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Abnormal spiral artery remodelling in the decidual segments during gestational endotheliopathy

Abstract: Objectives: In early human pregnancy placental trophoblasts migrate along uterine spiral arteries (SAs) and remodel these vessels into wide-bore conduits in a process essential for successful pregnancy. This work examined the consequences of the preclinical and manifest forms of gestational endotheliopathy (GE) on the adequacy conversion of the SAs and the main characteristics of the trophoblast migration.

Study design: 58 specimens of the placental tissues were obtained at 6–9 weeks of physiological pregnancy and pregnancy with gestational endotheliopathy. There were investigated histometrical and morphometrical parameters that were reflected the processes of optimal transformation of SAs during the first trimester.

Results: It was found that pregnancy with gestational endotheliopathy was accompanied by the significant decrease of the values of perimeter, cross-sectional area, and lumen in the SAs. In addition, we obtained reduction of intensity of th e vascular invasion internally cytotrophoblast and depression of the interstitial trophoblast invasion in GE, also.

Conclusion: Abnormal transformations of the SAs was more common in specimens of the placental tissues from women with GE.

Keywords: gestational endotheliopathy, spiral arteries, trophoblast migration, perinatal pathology.

Introduction

At the onset of pregnancy major physiological changes need to occur in the vasculature of the uterine wall in order to establish a functional interface between the maternal and fetal circulations. Early in pregnancy, extravillous cytotrophoblast

cells invade the decidualized uterine endometrium and the inner third of the myometrium[1]. They migrate along the maternal spiral arteries (endovascular invasion), replace the endothelium and musculoelastic tissues, and transform the arteries into large low resistance vessels that are no longer responsive to vasomotor influences. Modification of the spiral arteries with the loss of the muscular vascular wall, invaded by the trophoblasts, represents the goal of the physiological vascular adaptation during human implantation. Inadequate remodeling and cytotrophoblast invasion of the spiral arteries are believed to promote the abnormal placental development seen in the future perinatal pathology[2].

In the first trimester (14 weeks) of pregnancy specialized placental cells termed trophoblasts grow out from the placental chorionic villi and invade into the decidua and its blood vessels [the spiral arteries (SAs)] as far as the myometrial segments. These events are essential for pregnancy, and their importance is exemplified when they are insufficient, resulting in complications such as the hypertensive disorder preeclampsia and perinatal loss. For approximately the first 10–12 weeks of gestation trophoblasts form plugs that occlude the SAs, allowing only the maternal plasma filtrate to pass through, resulting in a high resistive index and decreased flow rate before 10–12 weeks of gestation[3]. Furthermore, as the process of SAs remodelling during this time involves the dedifferentiation or removal of the smooth muscle layer surrounding the SAs, these arteries also lose the ability to dilate or constrict in order to regulate their shear stress. The trophoblast plugs dissipate between 10 and 12 weeks of gestation, allowing maternal blood to flow freely to the placenta, lowering the resistance and increasing the flow rate in the unplugged arteries. Trophoblast migration down the SAs is dependent on trophoblast–endothelial cells interactions. However, the mechanisms by which trophoblast migration is regulated remain unclear. It is often assumed that trophoblasts migrate down the SAs retrograde to flow, but aside from the presence of trophoblasts in the arteries, little direct evidence exists to support this claim. The occlusion of the SAs by trophoblast plugs in the first trimester means that blood flow through these vessels is likely to be very slow during this time, and our previous work has shown that this may create an environment favourable for the remodelling of the SAs[4]. As a central

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[1] Dunk C, Huppertz B, Kingdom J: Development of the placenta and its circulation. Edited by Rodeck CH, Whittle MJ. London, Churchill Livingstone Elsevier. – 2009. – P. 69–96.

[2] A novel in vitro model of trophoblast-mediated decidual blood vessel remodeling/C. Dunk, L. Petkovic, D. Baczyk, et al.//Lab Invest. – 2003. – Vol.83. – P.1821–1828.

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player in clinically significant allograft rejection, coagulation, not surprisingly, has been also implicated in the pathogenesis of obstetric compromise, including endotheliopathy related fetal death, and preeclampsia. Failed re-growth of the maternal endothelium over the converted uteroplacental vascular wall of fibrinoid material and embedded trophoblasts, and protracted exposure of the maternal vascular wall to the maternal circulation, has been identified in preeclampsia. Therefore, in this study we aimed to investigate the histometrical parameters of the spiral arteries in the first trimester of pregnancy (in physiological pregnancy and with gestational endotheliopathy), which allows to assess the adequacy of gestational transformation of the spiral arteries.

Materials and Methods

Placentae and decidua parietalis (without prior invasion) were obtained, following written informed consent from patients undergoing first trimester elective terminations at the Vinnytsya maternity hospital № 1, between 2012–2013. This investigation and collections of human tissues conformed with the principles outlined in the Declaration of Helsinki, and was approved by the Vinnytsya National Medical University Local Research Ethical Committee.

The tissue was collected at 6 to 9 weeks (n=58). The specimens were established by placement of placental villi on the apical epithelial surface of patient-matched decidual explants. The specimens of placental tissue were fixed in 10% of buffered formalin solution. After posting, the specimens were embedded in paraffin. Paraffin sections of 3 mm thickness were stained with hematoxylin and eosin. After microscopy investigation were selected histological specimens and components with uteroplacental area and spiral arteries, when we were determined hystometrical parameters (perimeter and cross-sectional area) of the spiral arteries. We were expected to average the value of perimeter and cross-sectional area of the spiral arteries with the most marked gestational changes[1].

