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Demographic and Clinical Characteristics and Risk Factors for Infantile Hemangioma

A Chinese Case-Control Study

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Objectives: To study the demographic and clinical features of infantile hemangioma in China; to learn in more detail the risk factors for developing this disease; and to identify clinical characteristics associated with complications, associated risks, and the need for systemic treatment.

Design: A case-control study of 1832 prospectively enrolled children with hemangiomas and 1832 controls matched for age, sex, region, and hospital attending the dermatology department between 2005 and 2008.

Setting: Two large hospitals in central south China.

Patients: A total of 1832 children with hemangiomas.

Main Outcome Measures: Demographic and clinical presentations were summarized and compared with data from previous studies of hemangiomas. Predictive clinical factors for complications and/or treatment and potential risk factors for infantile hemangioma were analyzed by logistic regression.

Results: The clinical features of our study patients were different from those of other race/ethnicity groups reported by previous studies with regard to the morphologic subtypes, complications, and predictors for complications and/or oral corticosteroid treatment. After adjustment, significant risk factors for hemangiomas included lower level of maternal education (odds ratio [OR], 0.61; 95% confidence interval [CI], 0.57-0.66), mother engaged in manual labor (OR, 1.29; 95% CI, 1.12-1.48), multiple gestation (OR, 1.20; 95% CI, 1.05-1.36), maternal medication use during the periconceptional period (OR, 2.08; 95% CI, 1.88-2.31), and a positive family history of hemangiomas (OR, 1.55; 95% CI, 1.40-1.72).

Conclusion: Besides yielding several new findings with respect to risk factors for hemangiomas, the current study also suggests that the Chinese clinical features of hemangiomas are somewhat different epidemiologically from those in the West.

Arch Dermatol. 2011;147(9):1049-1056.

Published online May 16, 2011.

doi:10.1001/archdermatol.2011.122

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INFANTILE HEMANGIOMAS ARE THE most common vascular tumors of childhood, characterized by an initial phase of rapid proliferation followed by an involutonal phase.^{1,2} Although the pathogenesis of hemangiomas is not well understood, epidemiologic findings and advances in the knowledge of angiogenesis have provided some clues, such as the theory of placental origin, the specific marker GLUT1 (glucose transporter 1), and the activation of angiogenesis factor ang2 (angiopoietin-2).³⁻⁶

Most infantile hemangiomas are small and innocuous, but a considerable number cause functional deficits, life-threatening conditions, or permanent sequelae.⁷⁻⁹ Furthermore, hemangiomas may have associated structural anomalies, in-

cluding PHACE syndrome, which represents a spectrum of associated anomalies (posterior fossa brain malformations, hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, and eye abnormalities).¹⁰⁻¹² For these cases, closer monitoring and earlier intervention to prevent permanent disfigurement are required. It is well recognized that lesion size, location, and particularly morphologic subtype are risk factors for potential complications and treatment.^{13,14} However, racial differences have been observed in the demographic and clinical features of infantile hemangioma.^{15,16} For example, Hispanics have a more common segmental subtype, more complex hemangiomas, and greater morbidity than all other racial and ethnic groups.¹⁶ Scanty information exists on the clinical characteristics predict-

ing complications and treatment of hemangiomas in Asian populations.

Epidemiologic studies have suggested that female sex, white non-Hispanic ethnicity, premature birth, and history of chorionic villus sampling are risk factors for developing infantile hemangioma.^{15,17-21} Other independent or related factors include placenta previa, increased maternal age, pre-eclampsia, multiple gestation, and low birth weight.^{15,21,22} Yet evidence for these associations comes entirely from Western populations. To our knowledge, no study has investigated the risk factors for infantile hemangioma in Asian countries, where environmental and genetic backgrounds differ considerably from those in the West. Many prenatal and perinatal factors, such as environmental factors, have not been examined previously, in part because hemangiomas are usually not apparent at birth and thus cannot be documented by conventional birth defect registries.²¹ As an important epidemiologic indicator, the socioeconomic status (SES) effects on pregnancy outcomes and other diseases have been widely studied,²³⁻²⁵ but to our knowledge, SES effects on infantile hemangioma have not previously been reported.

