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Influence of Placental Metalloproteinase-9 Protein on the Branching Architecture of Chorionic Blood Vessels of Human Placenta

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ABSTRACT

Introduction: *In human placenta, two different branching patterns of chorionic blood vessels exist. In the dispersal type, the chorionic blood vessels undergo successive divisions with gradually diminishing caliber as the blood vessels traverse towards the placental margins. In the magistral type, the blood vessels traverse without appreciable decrease in diameter. We hypothesize, that matrix-degrading enzymes secreted by cytotrophoblasts may influence the branching patterns of these chorionic blood vessels. We, therefore, determined if placental expression of matrix metalloproteinase-9 (MMP-9) protein differed between the two vascular patterns of chorionic blood vessels of human placenta.*

Methods: *26 full-term delivered placentas were collected from normotensive women. Chorionic villi (CV) were isolated. CV MMP-9 protein was analyzed using human MMP-9 monoclonal antibody based ELISA kits. A novel method was used to determine the vascular patterns of the placentas from placental photographs. Independent t test was used for statistical analysis. $P< 0.05$ was considered significant.*

Results: *The branching pattern of the chorionic blood vessels was 54% dispersal and 46% of the magistral types. In placentas with dispersal type of branching pattern, MMP-9 protein expression was significantly higher ($p=0.035$). Women who delivered placentas with magistral type of branching pattern, the mean newborn weight was found to be significantly higher ($p=0.039$).*

Conclusion: *The study introduces a novel method to investigate chorionic vascular network of human placenta. Our findings underscore the importance of CV MMP-9 protein in affecting the placental branching architecture of chorionic blood vessels in humans. In the magistral type, the calibers of the chorionic blood vessels from the point of insertion of the umbilical cord to the placental margins remained more or less unchanged. We suggest, that this unchanged caliber of blood vessels in the magistral type, may have allowed better nourishment and oxygen to be catered to the fetus; resulting in fetal weight gain.*

Keywords

ELISA, Dispersal type, GIMP, Magistral type, MMP-9 protein, Newborn weights, Placental vasculature.

Introduction

Human placenta is marked on the maternal side by the basal plate and on the fetal side by the chorionic plate. Blood vessels branching from the umbilical arteries and vein traverse along the

chorionic plate as chorionic blood vessels. The placenta serves as the interface between the mother and the fetus and carries out several key functions during pregnancy, including gas exchange, nutrient and metabolic transfer, hormone secretion and fetal protection. These functions mainly take place in the capillary system of the placenta. Hence, the structural anatomy of the fetal vasculature of human placenta has been of great interest to many investigators in the past. Several methods have been used in the past to study the structure of placental vasculature using term delivered placentas. The methods used include corrosion techniques that have used latex or plastic casts, injection of gelatin dye, microscopy and angiography [1-6]. Imaging methods e.g., Power Doppler and three-dimensional sonography have also been used to study the structure of human placental vasculature in vivo, [7-9]. The common features that these studies revealed were that the feto-placental vasculature originates at the insertion point of the umbilical cord; thereafter the blood vessels branch as they traverse the surface of the chorionic plate to reach the placental periphery. Smaller arteries of these branches constitute the cotyledon vessels or intraplacental vessels that ultimately perfuse the cotyledons. Two distinct types of vascular architecture have been described by these studies. In placentas where the umbilical cord insertion point is at the center of the chorionic plate, the branches tend to continuously divide symmetrically to create a dichotomous pattern. In placentas where the umbilical cord is inserted marginally on the chorionic plate, the vascular architectural pattern is more monopodial, meaning that the blood vessels tend to course for a distance towards the placental periphery with an almost constant diameter, giving off branches of reduced diameter at intervals to the side [10]. Two other terminologies have also been used in describing the branching architecture of chorionic blood vessels of human placenta. When the branching vascular network courses from the central cord insertion point and profusely divides as it courses towards the placental periphery, the branching network is referred to as dispersal. When the network of chorionic blood vessels initiating at a marginal cord insertion point courses towards the opposite edge of the placenta without major branching, the branching network is referred to as magistral [11].

The extracellular matrix provides structural support and information to cellular structures imbedded within it. As the chorionic blood vessels evolve, the extracellular matrix needs to be continually degraded to transform the structural scaffold. Matrix metalloproteinases (MMPs) are key enzymes that efficiently participate in the extracellular matrix transformation process [12]. Previous studies have revealed that there are many MMPs found in human placentas. However, MMP-2 and MMP-9 are the ones most studied [14]. In our previous study, MMP-9 protein expression was identified in human placenta early in the first trimester, and the protein expression was found to progressively increase with an increase in gestational age [15].

