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REVIEW

Accelerated growth of hemangioblastoma in pregnancy: the role of proangiogenic factors and upregulation of hypoxia-inducible factor (HIF) in a non-oxygen-dependent pathway

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Abstract Hemangioblastomas (HBs) are benign, highly vascular tumors, often characterized by loss of function of the von Hippel–Lindau (vHL) gene. They are the most common central nervous system tumor observed in vHL syndrome. Loss of function of the vHL gene creates a "pseudo-hypoxic" state, causing overactivation of hypoxia-inducible factor (HIF) and vascular endothelial growth factor (VEGF)-related pathways. In some cases, HBs can rapidly increase in size during pregnancy to then present acutely, which most frequently occurs after the 20th gestational week. These changes in size usually occur from enlargement of the cystic component of the HB. Due to their preferred location in the posterior fossa near critical structures as well as along the spinal cord, such cases can present with severe neurological deficits, requiring urgent surgical intervention in a multidisciplinary setting. However, the reasons for this acute flare-up during pregnancy remain poorly understood, as are the reasons why this occurs in only a subset of tumors. Unveiling the etiology for this clinical scenario can affect the treatment of HBs, as it will contribute to the understanding of the pathophysiology of such a transformation from a quiescent lesion to a symptomatic one, not only in the setting of pregnancy. Identifying the correct triggers and the conditions initiating and mediating this switch will enable us to develop preventive medications which should allow us to keep the tumor in its quiescent phase. In this pathophysiological review, we investigate the association between HB growth and pregnancy based on an analysis > 40 such published cases. We suggest that the proangiogenic state of pregnancy is the leading etiology for this striking association, and to support the argument, we discuss its potential impact on HIF overexpression in a non-hypoxic manner through activation of the PI3K/Akt/mTOR pathway by proangiogenic factors. Specifically, we discuss the involvement of placental growth factor (PlGF) and its receptor vascular endothelial growth factor receptor 1 (VEGFR-1) in various pathologic processes that can lead to the formation and growth of peritumoral edema and cysts, which are the primary causes for the development of any symptoms in HB. Both PlGF and VEGFR-1 are expressed at increased levels during pregnancy, and both have been reported as part of various pathological processes, including angiogenesis and tumorigenesis. The unique feature that both do essentially not show any significant negative impact on regular physiological processes makes them attractive therapeutic targets since very little side effects are expected. Further research into the effects of anti-PlGF or anti-VEGFR-1 therapy in HB is therefore recommended.

Keywords Hemangioblastoma · Pregnancy · Angiogenesis · Vascular permeability · Placental growth factor

Introduction

Phacomatoses are a hereditary group of diseases characterized by the presence of disseminated hamartomas in neuroectodermally derived tissues [58]. One of these autosomal dominantly inherited disorders is the von Hippel–Lindau disease (vHLD). In vHLD, there is characteristic abnormal growth and proliferation of blood vessels in multiple organ sites [31]. The vHL protein is involved in the ubiquitination and degradation of the hypoxia-inducible factor 1alpha (HIF-

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1α) in an oxygen-dependent pathway. Loss of the vHL protein (causing a "pseudo-hypoxic" state) results in stabilization of HIF-1α and increased expression of many HIF-1α target genes, such as vascular endothelial growth factor (VEGF), that are important in regulating angiogenesis, cell growth, or cell survival [3]. Importantly, overactivation of HIF can also happen in a *growth factor*-dependent pathway, independent of any hypoxia-induced stabilization of HIF-1α [32].

Hemangioblastoma (HB) is the most common vHL-related tumor of the nervous system. Overall, 5–20% of HBs are associated with vHLD, and cerebellar HBs are seen in 30–50% of vHLD patients [103]. The female/male ratio is approximately 1.6:1, and 74% of cases manifest themselves over the age of 30 [64]. Cerebellar HBs constitute 1.25–2% of brain tumors and 7.3–12% of posterior fossa tumors [105]. Nearly 75% of symptomatic lesions are cystic, compared to 13% of non-symptomatic lesions [40, 140].

Symptomatic HBs have been repeatedly reported in association with pregnancy, when they seem to present with accelerated growth, causing either exacerbation of known, subtle symptoms or the acute appearance of new ones [43]. Nevertheless, this association remains a matter of controversy. One reason for this comes from the fact that many cases were only described as anecdotal case reports. Furthermore, when existing lesions were followed carefully during pregnancy with imaging and clinical assessments, no significant changes in size or symptoms were found [149].

Another reason for questioning these interaction stems from the fact that even if any association does exist, its pathophysiology is far from being understood. Various hypotheses were proposed in an attempt to explain this phenomenon [121]. According to a first hypothesis, rapid expansion or engorgement of the vascular beds during pregnancy could cause rapid enlargement of this highly vascular tumor. This is considered to presumably be the result of a generalized increase in circulating blood volume as well as the tendency to retain extracellular and intracellular fluid during pregnancy [95]. Another hypothesis includes direct (pregnancy-related) hormonal effects on tumor growth rates, mediated by hormonal receptors [138]. Yet, a third theory suggests involvement of proangiogenic growth factors. In either case, the exact etiology remained unknown and, for each theory, the supporting evidence is weak. Uncovering and understanding the principal etiology of this clinical phenomenon is important as it may help to elucidate the pathogenic determinants of these tumors, perhaps leading to novel medical treatments that can be used in patients not suitable or eligible for surgery. To this end, we have performed a comprehensive review and analysis of data on all published reports describing an association between symptomatic HB and pregnancy. Based on the accumulated data, a strong association between pregnancy and symptomatic presentation of HB is demonstrated. Given the unique physiological alterations of pregnancy, we suggest that the proangiogenic state of pregnancy is the main etiological factor responsible for the observed rapid changes in the size of these tumors, especially their cystic component.

We will describe how an increase in tumor vessel permeability as well as an increase in overall tumor vascularity through both angiogenesis and (uniquely) vasculogenesis can explain these characteristic changes during pregnancy. Finally, we will discuss the underlying physiological mechanism on a molecular level, as we formulate a correlation between the upregulation of HIF-1α in a growth factor-dependent manner (via the PI3K/Akt/mTOR pathway, which is overactivated in many phacomatosis-related tumors) and high levels of a unique proangiogenic factor: the placental growth factor (PlGF).

VEGF, PlGF, and VEGFR-1: a brief introduction

VEGF signaling pathways play important roles in angiogenesis. It binds to two tyrosine kinase receptors: vascular endothelial growth factor receptors (VEGFR) 1 and 2. While most of the biological effects of VEGF are mediated by activation of VEGFR-2 [147], VEGFR-1 functions as an inert "decoy" by binding VEGF and thereby regulating its availability. Such a decoy function might be particularly attributed to the soluble VEGFR-1 (sVEGFR-1) [21]. VEGFR-1 is expressed in endothelial cells, as well as in monocyte/macrophages, hematopoietic stem cells, and some tumor cells [42, 145].

VEGF is a unique growth factor since it does not only induce endothelial cell proliferation (promoting angiogenesis) but also exhibit permeability-modulating capabilities. In fact, it was initially discovered as a "vascular permeability factor" that rendered venules and small veins hyperpermeable to circulating macromolecules [27] and is one of the most potent vascular permealizing agents currently known [126]. Its expression levels are upregulated in hypoxia, mainly through activation by HIF-1α [26].

PlGF is a member of the VEGF subfamily, playing key roles in both angiogenesis and vasculogenesis [10]. PlGF has been the second member of VEGF family which was discovered, and it displays 53% homology with VEGF [131]. The name refers to placenta since it was cloned from a human placental cDNA library [89]. The human PlGF gene maps to chromosome 14q24. Like the other members of VEGF family, different isoforms exist which are due to alternative splicing of the respective gene. Four isoforms, PlGF 1–4 [30], are known of which PlGF-1 is the most active one.

