Received: 14 January 2022 | Revised: 22 February 2022 | Accepted: 27 February 2022

DOI: 10.1002/hsr2.566

OBSERVATIONS

Health Science Reports Open Access WILEY

Consecutive chorioangiomas in the same pregnancy: A clinical case and review of literature

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Abstract

Background and Aims: Aetiopathogenesis of chorioangioma is already unknown. Among the risk factors, hypoxia, environmental and genetic factors are believed to induce the overexpression of angiogenic cytokines promoting vascular proliferation. We reported a case of prenatally diagnosed 67 mm-wide placental chorioangioma, which occurred at 32 weeks of gestational age, infarcted, and followed by the onset of a second infarcted chorioangioma at 35 weeks of gestational age. Besides, we discussed the hypothesis of chorioangioma aetiopathogenesis and behavior through a literature summary.

Methods: We carried out a literature search of chorioangioma cases without a time interval. Therefore, we carried out a literature summary on chorioangioma risk factors and etiology, by selecting articles within a time interval from 1995 to 2021.

Results: This is the first case of two consecutive chorioangiomas in the same pregnancy published in the literature. We found a possible genetic predisposition in women developing chorioangioma while infarction may be related to the abnormal structure of tumor vessels. The onset of a second lesion could reflect hypoxic stimuli following infarction and involves hypoxia-induced factor-1alpha, vascular endothelial growth factor, transforming growth factor-beta, and soluble Fms-like tyrosine kinase-1 pathways. Chorangiosis can be coexistent and may reflect a mutual etiology in susceptible individuals.

Conclusion: In a predisposed placenta, that previously generated a chorioangioma, infarction of the chorioangioma should not represent a sign for pregnancy termination, but a marker for closer monitoring to early detect the possible onset of a second chorioangioma and a higher risk of umbilical cord thrombosis.

KEYWORDS

chorangiosis, infarcted chorioangioma, multiple chorioangiomas, placental chorioangioma, pregnancy, pregnancy complications

1 | BACKGROUND AND AIMS

Chorioangioma is the most common nontrophoblastic benign tumor of the placenta, found in 0.16%–1% of the placentae submitted to histologic analysis.[1] Still poorly known environmental and genetic factors, being associated with the quite rare recurrent pattern of the tumor, could probably contribute to the pathogenesis of chorioangioma.[2] Altitude, acting via hypobaric hypoxia, could induce the overexpression of angiogenic cytokines (e.g., vascular endothelial growth factor [VEGF]), in turn, responsible for excessive placental vascular proliferation.[3] Interestingly enough, pregnancies with a female foetus[4] and multiple pregnancies[5] appear to be more frequently affected by chorioangioma.

As their incidence is quite limited, a small number of chorioangiomas were reported, and very little is known about the natural history of this placental vascular abnormality. Chorioangiomas, in general, are not clinically evident, and pregnancy is carried on without any maternal or fetal risk. However, in a small proportion of cases, namely 1:3500–1:9000 pregnancies, chorioangioma reaches a rather big size (>4 cm diameter)[4]; these so-called "giant chorioangiomas" may be associated with serious antenatal complications, such as fetal anemia, hydrops fetalis, polyhydramnios, antepartum hemorrhage, preterm labor and birth, intrauterine fetal growth restriction (IUGR), and increased perinatal mortality.[6]

Herein we describe a rare case of large placental chorioangioma diagnosed at 32 weeks of gestational age, that underwent infarction a few days later, and was then followed by the onset of a second, smaller chorioangioma at 35 weeks, already infarcted. As we did not find in literature any other similar case of two consecutive chorioangiomas in the same pregnancy and, considering the rarity of the diagnosis, we decided to share our experience. Moreover, we discuss the aetiopathogenesis of the disease in view of the available literature, and we hypothesize possible causes and consequences of the occurrence of two chorioangiomas in the same pregnancy, both evolving into infarction.

1.1 | Clinical case

A 35-years-old Native-American primigravida underwent routine ultrasound examination at 32 weeks of gestational age, during which it was diagnosed a large round chorioangioma (67 mm diameter) located in close proximity of the umbilical cord insertion. The chorioangioma appeared as a regular round-shaped area, with nonhomogeneous echogenicity, supplied by a clearly visible afferent blood vessel (Figure 1).

