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# Congenital hemangioma: Evidence of accelerated involution

[Original Article]

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Outline



Graphics



## Abstract

Objective: To study the course of hemangiomas that proliferate in utero, are fully grown at birth, and begin to regress during early infancy.

Design: We analyzed retrospectively 31 infants with congenital hemangioma seen at Tarnier-Cochin Hospital (Paris) and Children's Hospital (Boston). Diagnosis was made by clinical and radiologic examination and, if necessary, by biopsy. Age, gender, location, appearance, and evolution were noted for each infant.

: Only 3 of 23 congenital hemangiomas were diagnosed in utero by ultra-sonography.
The three most common morphologic forms were raised violaceous tumor with ectatic veins (n = 8), raised grayish tumor with multiple tiny telangiectasias, surrounded by a pale halo (n = 8), and flat infiltrative tumor with violaceous overlying skin (n = 5). Two congenital hemangiomas had associated thrombocytopenic
coagulopathy (Kasabach-Merritt phenomenon). All the untreated congenital hemangiomas (n = 24) regressed by the time the infants were 14 months of age, leaving either atrophic skin or extra skin. Seven congenital hemangiomas

required therapy for complications: three tumors responded to systemic corticosteroid administration and four were resected.

Conclusion: Hemangiomas can proliferate in utero and manifest as fully developed tumors at birth. These congenital hemangiomas can regress rapidly. This phenomenon raises new questions about the pathogenesis of this tumor. (J Pediatr 1996;128:329-35)

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Hemangiogenesis seems to be triggered postnatally; most tumors appear during the first 4 weeks of life, whatever the infant's gestational age. This has suggested to some investigators that hemangiomas grow because of either deprivation of maternal hormones or excessive postnatal oxygen therapy. [1,2] A possible clue to the pathogenesis of hemangiomas is their increased frequency (23 percent) in premature infants who weigh less than 1000 mg. [3]

Most often, a nascent hemangioma appears in the neonatal nursery as either an erythematous macule, a localized telangiectasia, a pale spot, or an ecchymosis-like
birthmark. [4,5] Hemangiomas, however, can be in "full bloom" at birth. [6] Such congenital tumors have been detected as early as the second trimester of pregnancy with high-resolution prenatal ultrasonography. [7-9] Unfortunately, these fetal tumors are often labeled incorrectly as either "cavernous hemangioma"
or "vascular malformation." [10-12] Conversely, prenatal vascular malformations have been mistakenly called "hemangioma." [13,14]

Our study was a collaborative investigation of 31 infants with congenital, fully grown hemangiomas, undertaken to (1) recount investigations used to make the diagnosis, (2) review the clinical findings and the natural course, and (3) explore possible reasons for the differences between prenatal and postnatal hemangiogenesis.

## METHODS

Sixteen infants with congenital hemangioma were identified at the Hospital Tarnier-Cochin Pediatric Dermatologic Unit, Paris, and 15 such tumors were registered in the Children's Hospital Vascular Anomalies Program, Boston. Photographs has been taken at birth and during subsequent months. Routine antenatal ultrasonography was done during 7 of 15 Boston pregnancies and during all 16 pregnancies in France.

Postnatal diagnosis was made by either physical examination, radiography, or histopathologic examination and confirmed by subsequent behavior of the tumor. Postnatal radiographic studies in 13 infants included ultrasonography with color Doppler examination (n = 7), computed tomography (n = 2), magnetic resonance imaging (n = 5), and angiography (n = 1). In eight infants the diagnosis was confirmed by a 3 mm punch biopsy. Age, gender, location, appearance, and evolution of the tumor were documented; the time to completion of involution, defined as no change in size or color for 6 months, was also noted.

## RESULTS

Clinical presentation. The gender ratio for congenital hemangiomas was 14 girls to 17 boys. This differs from the usual 3:1 ratio for hemangiomas that develop postnatally. The tumors were located in the craniofacial area (n = 13), the

lower limbs (n = 13), the upper extremities (n = 3), and one each on the abdomen and the sacrococcygeal area.

The majority of congenital hemangiomas manifested as three morphologic variations: (1) raised violaceous tumor, with large radial veins (n = 8) Figure 1, Figure 2 hemispheric tumor covered with multiple tiny cutaneous telangiectases,
surrounded by a pale rim (n = 8) Figure 2, and Figure 3 pink-to-violaceous tumor, firm to palpation because of dermal or hypodermal infiltration (n = 5) Figure 3. Tumors of the third variety were usually located in the lower extremity (3/5). Two infants had a soft, deep congenital hemangioma with normal overlying skin; both were located in the neck area Figure 4. One forehead hemangioma underwent rapid necrosis within a few days after birth, with subsequent sloughing of the tumor, which left an atrophic scar. A thrill was noted in a small abdominal tumor and in two large (6 X 6 cm) hemangiomas, both of which were complicated by Kasabach-Merritt coagulopathy Figure 3. Ulceration was present in two of the fully grown hemangiomas; another tumor had a central scar at birth. Four infants with congenital hemangioma had minor abnormalities of adnexal structures: alopecia (n = 1), transient hypertrichosis (n = 2), and transient milia (n = 1).

