On infantile hemangiomas
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Epilogue
The work presented in this thesis represents the quest for answers on basic questions like ‘what is the prevalence of infantile hemangiomas’ and ‘what is the impact of infantile hemangiomas’.

As reported in chapter 2, we found a prevalence of infantile hemangiomas of 9.9% in the general population. Interestingly, only 7 per cent of these children were referred to a consultant e.g. dermatologist, pediatrics or plastic surgeon. Higher prevalences of multiple infantile hemangiomas, presence of a precursor lesion, a complicated course, or location in the head and neck area were seen in this referred group. Better insight in characteristics of the children in the general population revealed that previous studies reported an overestimation of infantile hemangiomas located in the head and neck area. As such, the reported prevalence of infantile hemangiomas in a hospital based study located in the head and neck area is a factor 1,5 higher in comparison with the general population. For infantile hemangiomas with a complicated course the difference is a factor 18.1 Since the time of this research and writing of chapter 2, important changes such as more general knowledge of infantile hemangiomas among children-well-fare doctors, general practitioners and parents, more active referral patterns, and new treatment options took place. Even though the potentially harming characteristics of infantile hemangiomas, obviously, have remained the same, these changes may help reduce its complication rate.

The results on the etiologic factors in the child well-fare center study as outlined in chapter 4 indicate amniocentesis, birth weight below 2500 grams, breech presentation, and being the first born in the family as a risk factor for developing infantile hemangioma. All other risk factors mentioned in literature are, again, mostly based on studies in hospital based populations. Hence, the observations regarding incubator treatment, female sex, Caucasian descent, prematurity, placental problems, low birth weight, invasive prenatal investigations, pre-eclampsia, breech presentation, caesarean section, and histopathological characteristics may have been biased by case selection. Still, the etiology of infantile hemangioma appears to unravel along one, or more, of the following lines of evidence.

1. Embolization of placental endothelial cells

Studies to refine pathological diagnosis of infantile hemangiomas showed that the endothelial cells of infantile hemangiomas are consistently and intensely immunoreactive for the erythrocyte-type glucose transporter protein, GLUT-1.3 This transporter isoform is undetectable in normal skin or subcutis but is highly expressed in normal endothelial cells at sites of blood-tissue barriers that may be found in the brain, eyes, nerves, and placenta.4-8 Further detection of endothelial and basement membrane antigens selectively expressed in neural and placental tissues (Glut-1, Lewis Y antigen, merosin, CCR6, indoleamine 2,3-dioxygenase, CD15) showed corresponding histochemical markers suggesting possible pathogenic associations between infantile hemangiomas
and these tissues. Hence, Glut-1 may be used to differentiate infantile hemangiomas from vascular malformations and other vascular tumors that were mentioned in chapter 1. The only exception to this rule are angiosarcomas that have a weak focal positive outcome of GLUT-1 and Lewis Y markers and, as stated in chapter 5, a biopsy needs to be taken and examined by a pathologist who is experienced in vascular anomalies in case of doubt regarding the clinical diagnosis.

This corresponding histological markers, furthermore, suggest a possible pathogenic associations between infantile hemangiomas and these tissues. Embolized placental endothelial cells from chorionic villi may reach the fetus through shunts that are characteristic of the normal fetal circulation. Intravascular embolization of placental cells is more likely to occur after placental injury. Such embolization of placental endothelial cells to the fetus would explain corresponding histochemical markers. It could also explain the fact that infantile hemangioma more often occurs after invasive prenatal investigations (chorion villus sampling) or disorders associated with possible damage to the placenta.

Subsequent molecular genetic investigations revealed no evidence of materno-fetal microchimerism in children with solitary infantile hemangiomas and infantile hemangiomas do not feature any maternal component. Still, the placental is a ‘conjoined organ’ of mother and fetus and has both maternal and fetal tissue and endothelial cells originating from fetal placental tissue, rather than maternal placental tissue, may be the source of the hemangiomas.

In women with preeclampsia, invading trophoblasts lead to reduction of blood flow of the placenta. This so called ‘maternal underperfusion’ is positively correlated with the prevalence of placental lesions, and preeclampsia occurs more frequently in first-pregnancies. Accepting placental lesions as a risk factor of infantile hemangioma, our observation that being the first born in a family poses a risk factor for developing an infantile hemangioma, would be in line with the observation of a higher incidence of preeclampsia in mothers of children with an infantile hemangioma.