Over the entire course of pregnancy, fetal growth was normal, without signs of cardiovascular compromise (e.g., ascites or hydrops), with normal doppler flowmetry of umbilical cord and middle cerebral artery, and a regular amount of amniotic fluid.

During the follow-up, at 34 weeks and 5 days of gestation, the placental lesion became hypoechogenic and increased moderately in diameter (73 mm), with no more evidence of vascularization, suggesting that a hemorrhagic infarction had occurred. The patient was hospitalized to undergo close maternal and fetal monitoring.

At 35 weeks + 4 days, in stable clinical conditions, the ultrasound scan showed a new finding within the placental structure that was not present in the previous US scan: a nonhomogenous rounded area, measuring 37 mm, appeared, and was diagnosed as a newly developed chorioangioma bearing ultrasonographic signs of infarction (Figure 2).

Given the presence of two sites of infarction in the same placenta, our concerns regarding the risk of umbilical cord thrombosis were raised and we decided to perform an urgent cesarean section; a live, healthy newborn girl weighing 2700 g was delivered. The baby appeared with adequate weight for gestational age and was at the 76th percentile. Apgar score was 9 at 1 min and 9 at 5 min. Umbilical cord artery pH was 7.33 with a base excess of −4.6. The placenta was easily removed, showing a little retroplacental hematoma, as a sign of a previous partial placental detachment. Estimated blood loss was 500 ml and the patient was discharged on the fourth day after intervention, in good health. The placenta was sent for histological examination: it was 18 × 17 cm in size and 800 g in weight, with central

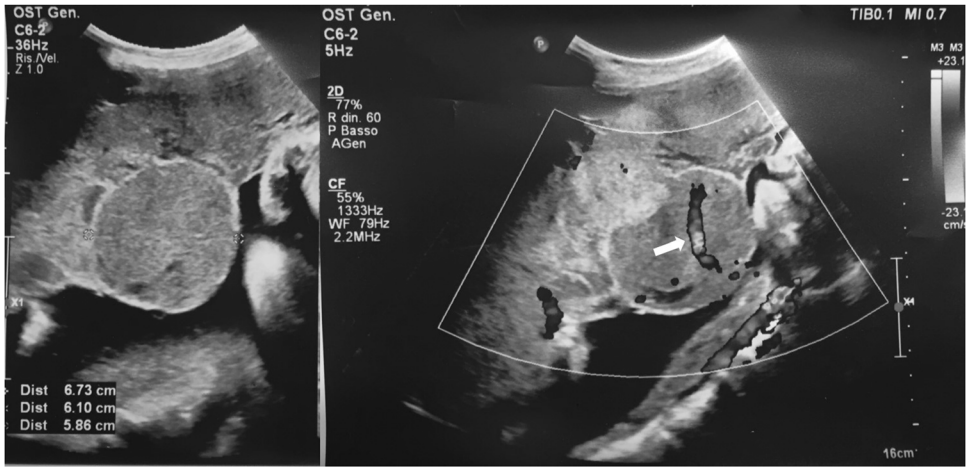

FIGURE 1 Ultrasound scan performed at 32 weeks and 4 days of gestational age, showed a regular-shaped rounded area, measuring 67 × 61 × 59 mm, with nonhomogeneous echogenicity and supplied by an afferent blood vessel (arrow)

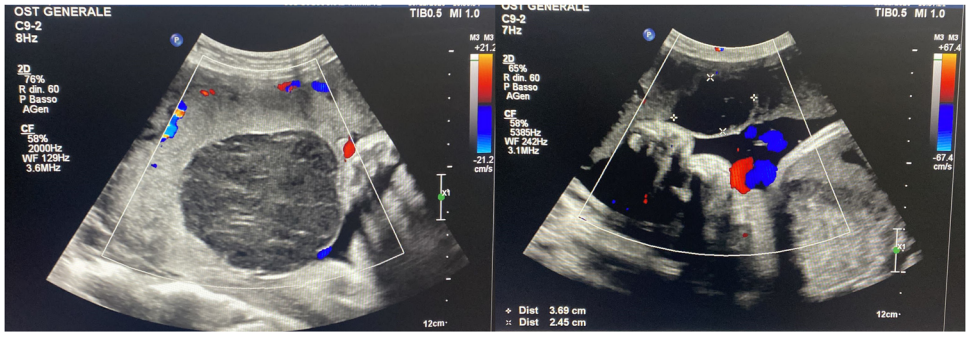

FIGURE 2 Ultrasound scan performed at 35 weeks + 4 days of gestational age, showing the original infarcted chorioangioma and the newly developed chorioangioma with signs of infarction

