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Original article

Analysis of CD31 expression and vascular parameters in human placentas from pregnant women with intrauterine growth restriction

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Summary

Introduction. Placental dysfunction is underlying cause in most of the intrauterine growth restriction and the pregnancy complications where the fetus does not achieve its genetically determined potential for growth. The critical process for the development of the placenta is angiogenesis. CD31 is an important endothelial adhesion protein that enables angiogenesis. The study aimed to analyze the CD31 expression and vascular parameters in normal placentas and IUGR placentas.

Methods. Thirty placental samples, fifteen IUGR placentas, and fifteen term normal placental samples were analyzed. The hematoxylin-eosin method and immunohistochemical method with anti CD31 antibody were used for the staining of the tissue sections. The analyzed vascular parameters were: capillary number density (CND), capillary area density (CAD), and capillary surface density (CSD).

Results. Between normal placentas and IUGR placentas there was no determined difference in CD31 expression. Positive intensive staining of CD31 was found in the endothelium of all blood vessels and no staining was observed in cytotrophoblast and syncytiotrophoblast cells. In IUGR placentas, CND of 2.55 capillary/1000 μm2 villous area was significantly decreased compared to normal placentas of 3.49 capillary/1000 μm2 villous area. CAD in IUGR placentas of 30.49 % was significantly decreased compared to normal placentas of 52.80 % villous area. CSD in IUGR placentas (92.81 μm/1000μm2) was significantly reduced compared to CSD in normal placentas (145.51 μm/1000μm2).

Conclusion. The localization and intensity of CD31 expression were not different between the IUGR and normal placentas. Histological vascular parameters of placental villi are decreased in the IUGR placenta. In case of intrauterine growth restriction, there is a reduced vascularization of the terminal villi of the placenta.

Keywords: placenta, intrauterine growth restriction, CD31 expression, vasculature

Introduction

The placenta is an organ that provides nutrients and oxygen for fetal development. Placental dysfunction is underlying cause in most of the intrauterine growth restriction, IUGR [1, 2]. Fetal growth restriction (FGR) is the complication of pregnancy where the fetus does not achieve its potential for growth that is determined genetically. IUGR occurs in 5–10% of all pregnancies. Increased perinatal morbidity and mortality are associated with IUGR. Also, serious health consequences in childhood and later in adulthood are associated with IUGR, including an increased risk for hypertension, cardiovascular diseases, obesity, diabetes mellitus type 2, and dyslipidemia [3, 4]. Various fetal and maternal factors may cause IUGR, but underlying insufficiency of the placenta is associated with the majority of the IUGR. It is believed that poor vascular development is associated with IUGR. Angiogenesis is a placental factor playing an important role [5, 6]. It is a critical process for the development of the placenta, as well as for all tissues [7–10]. The capillary network is formed with angiogenesis in which branching, sprouting, and lateral outgrowth of new vessels from pre-existing tubes occur. Different changes occur during this process, including increased endothelial cell proliferation, migration, the formation of endothelial cell tubes, increased vascular permeability, and finally, the coating of the outer surface of the capillary by pericytes and the formation of a stable vessel. CD31 is a transmembrane protein and is a member of the immunoglobulin family. It is an important endothelial adhesion protein that enables endothelial integrity and angiogenesis [11–13]. CD31 participates in the migration of endothelial cells and consequently the formation of new vascular vessels. It is a junctional protein containing an extracellular domain, a transmembrane domain, and a cytoplasmic domain (exons 9-16). The cytoplasmic domain is functionally the most important domain that can undergo alternative splicing and result in different isoforms. The mechanism by which CD31 enables cell migration appears to be due to altering the cytoskeleton. Antibodies against CD31 inhibit the capability of the endothelial cells for the formation of the tube-like structures which are the initial form of new blood vessels. In IUGR placentas hypoxic damages have been recorded and analyses of vascular growth are necessary.

In studies that have investigated the placental vasculature in IUGR, histological abnormalities in chorionic arteries have not been found, but in the stem villous arteries obliteration of vessels lumen and hypertrophy have been found [14]. The reports on the vascularity of the terminal villus varied. In the part near the placental center, a significant difference in microvascularity was not observed between the IUGR placenta and the normal term placenta. The results of previous studies indicate the presence of decreased placental vascularisation in the periphery of IUGR placentas [14, 15]. The study has aimed to investigate the expression of CD31 and the vascular parameters in the placentas of pregnant women with uncomplicated term pregnancies and placentas of pregnant women with IUGR.