2. Tissue hypoxia
Risk factors for infantile hemangioma like prematurity, multiple gestations (twins, triplets etc), incubator treatment and breech presentation provide links to tissue hypoxia that is a powerful cause of angio- and vasculogenesis. Placental hypoxia is also associated with infantile hemangioma. Insufficient placental function is an important cause for low birth weight, the single most important risk factor for infantile hemangioma showed in vitro that the combination of hypoxia and estrogen has a synergistic effect on infantile hemangioma endothelial cell proliferation, giving a possible explanation for the well-known female predominance of infantile hemangioma. Hypoxia is a potent mobilizer of endothelial progenitor cells (EPC’s) that are numerous in neonates. Increased EPC levels are also objectified in perinatal conditions such as preeclampsia, which is (again)
related with maternal underperfusion of the placenta. Hypoxia secondary to dysplastic arteries would explain the segmental occurrence of infantile hemangioma. Infants with segmental infantile hemangiomas (with or without PHACES) tend to be full term and of normal birth weight. This and the even greater female predominance among them suggest a different pathogenesis than that of localized infantile hemangioma. Arterial anomalies are the most common abnormalities seen in PHACES syndrome.21 The positive correlation between infantile hemangioma and retinopathy of prematurity (ROP) also supports this hypoxia-hypothesis. Infantile hemangioma and ROP share features like active endothelial sprouts in the early proliferation phase that involute over time, exclusive perinatal presentation, and increasing incidence with decreasing birth weight. ROP is also correlated with increased with histological chorioamnionitis. The latter is a relatively frequent complication in pregnancy characterized by the presence of numerous inflammatory cells in the amnion membranes, placental plate, umbilical vessels and decidua. Histological chorioamnionitis is a risk factor for preterm birth and very low birth weight infant. Still, possible relationship between chorioamnionitis and infantile hemangiomas is not yet investigated.

Most interesting is the similarity of infantile hemangioma and ROP in their response to propranolol and topical timolol.24 Glut-1 has shown to be expressed in vasoproliferative tissue of ROP and can be used to distinguish ROP from proliferative diabetic retinopathy.25 Glut-1 is a facilitative glucose transporter that is an important sensor of hypoxia. Glut-1 is up regulated by hypoxia in placental tissue, infantile hemangioma tissue and mysenchymal tumors as a result of increased activation of proteins such as hypoxia inducible factor 1α (HIF 1α).26

### 3. Increased angiogenic and vasculogenesis activity

Infantile hemangioma endothelial cells have reduced expression of vascular endothelial growth factor receptor 1 (VEGFR 1). This results in activation of VEGFR2 and downstream signaling pathways, which in turn leads to stimulation of angiogenesis. Vasculogenesis in addition to, or rather then, stimulated angiogenesis plays a role in the pathogenesis in infantile hemangioma as well.27-29 Vasculogenesis is proven to occur after birth when new blood vessels arise from circulating bone marrow-derived endothelial progenitor cells (EPC).27;30;31 EPC express hypoxia inducible factor 1α (HIF 1α), which in turn promotes local production of factors including vascular endothelial growth factor (VEGF) and stromal cell derived factor 1α.26 Several genes with anti-angiogenic activity have been identified on chromosome 21. Our observations of an extreme low incidence of infantile hemangiomas in among children with Down syndrome, reported in chapter 3, support the hypothesis that systematic up-regulation of this and other chromosome 21 related anti-angiogenic regulators prevent the development of infantile hemangiomas.
4. Renin angiotensin aldosterone system
The mechanism of the accidently discovered propranolol is a major lead to discover the true etiology of infantile hemangiomas. Propranolol is a non-selective beta-blocker. The assumed working mechanism of propranolol on infantile hemangioma is quadruplicate.\textsuperscript{32;32;33}

1) Firmness of the tumor and the color intensity will reduce as a result of beta-blocker induced vasoconstriction.
2) Inhibition of angiogenesis occurs by the suppression of the pro-angiogenic growth factors like vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF).
3) Induction of apoptosis of endothelial cells will appear as a result of hypoxia and the suppressed expression of Glucose transporter type 1 (GLUT-1) on the cell membrane.
4) Renin angiotensin aldosterone system (RAAS) is inhibited, which leads to a reduced level of angiotensin II and VEGF concentrations. This results in an inhibition of the hemangioma endothelial progenitor cells that prevent further proliferation of the hemangioma.

The role of the RAAS in infantile hemangioma is supported by the clinical observation of a higher incidence of hemangioma in premature babies, female infants and in the Caucasian population.\textsuperscript{33}

None of these theories can be solely responsible for the development of infantile hemangiomas. All factors mentioned above are interrelated. For example hypoxia leads to, inter alia, angiogenesis. Hence, a combination of two or more of the etiological pathways is plausible.