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Figure 1. Violaceous, lobulated, firm congenital hemangioma of cheek, seen at birth (left). Tumor nearly became involuted by 7 months of age (right).
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Figure 2. Raised congenital hemangioma of calf, with central telangiectases and pale peripheral halo (left). Note dermal atrophy 8 months later (right).
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Figure 3. Large, high-flow congenital hemangioma of thigh, complicated with Kasabach-Merritt phenomenon (left), resembles infantile sarcoma. [24] Note rapid regression after only 2 weeks of corticosteroid therapy (right) (drug therapy was discontinued 2 weeks later).
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Figure 4. Deep, soft cervical hemangioma, mimicking lymphatic malformation (left). Only fibrofatty residuum and extra skin remain at 10 months of age (right).
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Diagnosis. Although routine antenatal ultrasonographic evaluation was done during 23 of 31 pregnancies, only three hemangiomas (Boston cases) were diagnosed prenatally at 12, 20, and 37 weeks of gestation, respectively. Each tumor had an echogenic vascular parenchyma Figure 5. Prenatal Doppler study (n = 3) revealed high vascularity and fast flow in these three hemangiomas.

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Figure 5. Antenatal sonogram showing large exophytic, inhomogeneous soft tissue mass arising from a 20-week fetal cranium. Note flattened left parietal bone.
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The diagnosis of congenital fully grown hemangioma was usually obvious by physical examination. Postnatal imaging was used if the diagnosis was equivocal.

Ultrasonography with color Doppler study of seven infants revealed an echogenic and well-circumscribed vascular mass in each instance. One 5 X 5 cm scalp hemangioma had ultrasonographic signs of a central calcified cyst surrounded by fatty tissue and enlarged draining vessels. There was no evidence of arteriovenous
shunting in this lesion. Two infants with congenital hemangioma underwent computed tomography and five infants had magnetic resonance imaging. Angiography was performed in one neonate because of concern that the mass was a sacrococcygeal
teratoma.

Punch biopsy was used to confirm the diagnosis in infants (n = 8) who had firm-to-hard lesions, to rule out infantile sarcoma or infantile myofibromatosis.

Treatments. The majority of congenital hemangiomas (24/31) did not require therapy. Corticosteroid (prednisolone) was used for three endangering lesions: (1) one associated with Kasabach-Merritt coagulopathy, (2) a large hemangioma deforming the ear, and (3) a periorbital hemangioma likely to cause corneal deformation, astigmatism, and amblyopia. The second hemangioma (sacrococcygeal), complicated by Kasabach-Merritt phenomenon and high-output congestive heart failure, received a trial of interferon alpha-2a and digoxin for 5 1/2 weeks. Surgical resection became necessary because of an equivocal response to pharmacologic therapy, ulceration, and sepsis. After excision, the infant's cardiac function and platelet count returned to normal and the tumor did not recur. A scalp hemangioma, surgically resected at 4 days of life, contained a calcified cyst filled with old blood. Histopathologic examination, with hematoxylinand-eosin staining, confirmed the diagnosis; there were admixed areas of proliferation and involution. Neonatal surgical resection also was done for two other congenital tumors, one for necrosis and another for auricular deformation.

Accelerated natural involution. Those congenital hemangiomas that did not require either pharmacologic treatment or surgical excision (n = 24) underwent spontaneous regression by 14 months of age. The involution was before 7 months of age in 12 of 24 infants. After regression, dermal and hypodermal atrophy was present in 8 of 24 children Figure 3. Of 24 involuted lesions, 5 had excess skin Figure 4; a scar was visible in 4 children Figure 3, and fibrofatty residuum predominated in 4 of 24 Figure 4. Of 24 children, 4 had either normal skin or minor telangiectasia after regression. A firm, fibrous nodule remaining in one child was surgically resected at 5 years of age. Follow-up evaluation was not possible for one infant.