We conducted this study of a relatively large sample of Chinese patients with infantile hemangiomas to understand their demographic and clinical features, to better characterize risk factors for developing the disease, and to identify clinical characteristics associated with complications, associated conditions (including visceral hemangiomas and other anomalies), and the need for therapeutic intervention.

METHODS

STUDY POPULATION

Children with a diagnosis of infantile hemangioma were prospectively enrolled from Xiangya Hospital, Central South University, and a maternal and child health hospital in Hunan province during January 1, 2005, through December 31, 2008. These 2 large hospitals provide care for a population of approximately 60 million people per year who live in the central south region of China.

CASES

The diagnosis of infantile hemangioma was confirmed by physical examination, clinical behavior of the lesions, and (when necessary) ancillary studies. Clinical follow-up continued until October 31, 2009. Inclusion criteria were (1) age 12 years or younger at the time of enrollment and (2) the presence of 1 or more infantile hemangiomas. Exclusion criteria were (1) presence of other vascular malformations in the absence of infantile hemangiomas; (2) unwillingness of parents to be interviewed; (3) inability to contact birth mother for interview; and (4) patients whose matched controls developed hemangiomas after enrollment.

CONTROLS

The inclusion criteria for controls were (1) outpatient status at the same department as case patients; (2) presence of recent-onset minor dermatologic conditions or purpose of visit for health checkup only; (3) absence of hemangioma lesions and other angiomatous lesions confirmed by trained dermatolo-

gists; and (4) history of attending the department closest in duration to that of the newly enrolled case. The controls were randomly selected and individually matched to the case patients for sex, date of birth (<2 weeks' difference), region (urban vs nonurban), and hospital. Control infants younger than 1 month were reexamined when they reached age 3 months to rule out the later development of hemangiomas. The proportions of urban and nonurban cases and controls were not significantly different among hospitals.

There were 4 case patients whose birth mothers were unable to be contacted for an interview. No parents of the remaining case patients refused participation. Another case patient was excluded because her matched control developed a hemangioma found on reexamination. The parents of 22 controls were unwilling to participate, and those controls were replaced. Finally, a total of 1832 patients and 1832 controls were enrolled.

The training sessions and questionnaire were standardized before interviewing. The standardized questionnaire with information on clinical presentation, SES, and prenatal and perinatal variables was administered to both case patients and controls by the investigator who was a trained physician and masked to the interviewee's group assignment. All birth parents were interviewed face to face in a similar manner.

Questionnaire information was categorized as clinical presentation, SES, and prenatal and perinatal characteristics. Clinical presentations included lesion size, number, location, morphologic subtype, treatment (eg, oral corticosteroid therapy, pulsed-dye laser), complications, associated anomalies, visceral involvement, and infantile hemangioma-related medical records. Characteristics of SES included the mother's and father's education level, annual household income, and occupations. Annual household income was measured in Chinese Yuan (¥) from the year before the mother became pregnant, and it was categorized as less than ¥2000, ¥2000 to ¥5000, ¥5000-¥10 000, and more than ¥10 000. Others SES characteristics included maternal and paternal ages and birth order.

Prenatal and perinatal characteristics were categorized as lifestyle, environmental, and biomedical variables. Lifestyle variables included maternal passive smoking, alcohol drinking, and tea drinking behavior; paternal smoking and alcohol drinking behavior; and presence of animals in the house. Environmental variables included diagnostic irradiation and/or ultrasonographic exposure; new house repair or relocation; frequent maternal use of microwave ovens and/or mobile telephones during pregnancy; and periconceptional noise exposure. Biomedical variables included low birth weight (<2500 g), prematurity (<37 weeks' gestational age), multiple gestation (twins or triplets), mode of delivery (vaginal, cesarean delivery), maternal anemia during pregnancy, previous miscarriage, prepartum complications (pre-eclampsia, threatened abortion, pregnancy-induced hypertension), placental abnormalities, infection (any type, respiratory tract, viral, fungal, genitourinary), stressful life events during pregnancy, conception via in vitro fertilization, history of infertility, chorionic villus sampling, use of folic acid-containing multivitamin supplements, periconceptional use of drugs, fever during pregnancy, excessive vomiting, maternal chronic illness, a history of hemangiomas in first-degree relatives, and a family history of inherited disease.