In the present study, we did not seek to characterize the branching architecture of the human placenta. Instead, this study was undertaken to test our hypothesis whether MMP-9 protein secreted by cytotrophoblasts may have a role in influencing the branching architecture of the chorionic blood vessels. Since two different types of placental vasculature exists in humans: dichotomous and monopodial [10] or dispersal and magistral [11], the collected placenta had to be classified into either of the two groups before the influence of MMP-9 protein on the branching architecture of the chorionic blood vessels could be determined. For the study, we have not used the conventional methods that have previously been used to examine the placental vasculature. A novel technique was used instead in which the placental photographs taken at the time of sample collection were converted to pencil sketches using a GNU Image Manipulation Program 2.10.12 (GIMP); and the original placental photographs and the pencil sketches were jointly reviewed to classify the placental vascular pattern. The details of the placental vasculature classification are provided in the method and result sections. Since vascular structure of the placenta may be impaired in pregnancy related pathologies [16,17], we had therefore restricted the focus of the present study on human term delivered placentas collected only from normal pregnancy.

Methods

In the present study, we have collected placentas from normotensive mothers who had normal systolic and diastolic blood pressure throughout gestation. To accentuate the normal pregnant state, we have added several other exclusion criteria to the study, e.g., placentas were not collected from mothers with missed abortion, or pregnancies complicated with diabetes, hypertension, chronic renal disease, chronic peripheral vascular disease, multifetal gestation or with major fetal anomalies; or from mothers who had ever used drugs during their lifetime. Even though the placental samples were collected prior the COVID-19 pandemic but placentas were not collected from mothers if they had any infection.

Term delivered placentas that would otherwise have been discarded was collected after vaginal or cesarean deliveries at 37-42 week of gestation. Placentas were collected within approximately 30 minutes of term deliveries. Placentas that were delivered overnight or when placenta sample collection could not be done within the 30-minute window they were not collected to keep the sample collection protocol consistent. Moreover, placentas delivered below 37 weeks of gestation were not collected because these placentas are considered preterm.

The investigative protocol for the study was approved by the Human Subject Ethics Committee of the Bronx Care Health System. The IRB protocol had allowed certain clinical information to be collected at the time of tissue collection without the identification of the patients' names and/or their medical record numbers. These included maternal age, race/ethnicity (self-reported), gestational age (as determined by ultrasound or by initial date of the last menstrual period), medicine(s) administered during pregnancy or during labour. Tissues and clinical information gathered during sample collection were deidentified before exiting the delivery suites.

The method by which each placenta was processed is as follows. Briefly, the adhering blood clots, the placental membranes and the umbilical cord were first removed, leaving only a short stump of the umbilical cord at the insertion point where it enters the placenta. The placenta was weighed and the weight was recorded. The placenta was then placed on the table with the fetal side facing upwards. A disposable measuring tape was placed at the bottom of the placenta to document its size, and a photograph of the placenta was taken. Each placenta was then flipped to expose the maternal side; and was then visually dissected into four quadrants (Qs). The section taken from the north-east region of the placenta was designated Quadrant 1, south-east section was designated as Quadrant 2, south-west section was designated as Quadrant 3 and north-west section was designated as Quadrant 4. Sections from each quadrant was removed one at a time, thoroughly washed, cut into smaller pieces and placed in a petri dish with normal saline. Chorionic villi were isolated from these placental pieces that were free of the basal plate and adhering blood vessels. A few chorionic villi pieces were placed in cryovials that were prelabeled with the placental ID and quadrant number. Cryovials from the same placental quadrant were placed in a plastic bag and was left on ice while the other quadrants were being processed. Finally, the four plastic bags containing the samples from each of the quadrants were placed in a larger plastic bag labelled with the placenta number, and was brought to the laboratory on ice. The chorionic villi samples from the same placenta were placed in individual freezer boxes and stored at -80^{o}C until assay.

On the day of the assay, chorionic villi samples were taken out of the -80^{0}C freezer in chronological order the placental tissues were collected. Chorionic villi samples were homogenized, centrifuged and the homogenate was used to determine MMP-9 protein expression by direct sandwich enzyme-linked immunosorbent assay (ELISA) [18]. The ELIZA kits were commercially available from R&D Systems, Minneapolis, MN; and had used monoclonal antibody to human MMP-9 protein as capture antibody. The manufacturer claims that the sensitivity of the ELISA assays for MMP-9 protein is 31.2 pg/ml. A Tecan infinite 200 Pro microplate reader (Tecan Systems Inc., San Jose, CA) set at 450 nm with wavelength correction set at 540 nm was used to measure the absorbance during the ELISA assay.

