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Exploring the association between chorangioma and infantile haemangioma in singleton and multiple pregnancies: a case–control study in a Swedish tertiary centre

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ABSTRACT

Objectives Placenta or placental chorangioma could be the origin site of infantile haemangioma since they share various histochemical and genetic characteristics with placental vascular tissue. The aim of the current study was to investigate the association between chorangiomas and infantile haemangiomas in singleton and multiple pregnancies.

Materials and methods An informative questionnaire enquiring about the presence or not of infantile haemangioma and including illustrative photos of haemangioma was sent to 469 (153 cases with chorangioma and 316 controls) mothers of 323 singleton (104 cases and 219 controls) and 146 multiple (49 cases and 97 controls) liveborn neonates registered in Sweden. Overall, 310 mothers (66.1%) from 216 singleton and 94 multiple pregnancies (96 cases and 214 controls) provided feedback and their consent to participate in the current case–control study.

Results The incidence of infantile haemangioma showed no statistically significant differences between cases and controls (18.8% vs 18.2%) or between singleton and multiple pregnancies (18.9% vs 17.0%). The frequency of pre-eclampsia was significantly higher in cases with chorangioma compared with controls (41.7% vs 24.3%, OR=2.22, 95% CI 1.33 to 3.71, p=0.0022) and in singleton compared with multiple pregnancies (33.3% vs 21.3%, OR=1.85, 95% CI 1.04 to 3.26, p=0.034), whereas there were no significant differences in the incidence of infantile haemangioma in neonates of mothers with or without pre-eclampsia or in neonates of mothers with multiple compared with singleton pregnancies.

Conclusion There was no association between placental chorangiomas and infantile haemangiomas. Multiple pregnancies or pre-eclampsia were not significantly related to higher incidence of infantile haemangioma.

INTRODUCTION

Chorangiomas (CAs) are the most common non-trophoblastic tumour-like lesions of the placenta, occurring in approximately 1% of pregnancies.[1 2] The majority of CAs is small or microscopic, and is found only after thorough morphological examination of the placenta. The clinical significance of microscopic CAs remains unknown.[1 3] Large lesions, more than 4 cm in diameter, are rare in obstetric practice, and can be diagnosed by prenatal ultrasound imaging or on routine pathological examination.[4] Large CAs are often associated with arteriovenous shunting within the placenta and are linked to a number of maternal and fetal complications, whereas the perinatal mortality rate associated with CAs has been reported as high as 30%.[2 3]

Infantile haemangiomas (IHs) are the most common tumours of childhood, occurring in 5%–10% of infants.[2] They are benign vascular tumours appearing generally within the first few weeks of life. IH typically grows rapidly during the first several months of life, followed by slow involution.[2] Although the life cycle of IHs is well described and several pathogenic mechanisms have been proposed to explain the origin of these tumours, the specific aetiology remains unknown.[5 6] IH shares various histochemical and genetic characteristics with

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placental endothelial cells; also a predictable life cycle of initial proliferation followed by apoptotic involution is similar to that of the placenta. These findings suggest the possibility that the placenta could be the origin site of IH.[5–7] Further, several case reports have described a correlation between the presence of placental CA and the incidence of neonatal haemangiomatosis.[8] This correlation could support the hypothesis of the metastatic niche theory, which proposes that CA or placenta itself secretes substances that prepare the implantation site where IH occurs, and that the IH precursor cells come from the placenta as a 'benign metastasis'.[6] Higher risk for CA and IH has been described in relation to increased maternal age, prematurity, pre-eclampsia and multiple pregnancies.[3 9 10] The aim of the present study was to investigate the association between CA and IH in singleton and multiple pregnancies.

MATERIALS AND METHODS

The current case–control study was based on 15 742 placentas, including 2112 (13.4%) from multiple pregnancies (2095 twin placentas and 17 triplet placentas), which were examined at the Section of Perinatal Pathology, Karolinska University Hospital, Stockholm, Huddinge, during the period of 1996–2012. Regional consensus indications for pathological examination of the placenta included prematurity <32 weeks, pre-eclampsia including HELLP (haemolytic anaemia, elevated liver enzymes and low platelet count) syndrome, repeated haemorrhage, abruption, fetal/neonatal asphyxia (Apgar <7 at 5 min and/or umbilical artery pH <7.0), non-immune hydrops, intrauterine growth retardation (IUGR), fetal or perinatal death, macroscopically abnormal placenta or umbilical cord, and suspicion of chorioamnionitis. Twin placentas were referred in cases of complicated pregnancy (prematurity, twin-to-twin transfusion syndrome and IUGR), whereas chorionicity alone was clearly not an indication for referral. Placentas were examined according to a standardised, detailed protocol including macromorphological and micromorphological analyses. At least one section from the umbilical cord and the membranes and two sections from macroscopically normal placenta were subjected to histopathological examination. Furthermore, all the macroscopically detected focal changes in the placentas were sampled.

