsədi erkən preeklampsiya olan qadınlarda plasentar qan dövrünün histomorfometrik xüsusiyyətlərinin öyrənilməsi olmuşdur. Erkən preeklampsiya zamanı biz plasentada stromanın sklerozu ilə distrofik dəyişikliklər, toxumaarası sahədə fibrinoidin çökməsi, irifokuslu fibrinoid nekroz, toxumaarası tromboz, angiomatoz, damar divarının diametrinin azalması və qalınlaşması ilə gedən arteriospazm müəyyən etmişik.

Особенности плацентарного ангиогенеза в ранней преэклампсии

РЕЗЮМЕ

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Ключевые слова: ранняя преэклампсия, плацента, гистоморфометрия, тромбоз, микроциркуляция, ангиоматоз.

Преэклампсия занимает третье место среди всех причин смертности во время беременности и второе место в перинатальной смертности: смертность по беременности и родам составляет 15-25% (в Украине - 12-17%).

Цель: исследование гистоморфометрических особенностей плацентарного кровотока у женщин с ранней преэклампсией. В женской плаценте с ранним ПЭ мы обнаружили дистрофические изменения вместе со склерозом стромы и осадением фибриноидов в кучевой строме и межпространственном пространстве, в том числе с крупнофокусным фибриноидным некрозом; межпространственный тромбоз, свайный ангиоматоз; артериоспазм вместе с уменьшением диаметра и увеличением толщины сосудистой стенки.