Determining the pattern of placental vasculature

The photographs of the placentas taken at the time of sample collection were used to classify the vascular patterns of the placentas. To better visualize the chorionic blood vessels GIMP was used and the placental photographs were converted into pencil sketches, which provided a greater visibility of the chorionic blood vessels. To classify the vascular pattern of the collected placentas, the classifications of two past studies were taken into account: the classification of Gordon, et al. [10], who had classified placental vasculature patterns as dichotomous and monopodial; and that of Prasad et al. [11], who had classified placental vasculature patterns into dispersal and magistral types. To classify the vascular pattern of the chorionic blood vessels for this study, five individual characteristics were taken into account: 1) location where the umbilical cord had inserted into the placenta; 2) the branching pattern; 3) diameter of the chorionic blood vessels as they coursed towards the placental margins; 4) the number of times the blood vessel branched irrespective of whether it was an artery or a vein; and 5) a greater importance was also given to the diameter of the blood vessels at the placental margins whether the diameter was significantly reduced or not.

Statistical Analysis

The statistical analysis to determine MMP-9 protein expression was as follows: First MMP-9 protein expression for each of the four placental quadrants was individually determined, and the average MMP-9 protein expression value of the four quadrants was then considered to be the MMP-9 protein expression of that placenta. Placentas were grouped based on chorionic blood vessel network patterns into: dispersal and magistral types. The statistical software package SPSS, version 26 (IBM Corporation, Armonk, NY) was used for statistical analyses; and Independent T test was used to analyze the results.

$P<0.05$ was considered significant.

Results and Discussion

For the study, 26 term delivered placentas were collected from normotensive women. To accentuate the normal state, several exclusion criteria were rigidly followed as described in details in the method section. The placentas were collected fresh within 30 minutes of term delivery. In the past, a number of techniques have been used to investigate the chorionic blood vessel patterns of human placenta to elaborate the mechanisms involved in maternal fetal exchange [1-6,9-11]. The methods used were laborious, time consuming and required extensive manipulation of the placentas to achieve results. In this study, we have implemented a novel method to investigate the chorionic vascular pattern in normal human placenta that does not require any manipulation of the placenta itself. A photograph of the placenta obtained at the time of collection was converted into a pencil sketch using GIMP to enhance the visibility of the placental vasculature. That the visibility of the placental vasculature could be enhanced in these pencil sketches is documented in figure 1 and 2. In figure 1, two original placental photographs taken at the time of sample collection are displayed. The top panel shows the placental photograph in which the umbilical cord insertion point was marginal; and the bottom panel for comparison shows a separate placental photograph in which the umbilical cord insertion point was central. In the center of the top and bottom panels in figure 1, the GIMP converted pencil sketches of the respective placentas are shown. The right hand edges of the panels show the pencil sketches of the placentas with the vascular branching points marked with round spots at the region where the blood vessels bifurcated. In figure 2, two other original placental photographs are shown just to reiterate the novelty of our method, and to demonstrate that the method does enhance the visibility of chorionic blood vessels without any manipulation. It would have been useful if we could display all 26 placentas collected for the