PlGF binds exclusively to VEGFR-1 with an affinity that is higher than VEGF. It does not bind to VEGFR-2 [107]. There is ample in vivo evidence for the role of PlGF as a proangiogenic factor [99, 154], including a mitogenic effect on endothelial cells [20]. Aside from having its own specific actions, PlGF is thought to enhance the response to VEGF by forming VEGF/PlGF heterodimers, which have been found to

be nearly as potent as VEGF homodimers in assays of mitogenesis [21]. In addition, PlGF has been proposed to stimulate angiogenesis by displacing VEGF from the "VEGFR-1 sink," thereby increasing the fraction of VEGF available to activate VEGFR-2 [107].

Plasma PlGF and VEGFR-1 levels can be influenced by systemic conditions such as pregnancy, obesity, and smoking [61, 80].

The role of PlGF as a vascular permeability factor is much less known. It is easy to state that PlGF increases permeability through its enhancing effects on VEGF. However, this might be an oversimplification. Below, we will discuss the role of PlGF in angiogenesis and vascular permeability, and we will show how it may correlate to the accelerated growth of HB in pregnancy. First, such accelerated growth needs to be corroborated.

Pregnancy-related hemangioblastomas: accelerated growth and acute presentation

> "Pregnancy appears to be a not uncommon provocative element in bringing tumors to light, more particularly perhaps angiomatous lesions" (Cushing 1928).

Ye and colleagues have investigated different clinical and radiological characteristics of HBs in nine vHLD patients who became pregnant during an observational period. When compared to a control group of vHLD females who did not get pregnant, no significant changes were found between the two groups in terms of symptoms and size of the tumors [149]. Nevertheless, many reports have suggested the notion of distinct pregnancy effects on HB size and consequently the timing of symptomatic presentation [14, 15, 19, 31, 34, 35, 43, 47, 49, 52, 53, 62, 64, 66, 67, 70, 72, 74, 78, 88, 95, 96, 100, 102, 103, 105, 108, 113, 115, 117, 121, 122, 155]. Figure 1 illustrates a similar case, treated in our institution.

It should be emphasized that nowadays, neuroradiological screening of patients with vHLD allows the identification of more than 75% of new lesions before they become symptomatic [28]. This permits early treatment (usually surgery; radiation therapy in some cases) as soon as a lesion enlarges or becomes symptomatic. For this reason, many patients are undergoing diagnosis and treatment prior to becoming pregnant, which substantially diminishes the number of cases that can potentially show tumor growths during pregnancy.

In addition, sequential imaging has demonstrated an association between pregnancy and tumor growth, as several stable and asymptomatic lesions which were adequately followed for many years showed substantial increase in size during pregnancy, mainly through enlargement of their cystic component [14, 43, 47, 49, 103].

Due to its rarity, it is hard to accurately estimate the incidence of pregnancy-related HB. HBs were reported to present in pregnancy in 3–50% of cases overall [40]. In 1967, Robinson described their experience with 23 cases of HB. Remarkably, half of the female patients presented during pregnancy [115]. Even though in most cases pregnancy did not have a deleterious effect on the progression of the symptoms and the final diagnosis was made after pregnancy (Table 1), the high presentation rate during pregnancy is striking. Frantzen et al. analyzed the effect of pregnancy on vHL-related tumors and observed that the progression score of cerebellar HB was significantly elevated in the immediate postpartum period in about 40% of cases [43]. In addition, overall vHLD interventions during pregnancy and in the first year after delivery were five times more frequent than in the 4 years preceding pregnancy [43]. In a retrospective study on 30 vHLD patients with a total of 56 pregnancies, other authors found that 25% (1/4) of known, preconception asymptomatic HB became profoundly symptomatic during pregnancy [47].

Table 1 summarizes the clinical data of 42 such reported cases on pregnancy-related HBs from the literature. There are four major points that highlight the correlation between pregnancy and symptomatic presentation of HB: first, type and duration of symptoms. HBs are benign, slow-growing lesions. Consequently, their symptoms are usually rather chronic and indolent. vHLD patients with symptomatic cerebellar lesions usually present with gait ataxia (64%) or dysmetria (64%). Headaches (12%), diplopia (8%), or emesis (8%) are much less frequent [140]. On the other hand, in our pooled cohort review, 95% of reported cases had headaches, diplopia, or emesis at presentation, and most usually all three together (Table 1). Moreover, signs and symptoms of increased intracranial pressure were common, and the overall presentation was much more acute in nature [47, 66, 72, 78, 95, 103, 117, 122]. In addition, radiologically proven obstructive hydrocephalus was found in 75% (17/23) of cases, a significantly higher number than the previously reported rate of 28% in surgically treated cases [63]. In two large series on symptomatic HB, the mean duration of symptoms before medical attention was sought was 8–13.5 months [28, 105]. This is significantly longer than the period observed in the current cohort, with 10 cases described as an "acute presentation" and another 16 cases with a mean duration of only 6 weeks (Table 1). Second, the timing of presentation during pregnancy shows clear predilection toward the second and third trimesters. Sixty-nine percent (20/29) of reported cases (since 1975) presented after the 20th gestational week (GW), and nearly 45% (13/29) presented after the 30th GW. We would have expected to encounter a higher rate of cases presenting at an earlier gestational age if indeed the co-occurrence of tumor and pregnancy was merely coincidental. In addition, 63% (12/19) of vHLD patients in this pooled cohort had their first presentation of disease during pregnancy, further supporting a close correlation between the two entities. Third, spontaneous resolution or decrease of symptoms after delivery/