Oral informed consent was obtained from parents of each participant. This study was approved by the ethics committee at each participating institution and conducted in accordance to the Declaration of Helsinki principles.

STATISTICAL ANALYSIS

A database was constructed with SES, prenatal, and perinatal variables for case patients and controls, and SPSS for Windows, ver-

sion 13.0, was used for all analyses (IBM SPSS, Chicago, Illinois). All odds ratios (ORs) were calculated using Cox regression by a method equivalent to conditional logistic regression, and presented are those that were statistically significant (95% confidence interval [CI] excluding 1.0). All variables presenting an association with infantile hemangioma with $P \leq .15$ were retained for subsequent multivariate analysis that also used conditional logistic regression to assess independent associations with infantile hemangioma. We used χ^2 tests and t tests to compare categorical variables and continuous variables, respectively. The data in which variables demonstrated nonparametric distributions were analyzed using the Mann-Whitney U test for unpaired samples and the Kruskal-Wallis test for more than 2 groups. Logistic regression models were used to address factors predicting complications and/or treatment together with adjustment of potential confounders. Using a 2-sample Z test of percentages, we compared the percentage values of the Chinese group with those of the historical controls.^{13,16}

RESULTS

CLINICAL FEATURES

Demographic and clinical characteristics by race and ethnic group have been described in previous studies of infantile hemangioma.^{13,16} The characteristics of the patients in the present study are summarized in **Table 1**. A total of 40.1% of our patients had lesions at birth, while 59.0% developed lesions within the first month of life. The vast majority of our patients were younger than 1 year (97.8%).

A total of 3012 hemangiomas were observed in 1832 case patients, and the clinical presentations of the 2125 most clinically significant hemangiomas (≤ 3 hemangiomas per patient) were analyzed. Similar to previous reports,^{13,16} lesions were classified into 4 groups: localized, segmental, indeterminate, and multifocal (Table 1). There was a striking prevalence of localized lesions in the study patients, and the most commonly involved site was the face, among which 759 were located periorificially (around the eyelids, nasal ala, tip of the nose, earlobes, and lips) (82.0%), followed by 90 on the anterior cheek (9.7%). Mucous membranes were involved in 402 lesions (18.9%). Some hemangiomas occasionally extended into more than 1 site. The proportion of involvement of other sites, number of lesions with complications, and number treated with oral corticosteroids are also listed in Table 1. Using the Z test, we found that the Chinese group was significantly different from historical controls^{13,16} with regard to morphologic subtypes and complications ($P = .001$) (Table 1).

Fifty hemangiomas with associated anomalies (including PHACE syndrome,¹⁰ cardiac anomalies without other evidence of PHACE syndrome, urogenital abnormalities, or spinal involvement^{16,26}) and/or hepatic hemangiomas (by abdominal imaging) were reported before enrollment (based on medical records) and during the study period (2.4%). No visceral involvements were detected in patients with multifocal hemangiomas.

There were no differences in the incidence of complications ($P = .18$) and increased number of lesions ($P = .08$) between preterm infants and term infants, but the incidence of associated anomalies (including PHACE

Table 1. Comparison of Demographic and Clinical Characteristics of All-Chinese and Combined-Race/Ethnicity Populations With Infantile Hemangioma^a

Characteristic	All Chinese (Present Study)	All Races and Ethnicities Combined ^{13,16}
Female to male ratio	1.77:1	2.4:1
Age at enrollment, mean (SD)	122.9 (200.3) days	11.8 months
Lesion size, mean (SD), cm ²	13.0 (15.4)	18.9 (66.7)
Lesion type		
Localized	1831 (86.2) ^b	1022 (66.8)
Segmental	60 (2.8) ^b	200 (13.1)
Indeterminate	221 (10.4) ^c	253 (16.5)
Multifocal	13 (0.6) ^b	55 (3.6)
Localization		
Head and neck	542 (25.5)	322 (21.0)
Face	926 (43.6)	630 (41.2)
Trunk	362 (17.0)	357 (23.3)
Extremities	280 (13.2)	281 (18.4)
Perineum	95 (4.5)	94 (6.1)
Lesions with complications ^d	650 (31.0) ^b	188 (40.0)
Ulceration	418 (19.7)	75 (21.0)
Obstruction (auditory canal, airway)	12 (0.6)	10 (2.8)
Threat to vision	220 (10.4)	27 (7.6)
Infection (along with ulceration)	85 (4.0)	14 (3.9)
Bleeding (along with ulceration)	26 (1.2)	27 (7.6)
Patients treated with corticosteroids	202 (11.0) ^c	130 (12.3)

^aUnless otherwise noted, data are number (percentage) of lesions.

