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CLINICAL REPORT

Maternal and Perinatal Factors of Importance for Occurrence and Severity of Infantile Haemangioma

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To determine which patient and maternal factors are associated with the occurrence and the severity of infantile haemangioma (IH), a single-centre retrospective observational study was conducted with 96 haemangioma patients and 143 age-matched control babies, born in the same hospital between March 2012 and March 2013. The IH patients were selected according to diagnosis from dermatologists, either consulted from the department of paediatrics or in outpatient setting. Unplanned female children whose mothers smoked and/or consumed alcohol when pregnant was more likely to have IH ($p < 0.0.05$). The higher the birth weight, the more superficial the haemangioma ($p = 0.023$), and localised lesions were more common in singleton babies ($p = 0.023$) and babies conceived by normal fertilisation ($p = 0.002$). The occurrence and severity of IH is not only influenced by patient factors but also by maternal factors especially care during pregnancy period. By controlling these factors, the incidence and severity of IH may be lowered.
Key words: infantile haemangioma; maternal factor; perinatal care.

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Infantile haemangioma (IH) is the most common benign vascular tumour of infancy. The pathogenesis is complex, and both genetic and perinatal factors are known to be associated. Various demographic studies have revealed many factors related to the incidence of IH such as female gender, white non-Hispanic race, low birth weight, product of multiple gestation and erythropoietin therapy (1–3). Not only patient factors but some maternal factors are also known to increase the incidence of IH, such as high maternal age, antenatal vaginal bleeding, preeclampsia, low maternal education level, maternal history of drug intake during pregnancy, amniocentesis and *in vitro* fertilisation (1, 3, 4).

Many studies of IH compared the severity based on the features and distribution of the lesion(s) itself. In summary, exophytic and deep haemangiomas are more likely to sustain their growth and leave residue or scar, and segmental haemangiomas usually grow larger, accompany more ulceration and need systemic therapy (5). However, virtually no study has been conducted to elucidate which patient-related and maternal demographic factors may affect the prevalence and the severity of IH.

In the present study, we noticed an unusually high occurrence of IH in institutionalised babies who were mostly born of single mothers whose pregnancies were unplanned and who subsequently gave up their babies for adoption. All babies from the specific infant welfare institution were designated to receive dermatological care at our hospital, and thus we conducted a retrospective case-control study of IH patients under 4 years of age, comparing the IH patients with a control group of babies born at our hospital without any major perinatal problems.

MATERIALS AND METHODS

The study was a hospital-based monocentric retrospective study. The study group of 96 haemangioma patients was compared with the control group of 143 age-matched babies without haemangioma and any major perinatal problem, born in the same hospital between March 2012 and March 2013. The haemangioma patients were selected according to diagnosis from dermatologists of Boramae Hospital, either consulted from the department of paediatrics or in outpatient setting. Full records of gestational and perinatal examination were available. This database study was approved by Institutional Review Board of Seoul National University Boramae Hospital (number: 26-2013-100) on Oct. 31st, 2013.

The following clinical data were systematically recorded for each patient: sex, age, gestational age at birth, birth weight, birth history, singleton/twin, fertilisation type, planned/unplanned pregnancy, maternal smoking/alcohol consumption/medication history, maternal underlying disease (diabetes mellitus/hypertension/preeclampsia), and treatment modalities. History of medication intake/smoking/alcohol consumption during pregnancy period was based on the mothers' recall. Since all patients were Korean, analysis about ethnicity was not conducted. The demographic data are described in Table I.

To evaluate the factors that influence the severity, we subdivided the patient group into several categories. We categorised the subgroups according to the severity as mild, moderate and severe. The indices of severity were depth (superficial, mixed, deep) (Fig. 1), type (localised, segmental, multifocal) (Fig. 2) and treatment modality (spontaneous regression, localised treatment, systemic treatment, localised and systemic treatment). We also analysed the location of the lesions since it is crucial in determining treatment modalities.