Methods

The study analyzed thirty placental samples, fifteen IUGR placentas, and fifteen normal term placental samples (from the 38th to the 40th week of gestation) of healthy pregnant women. The obtained placentas were without visible macroscopic changes and damage. From all placentas, one tissue sample size 1x1 cm was taken at a medium distance from the center and margin of the placenta. The samples represent whole-thickness placental pieces from basal to chorionic plates. Tissue sections 5 μm thick were made. The standard hematoxylin-eosin method and immunohistochemical staining method

with anti CD31 antibody (Dako) were used for staining of tissue sections. Antibody unmasking was performed for 20 min in citrate buffer at pH 6.0. Thereafter, tissue sections were incubated with a 3% hydrogen peroxide solution for 10 minutes at room temperature to block endogenous peroxidase activity [16]. Phosphate buffer (Dako, EnVsion FLEX WASH BUFER) was used to wash the tissue section three times for two minutes. UV block for five minutes to block nonspecific background staining was used. Incubation with primary antibody (monoclonal ab-CD31, clone JC / 70A 1:100) was performed for 30 minutes at room temperature. At room temperature, the incubation with the primary antibody (monoclonal ab-CD31, clone JC / 70A 1: 100) for 30 minutes was performed. The UltraVision LP Detection System (Thermo Scientific) was used for visualization. After washing with wash buffer three times for three minutes, DAB chromogen was used and the reaction was monitored under a microscope. Mayer hematoxylin was used as a counterstain.

The obtained samples were photographed using a Leica DM 6000 microscope. Vascularization was analyzed on microphotographs made at x200 magnification by using Image Analysis LAS V4.3 software. The following parameters were analyzed on CD31 positive capillaries within the terminal villi: capillary number density (CND) as a total number of capillaries per tissue area unit, capillary area densities (CAD) as the total area of the capillary as a proportion of total tissue area, and capillary surface density (CSD) as the total circumference of the capillary per tissue area unit, as previously described by Borowicz P. et al. [6]. The obtained data were statistically analyzed with Levene's test and t-test, using a licensed version of SPSS software 19.0.

Results

Normal placentas were obtained from fifteen women with an uncomplicated pregnancy who delivered in term and whose life age was 32.51 ± 6.07 years. The life age of pregnant women with IUGR was 32.36 ± 5.95 years (Table 1). The mean gestational age at delivery of non-IUGR pregnancies was 38.49 ± 0,55 weeks and the mean gestational age of pregnant women with IUGR was 35.04 ± 3.11 weeks. In pregnant women with IUGR, the following were present: pregnancy-induced hypertension (PIH) in two pregnant women (13.33%), anemia in three pregnant women (20.00%), Rh incompatibility in two pregnant women (13.33%), coagulation disorder (thrombophilia) in two pregnant women (13.33%), hypothyreosis in three pregnant women (20.00%), bronchial asthma in one pregnant woman (6.67%), smoking in two pregnant women (13.33%), uterine anomaly (septum uteri, or uterus bicornis) in two pregnant women (13.33%), oligohydramnios in three pregnant women (20.00%), umbilical cord around the neck of the fetus (funiculus umbilicalis circum colli - FUCC) in three pregnant women (20.00 %). Some pregnant women had two or more of the listed risk factors.

Histological analysis of IUGR placentas showed increased syncytial knots, the sparser arrangement of terminal villi, and reduced vascular structures compared to normal placentas (Figure 1).

In all analyzed placentas the blood vessels of the chorionic plate and stem villi were overlaid with CD31 positive endothelium. Also, the endothelium of blood vessels of the intermediate villi and the capillaries in the terminal villi were CD31 positive. Cytotrophoblast cells and syncytiotrophoblast cells in all analyzed placentas were not positive for CD31 (Figure 2). There was no difference in the intensity and localization of CD31 expression between normal placentas and IUGR placentas (Figure 2).

Vascular density was analyzed in normal placentas and IUGR placentas (Table 1).