^b $P < .05$ compared with all races and ethnicities combined.

^c $P > .05$ compared with all races and ethnicities combined.

^dIncludes complications prior to and during the study period.

syndrome, cardiac anomalies without other evidence of PHACE syndrome, or urogenital abnormalities) was increased in preterm infants compared with that in term infants ($P < .001$).

PREDICTIVE FACTORS FOR COMPLICATIONS AND/OR TREATMENT

In analyzing the predictive role of lesion size, we found that hemangiomas with complications were larger than those without complications (Mann-Whitney U test, $P < .001$), and hemangiomas requiring oral corticosteroid treatment were also larger than those did not require oral corticosteroid treatment (Mann-Whitney U test, $P < .001$). For each 10-cm² increase in hemangioma size, there were 9% (OR, 1.096) and 28% (OR, 1.315) increases in the likelihood of having complications and oral corticosteroid treatment, respectively ($P < .001$ for all).

After controlling for hemangioma size, we found that facial hemangiomas were 2.66 times more likely to have complications (OR, 2.66; 95% CI, 2.12-3.33 ($P < .001$)) and 3.42 times more likely to receive oral corticosteroid treatment (OR, 3.42; 95% CI, 1.43-8.15) ($P < .001$) than nonfacial hemangiomas. However, hemangioma subtype was not a predictor for oral corticosteroid treatment or for the development of complications after size and location were controlled for.

Large, deep, and tumorlike hemangiomas located on the anterior cheek (**Figure**), which were categorized as indeterminate lesions according to previous literature,^{13,16} were 7.28 and 9.27 times more likely to receive



Figure. Frontal (A) and oblique (B) views of a large, deep, tumorlike hemangioma located on the right anterior cheek of an 8-week-old infant. The patient had been treated with oral prednisone for 1½ months.

Table 2. Main Characteristics of Case and Control Patients

Characteristic	Case Patients			Control Patients			P Value ^a
	Total (n=1832)	Urban (n=779)	Nonurban (n=1053)	Total (n=1832)	Urban (n=779)	Nonurban (n=1053)	
Age, mean (SD), d	122.9 (200.3)	117.4 (231.5)	127.0 (173.7)	123.8 (200.5)	117.9 (231.6)	128.1 (173.9)	.90 ^b
Female to male sex ratio	1.77	1.95	1.65	1.77	1.95	1.65	>.99 ^c

^aComparisons between all case patients and all control patients (regardless of urban/nonurban status).

^bt Test.

^cPearson χ^2 test.

oral corticosteroid treatment (OR, 7.28; 95% CI, 2.25-23.6) ($P = .001$) and have associated anomalies (including PHACE syndrome, cardiac anomalies without other evidence of PHACE syndrome, urogenital abnormalities, or spinal involvement) (OR, 9.27; 95% CI, 4.28-20.07) ($P < .001$), respectively, than all other subtypes after size was controlled for. When comparing outcomes between subtypes, we found that this subtype had higher rates of associated anomalies than segmental, localized, multifocal, and the other indeterminate hemangiomas (Kruskal-Wallis test, $P < .001$).

RISK FACTORS FOR INFANTILE HEMANGIOMA

Controls appeared well matched to case patients for age, sex, region (urban and nonurban), and hospital (**Table 2**). Socioeconomic, prenatal, and perinatal characteristics of the 1832 patients and 1832 control subjects are listed in **Table 3**. Crude and adjusted ORs of the socioeconomic, prenatal, and perinatal measures in relation to infantile hemangioma are listed in **Table 4** and **Table 5**, respectively.

