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The Determination of Normal Percentages of Syncytiotrophoblastic Knots in Various Regions of Placenta: Where to Count the Syncytial Knots

Sinsityotrofoblastik Düğümlerin Plasentanın Farklı Bölgelerindeki Normal Yüzdelerinin Belirlenmesi: Sinsityal Düğümleri Nereden Sayalım

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ABSTRACT

Objective: The marginal, basal and subchorial regions of the placenta are considered to be more hypoxic than other regions. Therefore, it is not recommended to determine the increase in syncytiotrophoblast knots, based on the major morphological change in placental hypoxia, from the samples taken from these regions. However, the normal count of knots at various regions of placenta is not investigated.

Material and Method: In this study we have sampled morphologically and clinically normal placenta with eccentric cord insertion from various sites, either close to cord entrance or away from it (marginal, non-marginal basal, non-marginal subchorial, and nonmarginal midparanchymal). The number of knots was calculated on a total of at least 100 villi for each placental sample. The normal amount of knots in different regions and comparison between them were investigated. Twenty-eight placentas with eccentric cord insertion were sampled in the same manner. Hot spots from the above mentioned regions were counted in a total of 100 villi.

Results: No significant difference was found between the dual comparison of the mean percentages of different regions (p: 0.148). The variety of hypoxia in different regions of the placenta could not be demonstrated in this study.

Conclusion: It is found that there is no difference in perfusion that can be morphologically demonstrated with increase in syncytiotrophoblast knot, between different regions of placenta.

Key Words: Hypoxia, Placenta, Syncytiotrophoblast

ÖZ

Amaç: Plasentanın marjinal, bazal ve subkoryal bölgelerinin diğer bölgelerine göre daha hipoksik olduğu düşünülür. Buna göre, plasental hipoksideki morfolojik bulgular temelinde sinsityotrofoblastik düğümlerdeki artışın bu bölgelerden alınacak örneklerden belirlenmesi önerilmez. Her şeye karşın plasentanın farklı bölgelerindeki düğümlerin normal sayısı incelenmemiştir.

Gereç ve Yöntem: Bu çalışmada, eksantrik kord girişli, morfolojik ve klinik açıdan normal plasentaların kord girişine yakın veya uzak, farklı alanlarından (marjinal, non-marjinal bazal, non-marjinal-subkoryal, non-marjinal midparenkimal) örnekler alındı. Düğümler, her bir plasental örnekte total en az 100 villüsten sayıldı. Farklı bölgelerdeki normal düğüm sayısı incelendi ve karşılaştırma yapıldı. Eksantrik kord girişli 28 plasenta benzer biçimde örneklendi. Yukarıda belirtilen bölgelerdeki sıcak noktalar total 100 villüsten sayıldı.

Bulgular: Farklı bölgelerin ortalama yüzdeleri dual karşılaştırıldığında anlamlı bir fark saptanmadı (p: 0,148). Bu çalışmada, plasentanın farklı bölgelerindeki hipoksi değişiklikleri gösterilemedi.

Sonuç: Yazarların düşüncesine göre plasentanın farklı bölgelerinde sinsityotrofoblastik düğüm artışı ile morfolojik olarak gösterilebilecek perfüzyon farklılıkları bulunmamaktadır.

Anahtar Sözcükler: Hipoksi, Plasenta, Sinsityotrofoblast

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INTRODUCTION

Tenney Parker Changes (TPC) are the major marker of maternovascular perfusion insufficiency. They are characterized by syncytial knot increase and villus clustering. Syncytial knot is a marked clustering of the syncytial nuclei under the light microscope. Studies performed with the electron microscope demonstrate various types of syncytial knots with different mechanisms of formation. These formation types usually cannot be differentiated under the light microscope. The syncytial knot increase has histomorphological significance (1). There is ongoing research among pathologists to designate the most appropriate definition of syncytial knots (2). The existence of syncytial knots in more than one third of the villi is defined as TPC. It is recommended to calculate the knot number from the midparenchymal region, because the basal, marginal and the subchorial regions are considered to be more hypoxic than the other regions (3). However, there is no standard regarding the normal number of knots from different regions. This study attempts to determine the normal amount of syncytial knots in different regions and to demonstrate whether a difference exists between them.