We enrolled pregnant women with gestational endotheliopathy (GE), that were diagnosed when microalbuminuria was more than 5,0 mg/mmol (screening test), and endothelium-dependent vasodilation was less than 10% (approving test)[2]. All the women had singleton pregnancies.

The specimens from pregnant women were distributed in three groups. The control group — specimens from women with physiological gestation (n = 22); the second group — pregnant women with GE, but without clinical manifestation (n =

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17); the third group — pregnant women with clinical manifestation of the gestational endotheliopathy (n = 19).

Statistical analysis was done on the basis of a standard STATISTICA package. Continuous variables, presented as means ± standard deviation (SD), as well as confidence intervals (95%, CI), were tested for normality and frequency distribution and were compared using the Student's t-test. The powers of the tests were estimated and $p<0,05$ was considered statistically significant.

Results

The placental bed is a highly dynamic vascular environment that in many ways is anatomically and functionally unique. Anatomically, the vasculature and supporting stroma were invaded by semi-allogeneic trophoblast epithelium, and vascular endothelium media and elastica were divested and replaced by fibrinoid. Functionally, the rate of uteroplacental blood flow increases manifold, even during the potentially vulnerable periods of extensive vascular remodeling. Any pathophysiologic impairment of the normal maternal vascular changes of pregnancy can result in abnormal hemodynamic supply of pregnancy.

When the study of the histometrical parameters in the decidual segment of the SAs has been found that among women with preclinical form of GE, the above parameters were statistically significantly lower ($p < 0,05$), than similar indicators that we were calculated among pregnant women with physiological pregnancy. The digital values of perimeter and cross-sectional area (CSA) in the SAs, among the pregnant women with preclinical form of gestational endotheliopathy were 0,57 ± 0,08 mm and 0,026 ± 0,007 mm^2, whereas during pregnancy without pathology parameters perimeter and CSA in spiral arteries were 0,90 ± 0,12 mm and 0,067 ± 0,01 mm^2 respectively.

We would like to note that histometrical indicators which have been calculated among pregnant women with clinical manifestation of GE had a statistically significant reduction (0,33 ± 0,05 mm (perimeter SAs) and 0,009 ± 0,002 mm^2 (CSA)) not only for specimens from women with physiological gestational process ($p < 0,05$), but also in comparison among pregnant patients with preclinical endothelial dysfunction ($p < 0,05$).

Furthermore, for physiological pregnancy, the lumen of SA in 73,0% had a strong expansion, while in the specimens that were obtained from pregnant women with preclinical GE, the preferences were for moderate expansion of the lumen of SAs — 71.0%. In the specimens of preparations from the pregnant women with the clinical manifestation of GE, the lumen of SAs was moderately advanced in 46,1% and not extended or expanded a little 53,9%.

Moreover, for physiological pregnancy, there were obtained the maximum values of intensity of the vascular invasion internally cytotrophoblast (VIICT) (83,15%). On the other hand for gestational endotheliopathy, in the majority of cases, only single

cells VIICT were found in the lumen of spiral arteries 69,6% and 55,8%, respectively, for pregnant women with pre-clinical and clinically manifest forms of GE.

Also, was noteworthy, that in specimens from pregnant women with physiological gestation, most of the indicators were found to the state when a moderate amount of cells were determined as for interstitial trophoblast cells (TIC), and as for stromal cells — 60,7%. However, incidences when the number of cells TIC prevailed over cells of stroma were not rare — 30,3%. In the histological preparations of pregnant women with manifest form of the GE, there were observed similar dynamics — 51,9% and 40,4%. In the specimens of SAs, that were obtained from women with preclinical form GE, the intencivity of interstitial cytotrophoblast invasion was decreased slightly, there was a relative balance between cases where we found the prevalence of TIC elements 56,5% and an equal ratio between TIC cells and stromal cells of 43,5%. These changes were associated with both the lag of physiological replacement of the musculo-elastic fibers of the arterial wall by the fibrinoid, and the preservation of the relative prevalence cells of the cytotrophoblast compared by the stromal cellular elements.

In summary, it was found that pregnancy with gestational endotheliopathy was accompanied by the significant decrease of the values of perimeter, cross-sectional area, and lumen in the SAs. In addition, we obtained reduction of intensity of th e vascular invasion internally cytotrophoblast and depression of the interstitial trophoblast invasion during GE.

Study of the normal physiological process of human decidual spiral artery transformation is critical to identify causative factors of impaired vascular remodeling and reduced utero-placental perfusion associated with gestational endotheliopathy. These results extend our understanding of the temporal sequence of events and mechanisms of remodeling, strongly supporting an integral role of the abnormal decidual vascular transformation in genesis of perinatal pathology.

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Myasthenia. Primary diagnosis. Complicacy in diagnostics

Myasthenia gravis is an autoimmune disease, characterized by muscle asthenia and pathologic fatigability, as a result of the neuromuscular conduction disturbances[1]. Recently, the morbidity of myasthenia increases, the popularity is 5–10 persons per hundred thousands[2].

T-lymphocyte sensitizing and the high-affine anti-acetylcholine receptors antibodies production play the main role in pathogenesis of myasthenia. Also, thymus is of great importance in immunopathogenesis. In a half of cases anti- acetylcholine receptors antibodies are absent, but anti-muscle kinase antibodies are revealed. This is

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