Table I. *Demographic data of patients and the results of statistical analysis comparing the risk factors of infantile haemangioma*

	Control group ($n=143$)	Study group ($n=96$)	Univariate analysis p-value
Gestational age, weeks, mean ± SE	37.4 ± 0.2	37.6 ± 0.3	0.564
Preterm or full term, *n* (%)			0.463
Preterm	43 (30.1)	24 (25.0)	
Full term	100 (69.9)	72 (75.0)	
Birth weight, kg, mean ± SE	2.8 ± 0.1	2.8 ± 0.1	0.956
Sex, *n* (%)			0.113[a]
Male	74 (51.7)	39 (40.6)	
Female	69 (48.3)	57 (59.4)	
Birth history, *n* (%)			0.083
Normal vaginal delivery	73 (51.0)	59 (62.8)	
Caesarean section	70 (49.0)	35 (37.2)	
Gestations, *n* (%)			0.576
Singleton	121 (84.6)	84 (87.5)	
Twin	22 (15.4)	12 (12.5)	
Smoking, *n* (%)			**<0.001**[b]
Yes	1 (0.7)	18 (18.8)	
No	142 (99.3)	78 (81.2)	
Alcohol, *n* (%)			**<0.001**
Yes	0 (0)	13 (13.5)	
No	143 (100)	83 (86.5)	
Medication[d], *n* (%)			0.116
Yes	14 (9.8)	16 (16.7)	
No	129 (90.2)	80 (83.3)	
Fertilisation type, *n* (%)			0.061
Normal	132 (82.3)	94 (97.9)	
In vitro fertilisation	11 (7.7)	2 (2.1)	
Parent type, *n* (%)			**<0.001**[c]
Planned	130 (90.9)	71 (74.0)	
Unplanned	13 (9.1)	25 (26.0)	
Underlying disease[e], *n* (%)			0.205
Yes	18 (12.6)	7 (7.3)	
No	125 (87.4)	89 (92.7)	

[a–c]Multiple logistic regression, OR (95% CI); p-value: [a] 1.88 (1.053–3.356); **0.033.** [b] 10.87 (1.229–100); **0.032.** [c] 2.237 (0.966–5.181); 0.06. [d] Medication by mother during pregnancy included most frequently common cold medication, followed by analgesics, antidepressant, antiepileptic, antitussive, appetite suppressant, sleeping pill and insulin. [e] Underlying diseases included most frequently gestational diabetes, hypertension and preeclampsia.
Significance are shown in bold.

Analyses were conducted using SPSS software, version 19. For continuous variables, mean values were compared using the two-sample *t*-test. For categorical variables, distributions of frequencies between samples were compared using the χ^2 test or the Fisher exact test (univariate analysis and multivariate logistic regression). Within the study group, we performed linear-by-linear association and cumulative logistic regression to evaluate factors that influence the severity of IH, comparing 3 groups in each index. Also we categorised the severity into 2 subgroups for each index, such as depth (superficial, mixed or deep), type (localised, segmental or multifocal), and treatment modality (localised, systemic or localised and systemic treatment). In every analysis, missing data were not counted. All p-values < 0.05 were considered to be statistically significant.

RESULTS

Compared to the control group, maternal smoking and alcohol consumption during pregnancy, and parent type (whether planned or unplanned pregnancy) were significantly more frequent in the study group by univariate analysis ($p < 0.001$) (Table I). With multiple logistic regression method, alcohol consumption lost its significance, and only female children whose mother smoked during pregnancy period was more likely to have IH ($p < 0.005$) (Table I).

Within the study group, analyses demonstrated that IH lesions of singleton babies were more likely to be localised compared with those of twin babies ($p = 0.014$), which means they tend to be milder in severity and more amenable to treatment. When the severity was categorised into 2 subgroups, the following results were obtained: the higher the birth weight, the more superficial the haemangioma ($p = 0.023$, OR [95% CI]: 0.419 [0.192–0.915]). Haemangiomas were more localised in babies who were singleton ($p = 0.023$, OR [95% CI]: 4.167 [1.135–15.301]) and conceived by normal fertilisation ($p = 0.002$). Babies of mothers who smoked, took alcohol or medication were more likely to have haemangioma in the head and neck. However, there was no statistically significant difference between 2 groups (Table II).

DISCUSSION

Haemangioma is the most common benign vascular tumour of infancy. The origin of IH is multifactorial, with genetic factors being part of the contributing trig-

