OBJECTIVE: Chorangiosis is an infrequently diagnosed placental lesion characterized by placental capillary proliferation. In this study we present 10 cases of chorangiosis with histological and immunohistochemical features and described the clinical effects on fetal outcome.

STUDY DESIGN: Ten cases of chorangiosis (7%) diagnosed in 150 placentas examined at our institution between 2002 and 2004 were evaluated. Chorangiosis was defined as the presence of a minimum of 10 villi, each with 10 or more vascular channels, in 10 or more areas of three or more random areas when using an x10 objective. Beside histopathological criteria, histochemical and immunohistochemical staining was also applied.

RESULTS: Chorangiosis was most commonly associated with cesarean section (60%), preterm birth and neonatal intensive care (40%), Apgar scores of 5 minute or less (30%), maternal disease and drug ingestion (30%). Also intervillous hemorrhage (80%), placental calcification (60%), placental growth retardation (40%), umbilical cord knots (40%), chorioamnionitis (40%), perivillous fibrin (40%) and umbilical vein dilatation (40%) were commonly observed placental findings in chorangiosis cases.

CONCLUSION: Chorangiosis should be considered as an important sign of placental injury associated with hypoxia in utero. Histopathological recognition of these lesions might help to determine the underlying and proximate causes of fetal injury.

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Key Words: Chorangiosis, Chorangiomatosis, Chorangiom, Villous capillary, Angiogenesis
preterm birth and neonatal intensive care, 4 (40%); Apgar scores of 5 minute or less, 3 (30%); maternal disease and drug ingestion, 3 (30%); premature rupture of the membranes, 2 (20%); toxemia or maternal hypertension, 2 (20%); neonatal death, 1 (10%); congenital anomaly, 1 (10%); diabetes mellitus, 1 (10%).

Of the 10 placentas with chorangiosis, the incidence of each of the following items were; intervillous hemorrhage 8 (80%), placental calcification 6 (60%), placentomegaly, 4 (40%), umbilical cord knots 4 (40%), chorioamnionitis 4 (40%), perivillous fibrin 4 (40%), umbilical vein dilatation 4 (40%), placental infarction 2 (20%), meconium staining of membranes 2 (20%), placental cyst 1 (10%); umbilical vein thrombosis 1 (10%).

Chorangiosis was defined in terms of the number of the capillary vascular loops in the terminal villi. Histopathologically we diagnosed chorangiosis (Figure 1a-b) by applying the criteria of Altshuler described above.1

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<th>Placental data</th>
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<td>Gestational age</td>
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<td>Umbilical vasculopathy</td>
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Histochemical stain for reticulin revealed a thin, well-defined basement membrane that surrounds capillaries (Figure 2).

Figure 1. Hypercapillarized terminal villi, each having 10 or more capillaries (a) H&E, x100, (b) H&E, x200.

Figure 2. Capillaries in chorangiosis are surrounded by a thin basement membrane (Reticulin, x100).

Figure 3. Immunostaining with CD 31 demonstrates more capillaries (Biotin streptavidin peroxidase, DAB, x400).
Immunohistochemically capillary endothelial cells showed uniform positivity with CD31; demonstrating more capillaries than were easily discernible by hematoxylin-eosin stain (Figure 3). The expression of PD-ECGF in the endothelial cells was present in five of our cases (Figure 4).

**Figure 4.** PD-ECGF positivity of capillary endothelia (Biotin streptavidin peroxidase, DAB, x200).

**Discussion**

In this study, we determined chorangiosis in approximately 7% of examined placentas, comparable to other reported series. Most placentas with chorangiosis were delivered ≤37 weeks’ gestation and it was not seen at less than 28 weeks. It may probably take time to develop chorangiosis, so this hypothesis would explain why we had seen chorangiosis in the advanced weeks.

Chorangiosis has been correlated with increased neonatal death, major congenital malformations, preterm delivery and placental abruption. It is frequently encountered in medical centers that care for high risk pregnancies. However, we had only one case with major congenital anomalies and neonatal death; but 40% of our cases with chorangiosis showed preterm delivery and required neonatal intensive care.

Association of chorangiosis with maternal disease and drug ingestion were also noted. In the present study, of the ten cases with chorangiosis, one patient had multiple sclerosis and two had thyroid dysfunction and had medical treatment throughout their pregnancies. Also a case with oligohydramnios and a case with polyhydramnios was present in our series.

Pre-eclampsia may also lead to chorangiosis by giving rise to tissue hypoxemia. Also in woman with hypertension, the frequency and extent of in f nction are increased. Two of our cases showed pre-eclampsia and at the same time showed placental infarction.