In normal placentas CND of 3.49 ± 1.39 capillary/1000 μm2 villous area was determined. The lowest determined value was 1,44 capil-

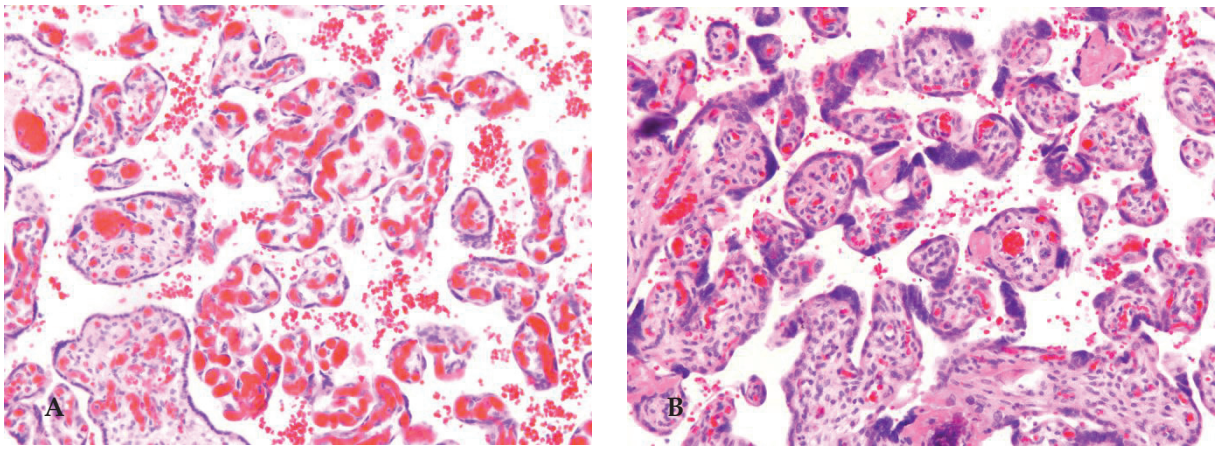

Figure 1. Placental villi: A. Normal term placenta, B. IUGR placenta (HE, x200)

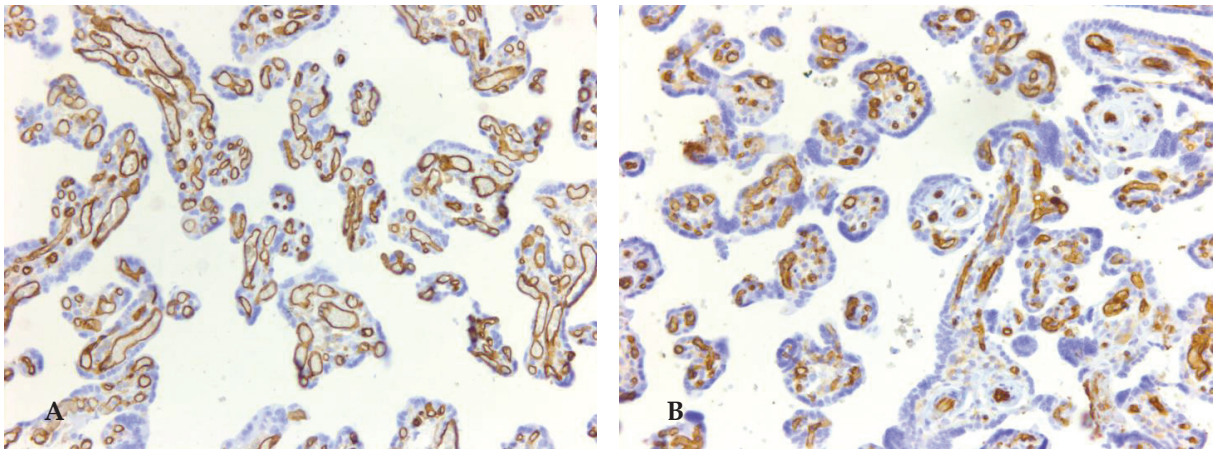

Figure 2. C D 31 positive endothelium in villi vessels A. Normal term placenta, B. IUGR placenta (anti-CD31, x200)

Table 1. Life age and gestational age at birth of pregnant women whose placenta was analyzed

		Placentas of the normal pregnancies		Placentas of the pregnancies complicated by IUGR	
	Number	M	SD	M	SD
Life age (years)	15	32.51	6.07	32.36	5.95
Placentas of the pregnancies complicated by IUGR (gestational weeks)	15	38.49	0.55	35.04	3.11

M - mean value, SD - standard deviation

lary/1000 μm2, and the highest value was 5.31 capillary/1000 μm2. In IUGR placentas CND of 2.55 ± 0.55 capillary/1000 μm2 villous area was determined. The lowest determined value was 1.26 capillary/1000 μm2, and the highest value was 3.20 capillary/1000 μm2. Compared to normal placentas, in IUGR placentas a statistically significant decrease in CND with the use of Levene's test for equality of variances was determined ($t = 2.459$, $df = 17.95$, $p = 0.024$).