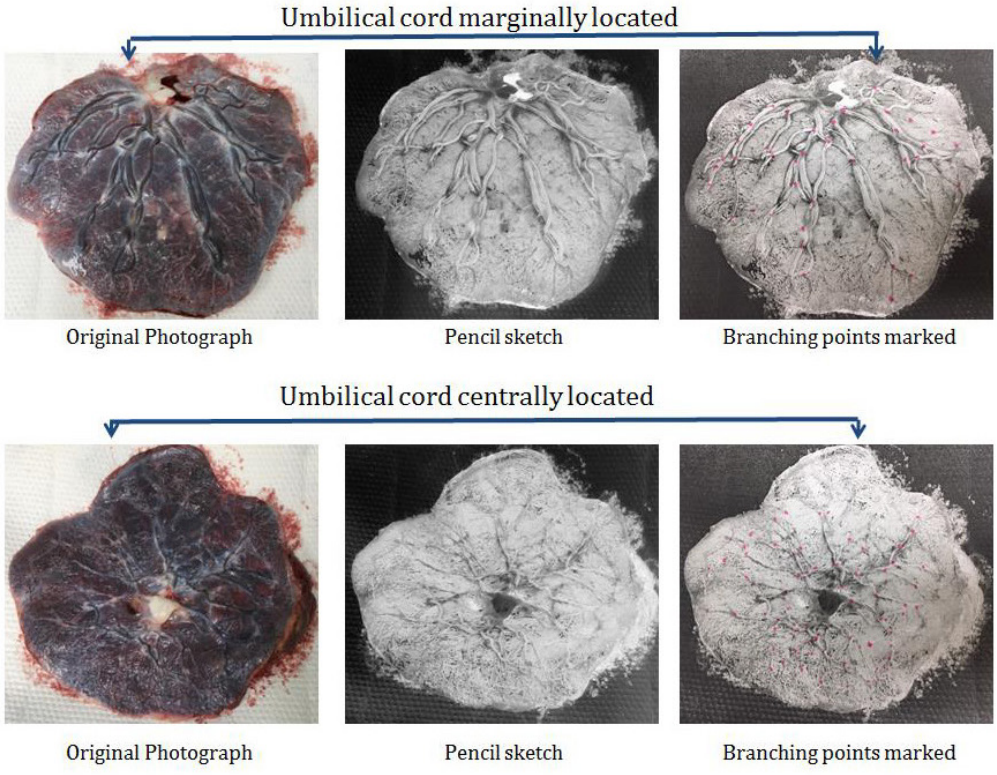

Figure 1: Original placental photographs and pencil sketches of human placentas.

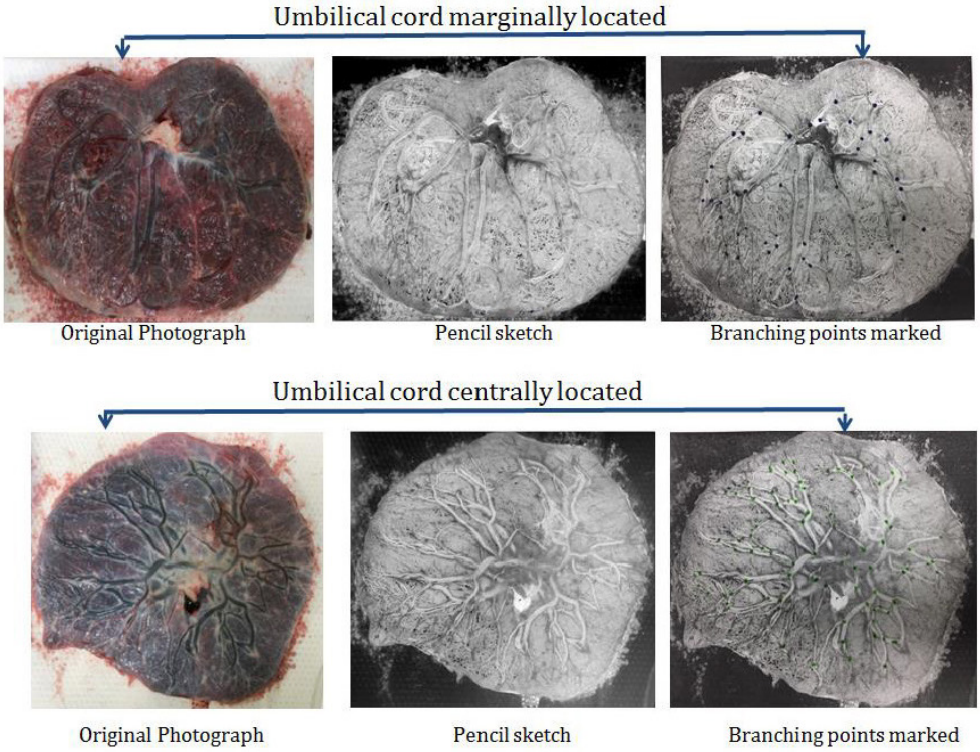

Figure 2: Original placental photographs and pencil sketches of human placentas.

study in the aforementioned format. It needs to be pointed out however that the branching points of the chorionic blood vessels were marked without making any attempt to differentiate between the chorionic arteries and the veins.

To classify the vascular pattern of the chorionic blood vessels for the study, two separate previous methods were combined: the method of Gordon et al. [10], who had classified placental vasculature into dichotomous and monopodial patterns; and that of Prasad et al, [11] who had classified placental vasculatures into dispersal and magistral types. The features that were taken into account to classify the vascular pattern of the chorionic blood vessels for this study included: 1) location where the umbilical cord had inserted into the placenta; 2) the branching pattern whether dichotomous or monopodial; 3) diameter of the blood vessels as they coursed towards the placental margins, taking into account whether the blood vessel traversed with a constant diameter on the chorionic plate before it branched; 4) the number of branches seen; and 5) whether the diameter of the chorionic blood vessel at the placental margins was significantly reduced compared to the diameter of the blood vessels at the insertion point.