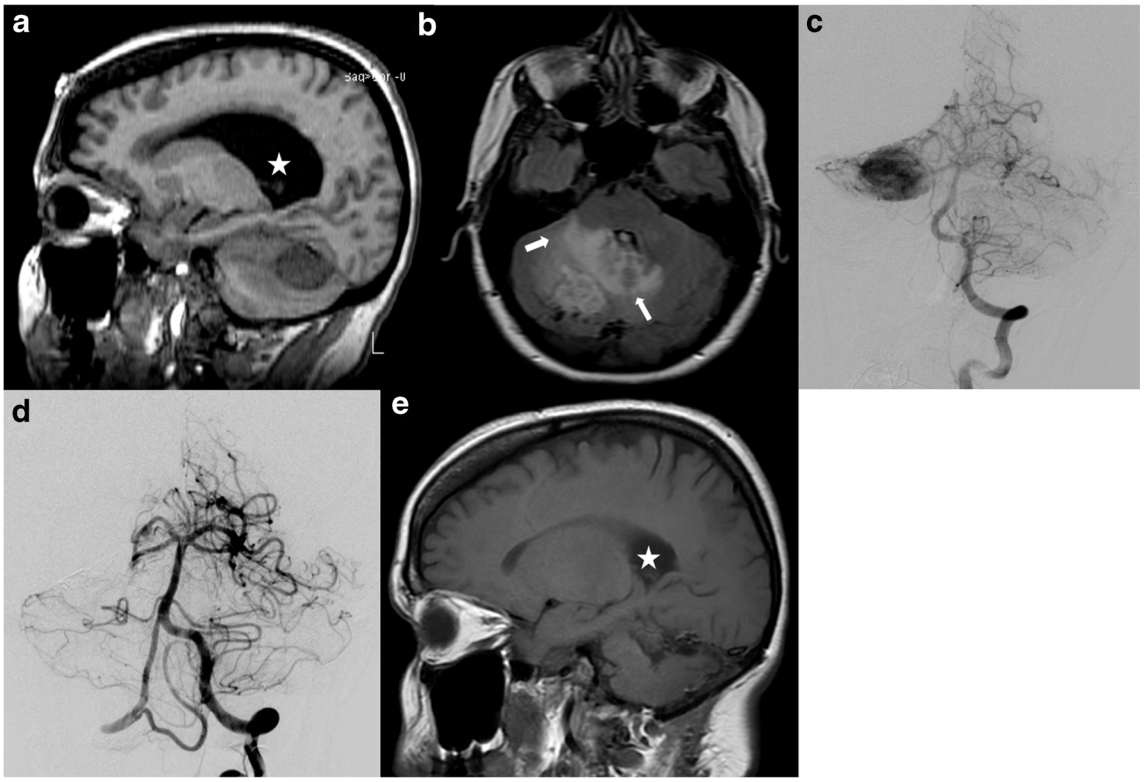

Fig. 1 A 40-year-old female, 16 weeks pregnant (gravida 1, para 0, 1 miscarriage), presented with headaches, vomiting, and blurry vision which developed over the course of few weeks. Her headaches were occipitally located and exacerbated by Valsalva and vomiting. She also developed new onset diplopia approximately 1 week prior to admission. On admission, her neurological examination was only positive for bilateral nystagmus as well as mild dysmetria. Non-contrast magnetic resonance imaging (MRI) of the brain revealed a 2.9 × 2.3 × 2.5-cm subtentorial mass, associated with surrounding edema with mass effect on the dorsal brain stem and partial effacement of the fourth ventricle resulting in hydrocephalus with transependymal edema, and tonsillar herniation. Slightly prominent subjacent flow void was also noted. There was no associated tumoral cyst. **a** Non-contrast, T1-weighted image, sagittal view. Significant obstructive hydrocephalus is demonstrated (*white star*). **b** Fluid attenuation inversion recovery (FLAIR) image, axial view. Significant hyperintensity surrounding the lesion is noticed, compatible with peritumoral edema (*arrows*). Patient underwent digital subtraction angiography (DSA) and tumor embolization using Onyx 18 (EV3, Inc., USA). **c** DSA images after left vertebral injection, anterio-posterior view, showing a markedly hypervascular infratentorial lesion. Two dominant pedicles arising from the right superior cerebellar artery were successfully embolized using Onyx 18 (EV3, Inc., USA). **d** DSA, same view, after an endovascular embolization of the lesion's main feeders. The vascular blush of the lesion can no longer be seen. The patient underwent tumor resection the following day (retrosigmoid approach). This was uneventful and gross total resection was achieved. **e** Non-contrast, T1-weighted image, sagittal view. There was no evidence of tumor residual (this was confirmed on a postpartum MRI with contrast). Ventricles are significantly smaller (*white star*). At term, the patient had a forceps-assisted vaginal delivery of a healthy infant at gestational age 39 weeks and 3 days. The patient delivered a healthy male baby, weighting 3395 g with Apgar scores of 9 and 9 (at 1 and 5 min). The delivery and postpartum hospital course were uncomplicated. Twenty months following surgery, the mother and child are alive and well, with no evidence of any neurological deficits or residual tumor on imaging. Thorough genetic counseling and workup found the patient to be negative for vHL

termination of pregnancy was reported repeatedly [49, 74, 95, 102, 115]. On the other hand, in a long follow-up of 160 (non-pregnancy related) cerebellar HB, no tumors or cysts spontaneously diminished in size during the observation period [140]. In addition, while an increase in the progression score in cerebellar HB was seen in the first measurements early after pregnancy, a *decrease* in progression score was found in the second MRI scan after pregnancy [43], emphasizing an intimate correlation between the two. Forth, HBs discovered in pregnancy were found in unusual locations. For example, multiple pregnancy-associated HBs were found in the filum terminale during pregnancy [102]. This further supports an altered environment during pregnancy which might be tumor growth permissive or inductive.

To conclude, even though not every HB is destined to grow during pregnancy, there is enough evidence to strongly suggest a correlation. As for now, it is unknown why some lesions react with a rather explosive growth while others remain quiescent [see "Pregnancy-induced "awakening" of quiescent hemangioblastomas" section].

Importantly, symptomatic HBs have something in common, regardless whether they are associated with pregnancy or not: the majority of symptomatic cases present with a significant cystic component. A previous study on the natural history of HB in vHLD patients showed that by the time symptoms appeared, the majority of mass effect-producing symptoms derived from the cyst, rather than from the tumor causing the cyst [140]. This is in accordance with findings in

Table 1 Pregnancy-related hemangioblastoma-summarized clinical data based on literature's review

Author, year	Maternal age (years)	G/P/A	Gestational age at presentation (weeks)	Symptoms and signs/duration (m)	vHL/first symptoms	Location / Size	Major Cystic component \ Edema	Remarks
This report	40	2/0/1	16	HA, N/V, diplopia; 8 w	No	R tentorial; 2.9 × 2.5	No/yes	OH
Satyarthee and Kumar, 2016 [121]	28	1/0	22	HA, N/V, diplopia, ataxia; 4 w	No	R cerebellar; 6 × 5	Yes	OH
Inoue et al., 2015 [62]	19	1/0	35	HA, N/V; acute	No	Vermis; "large"	Yes	OH
Hallsworth et al., 2015 [49]	37	2/1	21	HA, ataxia; NA	Yes/no	NA	NA/yes	Pt with known cerebellar HBs, stable for several years. New peritumoral edema. Spont. Resolution of S&S PP.
Capone et al., 2013 [19]	38	NA	38	LBP, dysesthesia; 8 w	Yes/no	T10–T11; 2.2 × 1	NA	Normal spinal MRI 3 y earlier
Frantzen et al., 2012 [43]	NA	1/0	32	HA, N/V, vertigo, ataxia, diplopia; NA	Yes/yes	R cerebellar; 4 cm	Yes	OH. Known 0.5-cm, non-cystic lesion prepregnancy became a 4-cm cystic lesion
	NA	1/0	NA	HA, V, ataxia, speech disorder, muscle weakness; NA	Yes/no	Cerebellar; NA	NA	OH
	NA	1/0	NA	Radiating lower back pain	Yes/yes	Spinal cord	NA	
Pereda Ríos et al., 2012 [108]	35	1/0	34	Diplopia, HA; 2 d	No	L cerebellar; 5 × 4	Yes/NA	OH
Hayashi et al., 2010 [52]	30	1/0	During delivery	HA during delivery, nausea, dizziness; 2 h	No	R cerebellar; 3.5 × 3	No (ICH)/yes	ICH with tumor (rec). Had resection of HB in the same location 6 y earlier. MRI 2 y earlier—no recurrence.
Hayden et al., 2009 [53]	24	2/1	10	UE numbness, burn marks; NA	Yes/yes	C1–C3; 3.9 × 1.5	Yes/yes	Diagnosis was made at GW 34. Pt deteriorated gradually.
Kenyon et al., 2009 [67]	33	4/2/1	28	Dizziness, HA, V, ataxia; 2 weeks	No	L cerebellar; 5 × 4	Yes/NA	OH
Rehman et al., 2009 [113]	27	NA	29	Preterm labor, ataxia, slurred speech, vertigo; 3 m	Yes/yes	R cerebellar; 4.1 × 3.6	Yes/yes	OH
Marta Ortega-Martinez et al., 2007 [102]	41	7/1/5	8	LBP, LE dysesthesia; NA	No	Filum terminale; 1.5 × 1 and S1; 1.5 × 1	No/NR	Spont. relief of S after abortion
Zilidis and Cadoux-Hudson, 2007 [155]	28	NA	12	HA; acute	Yes/yes	NA	Yes/NA	OH
Kurne et al., 2003 [74]	34	3/2	33	Paraplegia, urinary and fecal incontinence, hypoesthesia below T10; 6 m	Yes/yes	T8–T10	No/NA	Pt had similar S&S during 2nd P. Resolved spont. postpartum
Erdogan et al., 2002 [35]	35	6/5	24	HA, N/V, respiratory arrest, quadriparesis; acute	NA	R cerebellar; 3.5	Yes/NA	OH
Boker et al., 2001 [14]	30	1/0	35	HA, dizziness; 5 w	Yes/no	L cerebellar; 5.5 × 5	Yes/yes	Multiple cerebellar and spinal HB 3 m prior to pregnancy, the largest was 1.8 cm OH.
Delisle et al., 2000 [31]	35	Multigravida	30	HA, diplopia, gait problems; 2 w	Yes/yes	L cerebellar; 5 × 3	Yes/yes	OH
Grimbert et al., 1999 [47]	32	NA	32	Intracranial HTN; acute	Yes/no	NA	NA	Pt had known cerebellar HB before pregnancy