MATERIALS and METHODS

Twenty-eight placentas received at Ağrı Women and Children's Hospital, Department of Pathology were chosen for the study. All the samples were term gestational placentas with eccentric cord entrances. The weight of the placentas varied between 414 and 470 grams, which was within normal limits (4). They were all reported as late 3rd trimester placentas that were morphologically normal. Descriptive additional diagnoses coexisted which did not affect the final diagnosis. The following cases thought to bias the study either clinically or morphologically were not included in the study;

• Cases with no eccentric entrances: central, marginal and other cord entrances were thought to have different perfusions than eccentric ones.

• Placenta-induced hypertension (PIH): It is reported that there is no uniform physiologic change in different vessels of decidua basalis and in various regions of a single vessel as well (3). That is why it is accepted that even normal placentas may demonstrate physiological conversion insufficiency that is frequently seen in cases with preeclampsia and SGA (Small for Gestational Age) (5). As the deficiency of physiological conversion may increase the perfusion variances in the placenta, PIH cases with normal morphology were excluded from the study.

• Cases with villous maturation score of other than 22 and 23: Villous maturation scores are included in the reports of our department. The scores of 22 and 23 are defined as normal late third trimester placentas as demonstrated by Benirske and Kaufmann (1) and shown in Figure 1 and Figure 2.

• Cases with chorioamnionitis: The endothelin amount is increased in chorioamnionitis which in turn results in fetal vasoconstriction and hypoperfusion (6). VEGF is a growth factor increasing inflammatory cell migration. Its expression is increased both in hypoxic cases and in chorioamnionitis (7,8). Chorioamnionitis cases were therefore excluded from the study even with scores of 22 and 23.

• Cases with morphological changes associated with hypoxia and decreased perfusion: TPC is not the single finding of hypoxia and cases with the following changes demonstrated even focally were therefore excluded from the study: Increased intervillous fibrin, distal villous hypoplasia, acute atherosis, mural hypertrophy of membrane arterioles, muscularised basal plate arteries, increased placental side giant cells, increased immature intermediate trophoblasts,

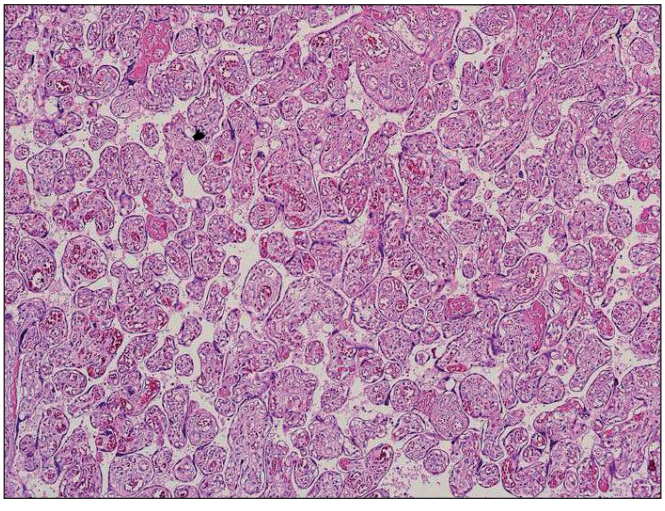

Figure 1: Score 22 (Villous maturation score) (H&E; x100).