hyperspiralized umbilical cord insertion. A red-violet, capsulated rounded mass of 9 cm was described in proximity of the site of insertion of the umbilical cord, to which it was connected by a high-flow vessel (Figure 3). A second rounded mass of 4 cm was located more marginally, 2 cm from the cord insertion (Figure 4); histological examination confirmed the diagnosis of chorioangioma for both masses. Rather interestingly, as it is a very rare situation, both chorioangiomas were infarcted, due to the thrombosis of the afferent vessel (Figure 5). Placental chorionic vessels were congested, with external walls affected by fibrosis and muscular hypertrophy, focal thrombosis, and vasculitis. Staminal villi vessels were partially congested, with hypertrophy of the muscular tunica and reduced caliber. The maturation of the villi was described as appropriate for gestational age, except for some immature areas with hyper-spiralized capillary vessels (Figure 6).

Basal decidua did not show any morphological abnormality. Overall, the observed vascular features were compatible with hemodynamic unbalance due to obstructed blood flow.

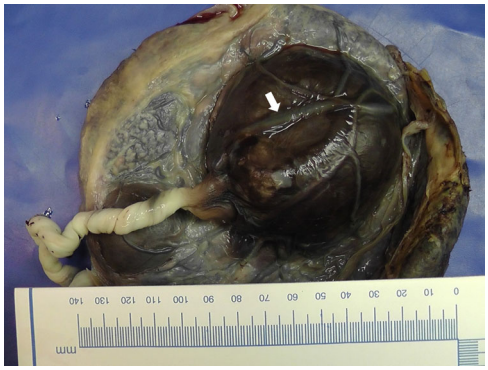

FIGURE 3 Macroscopic placenta with two chorioangiomas. Macroscopic imagine of 18 × 17 cm placenta, with central hyperspiralized umbilical cord insertion; in the picture is visible a capsulated rounded mass of 9 cm in the proximity of the site of insertion of the umbilical cord to which it appeared linked by a high-flow vessel (arrow) and a second rounded mass of 4 cm located at 2 cm from the cord

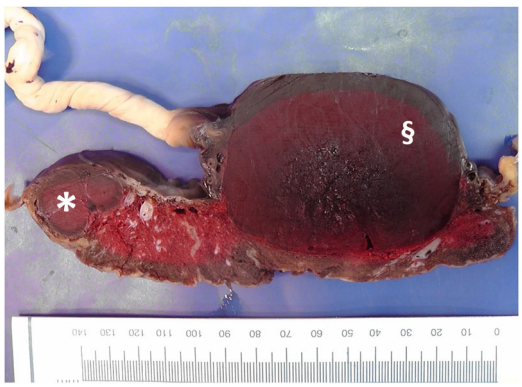

FIGURE 4 Sliced macroscopic view of the placenta with chorioangiomas. In the picture are shown the two congested chorioangiomas (marked with * and §)

2 | METHODS

We carried out a literature search in January 2021 from MEDLINE, EMBASE, and PUBMED, using keywords "placental chorioangioma," "placental chorangiosis," "multiple chorioangiomas," "consecutive chorioangioma," "villous capillary lesions," "placental lesions," "chorioangioma thrombosis" without a time interval. Therefore, we carried out a literature summary on chorioangioma risk factors and etiology from MEDLINE, EMBASE, and PUBMED, using keywords "chorioangioma risk factors," "chorioangioma etiology," "chorioangioma aetiopathogenesis," "chorioangioma AND hypothesis" by selecting articles within a time interval from 1995 to 2021.

