

LYMPHSPIRATION

ARE THERE LYMPHATIC VESSELS IN THE PLACENTA?

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ABSTRACT

The role of lymphatics in placentation has been scantily studied and the true existence of placental lymphatics is under debate. Numerous blood and lymphatic-lineage molecule markers are now available and they are expressed in human placental tissue. D2-40 expression at the placental stromal level seems to indicate that network-forming, podoplanin-expressing cells may act as a reticular-lymphatic-like conductive network. This exciting area at the intersection of perinatology and lymphology needs further investigation.

Keywords: placenta; lymphatics; immunohistochemistry, D2-40 podoplanin

The placenta is the interface between mother and developing fetus, allowing nutrient uptake, waste elimination, and gas exchange via the mother's blood supply. Proper vascular development in the placenta is fundamental to ensuring a healthy fetus and successful pregnancy. The functional unit of the placenta is the chorionic villus containing the layers of syncytiotrophoblasts/cytotrophoblasts, villous stroma, and fetal vascular endothelium that separate maternal blood from the fetal circulation. Maternal

tolerance of the semi-allogeneic fetus and fluid balance between maternal and fetal compartments (1) are fundamental biological processes linked to placental functions. The lymphatics play a role in both of these functions. Although these important placental functions have been under investigation for a long time, the role of lymphatics in placentation has been scantily studied and the true existence of placental lymphatics is under debate. Furthermore, the few available data are contradictory.

Thus, the main query might be: are there lymphatics in the human placenta? And, moreover, how can we approach this problem?

During pregnancy, utero-placental blood flow increases progressively, with estimates ranging from 600-700 ml/min near term. In addition to uterine blood vessel adaptation, important changes in the uterine lymphatic vessel system are also involved in vascular remodeling during pregnancy (2). Remodeling of the uterine arteries is a key event in early pregnancy that begins after implantation. The trophoblast differentiates into villous trophoblasts and extravillous trophoblasts. Villous "trees" are the main structure of the placenta. Based on the developmental stage, as well as on villous structure, vessel branches, histologic features, and vessel-cell

TABLE
Lymphatic Markers Expressed in the Human Placenta (modified from refs 7 and 9)

LYMPHATIC MARKERS EXPRESSED IN THE HUMAN PLACENTA						
Marker	EXAMINATION BY WESTERN BLOT (protein)			EXAMINATION BY Mrna-PCR		
	Trophoblast Cells	Villous Core Endothelium	Villous	Trophoblast	Villous Core Endothelium	Villous
LYVE-1	Positive	Mild positive	Absent	Positive	Mild positive	Absent
CD-44	Absent	Absent	Absent	Absent	Absent	Absent
VEGF-A	Uncertain	Uncertain	Absent	Positive	Positive	Absent
VEGF-D	Uncertain	Uncertain	Absent	Positive	Positive	Absent
Flt-1	Uncertain	Uncertain	Absent	Positive	Positive	Absent
VEGF-C	Uncertain	Uncertain	Absent	Mild positive	Positive	Absent
KDR	Uncertain	Uncertain	Absent	Mild positive	Positive	Absent
VEGFR-3	Mild positive	Positive	Absent	Mild positive	Positive	Absent
PROX-1	Absent	Absent	Absent	Absent	Absent	Absent
CD-31	Absent	Positive	Absent	Uncertain	Uncertain	Uncertain
D2-40	Absent	Absent	Strongly positive	Absent	Absent	Positive

type components, at least five types of villi have been described: stem villi, immature intermediate villi, mature intermediate villi, terminal villi, and mesenchymal villi. Research performed without the use of immunohistochemical methods provided conflicting results showing the presence or absence of the lymphatic vasculature in the endometrium, in the functional zone, or in the basalis region of the human endometrium (3-5). More recent studies carried out using immunohistochemical techniques demonstrated the presence of lymphatic vessels in the uterine wall (6), thus seeming to affirm that the lymphatic system plays an important role at the implantation site and in vessel remodeling and fluid homeostasis in the uterus during pregnancy. Recent developments have shown that numerous blood and lymphatic-lineage molecule markers,

including VEGF-A, -C, and -D, Flt-1, KDR, VEGFR-3/Flt-4, CD-31, CD-44, Prox-1, and D2-40 podoplanin are expressed in human placental tissue, and that the expression and localization of these lymphatic markers are compartmentally different within the villous tissue (*Table*) (7-9).

Despite the role played by lymphatics with regard to vessel remodeling and fluid homeostasis in the uterus during pregnancy, no certain knowledge exists on the presence of lymphatic vessels in the placenta, thus making it difficult to understand how placental fluid homeostasis is regulated (8, 10). In a study on hydrops fetalis, we recently observed that the D2-40 marker was positive in the stromal area of villous tissue sections of the at-term /near-term hydropic placenta (*Fig.*). These very preliminary results, together with recent evidence confirming our

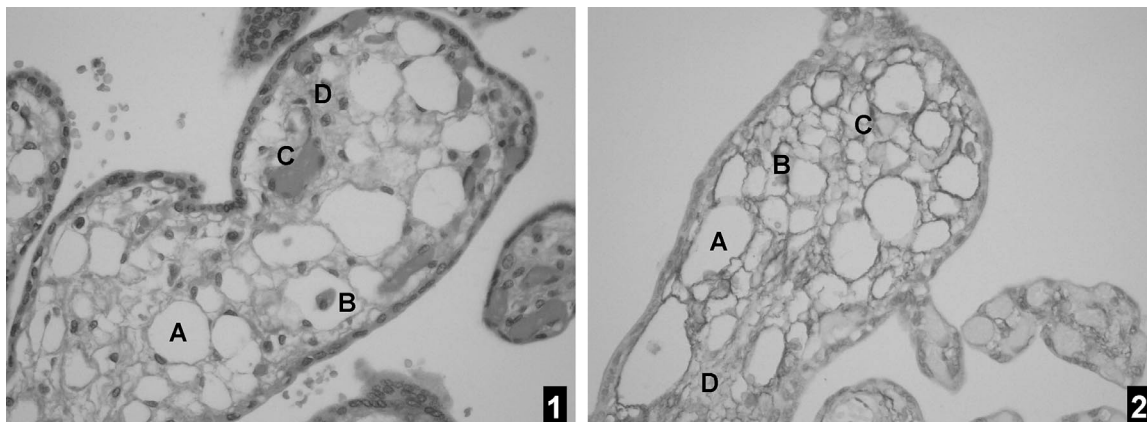


Fig. Immature intermediate villi from an at term hydropic placenta. Panel 1) Hematoxylin and Eosin (HE) staining (10x). Panel 2) Immunohistochemical D2-40 staining expression in placental immature intermediate villous tissue (10x). D2-40 is a selective marker of lymphatic endothelium. Tissue was formalin fixed, paraffin-embedded, and stained with D2-40 (1:120) for 60 min at room temperature. Podoplanin is a transmembrane mucoprotein that is recognized by the D2-40 monoclonal antibody. A: Ectasia. B: Hofbauer cell. C: Blood vessel. D: Stroma.

observation (9) point to the possible involvement of lymphatic vessels in the placental functions. The D2-40 expression at the placental stromal level seems to indicate that network-forming, podoplanin-expressing cells which do not form regular lymphatic vessels may act as a reticular-lymphatic-like conductive network positively involved in placental fluid homeostasis. Many questions are still awaiting answers. This is a fascinating research area of investigation for all who are involved in perinatology and lymphology.

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