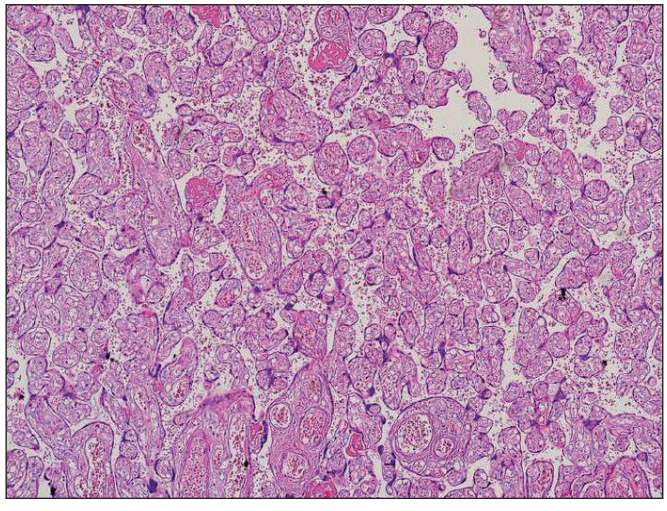

Figure 2: Score 23 (Villous maturation score) (H&E; x100).

thin umbilical cord, laminar necrosis, and microscopic chorionic pseudo cysts (2, 9, 10).

Placentas were kept in a solution of 10% formaldehyde for a night and were cut into two segments from the cord entrance parallel to its longitudinal axis (Figure 3). Six blocks were taken from each case. The sampling regions were as follows;

1X: Marginal zone close to cord insertion.

1: Non-marginal zone close to cord insertion.

2: Non-marginal zone far from cord insertion.

2X: Marginal zone far from cord insertion (Figure 4).

O: Fetal membranes and cord.

T: Horizontally sampled placental base.

After this sampling, the placentas were dissected parallel to the first incision and additional samples were taken from regions with an unusual appearance. In order to increase the standardization in perfusion, the central regions of maternal cotyledons at the opening site of the uterine arteries were chosen. All the samples were cut in 5 micron thickness and stained with hematoxylin and eosin. The pathologist investigated the samples. All the counting was done from the hot spots and knot numbers were determined from at least 100 villi for each dissected sample. Each syncytial knot and syncytial knot bridging was calculated as 1 point. During these scorings, accumulations with crowded nuclei, which are easily seen in 10x magnifications, were counted without question. For smaller knots, the inclusion presence of at least 6 nuclei was required. The compact accumulation of the nuclei was stipulated. Only the knots on terminal villi were counted. Syncytial knots existing on more than 1 villus due to slicing were also included in the study if they met the criteria above. Each syncytial knot was scored as 1. Syncytial knots including at least 6 nuclei and combining more than two villi were defined as syncytial knot bridging. Each syncytial knot bridging was scored as 1.

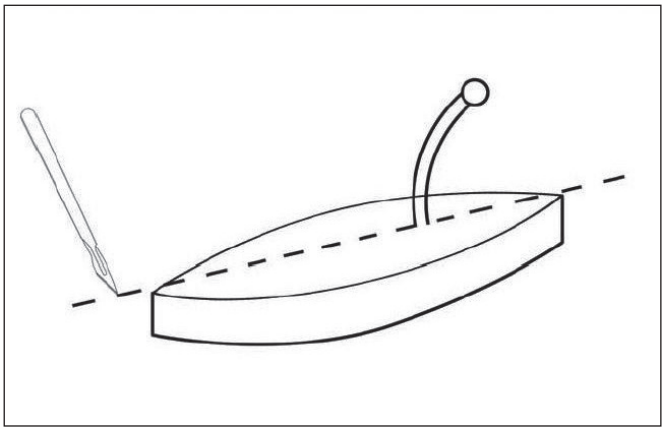

Figure 3: The dissection of placenta in this study.