SOCIOECONOMIC CHARACTERISTICS

In univariate analysis (Table 4), less maternal education, less paternal education, mother engaged in manual labor, household income, and birth order were statistically associated with infantile hemangioma ($P < .001$ for all). Adjusted results of this study (Table 5) show a decreased infantile hemangioma association with higher ma-

ternal education (adjusted OR, 0.61; 95% CI, 0.57-0.66). In addition, mother engaged in manual labor posed a 1.29 greater risk of infantile hemangioma (adjusted OR, 1.29; 95% CI, 1.12-1.48), but the associations of paternal education, household income, and birth order with infantile hemangioma risk were statistically nonsignificant after adjustment.

PRENATAL AND PERINATAL CHARACTERISTICS

Among the environmental and lifestyle variables investigated, none emerged as a statistically significant risk predictor in univariate and multivariate analyses. However, univariate analysis revealed several biomedical variables that were positively associated with infantile hemangioma, including low birth weight, prematurity, multiple gestation, previous miscarriage, maternal respiratory tract infection, periconceptional use of drugs, and a positive family history in first-degree relatives (Table 4). In multivariate analysis (Table 5), there was a borderline association between multiple gestation and infantile hemangioma (adjusted OR, 1.20; 95% CI, 1.05-1.36). Among the risk factors, periconceptional use of drugs was the strongest risk factor (adjusted OR, 2.08; 95% CI, 1.88-2.31).

COMMENT

This study, which was conducted in China, reaffirms previous findings regarding female sex predominance, fam-

Table 3. Distribution of 1832 Patients With Infantile Hemangioma and 1832 Age-, Sex-, Region-, and Hospital-Matched Controls^a

Characteristic	Cases (n=1832)	Controls (n=1832)
Socioeconomic Variables		
Maternal age at delivery, y		
<20	31 (1.7)	27 (1.5)
20-29	1269 (69.3)	1307 (71.3)
30-34	399 (21.8)	372 (20.3)
35-39	101 (5.5)	89 (4.9)
>39	32 (1.7)	37 (2.0)
Paternal age at delivery, y		
<20	19 (1.0)	22 (1.2)
20-29	1262 (68.9)	1285 (70.1)
30-34	398 (21.7)	377 (20.6)
35-39	107 (5.8)	97 (5.3)
>39	46 (2.0)	51 (2.8)
Maternal education		
College or higher	46 (2.5)	221 (12.1)
Senior high school/vocational	72 (4.0)	640 (34.9)
Junior high school	502 (27.4)	639 (34.9)
Primary school	1186 (64.7)	327 (17.8)
Illiterate/semiliterate	26 (1.4)	5 (0.3)
Paternal education		
College or higher	90 (4.9)	299 (16.3)
Senior high school/vocational	176 (9.6)	558 (30.5)
Junior high school	658 (35.9)	675 (36.8)
Primary school	895 (48.9)	294 (16.0)
Illiterate/semiliterate	13 (0.7)	6 (0.3)
Maternal occupation		
Manual labor	247 (13.5)	72 (3.9)
Other occupation	1155 (63.0)	1271 (69.4)
Unemployed	430 (23.5)	489 (26.7)
Paternal occupation		
Manual labor	183 (10.0)	157 (8.6)
Other occupation	1283 (70.0)	1244 (67.9)
Unemployed	366 (20.0)	431 (23.5)
Household income, ¥		
<2000	89 (4.9)	19 (1.0)
2000-5000	1080 (59.0)	343 (18.7)
5000-10 000	528 (28.8)	633 (34.6)
>10 000	135 (7.4)	837 (45.7)
Birth order		
1	1197 (65.3)	1382 (71.4)
≥2	635 (34.7)	450 (24.6)
Prenatal and Perinatal Variables		
Lifestyle variables		
Maternal smoking		
Yes	48 (2.6)	26 (1.4)
No	1784 (97.4)	1806 (98.6)
Paternal smoking		
Yes	749 (40.9)	703 (38.4)
No	1083 (59.1)	1129 (61.6)
Maternal alcohol drinking		
Yes	66 (3.6)	83 (4.5)
No	1766 (96.4)	1749 (95.5)
Paternal alcohol drinking		
Yes	326 (17.8)	334 (18.2)
No	1506 (82.2)	1498 (81.8)
Maternal tea drinking		
Yes	37 (2.0)	45 (2.5)
No	1795 (98.0)	1787 (97.5)
Frequent Maternal passive smoking		
Yes	217 (11.8)	199 (10.9)
No	1615 (88.2)	1633 (89.1)
Presence of animals in house		
Yes	194 (10.6)	187 (10.2)
No	1638 (89.4)	1645 (89.8)