Table 1 depicts in details our systematic approach how we have examined the placental vasculature of all 26 placentas, using both the original placental photographs and their respective pencil sketches, before any conclusions regarding the classification was drawn. We have found that in 10 placentas the insertion point was marginally located; in the remaining 16, the insertion point was central. In two placentas (#2 and #6 of Table 1) even though the insertion point was marginally located the placentas showed branching pattern of the dichotomous type. In 11 placentas, the branching pattern was noted to be monopodial while in the remaining 15 the pattern was dichotomous types. GIMP was also used to measure the diameter of the chorionic blood vessels; and the disposable ruler of each placental photograph was used for calibration. The diameter of the chorionic blood vessels at the insertion points ranged from 1.3 mm to10.3mm, the diameter of the chorionic blood vessels at the placental margins ranged from 0.7 mm to 6.1 mm; and the length of blood vessel traversed without bifurcation was found to range from 6 mm to 100 mm. The number of branches varied between placentas; and the number of spots at the bifurcations points of the chorionic blood vessels that were counted ranged from 28 to 91. The findings revealed that in case of centrally located insertion

Table 1 Placental vasculatural characteristics used to classify the placentas into dispersal and magistral types

Placenta #	Location of Insertion Point	Branching pattern	Diameter of blood vessel as it coursed towards placental margins	Number of branches	Diameters of blood vessels at placental margins significantly reduced	Placenta classified as
1	Marginal	Monopodial	Remained more or less unchanged	42	No	Magistral
2	Marginal	Dichotomous	Gradually reduced	74	Yes	Dispersal
3	Central	Dichotomous	Gradually reduced	84	Yes	Dispersal
4	Central	Monopodial	Remained more or less unchanged	49	No	Magistral
5	Central	Dichotomous	Remained more or less unchanged	87	No	Magistral
6	Marginal	Dichotomous	Gradually reduced	91	Yes	Dispersal
7	Central	Dichotomous	Gradually reduced	61	Yes	Dispersal
8	Central	Dichotomous	Gradually reduced	62	Yes	Dispersal
9	Marginal	Monopodial	Remained more or less unchanged	49	No	Magistral
10	Marginal	Monopodial	Remained more or less unchanged	55	No	Magistral
11	Central	Dichotomous	Gradually reduced	66	Yes	Dispersal
12	Marginal	Monopodial	Remained more or less unchanged	28	No	Magistral
13	Central	Dichotomous	Gradually reduced	59	Yes	Dispersal
14	Marginal	Dichotomous	Gradually reduced	83	Yes	Dispersal
15	Central	Dichotomous	Gradually reduced	83	Yes	Dispersal
16	Central	Dichotomous	Gradually reduced	75	Yes	Dispersal
17	Central	Dichotomous	Gradually reduced	86	Yes	Dispersal
18	Marginal	Monopodial	Remained more or less unchanged	73	No	Magistral
19	Central	Monopodial	Remained more or less unchanged	64	No	Magistral
20	Central	Dichotomous	Gradually reduced	63	Yes	Dispersal
21	Central	Dichotomous	Gradually reduced	73	Yes	Dispersal
22	Central	Monopodial	Remained more or less unchanged	65	No	Magistral
23	Marginal	Monopodial	Remained more or less unchanged	78	No	Magistral
24	Central	Monopodial	Remained more or less unchanged	49	No	Magistral
25	Central	Dichotomous	Gradually reduced	61	Yes	Dispersal
26	Marginal	Monopodial	Remained more or less unchanged	40	No	Magistral

point, the chorionic blood vessels bifurcated frequently, whereas in case where the insertion point was marginal, the bifurcations of the blood vessels were comparatively less. In some placentas, the diameters of the chorionic blood vessels at the insertion points were more or less maintained as the blood vessels coursed towards the placental edge, however in others the diameters of the blood vessels gradually decreased with each subsequent bifurcation. At the placental margins, the diameters of the blood vessels of some placentas were found to be significantly reduced. Taking into consideration all the features, 12 placentas in the study could be categorized as magistral (46%) and the remaining 14 as dispersal types (54%). In figure 3 all 12 placentas that were classified as magistral types are shown; and figure 4 shows the remaining 14 placentas that were classified as the dispersal types. Placentas with vasculature pattern of the dispersal types had significantly higher (p=0.010) number of branches (73 $\pm$11), compared to of the magistral types (57 $\pm$16) Table 2. The findings of the present study concur with other reports that stated that the incidence of dispersal pattern of placental vasculature is more common in humans, and the number of branches in these placentas is comparatively higher compared to the magistral types [10].