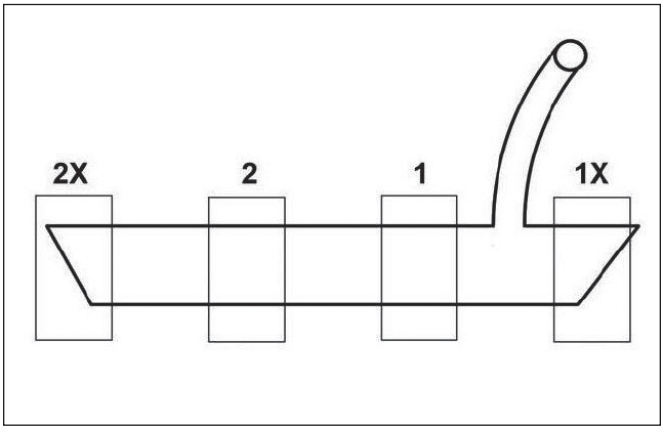

Figure 4: Illustration of zones sampled in the study. 1X, marginal zone close to cord insertion; 2x, marginal zone far from cord insertion; 1, central zone close to cord insertion; 2, central zone far from cord insertion.

When the intense regions were selected, the regions closest to the choriobasal unit in the marginal regions were preferred for counting. For subchorial counting the closest regions to chorial plaque, for midparenchymal counting the 1/3 sectional part of the placental thickness, and for basal counting the closest regions to the basal plaque were preferred. SPSS version 16.0 Statistical Analysis Software was used to analyze the relation between variants. Variations among groups were determined using the Mann-Whitney U test. The Kruskal-Wallis test was used for comparison of more than two groups. Probabilities of less than or equal to 0.05 were accepted as significant.

RESULTS

The clinical and pathological characteristics (the type of birth, the direction of cord turn, additional microscopic characteristics and villous maturation scores) of the 28 cases included in the study are demonstrated in Table I.

Villus counting from the previously defined regions, their number of included syncytial knots present, and the percentages of these are demonstrated in Table II. The group statistics are listed in Table III and Table IV. Mean parameters were calculated for every region. No significant difference between the mean parameters of the regions were demonstrated with Kruskal-Wallis test (p:0.148). No significant difference between the mean parameters of regions close to and away from cord entrance were found (p:0.101, and p:0.282, respectively). No significant differences between the mean parameters of marginal, subchorial, basal, and midparenchymal counting of regions close to and away from cord entrance were found (p:0,594, p:0,706, p:0,577, and p:0,577 respectively).

Table I: The clinical and pathological characteristic of cases used in this study

	Delivery route	Cord turn	Additional microscopical features	VMS
1	VD	L	x	22
2	C/S	L	x	23
3	C/S	L	Focal stem villus calcification	22
4	VD	L	x	23
5	VD	R	Cylindric change in amnion epithelium	22
6	C/S	L	Subcorial fibrinoid excess	23
7	C/S	L	x	22
8	C/S	R	Amniotic epithelium proliferation	22
9	C/S	R	x	22
10	C/S	L	Amniotic mesencymal pigmented macrophages	23
11	C/S	L	x	22
12	VD	L	x	22
13	C/S	L	Ductus vitellus remnant	22
14	C/S	L	x	22
15	C/S	L	x	22
16	C/S	L	x	22
17	VD	L	x	22
18	C/S	L	Intravillous fibrinoid excess	22
19	C/S	L	x	22
20	C/S	L	x	22
21	C/S	L	Subcorial focal chronic infarct	22
22	C/S	L	x	22
23	C/S	L	x	22
24	C/S	R	x	22
25	VD	R	x	22
26	C/S	R	x	22
27	C/S	R	x	22
28	C/S	L	x	23

C/S: Cesarean section, **VD:** Vaginal Delivery, **VMS:** Villous maturation score.