(continued)

ily history of hemangiomas, low incidence of associated anomalies, and good overall prognosis in patients with infantile hemangioma.^{4,13,16,27-29} Our data also demon-

Table 3. Distribution of 1832 Patients With Infantile Hemangioma and 1832 Age-, Sex-, Region-, and Hospital-Matched Controls^a (continued)

Characteristic	Cases (n=1832)	Controls (n=1832)
Environmental Variables		
Diagnostic irradiation during pregnancy		
Yes	12 (0.7)	10 (0.5)
No	1820 (99.3)	1822 (99.5)
Diagnostic ultrasonography during pregnancy		
Yes	1303 (71.1)	1265 (69.1)
No	529 (28.9)	567 (30.9)
Frequent noise exposure during pregnancy		
Yes	60 (3.3)	82 (4.5)
No	1772 (96.7)	1750 (95.5)
New house repair or relocation during pregnancy		
Yes	170 (9.3)	135 (7.4)
No	1662 (90.7)	1697 (92.6)
Frequent use of mobile telephone during pregnancy		
Yes	209 (11.4)	252 (13.8)
No	1623 (88.6)	1580 (86.2)
Frequent use of microwave ovens during pregnancy		
Yes	38 (2.1)	58 (3.2)
No	1794 (97.9)	1774 (96.8)
Biomedical Variables		
Low birth weight		
Yes	167 (9.1)	29 (1.6)
No	1665 (90.9)	1803 (98.4)
Prematurity		
Yes	160 (8.7)	27 (1.5)
No	1672 (91.3)	1805 (98.5)
Multiple gestation		
Yes	316 (17.2)	11 (0.6)
No	1516 (82.8)	1821 (99.4)
Mode of delivery		
Vaginal	1247 (68.1)	1310 (71.5)
Cesarean	585 (31.9)	522 (28.5)
Previous miscarriage		
Yes	641 (35.0)	331 (18.1)
No	1191 (65.0)	1501 (81.9)
Anemia during pregnancy		
Yes	433 (23.6)	368 (20.1)
No	1377 (75.2)	1428 (77.9)
Unknown	22 (1.2)	36 (2.0)
Prepartum complications (pre-eclampsia, threatened abortion, pregnancy-induced hypertension)		
Yes	184 (10.0)	172 (9.4)
No	1648 (90.0)	1660 (90.6)
Placental abnormalities		
Yes	31 (1.7)	19 (1.0)
No	1801 (98.3)	1813 (99.0)

(continued)

strate that lesion size and location, but not morphologic subtype, were major predictors of complication and/or systemic treatment in our Chinese patient population. Specifically, we observed that large and deep hemangiomas with tumorlike appearances located on the anterior cheek were predictors of steroid therapy and associated anomalies. It is well recognized that facial hemangiomas occur in 2 distinct patterns of tissue involvement: (1) a focal, tumorlike lesion; and (2) a diffuse, plaque-like lesion with a segmental pattern, which is considered to be associated with visceral hemangiomas.^{1,11,30} However, in the present study, magnetic resonance imaging angiography and abdominal imaging were not

Table 3. Distribution of 1832 Patients With Infantile Hemangioma and 1832 Age-, Sex-, Region-, and Hospital-Matched Controls^a (continued)