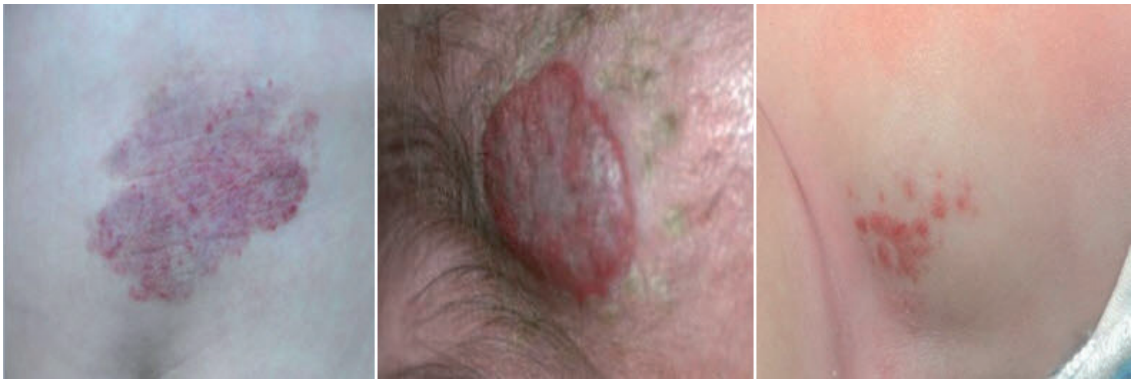

Fig. 1. Infantile haemangioma. Depth: superficial (left), mixed (middle) and deep (right).

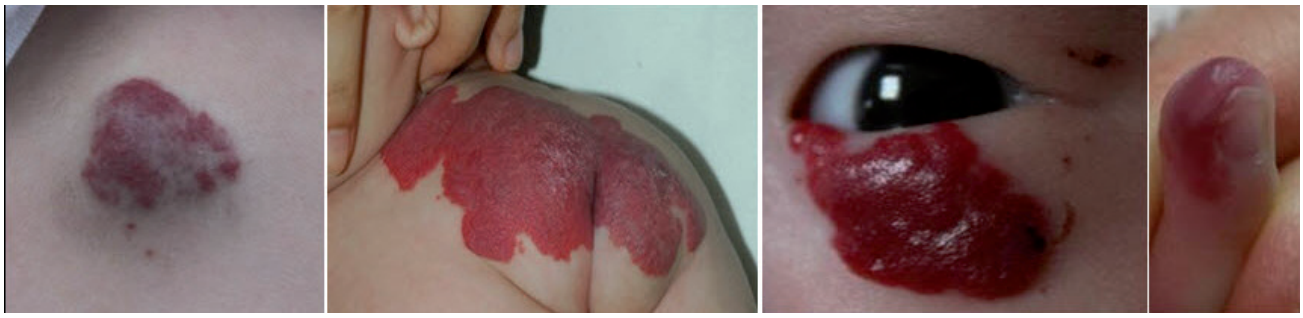

Fig. 2. Infantile haemangioma. Type: localised (left), segmental (middle) and multifocal (on lower eyelid and fingertip – right).

gers. In the present study, we identified 4 independent factors associated with the occurrence of IH, namely, female gender, unplanned pregnancy, maternal smoking and alcohol consumption history while pregnant. Also, product of multiple gestations, low birth weight, and fertilisation type were shown to be factors that influence the severity of IH.

Since the *p*-value of maternal alcohol consumption history was larger than 0.05 in multivariate analysis, its effect on the severity of haemangioma may be underestimated. However, in the patient group, 76.9% (10/13) of mothers who consumed alcohol during pregnancy period smoked, and 55.6% (10/18) who smoked during pregnancy period also drank alcohol, whereas 90.4% (75/83) of mothers who did not consume alcohol during pregnancy did not smoke, and 96.2% (75/78) who did not smoke during pregnancy period did not consume alcohol. We can conclude that maternal smoking and alcohol consumption during pregnancy are highly correlated, and their influence on the severity of IH is mutual.

Consistent with previous studies, IH was more prevalent in the female in this study; however, so far there has been no evidence of haemangioma linked with the X chromosome (1, 5). In the present series, 31 female patients had multiple IHs or IHs on face or in anogenital area compared to 20 male patients. The fact that these lesions are more noticeable and/or their potential to impair vital function may have led to more visits to dermatologists and hence a higher incidence of IH in female in this series.

The results that unplanned children and children whose mothers smoked or drank alcohol while pregnant are more likely to have IH may be explained in a consistent context since normally women quit smoking and stop drinking when they plan to have a baby because of well-known adverse effects on the offspring (6). On the other hand, smoking has a protective effect on preeclampsia due to its proangiogenic effects, as documented by the increased placental growth factor in cigarette dose-dependent manner, and decreased soluble endoglin and anti-angiogenic soluble vascular endothelial growth factor (VEGF) receptor 1 (7). This pro-angiogenetic effect of cigarettes can be understood as a reaction to anaemia and hypoxia.