DISCUSSION

A syncytial knot, primarily defined under the light microscope, is defined as significant clustering of syncytial nuclei (Figure 5). Increase in syncytial knots and clustering of villus are defined as Tenney Parker Changes (TPC). TPC are primarily described as the determinant of preeclampsia. They are attributed to demonstrate placental ischemia later on. They have been associated with Factor 5 mutations lately (11,12). Syncytial knots are classified into three categories according to their mechanisms of formation. However, differentiation of these under the light microscope is quite difficult (1,13). Instead of being trophoblastic proliferations, most of the knots appear as slice artifacts of deformed villi due to villous angiogenesis, specifically during the last trimester. However, whatever their etiologies are, syncytial knots are known to demonstrate changes in trophoblastic turnover (3). Syncytial knots and bridging have various definitions in different studies. Baergen et al. have defined syncytial knots as clusters of 5 or more nuclei and only in terminal villi (14). However, it is reported that some of the counted villi do not meet the criteria and possess less than 5 nuclei. Syncytial bridging is described as one of the 4 etiological types of syncytial knots and the real bridging is described as a rare condition originating from fusion of 2 villi. The contact of the surfaces of the chorionic villi is designated as "touching" in the same study. Syncytial knots are defined as an increase in syncytiotrophoblastic nuclei, and the bridging as villous agglutination in the study of Redline et al. According to this, villous agglutination is

Table II: The number of syncytiotrophoblastic knots and villi, their percentages (pct) counted at various areas

	1X	1X (%)	1Sub	1Sub (%)	1Mid	1Mid (%)	1Bas	1Bas (%)	2X	2X (%)	2Sub	2Sub (%)	2Mid	2Mid (%)	2Bas	2Bas (%)
1	54/347	15.56	13/159	8.17	31/230	13.47	18/139	12.94	25/205	12.19	18/125	14.4	26/200	13	40/185	21.62
2	5/141	3.54	12/208	5.76	46/320	14.37	36/272	13.23	33/275	12.13	16/120	13.33	65/260	25	44/234	18.8
3	25/162	15.43	27/220	12.27	33/200	16.5	23/165	13.93	44/250	17.6	32/285	11.22	47/284	16.49	46/171	26.9
4	58/163	35.58	38/405	9.38	78/200	38.42	51/272	18.75	95/360	26.38	33/140	23.57	66/292	22.6	34/170	20
5	45/252	17.85	24/122	19.67	25/185	13.51	28/200	14	25/142	17.6	40/200	20	31/182	17.03	51/190	26.84
6	23/216	28.7	42/204	20.58	30/138	21.73	28/184	15.21	41/166	24.69	97/237	40.92	55/215	25.58	80/201	39.8
7	34/160	21.25	20/245	8.16	36/249	14.45	24/134	17.91	17/173	9.82	30/178	16.85	34/252	13.49	82/258	31.25
8	42/237	17.72	11/154	7.14	23/237	9.7	40/290	13.79	25/220	11.36	20/193	10.36	22/255	8.62	10/229	4.36
9	70/277	25.27	25/273	15.33	16/235	6.8	18/308	5.84	60/202	29.7	9/162	5.55	28/186	15.05	28/213	13.02
10	70/213	32.86	13/165	7.92	17/200	8.5	37/208	17.78	27/227	11.89	18/185	9.72	32/197	16.24	24/217	11.05
11	22/163	13.49	40/191	20.94	8/150	5.33	16/169	9.46	30/186	15.95	24/160	15	25/310	8.06	30/272	11.02
12	21/230	9.13	20/194	10.3	18/232	7.75	14/199	7.03	51/257	19.84	11/290	3.79	58/255	22.74	23/185	12.43
13	126/341	36.95	30/300	10	66/290	22.29	42/305	13.77	67/254	26.37	5/237	2.11	18/255	7.05	29/250	11.6
14	9/195	4.61	10/184	5.43	9/180	5	12/142	8.45	30/232	12.93	6/190	3.15	13/234	5.55	21/174	12.06
15	25/260	9.61	18/212	8.49	22/358	6.14	18/315	5.71	10/146	6.84	28/190	14.73	40/277	14.44	28/145	19.31
16	109/290	37.58	91/213	42.72	86/298	28.85	96/328	29.26	50/280	17.85	64/242	26.44	65/292	22.18	66/338	19.52
17	108/370	29.18	26/250	10.4	69/420	16.42	76/376	20.21	56/270	20.74	50/197	21.38	38/315	12.06	33/296	11.14
18	195/410	47.56	64/371	17.25	90/304	29.6	85/335	25.37	118/386	30.56	53/357	14.84	53/283	18.72	81/350	23.14
19	99/272	36.39	61/209	29.18	531/350	15.14	109/374	29.14	175/300	58.33	54/184	29.34	149/348	42.81	44/292	15.06
20	92/290	37.72	29/214	13.85	70/310	22.58	62/336	18.45	110/355	30.98	63/445	14.15	70/294	23.8	80/285	28.07
21	63/412	15.29	88/291	30.34	96/492	19.51	69/312	22.11	60/372	16.12	117/297	39.39	110/468	23.5	57/300	19
22	56/310	18.06	69/267	25.84	46/203	22.66	105/290	36.2	50/259	19.3	87/360	23.83	68/332	20.48	47/284	16.54
23	90/176	51.13	58/146	39.72	49/222	22.07	30/119	25.21	78/203	38.42	48/335	14.32	51/231	22.07	48/276	17.4
24	111/332	33.43	131/655	20	88/335	26.26	58/223	25.11	87/348	25	30/300	10	99/512	19.33	70/272	25.73
25	44/186	23.65	47/262	17.93	66/277	23.82	77/256	30.07	44/157	28.02	37/263	14.06	38/240	15.83	53/250	21.2
26	45/237	18.98	47/225	20.88	124/354	35.02	97/334	29.04	116/300	38.66	63/203	31.03	70/160	43.75	84/276	30.43
27	65/307	21.17	77/415	18.55	62/335	18.5	75/250	30	76/219	34.7	110/495	22.22	106/345	30.72	119/286	41.6
28	90/330	27.27	102/437	23.34	159/338	47.04	84/412	20.38	82/280	29.28	150/582	25.77	132/444	29.72	88/305	28.85