CAs were diagnosed in 170 cases (121 singletons and 49 multiple pregnancies) and were coded as haemangiomas according to the Systematised Nomenclature of Medicine. Histological slides of CA cases were rereviewed by two perinatal pathologists (NP and MS) and the diameter of CA was measured. From a cohort of 3000 selected placentas that have been morphologically examined during the period of 2012–2013, 242 singleton and 98 multiple placentas without CAs were selected in our study as controls. The controls were matched with the cases by stratification of the gestational age (group 1: 20–23 gestational weeks; group 2: 24–28 gestational weeks; group 3: 29–32 gestational weeks; group 4: 33–37 gestational weeks; and group 5: 38–43 gestational weeks). Gestational age was retrieved from medical records and evaluated according to ultrasound examinations performed in the beginning of the second trimester. Prematurity was defined as delivery before the 37th week of gestation. Birth weight adequacy to gestational age was evaluated according to Swedish growth charts (mean±2 SD).

An informative questionnaire with illustrative photos of IH was prepared and approved by a local ethics committee (online supplementary file 1). Maternal contact data were collected from the electronic database TakeCare, and the clinical status of respective infants was checked in the electronic database ObstetriX. The questionnaire was sent to 469 (153 cases with CA and 316 controls) mothers of 323 singleton (104 cases and 219 controls) and 146 multiple (49 cases and 97 controls) liveborn neonates registered in Sweden. In total 323 (68.9%) answers were received, of which 13 (4 cases and 9 controls) chose to be excluded from the study. Thus, 310 (66.1%) patients (96 cases and 214 controls) of 216 singleton (64 cases and 152 controls) and 94 multiple (32 cases and 62 controls) pregnancies were included and enrolled into a case–control study. The Regional Ethical Review Board in Stockholm approved the study.

Statistical analysis

Statistical analysis was performed using the R V.3.0.3 software (R Foundation for Statistical Computing, Vienna, Austria). Pearson's X^2 and Fisher's exact tests were used where appropriate. Univariate logistic regression analysis was applied to estimate OR values with 95% CIs for variables (pre-eclampsia and small for gestational age (SGA)), which displayed statistically significant association (p<0.05) with the studied cohort on the contingency tables analysis, whereas multivariate logistic regression analysis was applied to model the relationship of risk factors (type of pregnancy, pre-eclampsia, SGA, gender and prematurity) on the incidence of CA cases.

RESULTS

The incidence of CA in our cohort of 15 742 placentas was 1.08%. The diameter of CA in cases with IH (n=18) ranged between 1 and 100 mm (mean±SD 21.6±24.7 mm), and in cases without IH (n=78) between 1 and 135 mm (mean±SD 20.2±26.6 mm).

There were no statistically significant differences in the incidence of IH either between cases with CA and controls (18.8% vs 18.2%), or between singleton and multiple pregnancies (18.9% vs 17.0%) (tables 1 and 2).

The frequency of multiple pregnancies with IH was higher in cases with CAs compared with controls (33.3% vs 25.6%); however, the difference did not reach the level of statistical significance (table 1).

In our cohort, the frequency of IH was higher in female compared with male neonates (22.3% vs 16.3%, p>0.05). The incidence of IH was higher in female neonates in

Table 1 The incidence of infantile haemangiomas in neonates of cases with CA and in controls without CA

	Cases with CA (N, %)	Controls (N, %)	p Value
IH			0.912
Yes	18 (18.8)	39 (18.2)	
Gender			0.638
Male with IH	8 (44.4)	14 (37.8)	
Female with IH	10 (55.6)	23 (62.2)	
Gender (male)			0.349
With IH	8 (18.8)	14 (18.2)	
Gender (female)			0.509
With IH	10 (19.2)	23 (23.9)	
Pregnancies			0.548
Singleton with IH	12 (66.7)	29 (74.4)	
Multiple with IH	6 (33.3)	10 (25.6)	
Singleton pregnancies			0.955
With IH	12 (18.8)	29 (19.1)	
Multiple pregnancies			0.748
With IH	6 (18.8)	10 (16.1)	
Pre-eclampsia			**0.002**
Yes	40 (41.7)	52 (24.3)	
Pre-eclampsia cases			0.832
With IH	10 (25.0)	12 (23.1)	
Prematurity			0.075
Yes	42 (43.8)	117 (54.7)	
Prematurity cases			0.436
With IH	13 (30.9)	29 (24.8)	
SGA			**0.00010**
Yes	51 (53.1)	64 (30.1)	
SGA cases			0.575
With IH	10 (19.6)	10 (15.6)	