Given the fact that children with low birth weight, placental problems, incubator treatments, breech presentation and caesarean section occur in a hospital based population, it should be preferred as a hospital based study. In all (premature) children in whom an infantile hemangioma arises, histopathological research of biopsies of the infantile hemangioma and ideally of their placenta should be performed and compared. Cooperation of gynecologist, department of neonatology, pathologist, pediatrician, dermatologist, and plastic surgeon is a condition sine qua non for such a study.

Pre-eclampsia is subdivided in preterm and term, in early and late and mild moderate and severe. In each subdivision different etiologic factors play an (more) important role. Further research to assess in which subgroup the prevalence of infantile hemangiomas is the highest and placental examination in this particular group offer useful tools to further specify the etiology. Again, cooperation between different specialists departments is necessary.

Unfortunately, infantile hemangiomas do not occur in animals. Still, animal models that allow investigation of the consequences of placental damage of various causes and the induction of embolization of placental endothelial cells, may be established.
Once the diagnosis infantile hemangioma is made, various treatment options will be considered. During the time of research and writing this thesis, new treatments like propranolol and timolol were discovered and changed the treatment completely. While, in the past, the ‘wait and watch’ was the first choice in treatment and corticosteroids were administered only in severe cases more active treatment with systemical or local applied beta-blockers is given currently. In chapter 6, we argued that extra attention is needed for infantile hemangiomas in the peri-orbital and cheek regions. The traditionally ‘wait and watch’ option for this self-limiting disease, furthermore, is obsolete in large, conspicuous, or complicated infantile hemangiomas. Future comparisons between treatment outcome of systemically versus locally administered beta blocker should show us the best flow charts for treatment.34 By mapping the risk factors for increased changes of complications of systemically and/or locally administered beta blockers, this specific group of children could be advised to start with the second line of treatment. As such, the choice between wait and watch, corticosteroids, surgery, and laser therapy should depend on the size and locations of the infantile hemangioma.

Second, the treatment outcome changed dramatically. With the known impact of infantile hemangiomas on conspicuous location or of those with a complicated course, early referral leading to early active treatment will prevent further proliferation and regression may be reached in an earlier stage. Such early induction of regression of the infantile hemangiomas by beta blockers decreases the maximum size of the hemangioma and its residual symptoms.

Moreover, we showed that less additional therapy is needed after propranolol treatment. More experience and a longer follow up will show whether, or not, propranolol also decreases the possible negative psychosocial consequences.

The physiological effects of hemangiomas are mapped in part two. The knowledge that most children with non visible and/or hemangiomas with a non-complicated course will have a good quality of life will set practitioners at ease. Still, accurate counseling and support of the parents is wanted by most parents. Use of propranolol leading to fewer outgrowths of the infantile hemangioma and earlier regression will also reduce their worries. To detect psychological burdens online programs as www.hetklikt.nu are developed to assist both parents and doctors. Online filling in of questionnaires will inform the doctors of potential psychosocial burdens so they can react adequately and support parents and children. A good doctor-patient relationship will encourage the online participation. Likewise, a proper functioning patients and parents association offers additional information to parents and contributes to better insight in the parents-doctor relationship. Compliant to the new treatment options, the found impact of infantile hemangiomas may be expected to be reduced in the future. With online questionnaires impact can be measured more accurately than by retrospective assessment and performing research will be easier and less time assuming.
The following conclusions and suggestions may be drawn from this thesis:

- The present prevalence of infantile hemangiomas is 9.9% in the general population. Only 6% of children with infantile hemangioma in the general population are referred to a general practitioner for the hemangioma, and 7% to a specialist in a hospital.

- The ‘wait and watch’ policy as the main treatment modality of infantile hemangiomas is to be considered obsolete.

- An over-expression of chromosome 21 related anti-angiogenic factors protects children against infantile hemangioma.

- Infantile hemangiomas in the peri-orbital and cheek region are underestimated as a risk factor of astigmatism leading to amblyopia.

- Propranolol is preferable to intralesional corticosteroid treatment in periorbital infantile hemangiomas because of the rapidity of improvement.

- Parents of children with conspicuous infantile hemangiomas or infantile hemangiomas with a complicated course need more attention in order to prevent and detect potential psychosocial burdens.
Chapter 9

Reference List

31 Drolet BA, Frieden IJ. Characteristics of infantile hemangiomas as clues to pathogenesis: does hypoxia connect the dots? Arch Dermatol 2010; 146(11):1295-1299.