X: Marginal zone; **1:** Peri-cord insertional zone; **2:** Far from cord insertional zone; **Sub:** Subchorial, **Mid:** Midparencymal, **Bas:** basal, **Pct:** Percentage

Table III: Group Statistics; mean percentages of various areas and their comparison between peri-cord insertional and far from cord insertional zones

Area		n	Mean percentage	SD	Std. error mean	p
x	1	28	24.46	12.24	2.31	0.594
	2	28	22.97	11.17	2.11	
sub	1	28	17.12	9.78	1.84	0.706
	2	28	17.55	9.96	1.88	
bas	1	28	18.86	8.31	1.57	0.577
	2	28	20.63	8.89	1.68	
mid	1	28	18.97	10.38	1.96	0.606
	2	28	19.85	9.25	1.74	

Table IV: Group Statistics; comparison between mean percentages of various areas (x, sub,bas, mid) within peri-cord insertional (1) and far from cord insertional (2) zones

Area		n	Mean percentage	SD	Std. error	p
1	x	28	24.46	12.24	2.31	0.101
	sub	28	17.12	9.78	1.84	
	bas	28	18.86	8.31	1.57	
	mid	28	18.97	10.38	1.96	
	Total	112	19.85	10.50	0.99	
2	X	28	22.97	11.17	2.11	0.282
	Sub	28	17.55	9.96	1.88	
	Bas	28	20.63	8.89	1.68	
	Mid	28	19.85	9.25	1.74	
	Total	112	20.25	9.91	0.93	

described as clustering of the adjacent distal villi (>2, <20) inside fibrin and/or bridging (micro infarcts) at the syncytial knots (2). Others have mentioned that the formation of syncytial knots and bridging are slicing artifacts due to deformed villi with vascular proliferations, and the syncytial knots and the bridging are not defined as separate forms (1). We have scored one, two, or more villi including significant knot accumulation as 1 in our study. Syncytial knots or bridging are not differentiated. Some of these were proposed to be the contact regions described by Baergen et al. (14). The real and the pseudo bridging, and the differences from the contact regions should be clearly defined in future studies.