The incidence of chorangiosis is higher in women living in high altitudes; this event seems to result from placental hypoperfusion. Hypoxia appears to stimulate both placental capillary proliferation and cytotrophoblast and can result in elevated maternal serum hCG levels.

Chorangiosis is predominantly a lesion of terminal villi. A number of angiogenic factors, vascular growth factors are thought to have a part in terminal villogenesis. Capillary and stromal overgrowth is characteristic of placentas in diabetes mellitus and Beckwith-Wiedemann syndrome, which can show mesenchymal dysplasia and villous capillary lesions. Although we found high frequency of placentomegaly (60%) among placentas with chorangiosis, just one of our cases had diabetes mellitus.

Chronic hypoperfusion or tissue hypoxemia is the well-known stimulus that cause growth factors such as VEGF, PDGF and TGF-β, produced by mesenchymal and trophoblastic cells. Initiation of angiogenesis depends on VEGF, while continued capillary growth and development depend on PDGF dependent differentiation of pericytes, which produces angiopoietins that control remodeling of the primary vascular plexus into a mature capillary bed. Finally endothelial cells and pericytes lead to the activation of TGF-β, which inhibits further growth and promotes terminal differentiation of the mature capillary. We demonstrated PD-ECGF reactivity in 5 of 10 cases. In negative cases, we might hypothesize that angiogenesis has become stable or perhaps is presently going on.

Another alternative proposal for the pathogenesis is that, the increase in the macrophage-derived growth factors, such as tumor necrosis factor-α may play a role in chorangiosis. In some series, villitis was demonstrated in chorangiosis cases. We noted an increase of the percentage of chorionamnionitis (40%) in our series; however villitis or necrotizing funisitis were not accompanied.

Increased intramural pressure related to venous obstruction at the umbilical cord and fetal cardiac level is thought to have part for the pathogenesis of chorangiosis and associations of cord anomalies, such as long umbilical cord, thrombosis of vessels and nuchal cord have been reported. And we observed three false and one true umbilical cord knots (40%) in ten of our cases that in our knowledge it had not been reported before. Also four of our cases showed dilatation of umbilical cord and one umbilical vein thrombosis.

In our study 60% of placentas with chorangiosis were associated with cesarean section, which was also proposed previously by Altshuler. In that study it was proposed that chorangiosis might result from placental circulatory changes or from factors that lead to obstetric decision for cesarean section.

The differential diagnosis between chorangiosis and other villous capillary lesions like chorangiomatosis and chorangioma is based on some histological criteria. Chorangio ma is defined as an expansive nodular lesion composed entirely of capillary vascular channels some of which can con-
tain mitotically active cells, intervening stromal cells and surrounding trophoblasts and are analogous to hemangiomas at other body sites. Chorangiomatosis is ascertained both at gross examination and an incidental findings at microscopic examination.\textsuperscript{7,13} Chorangiomatosis is a more heterogeneous and less well-defined lesion with features described as having intermediate features between chorangioma and chorangiosis.

Chorangio and chorangiomatosis is distinguished from chorangiosis by the presence of increased stromal collagenization and cellularity, and surrounding perivascular cells. Also reticulin network will aid the differential diagnosis between chorangiomatosis and chorangiosis. While the former had a loose poorly cohesive lattice of fibrils, capillaries in the latter were each surrounded by a thin, well-defined basement membrane, histochemically demonstrated by reticulin, as in our cases.\textsuperscript{2,6}

Chorangiosis should also be differentiated from congestion, and from tissue ischemia with shrinkage of villi. Normal villi contain no more than five vascular channels\textsuperscript{1,14} and in congestion vasculature is numerically normal.

Features associated with chorangiosis in this study generally agree with other studies including placentomegaly, umbilical cord problems, preterm birth and neonatal intensive care, low (5 minute or less) Apgar scores, maternal disease and drug ingestion and the presence of cesarean section. We had also demonstrated chorangiosis cases together with umbilical cord knots, chorioamnionitis, placental calcification and perivillous fibrin deposits with a high percentage.

In summary, the cause of chorangiosis is still not well-known, but chronic hypoperfusion or tissue hypoxemia combine with maternal, placental and fetal factors may produce this pathologic condition. Whatever its cause it should be considered as an important clinical sign of fetal injury. Histopathological recognizing of these lesions might help to clarify the causes of many adverse pregnancy outcomes and would aid the improvement in the management of the subsequent pregnancies.

References