Characteristic	Cases (n=1832)	Controls (n=1832)
Biomedical Variables (continued)		
Infection		
Any (n = 0 or ≥1)		
Yes	124 (6.8)	89 (4.9)
No	1708 (93.2)	1743 (95.1)
Respiratory tract		
Yes	438 (23.9)	353 (19.3)
No	1394 (76.1)	1479 (80.7)
Viral		
Yes	35 (1.9)	21 (1.1)
No	1797 (98.1)	1811 (98.9)
Fungal		
Yes	105 (5.7)	108 (5.9)
No	1727 (94.3)	1724 (94.1)
Genitourinary		
Yes	111 (6.1)	82 (4.5)
No	1721 (93.9)	1750 (95.5)
Stressful life events during pregnancy		
None	1805 (98.5)	1803 (98.4)
Mild	16 (0.9)	10 (0.6)
Severe	11 (0.6)	19 (1.0)
Conceived via in vitro fertilization		
Yes	22 (1.2)	23 (1.3)
No	1810 (98.8)	1809 (98.7)
History of infertility		
Yes	31 (1.7)	26 (1.4)
No	1801 (98.3)	1806 (98.6)
Chorionic villus sampling		
Yes	7 (0.4)	10 (0.5)
No	1825 (99.6)	1822 (99.5)
Folic acid-containing multivitamin supplement use		
Yes	395 (21.6)	441 (24.1)
No	1437 (78.4)	1391 (75.9)
Periconceptual use of drugs ^b		
Yes	725 (39.6)	100 (5.5)
No	1107 (60.4)	1732 (94.5)
Maternal chronic illness		
Yes	30 (1.6)	28 (1.5)
No	1802 (98.4)	1804 (98.5)
Excessive vomiting		
Yes	225 (12.3)	177 (9.7)
No	1607 (87.7)	1655 (90.3)
Fever during pregnancy		
Yes	86 (4.7)	31 (1.7)
No	1746 (95.3)	1801 (98.3)
A history of hemangiomas in first-degree relatives		
Yes	675 (36.8)	25 (1.4)
No	1157 (63.2)	1807 (98.6)
A family history of inherited disease		
Yes	12 (0.7)	15 (0.8)
No	1820 (99.3)	1817 (99.2)

^aUnless otherwise indicated, data are reported as number (percentage) of subjects.

^bThe periconceptual period refers to the month before conception and the first 3 months after conception.

routinely performed, so it is highly likely that cases with structural anomalies were missed, especially those with segmental hemangiomas. Moreover, these results should be interpreted cautiously. The confidence intervals were wide because the sample size of this morphologic subtype was small, and further research is warranted to identify this association.

Although a high percentage of facial hemangiomas probably represents an ascertainment bias, it is interest-

Table 4. Univariate Analysis of SES, Prenatal, and Perinatal Characteristics of Patients and Controls

Risk Factor	Crude OR (95% CI)	P Value
Maternal education level	0.50 (0.47-0.53)	<.001
Paternal education level	0.63 (0.60-0.67)	<.001
Mother engaged in manual labor	1.64 (1.43-1.88)	<.001
Household annual income	0.53 (0.50-0.56)	<.001
Birth order	1.26 (1.15-1.39)	<.001
Low birth weight	1.80 (1.53-2.10)	<.001
Prematurity	1.79 (1.53-2.11)	<.001
Multiple gestation	2.15 (1.91-2.43)	<.001
Previous miscarriage	1.50 (1.36-1.65)	<.001
Maternal respiratory tract infection	1.14 (1.03-1.27)	.01
Periconceptual use of drugs	3.23 (2.95-3.55)	<.001
A family history of hemangiomas	2.51 (2.28-2.76)	<.001

Abbreviations: CI, confidence interval; OR, odds ratio; SES, socioeconomic status.

Table 5. Multivariate Analyses of SES, Prenatal, and Perinatal Characteristics of Patients and Controls^a

Characteristic	Adjusted OR (95% CI) ^a	P Value
Maternal education level	0.61 (0.57-0.66)	<.001
Mother engaged in manual labor	1.29 (1.12-1.48)	.006
Multiple gestation	1.20 (1.05-1.36)	<.001
Periconceptual use of drugs	2.08 (1.88-2.31)	<.001
A family history of hemangiomas	1.55 (1.40-1.72)	<.001

Abbreviations: CI, confidence interval; OR, odds ratio; SES, socioeconomic status.

^aEducation and occupation were adjusted by each other plus by the covariates multiple gestation, periconceptual use of drugs, and family history of hemangiomas.

ing that facial hemangiomas in our patients were more likely to be located periorificially, which may predispose to cosmetic problems. It was not the increased number of hemangiomas but the incidence of associated anomalies that was increased among preterm infants in our study patients, and this is in disagreement with a previous study.³¹ Compared with historical controls, localized lesions were more common and complications were relatively low in our patients. Despite the potential referral bias in our department, no symptomatic visceral involvements in our study patients were documented, and severe life-threatening complications were very rare.