## DISCUSSION

Large clinical studies of hemangiomas report no correlation between the rapidity of involution and the infants' age at onset of tumor appearance. [15-18] In an earlier review, we noted rare cases of accelerated involution and presumed that these were curiosities. [6,19] We had failed to differentiate nascent hemangiomas
(those beginning proliferation at birth) from congenital, fully grown hemangiomas
that had proliferated in utero. Intrauterine hemangiogenesis has been recognized since the routine use of antenatal ultrasonography [7-11,20]; the earliest diagnosis was made at 14 weeks of gestation. [8] The earliest in our series was noted at 12 weeks of gestation. Detection of a hemangioma by antenatal ultrasonographic examination depends on the gestational age, the fetal position,

and the location and size of the hemangioma, as well as the sonographer's skill. Whenever a parenchymal mass is noted by antenatal ultrasonography, Doppler study can be done to determine the degree of vascularity of the lesion. Hemangioma appears as a fast-flow parenchymatous mass. Once such a mass is discovered, we recommend that it be monitored ultrasonographically every 2 to 4 weeks. Shunting through a large intrauterine hemangioma can cause hydrops fetalis, a complication
associated with a high mortality rate. [11,20,21] Therefore periodic prenatal evaluation with ultrasonography and cardiac studies is necessary. Planned early delivery, sometimes cesarean-section, may be indicated to prevent dystocia, bleeding, or laceration of the tumor during vaginal delivery.

These congenital hemangiomas did not grow further after birth, thus seeming to be either at or past their proliferative peak. Typically, these fully developed tumors are raised, pink to violaceous in color, and firm to hard on palpation. Some lesions have deep dermal and hypodermal infiltration or exophytic nodules. Central ulceration or scar is sometimes present. Ultrasonography with color Doppler, magnetic resonance imaging, or both demonstrate fast blood flow and parenchyma. [22,23] Calcification is rare but is sometimes seen in the involuting phase of hemangioma that manifests postnatally. However, we found this dystrophic change in one fully grown tumor. A biopsy should be done whenever malignancy is suspected.

Other congenital (intrauterine) fetal masses can be confused with hemangioma: arteriovenous malformation, [6] venous malformation, [13,14] ventral abdominal wall defect, [9] infantile fibrosarcoma, [24] infantile myofibromatosis, [25] lymphatic malformation, [26] "Kaposi-like" hemangioendothelioma, [27] teratoma, [28] congenital hemangiopericytoma, [29] lumbar lipomyelomeningocele, [30] and encephalocele. [8]

The congenital hemangiomas in our series, like all hemangiomas, invariably regressed. However, their involution began earlier, usually just after birth, and proceeded more rapidly, on average between 6 and 14 months. Accelerated involution often resulted in dermal and subcutaneous atrophy. Despite intrauterine
onset, these tumors can cause typical postnatal proliferating phase complications,
such as ulceration, obstruction of a vital organ, platelet-trapping coagulopathy (Kasabach-Merritt phenomenon), and congestive heart failure, [31] that require pharmacologic therapy. A reported case of a congenital hemangioma, diagnosed at 22 weeks of gestation, was complicated by Kasabach-Merritt phenomenon [32]; there were two such cases in our series. The majority of congenital hemangiomas in this series (90 percent) did not require treatment. This percentage is similar to that for cutaneous hemangiomas arising postnatally.

Should a hemangioma that threatens the life of the fetus be treated pharmacologically?
The possible effects of corticosteroids on the developing fetus are well known, and include premature closure of the ductus arteriosus, diminished glomerular filtration with salt retention, and gastrointestinal complications. [33] Interferon alpha-2a is an effective antiangiogenic drug, but the interferon family also regulates growth and differentiation, [34] Thus, on the basis of current knowledge, probably neither of these drugs should be given during pregnancy unless there is a real threat to the life of an otherwise healthy fetus. If a potent antihemangiogenic drug were available, it could potentially be given to the fetus directly through an injection in the umbilical vein.

The occurrence of intrauterine hemangiogenesis as early as the late first trimester suggests reevaluation of the paradigm of postnatal onset. Proliferation
and involution can be envisioned by the concept that these tumors are "angiogenesis
dependent." [35,36] A proliferative-phase hemangioma is characterized by high expression of angiogenic stimulators (i.e., vascular endothelial growth factor and basic fibroblast growth factor [37]) and low expression of interferon beta, an inhibitor of angiogenesis (Fidler IJ: unpublished data). In vitro and in vivo assays demonstrate that vascular endothelial growth factor and basic fibroblast growth factor stimulate angiogenesis and that interferon inhibits angiogenesis by lowering the concentration of basic fibroblast growth factor. [38,39] Vascular endothelial growth factor also has been implicated as an inducer of endothelial proliferation during embryonic angiogenesis. [40] Furthermore, interferon alpha is found in amniotic fluid, [41] the fetoplacental unit, [42] and placental blood. [43] Trophoblastic interferon also regulates embryonic differentiation of trophoblastic cells and down-regulates nontrophoblastic cells. [44] Trophoblast produces a sixfold higher level of interferon in the first trimester than in the third trimester. [45] Perhaps an intrauterine hemangioma results from a low concentration of trophoblastic interferon in a localized area of the developing fetus. Thus the postnatal appearance of hemangioma might result from a sudden decrease in trophoblastic interferon as the infant separates from the placental circulation.

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