Table 3 depicts some of the maternal characteristics of the women from whom placentas were collected. Age, gestational age in days, placental weight, placental length, systolic and diastolic blood pressure was all remarkably similar between the two groups. The vascular pattern of the placenta that was delivered by cesarean sections was similar to those delivered vaginally. It needs to be pointed out that the higher number of cesarean sections seen in the study was because it was easier to collect placental samples in a timely manner from a scheduled cesarean section than from spontaneous vaginal delivery. Majority of the women from whom placentas were taken for the study were Hispanic, and ethnicity was not found to influence the distribution patterns of the chorionic blood vessels.

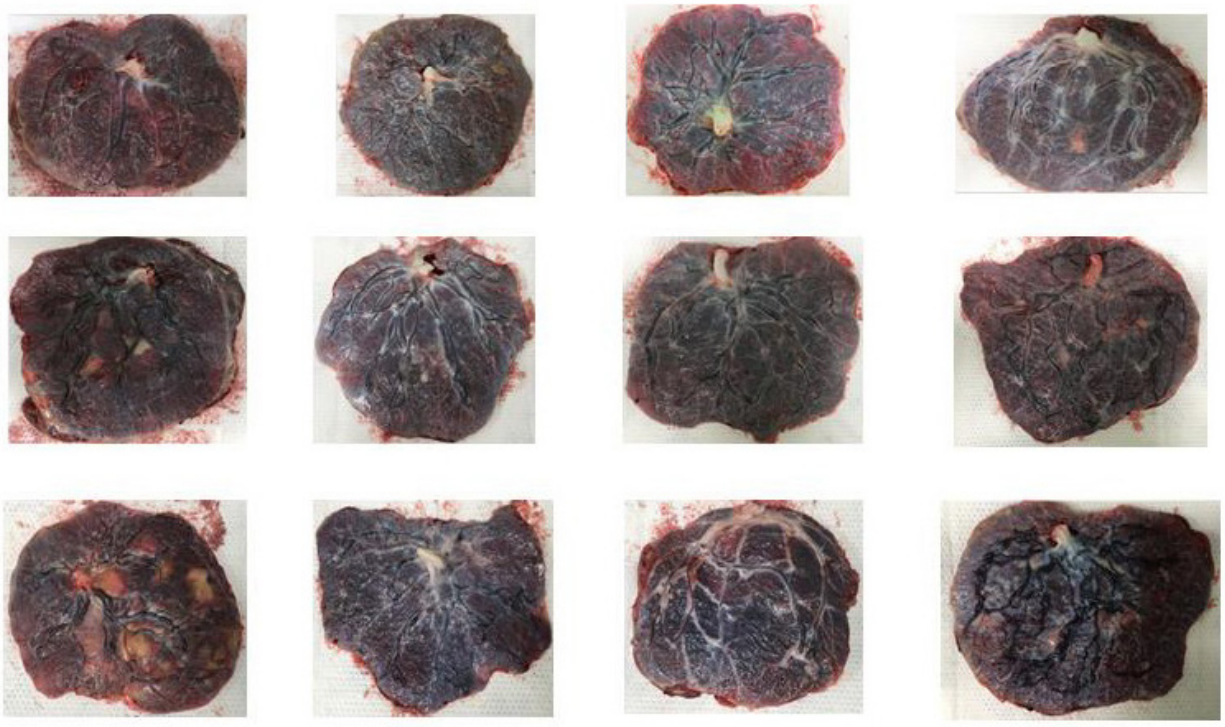

Figure 3: Human placentas with magistral type of branching pattern of the chorionic blood vessels.