Table 1 (continued)

Author, year	Maternal age (years)	G/P/A	Gestational age at presentation (weeks)	Symptoms and signs/duration (m)	vHL/first symptoms	Location / Size	Major Cystic component \ Edema	Remarks
Othmane et al., 1999 [103]	21	1/0	1 week after delivery	HA, papilledema; acute	Yes/no	L cerebellar; 4 × 3	Yes/NA	OH; no lesions on previous brain MRI scans
Naidoo Bhigjee, 1998 [95]	26	NA	21	HA, N/V, ataxia, diplopia; papilledema; 2 w	Yes/yes	R cerebellar; 2.9 × 2.3	Yes/no	OH
	26	NA	33	HA, ataxia; acute	Yes/yes	L cerebellar; 4.5 × 4	No/yes	Same pt. as above, presented again later during same pregnancy with a 3-fold increase in size of L lesion. Spont. regression PP
Korula et al., 1998 [70]	33	1/0	32	HA, N/V, dizziness; 2 w	NA	Vermis	Yes/NA	OH
Ogasawara et al., 1995 [100]	23	3/0	35	Paraplegia, urinary retention; acute	Yes/yes	T4–T5	NR	Lesion caused intramedullary hemorrhage
Nathan et al., 1995 [96]	28	NA	2nd trimester	Ataxia, left-sided weakness, N/V; 4 w	No	L cerebellar; 4 × 3.5	Yes/NA	
Kuhnigk and Danhauser-Leistner; 1994 [72]	31	NA	28	Increased ICP; acute	Yes/no	Cerebellar/NA	NA	
Lechowski et al., 1992 [78]	28	NA	31	Increased ICP	NA	NA	NA	
Romansky et al., 1992 [117]	20	NA	8th month	HA, N/V, ataxia, blurred vision, papilledema; 2 w	NA	L cerebellar; 4.5	No/yes	OH
Kasarskis et al., 1988 [66]	18	2/1	2nd month	HA, ataxia, blurred vision, N/V, lethargy; 1 m	NA	R cerebellar; 2.5 × 2	No/yes	OH
Jeffreys et al., 1975 [64]	NA	NA	3rd month	NA	NA	NA	NA	
Palmer, 1972 [105]	NA	NA	6th month	NA	NA	NA	NA	Symptoms recurred 10 d after delivery. After surgery, pt. had 3 recurrences and 2 more pregnancies but they were not correlated.
Bourdillon and Hickman, 1967 [15]	25	2/1	4 w	N/V	Yes/yes	NA	Yes (at time of surgery. No images at time of diagnosis)	V persisted till 20th GW when pregnancy was terminated. Next pregnancy also terminated d/t V. Tumor removed at age 30.
Robinson et al., 1965 [115]	26	3	2nd month	NA	NA	NA	No/NA	
	24	2	8th month	NA	NA	NA	Yes/NA	
	36	3	3rd month	NA	NA	NA	No/NA	
	35	4	1st month	NA	NA		Yes/NA	
	42	4	8th month	HA, V, ataxia, double vision; 2 m	NA		Yes/NA	Spontaneous remission after delivery
	26	3	7th month	V, double vision, ataxia; NA	NA	R cerebellar; 1.5	Yes/NA	Spontaneous remission 5 m after delivery. No symptoms in a follow-up pregnancy.
	27	2/1	5th month		NA	L cerebellar; 4 × 2	Yes/NA	OH

Table 1 (continued)

Author, year	Maternal age (years)	G/P/A	Gestational age at presentation (weeks)	Symptoms and signs/duration (m)	vHL/first symptoms	Location / Size	Major Cystic component \ Edema	Remarks
Scarcella et al., 1961 [122]				HA, N/V, dizziness, ataxia, papilledema; 3 weeks				
Dupperat et al., 1945 [34]	34	1/0	1 d postpartum	HA	NA	NA	NA	Sudden death 11 d postpartum
Moller, 1944 [88]	26	2/1	6–7 months	HA, N/V, vertigo; 4 m	Yes/yes	NA/vermis	Y/NA	

A abortion, *cm* centimeters, *d* days, *G* gestation, *GW* gestation week, *HA* headache, *HB* hemangioblastoma, *HTN* hypertension, *ICP* intracranial pressure, *L* left, *LBP* low back pain, *LE* lower extremities, *m* months, *MRI* magnetic resonance imaging, *N* nausea, *NA* non-available, *OH* obstructive hydrocephalus, *P* pregnancy, *PP* postpartum, *PT* patient, *R* right, *spont* spontaneous, *S&S* signs and symptoms, *V* vomiting, *vHL* von Hippel–Lindau, *w* weeks

the current cohort, as 70% (21/30) of relevant cases demonstrated a large cystic component (Table 1). Overall, a strong correlation exists between the growth rate of the tumor, the presence of a cyst, and the appearance of symptoms for both pregnant and non-pregnant cases [140]. We will therefore need to consider the detailed pathophysiology of cyst formation in HB.

Hemangioblastoma-related cysts: vasculogenesis, angiogenesis, and vascular hyperpermeability

> "The more primitive masses which do begin as isolated masses or islands of cells but must first produce endothelium and plasma, I shall call angioblasts" (Sabin 1920).

> "To angioblast, however, I prefer the term haemangioblast. This expresses the fact that both endothelium and blood develop from the solid mass, whereas the term angioblast strictly refers only to the vessels, i.e. to the endothelium" (Murry 1932).

In tumors, the process of angiogenesis is strongly correlated with increased vascular permeability [94]. Fluid leakage in tumors takes place in newly formed, highly abnormal blood vessels postangiogenesis. Increased vascular permeability has several radiological and clinical consequences, such as contrast enhancement, the formation of vasogenic brain edema, and the formation of tumor-related cysts [7]. In tumors of the nervous system, it can also cause elevated levels of proteins in the cerebrospinal fluid (CSF), even in the presence of small, benign tumors. This was demonstrated in two other phacomatosis-related tumors, namely vestibular schwannomas (associated with neurofibromatosis 2) and subependymal giant cell tumors (associated with tuberous sclerosis complex) [77]. HBs were also described to occur in association with high CSF protein levels, including in pregnant patients [15]. In a large series, the CSF protein content was raised to above 45 mg% (normal 15–45 mg%) in 21 of 30 eases investigated, the highest levels reaching a value of 480 mg% [105]. In addition, nearly 80% of HBs are associated with either peritumoral edema or cyst formation [7, 45]. Taken together, it is highly suggestive that the formation and the growth of the cystic component (including during pregnancy) are secondary to increased vascular permeability.