Table 2. Histological vascular parameters in normal term placentas and IUGR placentas

		CND (capillary/1000 μm2 villous area)			CAD (%)			CSD (μm/1000 μm2 villous area)		
	N	Min	Max	MV	Min	Max	MV	Min	Max	MV
Normal placentas	15	1.44	5.31	3.49	41.20	68.13	52.80	102.44	217.56	145.51
IUGR placentas	15	1.26	3.20	2.55	19.90	45.95	30.49	71.93	125.44	92.81

N - number of analyzed placentas, Min - the lowest value, Max - the highest value, M - mean value

CAD in normal placentas was 52.80 ± 7.91 %, and in IUGR placentas was 30.49 ± 6.54% (Figure 3). In normal placentas, the lowest determined value was 41.20%, and the highest value was 68.13%. In IUGR placentas the lowest determined value was 19.90%, and the highest value was 45.95%. Between normal placentas and IUGR placentas a statistically significant difference with the use of the t-test was determined. CAD was significantly reduced in the IUGR placentas (t = 8.42, p = 0.0001).

CSD in normal placentas was 145.51 ± 31.39 μm/1000 μm2 villous area, and in IUGR placentas it was 92.81 ± 20.86 μm/1000 μm2 villous area. In normal placentas, the lowest determined CSD value was 102.44 μm/1000 μm2 villous area, and the highest CSD value was 217.56 μm/1000 μm2 villous area. In IUGR placentas the lowest determined CSD value was 71.93 μm/1000 μm2 villous area, and the highest CSD value was 125.44 μm/1000 μm2 villous area. Compared to normal placentas CSD in IUGR placentas was significantly reduced (t=5.415, df=28, p=.000).

Discussion

The important cause of perinatal morbidity and mortality is IUGR. The IUGR will occur in 5–10% of all pregnancies, while in countries with low income the incidence is 15–20%. IUGR is present in 26% of stillbirths and influences adult health in long term [2–5]. Because of that, it is important to diagnose IUGR accurately and on time and to properly manage pregnancy complicated with IUGR.

Intrauterine fetal growth can be impaired by fetal, placental, maternal, and environmental factors. Considering the time of diagnosis and Doppler ultrasound parameters, IUGR is divided into early-onset IUGR and late-onset IUGR. Early IUGR accounts for 20–30% of all IUGR and is associated with preeclampsia in 50% of cases. Late-onset IUGR accounts for 70–80% of all IUGR and is associated with preeclampsia in 10% of cases. The placenta plays an important role because insufficient placental function leads to abnormal fetal growth. In the background of placental insufficiency is the abnormal development of the placenta. In IUGR placentas there are histological changes including syncytial knots, the sparse arrangement of terminal villi, and reduced vascular structures. Histological changes in IUGR placentas, which are hypoxic lesions that occurred by reducing utero-placental or feto-placental flow, were determined in previous studies: widespread infarct areas, increased syncytial knots, the absent or reduced lumen of the blood vessel, vascular thrombosis, villous hypoplasia [1,15,17].

The placental factor that could be the cause of the development of IUGR is inadequate angiogenesis in the placenta and decreased maternal-fetal blood flow [1,15]. In this study, positive intensive staining of CD31 was found

in endothelial cells of all placental blood vessels and no staining was observed in cytotrophoblast and syncytiotrophoblast cells. There was no difference in the intensity and the type of cells positive for CD31 expression between normal placentas and IUGR placentas. In literature, the study that analyzed the expression of CD31 in IUGR placentas by immunohistochemistry found no differences between normal and IUGR placentas [10]. CD31 is an important endothelial adhesion protein that mediates angiogenesis. It is the main endothelial marker for the analysis of vascular growth. Due to the fact that hypoxic damage has been recorded in IUGR placentas, analyses of vascular growth in the placenta are necessary. This endothelial marker was used to analyze placental microcirculation in IUGR placentas.

The present study showed the hypovascularity of terminal villi at a medium distance between the center and the periphery of the IUGR placenta. CND (the parameter that indicates the number of capillaries in the villi), CAD (the parameter that indicates the size of the villous part built by the capillaries), and CSD (the parameter that indicates the size of the circumference of villous capillaries), were reduced in IUGR placentas. CND in IUGR placentas (2.55 ± 0.55 capillary/1000 μm2villous area) was significantly reduced compared to normal placentas (3.49 ± 1.39 capillary/1000 μm2 villous area). Also, CAD and CSD in IUGR placentas (30.49 ± 6.54 %; 92.81 ± 20.86 μm/1000 μm2 villous area) were significantly reduced compared to normal placentas (52.80 ± 7.91 %; 145.51 ± 31.39 μm/1000 μm2 villous area).