Bold font indicates significant differences (p<0.05).
CA, chorangioma; IH, infantile haemangioma; SGA, small for gestational age.

Table 2 The incidence of IH in neonates of mothers with singleton and multiple pregnancies

	Singleton (N, %)	Multiple (N, %)	p Value
IH			0.682
With IH	41 (18.9)	16 (17.0)	
Gender			0.771
Male with IH	16 (39.0)	6 (42.9)	
Female with IH	25 (60.9)	8 (57.1)	
Gender (male)			0.667
With IH	16 (15.5)	6 (18.8)	
Gender (female)			
With IH	25 (23.4)	8 (19.5)	0.614
Pre-eclampsia			**0.032**
Yes	72 (33.3)	20 (21.3)	
Pre-eclampsia cases			0.382
With IH	19 (26.4)	3 (15.0)	
Cases (CAs) versus controls			0.548
Cases with IH	12 (29.3)	6 (37.5)	
Controls with IH	29 (70.7)	10 (62.5)	
Cases (CAs)			1
With IH	12 (18.8)	6 (18.8)	
Controls			0.612
With IH	29 (19.1)	10 (16.1)	
Prematurity			0.125
Yes	117 (54.2)	42 (44.7)	
Prematurity cases			0.655
With IH	32 (27.4)	10 (23.8)	
Without IH	89 (72.6)	32 (76.2)	
SGA			**0.021**
Yes	71 (33.0)	44 (46.8)	
SGA cases			0.403
With IH	14 (19.7)	6 (13.7)	

Bold font indicates significant differences (p<0.05).
CA, chorangioma; IH, infantile haemangioma; SGA, small for gestational age.

singleton compared with multiple pregnancies (60.9% vs 57.1%, p>0.05), and lower in female neonates in cases with CAs compared with controls (55.6% vs 62.2%, p>0.05) (tables 1 and 2).

The frequency of pre-eclampsia in our study was significantly higher both in cases with CAs compared with controls (41.7% vs 24.3%, OR=2.22, 95% CI 1.33 to 3.71, p=0.0022) and in singleton compared with multiple pregnancies (33.3% vs 21.3%, OR=1.85, 95% CI 1.04 to 3.26, p=0.034). However, the co-occurrence of IH and pre-eclampsia in cases with CAs compared with controls (25.0% vs 23.1%) and between singleton and multiple pregnancies (26.4% vs 15%) did not reach the level of statistical significance (tables 1 and 2). Overall, in the studied cohort, the incidence of IH showed no statistically

significant difference between patients with and without pre-eclampsia (23.9% vs 16.1%, p>0.05).

The incidence of SGA neonates was significantly higher in cases with CA compared with controls (53.1% vs 30.1%, OR=2.63, 95% CI 1.60 to 4.33, p=1.28e-04), as well as in multiple compared with singleton pregnancies (46.8% vs 33.0%, OR=1.78, 95% CI 1.08 to 2.92, p=0.021). However, there was no statistically significant association between SGA and IH in either studied group (tables 1 and 2). Prematurity did not show any statistically significant differences between cases and controls or multiple and singleton pregnancies as study groups were matched by gestational age (tables 1 and 2).

Table 3 Multivariate logistic regression analysis for chorangiomas

Variables*	OR (95% CI)	p Value
SGA	**2.08 (1.19 to 3.63)**	**0.010**
Gender (female)	1.20 (0.70 to 2.04)	0.495
Prematurity (yes)	**0.51 (0.29 to 0.90)**	**0.021**
Pre-eclampsia (yes)	**2.09 (1.15 to 3.79)**	**0.015**
Pregnancies (multiple)	1.36 (0.74 to 2.47)	0.311

Bold font indicates significant results (p<0.05).
*The references for variables entered into the model were as follows: SGA (no SGA); gender (male); prematurity (no prematurity); pre-eclampsia (no pre-eclampsia); pregnancies (single).
SGA, small for gestational age.