In his early (1949) discussion regarding high protein contents of cysts in HB, Broager supported the theory of *Lindau*, suggesting that cyst formation is the result of a transudation from the vessels of the tumor [16]. This fits perfectly well with the much later evidence correlating increased vascular permeability with angiogenesis and increased VEGF levels in HB [29, 45].

However, specifically in HB, a second mechanism for cyst enlargement may exist. Blood vessels are constructed by two processes, namely, vasculogenesis (formation of new blood vessels de novo) and angiogenesis (formation of new blood vessels from previous ones) [114]. In vasculogenesis, blood vessels and blood cells share a common progenitor, the hemangioblast [54]. The thought that hemangioblasts are the precursor cells or cell of origin of HB is not new and dates to the early decades of the previous century. In 1931, Lindau [83], after reviewing Sabin's work on the development of cerebral circulation [119], suggested that HB arose from portions of vascular mesenchyma, destined to form choroid plexus of the fourth ventricle, which were isolated and incorporated into the developing cerebellum during the third fetal month. Nearly 30 years later, the group by Stein et al. found that the solid portions of HB are composed of an admixture of adult capillary and cavernous vascular channels and other *immature*, *vasoformative tissue*. Furthermore, it was suggested that tumor-related cysts are the result of a process of differentiation of blood vessels and the formation of primitive plasma from masses of hemangioblasts [130]. It took another six decades before it was finally shown that vHL-associated HBs are derived from embryologic multipotent cells which were indeed the hemangioblasts [106]. This discovery has led to further important discoveries: First, it was shown that hemangioblast also serves as the progenitor cell for other vHL-associated tumors such as renal cell carcinoma (RCC), supporting the extremely close clinical, histological, and molecular relationships between these two tumors [153]. In addition, it was demonstrated that isolated vascular structures and blood vessels within HB are a result of both "hypoxia"-induced angiogenesis (secondary to inactivation of the vHL gene), as well as tumor-derived vasculogenesis, emphasizing the active role of hemangioblasts in tumorigenesis of HB [153]. Importantly, this may imply that factors that enhance or initiate hemangioblast activation can positively affect the growth of HB through vasculogenesis. Thus, it can well be that the pathophysiology of accelerated cyst formation, found in the majority of pregnancy-related cases, is a combination of two underlying processes: an increased vascular permeability (accompanied angiogenesis) as well as the production of the so-called primitive plasma (accompanied vasculogenesis).

This raises a question: Can hemangioblasts be activated during pregnancy?

In 2002, the group by Hattori et al. have suggested that the accumulation of hemangioblasts within the yolk sac in VEGFR-1$^{-/-}$ mice may be due to impaired cell migration. In a series of experiments, these authors were able to show that a subgroup of human hematopoietic stem cells (HSC; CD34^{+}) expresses VEGFR-1 and that inhibition of VEGFR-1 blocks their cell cycling, differentiation, and migration. Moreover, the authors have shown that PlGF promotes recruitment of VEGFR-1^{+} HSCs from a quiescent to a proliferative bone marrow microenvironment, favoring differentiation, mobilization, and reconstitution of hematopoiesis [50]. The observation that PlGF not only activates angiogenic pathways (directly or through its association with VEGF) but in fact can promote recruitment of hemangioblasts as the cell of origin of HB is exciting since it implicates a unique way by which excess of PlGF and/or VEGFR-1 can enhance the growth of this tumor during pregnancy. Figure 2 summarizes the pathophysiology of HB's cyst enlargement and the possible ways by which pregnancy might accelerate its growth. Excess levels of PlGF and VEGFR-1 during pregnancy are discussed next.

Increased vascular permeability in normal and pathological pregnancies

Physiologic angiogenesis plays an important role in endometrial growth, embryo implantation, and placentation. There are striking similarities between blastocyst implantation and tumor growth and invasion, especially in their ability to access the host vasculature and to recruit blood supply [156]. The uterus vasculature undergoes three main adaptive changes during pregnancy: vasodilation, increased permeability, and growth and development of new vessels (i.e., vasculogenesis). These changes are dependent on the release of proangiogenic factors (i.e., VEGF, PlGF, and others) by the endometrium, decidua, and placenta [136, 156].

Changes in vascular permeability during pregnancy can lead to pregnancy-related complications, some of which can be life-threatening. Pathologic conditions such as pregnancy-induced hypertension (PIH), preeclampsia, eclampsia, and posterior reversible encephalopathy syndrome (PRES) can produce severe neurologic symptoms, some of which are associated with blood–brain barrier (BBB) disruption and increased permeability as their central etiology [25]. Nevertheless, and despite the presence of these proangiogenic factors, most pregnancies do not lead to BBB disruption and brain edema. In fact, in normal pregnancy, capillary permeability is *not* altered from that of non-pregnant subjects, despite the presence of proangiogenic factors [17]. In normal pregnancy, all compartments of the extracellular fluid volume (ECFV) are increased from that of non-pregnant women, but these increases are proportionally similar so that the plasma volume/interstitial fluid volume (PV/ISFV) ratio does not change significantly. On the other hand, it has been observed in women with, e.g., PIH, that there is a significant reduction in the PV/ISFV ratio without a significant change in total ECFV from that of normal pregnancy, i.e., the reduced PV resulted from a loss of plasma to the interstitial space due to increased capillary permeability and/or altered Starling forces. Interestingly, this increased capillary permeability in complicated pregnancies was found during the third trimester [17]. Can this abnormal vascular permeability found in some pregnancies cause accelerated growth of tumor-related cysts and is

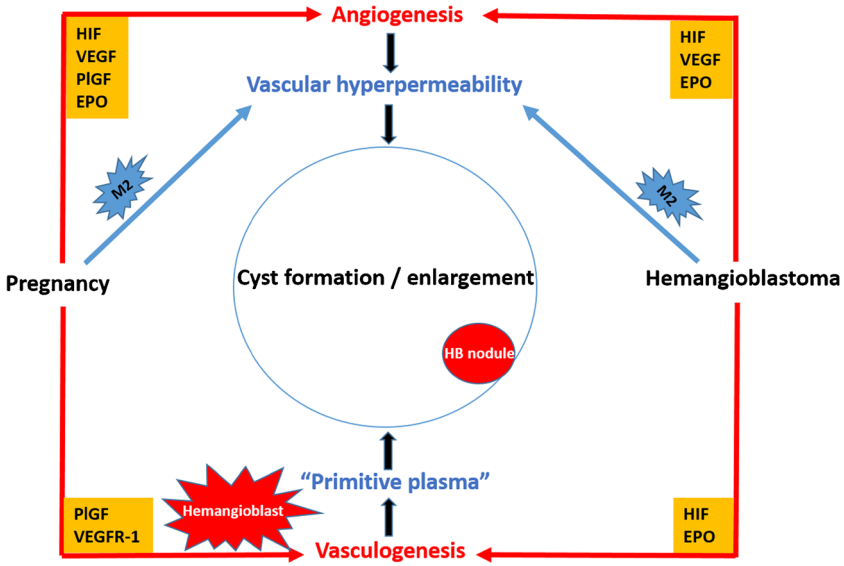

Fig. 2 Different mechanisms causing cyst formation in hemangioblastoma and the possible growth accelerating effects seen in pregnancy. Please refer to text ("Hemangioblastoma-related cysts: vasculogenesis, angiogenesis, and vascular hyperpermeability"; "PlGF and VEGFR-1 in pathologic angiogenesis and tumorigenesis"; and "Pregnancy-induced "awakening" of quiescent hemangioblastomas" sections) for a detailed explanation

it all related to abnormal levels of proangiogenic factors in the late stages of pregnancy?