With respect to risk factors, to our knowledge, our data are the first to demonstrate that SES variables including lower level of maternal education and mother engaged in manual labor are independent risk factors for infantile hemangioma. Mothers with a high level of education may be more likely to gain ability to access and interpret information on reproduction and pregnancy. Occupation may influence pregnancy outcomes via workplace hazards exposure and psychosocial factors, thereby indirectly affecting the risk of infantile hemangioma or other diseases.^{24,25,32,33}

Low birth weight and prematurity have been considered potential risk factors for developing hemangiomas, but our findings show that multiple gestation rather than prematurity or low birth weight is an independent risk factor for developing hemangiomas, owing at least in part

to ethnic and/or racial differences. Interestingly, it has been reported that Chinese women are less likely to have low-birth-weight infants than are white women.³⁴

Although use of drugs was not increased in the hemangioma group in 1 previous report,²¹ maternal medicine use during the periconceptional period was positively associated with hemangiomas in our study. These drugs, including prescription drugs and nonprescription drugs, were categorized as follows: antibiotics, Chinese herbal medicines, antifungal drugs, progesterone, others (including oral contraceptive medications, nonsteroidal anti-inflammatory-containing multiple medications, clomiphene, and ethamsylate), and unknown. There were 846 mothers who took medicines in combination (46.2%). We did not find an association between risk of infantile hemangioma and each type of medication when they were used alone (data not shown). There remains a need to further study the possible role of maternal use of drugs in infantile hemangioma.

One major limitation of the current study is the potential for recall bias, and so we took a number of steps to minimize the potential sources of error. First, the matching design, to some degree, offsets exposure misclassification. Second, the questionnaire was standardized both for case patients and controls by uniformly trained interviewers. Third, the use of hospital controls assured a high level of cooperation from the parents of case patients.^{23,35} In addition, we conducted the interview when the participants first presented to the clinics, and the recall periods in both cases and controls were shorter than those reported in a previous study.²²

Another limitation is that hospital-based cases do not represent the total distribution of infantile hemangioma occurring in the general population. However, most of the lesions in this study were localized hemangiomas (86.2%), which are the most common and the most likely subtype to be encountered in a primary care setting.²¹ Furthermore, these data were collected consecutively from general dermatology practices, which should be more generalizable than those from pediatric dermatology practices. In addition, each control was chosen based on a history of attending the department closest in duration to that of the newly enrolled case.

In conclusion, this study shows that in Chinese patients with infantile hemangioma, lesion size and location are significant prognostic factors for complications and steroid therapy. Moreover, in the population studied, patients with large facial hemangiomas needed more careful monitoring and systemic therapy. Furthermore, our study suggests that social inequalities and several new biomedical risk factors have a role in the development of infantile hemangiomas in a Chinese population. These results may help provide clues to prevention actions and further study on the origins of this vascular tumor.

Accepted for Publication: March 16, 2011.

Published Online: May 16, 2011. doi:10.1001/archdermatol.2011.122

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Financial Disclosure: None reported.

Funding/Support: This study was supported in part by grant 2009sk3178 from the Social Development Support Program of Hunan Province, China.

Role of the Sponsors: The sponsors had no role in the design and conduct of the study; in the collection, analysis, and interpretation of data; or in the preparation, review, or approval of the manuscript.

Additional Contributions: Jianyang Hu, MD, and her colleagues at the maternal and child health hospital of Hunan province, Changsha, Hunan, contributed to this work. Linyong Xu, MD, provided statistical expertise.

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Archives Web Quiz Winner

For a complete presentation of this case and an in-depth discussion of the entity, please see next month's edition of the *Archives*. Congratulations to the winner of our June quiz, Jaume Querol Riu, MD, Santa Coloma de Gramenet, Spain. The correct answer to our June challenge was *myxoid dermatofibrosarcoma protuberans*. For a complete discussion of this case, see the Off-Center Fold section in the July *Archives* (Kunisada M, Nagai H, Shimizu H, Yogiarti F, Nishiyama S, Nishigori C. Double-headed nodules on the abdomen. *Arch Dermatol.* 2011;147[7]:857-862).

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