In multivariate analysis, pre-eclampsia (OR=2.09, p=0.015), SGA (OR=2.08, p=0.01) and prematurity (OR=0.51, p=0.021) were found to have an impact on the incidence of CA cases (table 3).

DISCUSSION

Many mechanisms and various hypotheses have been proposed to explain the aetiology of IHs, which still remains unclear. According to the placental hypothesis, IH originates from placental progenitor cells.[11] This theory is supported by molecular biology and immuno-phenotyping data, as well as indirect clinical associations.[5] IH and placental vasculature share expression of several cell surface markers including the GLUT1, Lewis Y antigenic FcyR11 and merosin, which are typically expressed only on tissues of neural or placental origin.[6] Also, remarkable similarities in microarray expression profiles of IH and placental tissue have been reported, supporting a possible relationship.[6] Further, expression of human chorionic gonadotropin and human placental lactogen by endothelium of proliferating but not involuting IH suggests that IH might origin from a placental chorionic villus mesenchymal tissue rather than from trophoblast.[6] According to the latter, one line of evidence for possible pathogenetic mechanism is that placental endothelial cells embolise to the fetal cutaneous vessels and proliferate in areas with relative hypoxia.[2 12] Another hypothesis of pathogenesis is that IH is caused by somatic mutation in a gene which mediates endothelial cell proliferation.[2] Several additional hypotheses regarding the origin of the IHs are discussed in the literature, including tissue hypoxia, and the theory of increased angiogenic and vasculogenic activity. Hypoxia is an important stimulus of angiogenesis and vasculogenesis through an increased expression of vascular endothelial growth factor (VEGF), placental growth factor (PlGF), Flt-1 (a high-affinity transmembrane receptor for both PlGF and VEGF) and sFlt-1 (a placental-derived, soluble fms-like tyrosine kinase 1 molecule), and therefore placental hypoxia could act as a trigger to activate the leader endothelial cells and initiate a cascade of reactions leading to IH and/or CA proliferation.[3 12 13]

IHs occur more often in Caucasian, premature, female infants who are born from multiple gestation and with low birth weight. Their mothers are usually of higher age and have a higher incidence of pre-eclampsia compared with the general population.[9]

In previous studies,[3 10] the presence of CA has been correlated with an increased maternal age and it has been associated with HELLP syndrome, pre-eclampsia, multiple gestation and preterm birth. The current study of high-risk pregnancies, although it confirms previously reported association between CA and adverse pregnancy outcomes, including pre-eclampsia and SGA neonates, did not show any significant associations between CA, prematurity, pre-eclampsia, SGA, multiple pregnancies or size of CA and increased risk of IH. However, since our study sample was restricted to high-risk pregnancies, the results may not be generalisable to all pregnancies. Female neonates were slightly more often affected by IH, but the finding did not reach the level of statistical significance. The mechanism by which female neonates show an increased risk of developing IH might be related to the higher levels of renin compared with male neonates. An increased level of renin leads to a higher level of angiotensin II within the IH, which in turn promotes the endothelial proliferation. Increased renin level is found also in Caucasians compared with blacks, premature compared with full-term infants, and children compared with adults. It could even explain the spontaneous involution of IH: the renin levels decrease as children grow older.[14]

Our current study demonstrated high incidence of IH (18.4%), compared with the incidence reported in the literature (5%–10%),[3] which could be explained by selection bias, as parents whose infants had IH probably were more keen to participate in the study. We should also consider that since the incidence of IH was reported directly by the parents and the diagnosis of IH was not confirmed by information from medical records, it might be higher than in medical records, as parents might record more IH cases, even those that did not require clinical attention. As far as we know, there is only one previous study addressing the epidemiological links between CA and IH.[5] In the latter study, the authors claim a very high (55%) incidence of IH in infants with CA-containing placentas, in support of the placental origin theory. However, the results of that study are difficult to interpret and are hardly comparable to ours because of the small sample size, incomplete pathological and clinical data and lack of appropriate control group.

In conclusion, the current study failed to demonstrate any correlations between CAs and IH, and that the occurrence of multiple pregnancies or pre-eclampsia was not associated with an increased incidence of IH. Overall, to the best of our knowledge, the current study is the largest case–control study so far investigating the coexistence of CAs and IHs, thus providing valuable insights into the clinical approach of placental CAs and IHs.

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