To address this, we will first discuss which proangiogenic factors are elevated during pregnancy. In normal pregnancy, serum VEGF increased approximately 30 days after embryo transfer and thereafter continued to rise in both singleton and twin pregnancies over a period of 20–40 days after which concentrations remained elevated [38]. In a study by Amburgey et al. [4], the concentration of peripheral VEGF, taken at 34th GW, was similar in plasma obtained in normal pregnant and preeclamptic patients (62.0 vs. 61.4 pg/mL, respectively), and this level was considerably higher than the level of VEGF found in non-pregnant women (15.0 pg/mL). These results are in concordance with other studies, showing increased levels of VEGF in early pregnant vs. non-pregnant individuals [37] as well as in preeclamptic patients [73, 128]. Others have shown that VEGF level in a PIH group (median = 109.19 pg/mL) was significantly higher than in both normal pregnant (median = 20.82 pg/mL) and non-pregnant (median = 4.92 pg/mL) groups [133]. However, these results are not conclusive. For example, Baker et al. have also shown elevated level of VEGF in preeclamptic subjects, but levels were *undetectable* in the normal pregnant females [8]. Furthermore, Lyall et al. found that plasma VEGF concentrations in the non-pregnant group were significantly *higher* than in both late pregnancy and preeclampsia groups (166, 12.89, and 2.34 pg/mL, respectively; $p < 0.0001$) [87]. Surprisingly, systemic low levels of VEGF in pregnancy were reported many times [81, 91, 104, 143]. It is hard to interpret these conflicting results. Although it seems logical to find higher levels of VEGF in pregnancy, the results tend to actually support low levels of circulatory VEGF. One possible explanation may be the presence of sVEGFR-1 [also known as solubale fms-like tyrosine kinase 1 (sFlt1)] in pregnancy. Some recent studies have revealed the presence of sVEGFR-1 in the blood of pregnant females but not in non-pregnant females or males [133]. Considering the fact that sVEGFR-1 has high binding affinity to VEGF, the resultant concentration of biologically active VEGF is difficult to interpret. This may serve as explanation of the discrepancy in the observed results of various studies.

In contrast to VEGF, high levels of both sVEGFR-1 and PlGF were found in the blood of pregnant women in different studies. In a longitudinal study in individuals with normal pregnancies, sVEGFR-1 levels were relatively constant until weeks 29 and 30, at which point they increased, peaking at week 40. An increase of 643 pg/mL per week was observed from weeks 30 to 40. Postpartum levels were low again [104]. These results are similar to findings in other longitudinal reports [23, 81, 91, 118].

PlGF is highly expressed in placental trophoblast throughout pregnancy. It is also present in maternal serum during pregnancy [82]. PlGF increased by 16 pg/mL per week from early pregnancy until weeks 29 and 30 and thereafter decreased by 14 pg/mL per week until week 40 [104]. Similarly, Krauss et al. found that PlGF levels in pregnant women rise steadily throughout pregnancy to reach levels exceeding 500 pg/mL after 30 weeks of gestation (levels of non-pregnant women usually measure < 50 pg/mL). Thereafter, values gradually decline until term. Of note, the PlGF level correlates with the incidence of certain complications, as 27.3% of women who developed preeclampsia had plasma PlGF levels less than 200 pg/mL beyond 22 weeks of gestation [71].

Can PlGF and VEGFR-1 affect cerebral vascular permeability? In 2010, Amburgey et al. showed that BBB permeability increases manifold after exposure to normal plasma obtained during late stages of pregnancy when compared to no plasma exposure ($p < 0.01$) [4]. Further findings have suggested that circulating factors in the plasma from preeclamptic women increase BBB permeability with important role for VEGFR tyrosine kinase activity in the process. The authors

could show that VEGF is not the only factor affecting BBB permeability during pregnancy, although it was not mentioned what the other factors were [4]. Two years later (2012), Schreurs et al. showed that BBB permeability measures were similar in both non-pregnant (NP) and late-pregnant (LP) rats, despite the finding that veins from LP rats showed increased VEGF messenger ribonucleic acid (mRNA) expression levels [124]. Exogenous VEGF initiated a significant increase in BBB permeability in NP states, while it did not affect BBB permeability in LP states. It was demonstrated that increased permeability in response to VEGF was prevented by LP plasma due to the presence of sVEGFR-1 [124]. This is probably one of the main mechanisms explaining why the majority of pregnancies are not associated with clinically significant brain edema. Beyond that, the authors made another important discovery: The observation that PlGF significantly increases BBB permeability and acts as a permeability controlling factor in the cerebral endothelium. Furthermore, PlGF required only VEGFR-1 activation to be effective [124]. It could be that PlGF was the "missing" circulating factor in the study by Amburgery et al. mentioned above [4].

So far, little is known about the signaling pathways of PlGF leading to increased BBB permeability. However, it is known that increase in VEGFR-1 to PlGF ratio during late stages of pregnancy is strongly associated with the development of preeclampsia [80, 81]. It could be that similar changes in the circulatory or cerebral levels of these proangiogenic factors affect the growth of highly vascular tumors such as HB.

It is unclear if the pathogenesis leading to PIH, preeclampsia, or PRES is related to the pathophysiology of accelerated growth of vascular tumors during pregnancy. Since preeclampsia is considered to be caused by endothelial dysfunction and changes in vascular permeability [80], it is tempting to correlate it with changes seen in vascular tumors during pregnancy. Interestingly, in a recently published (2015) retrospective cohort study on pregnancy-related nervous system complications in women with rare tumor suppressor syndromes, patients with neurofibromatosis 2 (NF2) or tuberous sclerosis complex (TSC) had a significantly increased risk of preeclampsia (adjusted odds ratio 3.5 and 2.8, respectively) and patients with vHLD had significantly increased risk of cerebrovascular disease (adjusted odds ratio, 12.5) [135].

As mentioned, most women do not develop preeclampsia or brain edema despite the increased levels of vascular permeability factors in pregnancy. On the same note, not every HB grows during pregnancy. This may implicate that a yet to be determined constellation of conditions (perhaps certain levels of circulating factors or additional genetic mutations) are required for this pathological cascade to occur. This will require further research. Regardless, it is clear that both PlGF and sVEGFR-1 are persistently expressed at high levels in the circulation of pregnant women, especially during the second half of pregnancy. In addition, changes in their levels are associated with certain pregnancy-related vascular diseases [80]. Finally, when acting together, these factors can increase angiogenesis and vascular permeability, a role that is accentuated in pathological states, including tumorigenesis.

PlGF and VEGFR-1 in pathologic angiogenesis and tumorigenesis

PlGF expression, unlike that of VEGF, is undetectable in most organs in healthy conditions [110], but is highly upregulated in various diseases and pathological conditions such as cancer and inflammation [69, 86, 137], myocardial angiogenesis and atherosclerosis [21, 22], sepsis [146], allergic asthma [12], diabetic wound healing [24], sickle cell disease [109], and preeclampsia [141] among others.

Under physiological conditions, the absence of PlGF has a negligible effect on vascular development, as can be seen, for example, in embryonic angiogenesis in mice which were not affected by deficiency of PlGF [21]. However, PlGF deficiency *reduced* pathological angiogenesis, permeability, and growth of collaterals in ischemia, inflammation, and cancer. This is an important observation, because unlike the essential role of VEGF in both physiological and pathological angiogenesis, the role of PlGF is restricted to pathological conditions and offers therefore a possible target for therapy [21].