Hussain et al. (8) detected changes in the pattern of gene expression in the umbilical cord tissue of smokers that can be understood in the context of foetal adaptation to a nutrient-poor or growth-limiting environment and anaemia. The association between IH and erythropoietin treatment in preterm infants also indicate that anaemia,

Table II. *Maternal factors that affected the localisation of infantile haemangiomas*

	Face *n* (%)	Head and neck *n* (%)	Trunk *n* (%)	Extremities *n* (%)	Anogenital area *n* (%)	Multiple *n* (%)	Total *n*	*p*-value
Smoking								0.361
Yes	3 (16.7)	4 (22.2)	3 (16.7)	5 (27.8)	0 (0.0)	3 (16.7)	18	
No	28 (35.9)	7 (9.0)	12 (15.4)	14 (17.9)	4 (5.1)	13 (16.7)	78	
Alcohol								0.278
Yes	2 (15.4)	4 (30.8)	2 (15.4)	3 (23.1)	0 (0.0)	2 (15.4)	13	
No	29 (34.9)	7 (8.4)	13 (15.7)	16 (19.3)	4 (4.8)	14 (16.9)	83	
Medication								0.589
Yes	4 (25.0)	3 (18.8)	3 (18.8)	4 (25.0)	1 (6.3)	1 (6.3)	16	
No	27 (33.8)	8 (10.0)	12 (15.0)	15 (18.8)	3 (3.8)	15 (18.8)	80	
Fertilisation type								0.871
Normal	30 (31.9)	11 (11.7)	15 (16.0)	19 (20.2)	4 (4.3)	15 (16.0)	94	
In vitro fertilisation	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	2	
Parent type								0.104
Planned	26 (36.6)	9 (12.7)	9 (12.7)	10 (14.1)	4 (5.6)	13 (18.3)	71	
Unplanned	5 (20.0)	2 (8.0)	6 (24.0)	9 (36.0)	0 (0.0)	3 (12.0)	25	
Underlying disease								0.461
Yes	5 (71.4)	0 (0.0)	1 (14.3)	1 (14.3)	0 (0.0)	0 (0.0)	7	
No	26 (29.2)	11 (12.4)	14 (15.7)	18 (20.2)	4 (4.5)	16 (18.0)	89	

which acts as stimulator of erythropoiesis, and angiogenesis, possibly provokes the development of IH (2).

Hypoxia is the best known stimulus capable of activating angiogenesis through an increased expression of VEGF (9). Abnormal signalling via VEGF receptors on haemangioma stem cells directs their proliferation and differentiation (10, 11). Therefore, IHs correlate with placental or perinatal hypoxia (9), and prematurity-related disorders can potentially cause an increase in the frequency of haemangioma.

Maternal alcohol intake during pregnancy is likely to cause lower birth weight and higher preterm birth (12). We can expect the group with alcohol consumption history to be more likely to have IH, since both lower birth weight and preterm birth are risk factors of IH.

The finding that offspring of multiple gestations is likely to have severe IH can be explained in 2 different ways, prematurity and progesterone. In *in vitro* fertilisation, the prevalence of multiple gestations is higher; therefore it can be understood in a similar manner.

In multiple gestations, babies have a higher risk to be born prematurely with lower birth weight. In haemangioma formation, an imbalance of angiogenic control mechanisms is important, and IH may result from prematurely removing a foetus from antiangiogenic factors of maternal and placental origin, explaining why twin babies may manifest severe haemangiomas (1). Also in twins, factors known to be correlated with birth weight, such as human placental lactogen, oestriol, and placental protein 5, are higher (13).

Progesterone is a known key hormone for pregnancy maintenance, and its effect in angiogenesis is supported by many studies. Progesterone increases VEGF protein expression, stimulates basic fibroblast growth factor, induces influx of matrix metalloproteinase 6 which is increased in IH, and decreases tissue inhibitor of metalloproteinase 1 and 2, which results in invasion of haemangioma-derived endothelial cells in embryonic tissue (14). In twin pregnancies, maternal serum progesterone levels are nearly twice those in singleton pregnancies (15). This may also increase the risk and severity of IH in twin pregnancies.

Admittedly, this study has some limitations. First of all, the number of patients is too small to represent the whole spectrum of IH patients. Secondly, the indices of severity were measured subjectively solely based on inspection by dermatologists. The monocentric retrospective nature of our study is also a limitation.

The authors declare no conflict of interest.

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