Table 2 Number of branches of the chorionic blood vessels in placentas with different vascular patterns

Types	N	Number of branches (Mean)	SD	P value
Dispersal	14	73	11	0.01
Magistral	12	57	16	

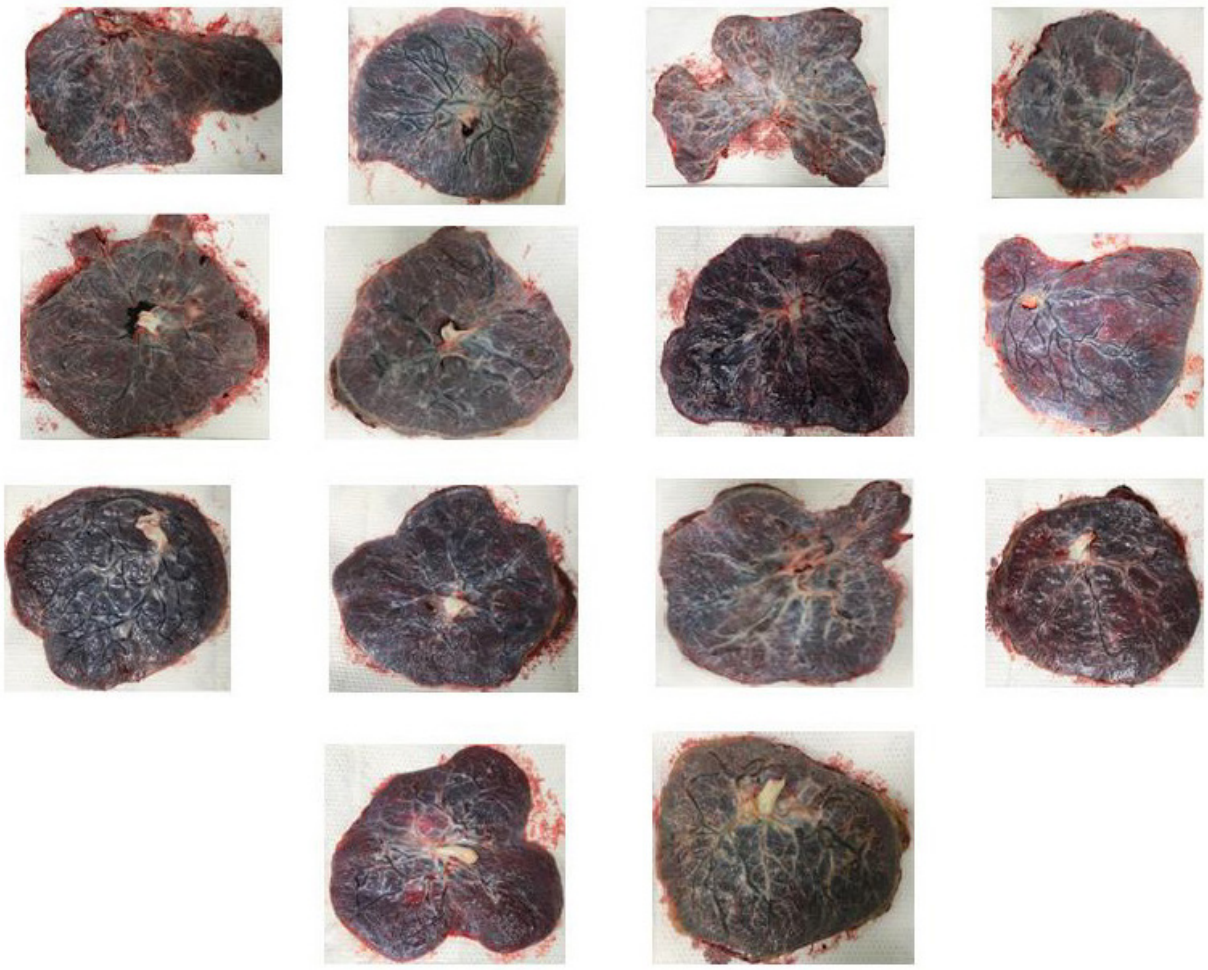

Figure 4: Human placentas with dispersal type of branching pattern of the chorionic blood vessels.

Table 3 Clinical characteristics of mothers from whom placentas were collected

Types	N	Age	GAD	Placental weight (gms)	Placental length (inches)	Systolic Blood Pressure (mm Hg)	Diastolic Blood Pressure (mm Hg)	Method of Delivery		Ethnic variations		
								C-section	Vaginal	Hispanic	Black	Other
Dispersal	14 (54%)	27±7	278±7	422±66	8.1±1.3	115±14	68±10	9	5	10	3	1
Magistral	12 (46%)	28±6	276±4	451±113	7.6±0.9	120±12	74±11	8	4	8	0	4

Table 4 MMP-9 protein expression in placentas with different chorionic blood vessel branching patterns

Types	N	MMP-9 protein expression (ng/100 mg tissue)	SD	P value
Dispersal	14	26.98	14.70	0.035
Magistral	12	17.07	6.63	