Unlike PlGF, which lack significant role under physiological conditions, the biological role of VEGFR-1 appears to be more complex. On one hand, VEGFR-1 null mutation resulted in early embryonic death at embryonic day 8.5, in the setting of disorganization of blood vessels and overgrowth of endothelial cells. On the other hand, genetic data indicate that downstream signaling of this receptor (through activation of its tyrosine kinase domains) is not required for angiogenesis during development [56]. In addition, it serves a dual function in angiogenesis, acting in either a positive or a negative manner under different biological conditions [56]. VEGFR-1 is a *positive* regulator using its tyrosine kinase under *pathological* conditions when the VEGFR-1 ligand (i.e., PlGF) is expressed at abnormally high levels [55]. An active role for VEGFR-1 during tumor angiogenesis has hence been suggested [93].

Plasma PlGF levels and tumor's PlGF mRNA and protein levels are associated with growth, progression, and survival of different solid malignancies [57, 90, 142, 151]. The first investigation conducted on PlGF expression in tumors was undertaken by Takahashi et al. [132]. Interestingly, these authors demonstrated that PlGF is expressed in hypervascular RCC, the tumor most closely resembling HB. In a study on embryonic stem cell-derived tumors, the group of Carmeliet et al. showed that when both tumor and host expressed PlGF, tumors were large and highly vascularized [21]. In a separate set of experiments, the same group showed that loss of PlGF impaired growth of VEGF-dependent tumors.

Several mechanisms were suggested to explain the role of PlGF in pathological angiogenesis [21]. First, PlGF and VEGFR-1 are minimally expressed in adult quiescent vasculature, but are markedly upregulated during pathological conditions [98]. Second, highly upregulated PlGF transmits its signal through VEGFR-1 by stimulating phosphorylation of specific VEGFR-1 tyrosine residues and thus induces the expression of distinct downstream targets [75]. Third, PlGF might enhance the angiogenic response to VEGF by forming VEGF/PlGF heterodimers [18]. Fourth, VEGF can amplify its effects on endothelial cells by inducing endothelial cell production of PlGF at the protein level [148]. Fifth, once PlGF has activated VEGFR-1, VEGFR-2 may be activated by mechanism of transphosphorylation [6]. Sixth, PlGF is a chemoattractant for inflammatory cells, a hallmark of pathological angiogenesis and collateral growth.

In primary nervous system tumors, PIGF mRNA was expressed in most hypervascular tumors (14/16 meningiomas and 6/7 gliomas), but only in 5/16 (31.3%) of hypovascular tumors [98]. In another study, PlGF mRNA was expressed in 4/16 meningiomas, and PlGF protein was detectable in most capillaries of these tumors, suggesting its role in tumor angiogenesis in human meningiomas [33]. Finally, PlGF concentrations were significantly higher in the blood plasma of high-grade meningioma patients than in the plasma of low-grade meningioma patients [60]. Interestingly, not all vascular tumors show high level of PlGF expression. For example, none of three metastatic hypervascular brain tumors expressed PlGF mRNA [98]. In a study on HB and hemangiopericytomas, increased levels of VEGF, VEGFR-1, and VEGFR-2 mRNAs were found in both tumors. However, while HBs express abundant PIGF mRNA (mRNA expression in clusters of large stromal cells), hemangiopericytomas showed little or no PIGF mRNA [51].

PlGF is produced by not only the malignant cells of tumors but also by endothelial cells [134, 150], smooth muscle cells [150], pericytes, cancer-associated fibroblasts [46], bone marrow progenitor cells [50], tumor-associated macrophages (TAMs), and various other inflammatory cells within the tumor stroma [41, 69, 150]. Furthermore, in several tumor models, a cancer cell–stroma crosstalk was documented, in which tumor cells induced stromal PlGF production [123, 129].

After anti-VEGF therapy, PlGF-VEGFR-1 signaling provides a major route for angiogenic rescue for tumors [68], making the inhibition of PlGF attractive in supplementing deficient anti-VEGF therapy. Fisher et al. have demonstrated that anti-PlGF blocking antibodies inhibit the growth and metastasis of various tumors in mice, including those resistant to VEGFR inhibitors. They also enhance the efficacy of chemotherapy and of VEGFR inhibitors [41]. Expression of functional VEGFR-1 in tumor cells is a major determinant of anti-PlGF antibody efficacy [147].

These studies emphasize the great significance of both PlGF and VEGFR-1 in the pathophysiology of tumors, including those of the nervous system. Their elevated expression during pregnancy may thus affect growth and aggressiveness of vascular tumors, even in those which were quiescent for many years.

Pregnancy-induced "awakening" of quiescent hemangioblastomas during pregnancy

Allelic losses and mutations of the vHL tumor suppressor gene play a significant role in both vHLD as well as sporadic HB tumorigenesis [65, 79, 127, 144]. The effect is an accumulation of HIF-1α, which, in turn, upregulates expression of VEGF [92, 144]. Bohling et al. confirmed high VEGF and PlGF mRNA expression in stromal cells of HB [13].

In vHLD, half of the HBs remain quiescent, while others become symptomatic with exponential growth or cyst formation following long periods of quiescence [39]. In addition, the presence of subclinical and radiologically un-diagnostic HB tumors in vHL patients at autopsy supports the concept that these tumors may be developmentally arrested but can be reactivated under appropriate conditions [139]. Such conditions were suggested to be circulating factors, including puberty—or pregnancy—related hormones [106].

Could this switch from quiescence to awakening be related to the observation of high levels of PlGF/VEGFR-1 in pregnancy?

As pointed out before, vHL plays a significant, oxygen-dependent, role in regulating HIF-1α expression. Loss of VHL (as it occurs in vHLD) simulates a hypoxic condition, leading to stabilization of HIF-1α and prevention of its degradation by proteosomes [32]. However, accumulating evidence demonstrates that stimulation of different cell types with growth factors, cytokines, vascular hormones, and viral proteins can also lead to the induction and activation of HIF-1α in *non*-oxygen-dependent pathways. Contrary to hypoxia, stabilization and inhibition of HIF-1α degradation do not seem to play a significant role in the non-hypoxic induction of HIF-1α. The main mechanism implicated in this induction is an increase in HIF-1α protein translation.

This increase in protein translation alone appears sufficient to shift the balance between synthesis and degradation toward an accumulation of normoxic HIF-1α [32]. Several studies have shown that activation of PI3K increases the rate of HIF-1α translation via the activation of ribosomal S6 protein by the PI3K/p70S6K/mTOR pathway [32]. VEGF is one of the growth factors that stimulates the PI3K/Akt/mTOR pathway [1], and it can create this effect even in the presence of VEGFR-1 alone (without VEGFR-2) [84]. Thus, it may well be that PlGF carries a similar effect—either directly through

its effects on VEGFR-1 or indirectly through its amplified effect on VEGF.

Bellik et al. were the first to describe a proliferative effect of PlGF and VEGFR-1 on cells through activation of the PI3K pathway, although that was demonstrated in a hypoxic environment [9]. Remarkably, two very recent (2016) studies were able to show for the first time that PlGF can directly stimulate the PI3K/Akt/mTOR pathway in a non-oxygen-dependent manner [152], including in tumors [2].

To summarize, we are suggesting that in pregnant women with HB, HIF-1α is locally overexpressed in the tumor, not only through the pseudo-hypoxic pathway created by the loss of vHL but also through the *oxygen-independent* pathway, caused by overactivation of the PI3K/Akt/mTOR cascade by proangiogenic factors. This unique "double trap" can explain the rapid and sometimes stormy growth of HB observed in pregnancy through the effects of HIF-1α on angiogenesis and vascular permeability.