The determination of the region where the counting will take place is another argument. While in Handbook of Placental Pathology eds. Faye-Peterson OM, Heler DS, Joshi recommends counting from the midparenchymal region and from the knots on terminal villi (3), another study suggests the slice to be taken from the 75% of the basal part and from the knots on proximal stem villi and distal villi (2).

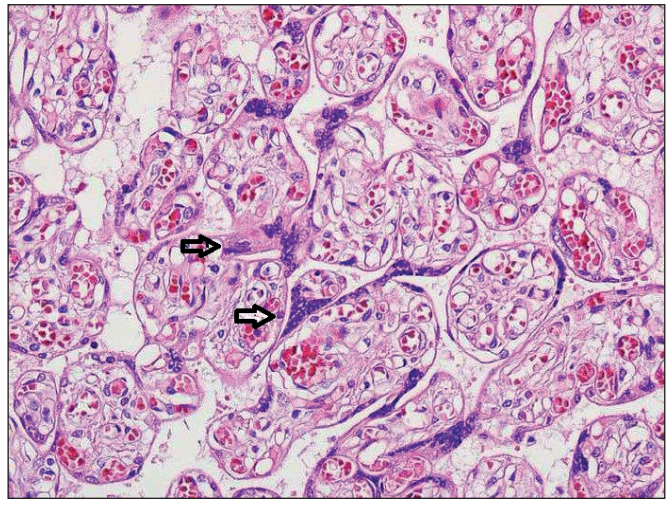

Figure 5: Syncytial Knots (Arrows) (H&E; x200).

Relative ischemia of marginal parts and the non-marginal parts of the basal and subchorial areas of the normal placentas have been reported (3). This thesis constitutes the basis of our study and our goals were to differentiate various areas according to their number of syncytial knots, and if there is a difference, to support the idea of relative ischemia and to contribute to the standardization of normal number of syncytial knots in various regions.

The theory of relative ischemia stems from physiological data about maternal circulation. The blood from the transformed arterioles entering the maternal circulation spouts into the subchorial region. This results in a fibrinoid accumulation defined as "subchorionic fibrinoid" and returns back to the basal area. It is reabsorbed from the open-ended veins (3). That is why the subchorial and the basal areas are the locations of blood accumulation. Another study has hypothesized that the collateral arterial circulation and the gestational arterial changes are fewer in the marginal regions (15). Besides, lesions like infarcts and x cell cysts that are classically known to be associated with hypoxia are reported to be more frequently seen in subchorial, basal and marginal regions.

No significant differences between the number of syncytial knots in any region were observed in our study. Although there is no significant increase in the number of syncytial knots in the marginal area or decrease in nonmarginal basal zones, these results should not be interpreted as non-existence of relative ischemia, as the minor changes in perfusion may not effect the morphology. The increase in syncytial knot number is not the only finding of hypoxia and does not necessarily coexist with the other morphological changes of hypoxia. The morphological findings of hypoxia vary according to the degree and onset of hypoxia (16-19). For example, TPC may not accompany chorioangiosis that is thought to be formed due to long-lasting low grade hypoxia (3). Although we have excluded the cases with known hypoxia-associated changes from our study, there may be other findings yet not defined and associated with hypoxia. Future studies are needed to clarify this issue. We have an ongoing study proposed to demonstrate the number of syncytial knots from the same regions used in this study and investigate from where the knot increase has started, in cases with a villous maturation score of 32.

As a conclusion no differences between the number of syncytial knots counted from various regions of the normal term human placenta are demonstrated. The thesis of increased ischemia in marginal, non-marginal basal and non-marginal subchorial regions of the term, clinically and morphologically normal placentas are not supported in this study.

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