Table 5 Newborn characteristics born to mothers with different chorionic blood vessel branching patterns of the placenta

Types	N	Newborn Sex	Newborn weights (Mean gms + SD)	P value
Dispersal	14	7 males	3157 ± 192	0.04
		7 females		
Magistral	12	7 males	3533 ± 544	
		5 females		

The MMP family of enzymes degrades the extracellular matrix and the basement membrane and the substrate specificities of these enzymes are broad and diverse [19]. During pregnancy, trophoblast cells need to invade the uterine basement membrane and extracellular matrix, to gain access to the uterine stroma; and there are reports that expression of both MMP-2 and MMP-9 proteins significantly increase in cytotrophoblasts in the first trimester of human pregnancy [20,21]. However, beyond six weeks of human gestation, the expression of MMP-2 protein in the cytotrophoblasts decline, while the expression of MMP-9 protein prevails [22]. In our previous study, we have demonstrated that placental expression of MMP-9 protein progressively increased with an increase in gestational age [15,18]. Since the extracellular matrix provides the structural support for the placental vasculature to grow, and the matrix needs to be continually degraded as pregnancy advance, we were interested in finding out whether MMP9 protein has a role in influencing the structural architecture of human placental vasculature. In the present study, placental MMP-9 protein expression was compared between placentas with chorionic vascular network patterns of the dispersal and magistral types, and the data are presented in Table 4. Placentas with vascular network pattern of the dispersal types was found to have significantly higher levels of MMP-9 protein ($p = 0.035$), compared to the magistral types. In the present study, we have compared the number of branches between placentas with chorionic blood vessel network pattern of dispersal and magistral types, and the data as presented in Table 2 show that the number of branches in placenta with dispersal type was significantly higher ($p=0.01$). Placentas with chorionic vascular pattern of the dispersal types (dichotomous) have been reported by investigators to branch more frequently than the magistral types (monopodial) [10,11]. In the present study, significantly higher number of branches was seen in placentas of the dispersal types. Hence, our findings support the notion that MMP-9 protein may have a role in influencing the branching architecture of chorionic blood vessels of human placenta. In placentas of the dispersal type, higher expression of MMP-9 protein may facilitate more the clearing of the connective tissue matrix components to make room for the placental vascular network to expand; allowing the chorionic blood vessel network to profusely branch out.

The daughter-to-mother diameter ratio of the chorionic blood vessel branching patterns was suggested by Gordon et al. [10], to reflect their different role in the distribution of fetal blood over the chorionic plate. Repeated symmetrical bifurcation of the vascular structure with high daughter-to-mother ratio as seen in the dichotomous types was suggested to be the delivering vessel trees; whereas the structures of the chorionic vessels which are asymmetric, with small daughter-to-mother diameter ratio; as seen in the monopodial types, the blood vessels were considered as distributing vessels.

Schordania has however specified that the vascular pattern of the placenta is genetically determined, and is dependent on the vascular characteristics of the mother [23]. He has suggested that placenta with vascular pattern of the magistral type delivers better-developed fetus, with greater weight and thoracic measurement compared to those of the dispersal type. In the present study, all women delivered normal healthy new-borns; and the average newborn weight born to mothers with placentas with chorionic blood vessel patterns of the magistral types was 3533 ± 544 grams. This weight was significantly higher ($p=0.04$) compared to the average new-born weight (3157 ± 192 grams) born to mothers who had placentas with chorionic blood vessel patterns of the dispersal types (Table 5). We agree with the suggestion made by Schordania that the unchanged caliber of blood vessels from the placental cord to the placental margins in the magistral types may allow better nourishment and oxygen to be delivered to the fetus, resulting in fetal weight gain.

Conclusions

In the present study, we report a novel method to study the chorionic vascular pattern of human placenta, which is unlike other techniques used in the past. The method is rapid and does not require any manipulation of the placenta. We hope our novel, rapid technique can be used in prospective studies to provide better insight into the placental vascular patterns in complicated pregnancies. The findings of the present study additionally demonstrate that the incidence of placental vascular network of the dispersal types is more common. Since the chorionic blood vessels in these placentas repeatedly branch and MMP9 protein expression in these placentas was found to be significantly higher, we suggest

that MMP-9 protein may indeed have a role in influencing the branching architecture of human placenta. Mothers, who delivered placentas with vascular pattern of the magistral type, were found to deliver new-born with significantly higher new-born weights. In future studies, the effect of other MMPs and their inhibitors on placental vasculature and on new-born weights may also be examined.

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