Moreover, a third "trap" may be activated in this setting: PlGF activates, attracts, and is essential to sustain the proangiogenic type 2 tumor-associated macrophages (M2) that release angiogenic molecules [125]. In tumors, M2-type TAMs increase angiogenesis and tumor cell intravasation/extravasation and growth and suppress antitumor immunity [116]. Histidine-rich glycoprotein (HRG), a host-produced antiangiogenic and immunomodulatory factor, was able to inhibit tumor growth and metastasis by skewing TAM polarization away from the proangiogenic, M2-like phenotype. Most importantly, it does so by decreasing the expression of PlGF and exerting its effect only if the tumor's stromal cells express PlGF [116]. In addition, Incio et al. showed that in obese mice, VEGFR-1 deletion led to a reduction in tumor progression associated with a shift in tumor cytokine profile and TAM polarization toward the M1 phenotype. Furthermore, PlGF blockade in obese mice reproduced these effects of VEGFR-1 deletion on the tumor immune environment and tumor growth [61]. This M2 polarization is affected by activation of nuclear factor-kappa B (NF-kB) [48, 120]. Activation of NF-kB requires activation of PI3K and its downstream targets, e.g., Akt [44]. In addition, biallelic inactivating mutations of vHL induce NF-kB activity [5]. Taken together, it is possible that pregnancy-induced high PlGF levels can enhance tumorigenesis in HB by further overactivating protumoral pathways that are already strongly activated by the loss of vHL function, i.e., HIF-1α and M2 macrophage overproduction (Fig. 2).

Finally, in addition to these enhancing mechanisms induced by PlGF, we should add the ability of PlGF to "awake" quiescent stem cells/progenitor cells. PlGF promotes the recruitment and maturation of angiogenesis-competent (VEGFR-1 positive) myeloid progenitors to grow and sprout into collateral vessels, leading to a 20-fold increase of these cells in the circulation [50, 85, 112]. Thus, the direct effect of PlGF on

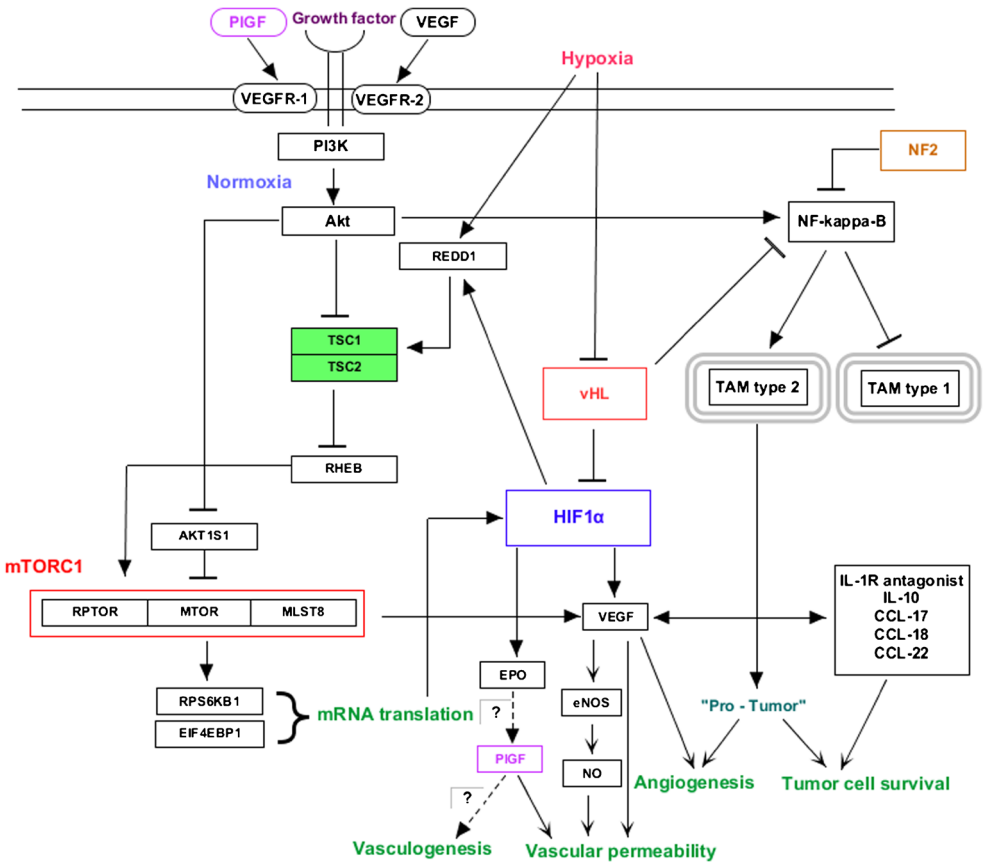

Fig. 3 Schematic illustration of the different molecular pathways involved in growth and progression of hemangioblastoma. Activation of HIF pathways can be done by an oxygen-dependent or a non-oxygen (=angiogenic factors) dependent manner. Please refer to text for a detailed explanation

recruitment of quiescent hemangioblasts can be another way by which it accelerates tumor growth, explaining the rapid growth of the cyst component of the tumor through the unique process of vasculogenesis. Figure 3 illustrates the relevant pathways in HB tumorigenesis.

These processes might have important clinical and therapeutical implications. Anti-PlGF therapy inhibits the growth and formation of metastasis in multiple tumor models. It also inhibits intratumoral macrophage infiltration and amplifies the effect of cytotoxic chemotherapy [97]. Importantly, anti-PlGF treatment does not seem to induce an antiangiogenic escape program (in contrast to anti-VEGFR-2 therapy) and demonstrates a superior safety profile when compared to VEGF(R) inhibitors [41]. Recently, the results of a phase I, dose escalation study of a humanized anti-PlGF monoclonal antibody in patients with advanced solid tumors was reported [76]. Interestingly, and despite the repeatedly made observation of increased expression levels of VEGF in HB, experience with the use of anti-VEGF treatments such as bevacizumab in HB is limited to just few case reports [59, 101]. This is in contrast to the growing experience with this treatment in, e.g., VS [11] and also contrasts with its established and approved role in RCC [36]. In 2009, at attempt was made to clinically evaluate the effects of bevacizumab on unresectable or recurrent HB in vHLD patients [NCT01015300]. Unfortunately, the trial was ended prematurely due to low accrual.

This is a missed opportunity in our eyes, and based on the large amount of available evidence presented here, we would strongly recommend to consider including anti-PlGF agents in similar clinical trials in the future. In this regard, it should be emphasized that a recent study found activation of several key angiogenic pathways in HB, in addition to VEGF/VEGFR-2 [111]. These pathways should also be considered in any future clinical trials.

Summary

In some cases, hemangioblastomas can rapidly increase in size and present acutely during late stages of pregnancy. The presentation can be accompanied by severe neurological deficits, requiring urgent surgical intervention in a multidisciplinary setting. The reasons for such acute flare-ups during pregnancy are poorly understood. Uncovering the etiology for this clinical scenario may contribute to the understanding of the pathophysiology of transformation from quiescent lesions to symptomatic ones, having implications that apply not only in the setting of pregnancy. Finding the correct triggers and mechanism that control this switch will enable us to find appropriate preventive medicines to keep these tumors in their quiescent phase.

In this review, we have laid out that HB growth is not only "associated" with pregnancy, but that the proangiogenic state of pregnancy itself may be the responsible underlying etiology. Specifically, we have analyzed the involvement of PlGF and its receptor VEGFR-1 in various pathologic processes that can lead to the accelerated growth of the cystic component as a primary cause for HB symptomatology during pregnancy. Their high specificity and their unique lack of any detrimental impact on other relevant physiological processes make them attractive future study objects for therapeutic interventions since side effects are expected to be minimal. Further research on the effects of anti-PlGF or anti-VEGFR-1 therapy in HB is therefore greatly needed.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee of Beth Israel Deaconess Medical Center and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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