In a normal placenta, Aughwane et. al analyzed vascular density in relation to the location from cord insertion to the placental edge. On histological analysis, a difference in villous vascular density with distance from the umbilical cord insertion was not determined [18]. Between birthweight and placental vascular malperfusion lesions, and also adverse neonatal outcome, there was a negative correlation [19]. The analysis of the macrovasculature in normal and FGR placentas, with the use of computed tomography angiography revealed no difference between normal and IUGR placentas [20].

In preeclamptic placentas, Li et. al directly counted and measured the CD31 stained capillaries with the use of digital image analysis that might estimate more precisely vascular changes in the placenta. They found no difference in CND between normal placentas (the medium value of 2.77 capillary/1000 μm2 villous area) and severe preeclamptic placentas (the medium value was 2.83 capillary/1000 μm2 villous area) [9].

In literature data about villous vascularity of IUGR placentas was determined with stereology measurements and they alter significantly in the different areas of IUGR placentas. In the area near the center of the placenta, between IUGR and normal placentas was no significant difference in vascularity. Significantly reduced vascularity of the villi was determined at the periphery of IUGR placentas [14]. In this study vascularity of terminal villi was analyzed at the medium distance between insertion of the umbilical cord and placental margin. At medium distance vascularity of terminal villi was reduced.

The results obtained in this study support the findings of altered angiogenesis and reduced vascularization of the terminal villi in the placentas from pregnancy with intrauterine growth restriction of the fetus.

Conclusion

The localization and intensity of CD31 expression in the IUGR placenta are not different compared to the normal placenta. Histological vascular parameters of placental villi are decreased in the IUGR placenta. In the intrauterine growth restriction decreased vascularity of terminal villi of the placenta is present.

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Ethical approval. The Ethics Committee of the University Clinical Center of Republic Srpska in Banja Luka approved the study and informed consent was obtained from all individual respondents. The research was conducted according to the Declaration of Helsinki.

Conflicts of interest. The authors declare no conflict of interest.

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Analiza ekspresije CD31 i vaskularnih parametara u humanim posteljicama od trudnica sa intrauterinim zastojem rasta

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Uvod. Disfunkcija posteljice se nalazi u osnovi većine intrauterinih zastoja rasta ploda, komplikacije trudnoće u kojoj fetus ne postiže svoj genetski određen potencijal za rast. Proces koji je kritičan za razvoj posteljice je angiogeneza. Cilj studije je bio da se analiziraju ekspresija CD31 i vaskularni parametri u normalnoj posteljici i posteljici kod intrauterinog zastoja rasta (intrauterine growth restriction - IUGR).

Metode. Trideset uzoraka posteljica, petnaest posteljica kod IUGR i petnaest uzoraka normalne terminske posteljice je analizirano. Hematoksilin-eozin metoda i imunohistohemijska metoda sa antiCD31 antitijelom su korišćene za bojenje tkivnih rezova. Analizirani su vaskularni parametri: numerička gustina kapilara (cappilary number density - CND), arealna gustina kapilara (capillary area density - CAD) i površinska gustina kapilara (capillary surface density - CSD).

Rezultati. Između normalnih posteljica i posteljica sa IUGR nije utvrđena razlika u CD31 ekspresiji. Intenzivno pozitivno CD31 bojenje je nađeno u endotelu svih krvnih sudova i nije uočeno pozitivno bojenje u citotrofoblastu i sinciciotrofoblastu. CND u IUGR posteljicama od 2,55 kapilara/1000 μm2 površine resice je značajno smanjen u poređenju sa normalnim posteljicama od 3,49 kapilara/1000 μm2. CAD u IUGR posteljicama od 30,49 % je značajno smanjen u poređenju sa normalnim posteljicama od 52,80 % površine resice. CSD u IUGR posteljicama (92,81 μm/1000μm2) je značajno smanjen u poređenju sa CSD u normalnim posteljicama (145,51 μm/1000μm2).

Zaključak. Lokalizacija i intenzitet ekspresije CD31 se nisu razlikovali između IUGR posteljice i normalne posteljice. Histološki vaskularni parametri resica posteljice su smanjeni u IUGR posteljici. Kod intrauterinog zastoja rasta ploda prisutna je smanjena vaskularizovanost terminalnih resica posteljice.

Ključne riječi: posteljica, intrauterini zastoj rasta, ekspresija CD31, vaskulatura