

# Hemangiomas Linked to Placental Abnormalities

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Vascular abnormalities of the placenta were strongly correlated with the incidence of infantile hemangiomas in a small group of very-low-birth-weight infants, Dr. Juan Carlos Lopez Gutierrez and his colleagues reported.

Abnormalities such as infarcts and hematomas might create a hypoxic intraplacental environment that stimulates

vasculogenesis and predisposes these infants to postnatal hemangioma growth, said Dr. Lopez and his associates of La Paz Children's Hospital, Madrid (*Pediatr. Dermatol.* 2007;24:353-5).

Although the study is too small to make absolute claims, it does seem to shed additional light on the prevailing theory of hemangioma pathogenesis: embolization of placental endothelial cells. "There are several different factors playing an important role in the pathogenesis of hemangiomas.

Just embolization of placental cells as the origin of hemangiomas is too simple a theory," Dr. Lopez said in an interview.

His case series suggests that placental lesions lead to a hypoxic environment that, in turn, stimulates the unopposed growth of escaped fetal endothelial cells. "Hypoxia is extremely important as a precursor lesion, and placental anomalies provoke a low-oxygen atmosphere, which is one—and probably the most important—of the suggested factors for hemangioma

development," Dr. Lopez said. His study included 26 very-low-birth-weight infants, 13 of whom developed infantile hemangiomas postnatally. The investigators examined each placenta macroscopically and microscopically.

Every placenta in the group of infants who developed hemangiomas was abnormal, they found. Two placentas showed massive retroplacental hematomas; seven showed extensive infarction; and four exhibited large dilated vascular cavitations, severe vasculitis, chorioamnionitis, and funiculitis. Cord insertion was marginal in eight, paracentral in three, and velamentous in two. Among the placentas showing infarcts, the area of ischemia was simple in two and multiple in five, with a mean infarct size of 15 mm. The infarcted areas resulted in decreased growth of peripheral villi in all tissues.

In contrast, all of the placentas of the infants without hemangiomas were free of lesions reflecting disturbed maternal-fetal circulation. Two placentas showed isolated villous immaturity. Cord insertion was central in four and paracentral in nine.

Hypoxia is an important angiogenic stimulator in fetal development. "The relatively low oxygen environment in which the human fetoplacental unit develops during the first trimester is necessary to induce vasculoangiogenesis via embryonic endothelial cells proliferation, as these cells are sensitive to hypoxia and acidosis," Dr. Lopez and his associates noted.

Prior research suggests that abnormal placentas increase the likelihood of infantile hemangiomas through shearing and embolization of placental tissue. Thus, the hypoxic environment created by placental insufficiency could be the trigger that turns on a vasculogenic response in any endothelial cells that have escaped into a fetus's circulation, they wrote.

Dr. Paula North, chief of pediatric pathology at the Medical College of Wisconsin, Milwaukee, pioneered the embolization theory of hemangioma pathogenesis and said that Dr. Lopez's study raises some valid issues. "The evidence from this study is a little bit circumstantial in supporting the placental origin theory," Dr. North said in an interview. "What it does suggest is the idea that any kind of placental injury would increase the shedding of vascular precursor cells from the placenta, which then migrate into the baby."

Once the placental cells enter the fetus, their migratory path and growth are probably influenced by their phenotype. "The cells that make up a hemangioma express a very interesting pattern of molecules that are highly relevant to the immune system," Dr. North said. "They express indoleamine 2,3-dioxygenase, which helps create a state of maternal immune tolerance to the fetus, and this could help protect the growing hemangioma from attack by activated T cells."

Hemangioma cells also express chemokine receptor 6. Normally expressed in dendritic cells, it might influence the area where shed placental endothelial cells eventually lodge, working "like a homing mechanism to bring the cells to the skin and liver," she said. ■

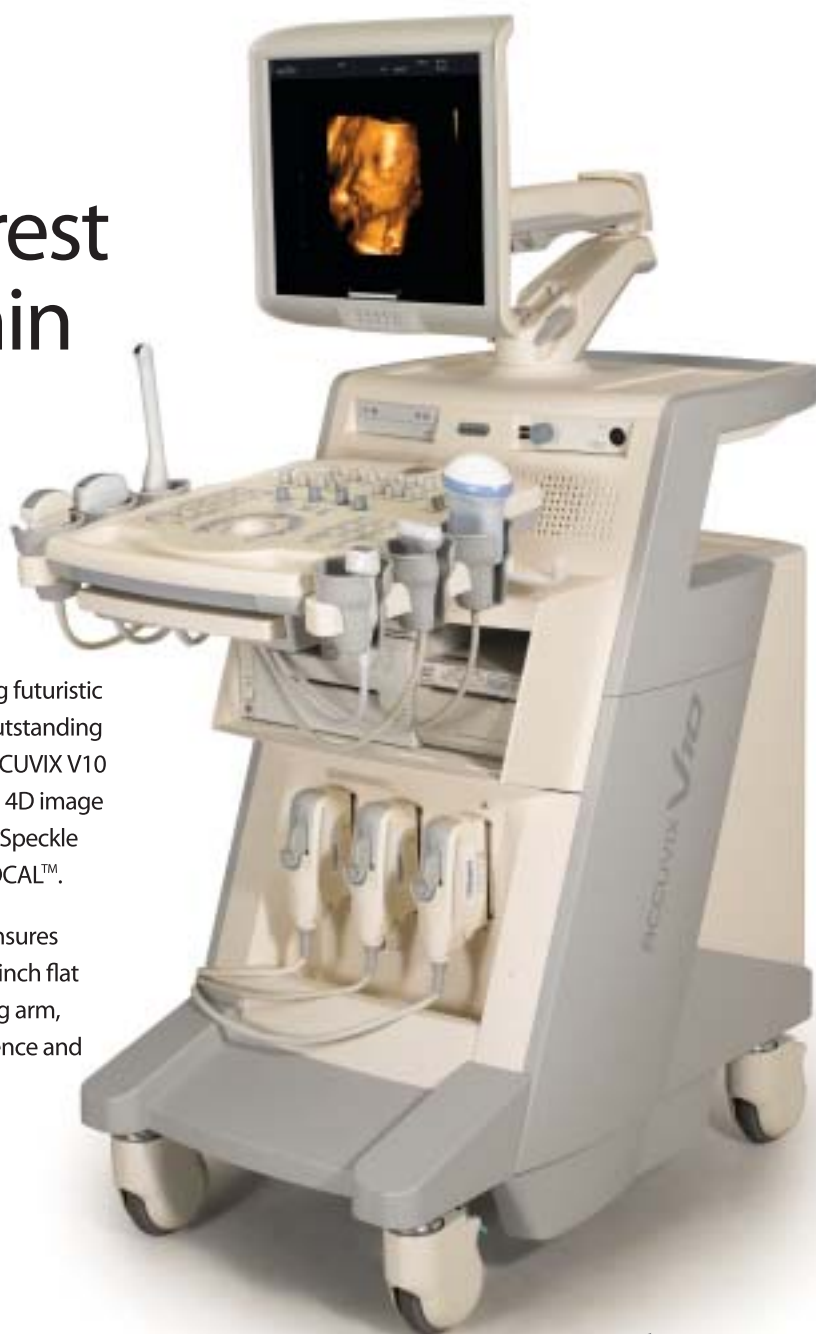
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