3 | RESULTS

The aetiopathogenesis of chorioangioma is still poorly known. Its incidence was observed to be higher in women living at high altitudes, leading to the hypothesis that hypobaric hypoxia could be involved in its genesis.[3] Indeed, some studies investigating the altitude-related fetal growth restriction speculated about some "constitutional" long-term adaptation of the placental development to high-altitude hypoxia, in turn leading to angiomatous vascular growth.[7,8] Actually, the patient considered in our case report was

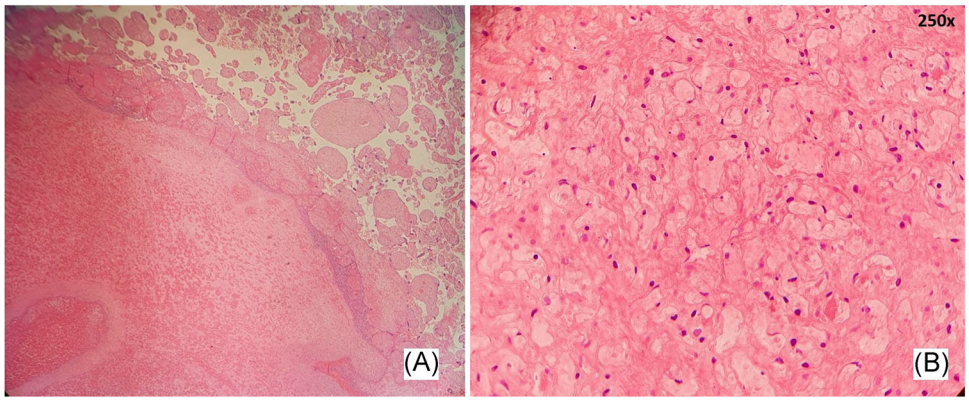

FIGURE 5 Chorioangioma microscopic aspect. The figure shows the histological slides of the chorioangioma, surrounded by thrombosed vessels (A) and ×250 magnification of chorioangioma microscopic structure (B)

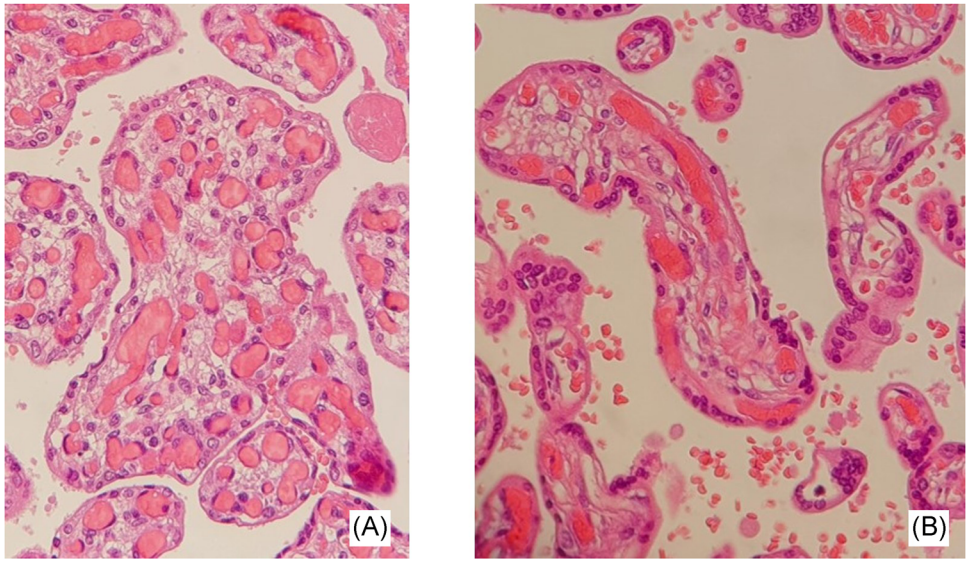

FIGURE 6 Hyperspiralized terminal villi vessels (chorangiosis) (A) and normal terminal villi vessels (B)

born in Peru and belonged to the Native American ethnic group and her baby showed adequate weight for gestational age according to Italian Neonatal Study chart.[9] Fetal growth should be assessed frequently in case of placental chorioangioma, to early detect fetal growth restriction and to schedule adequate timing for delivery; the normal fetal growth in our case suggests a good maternal response to hypoxia, possibly related to a genetic predisposition toward activating a good response to hypoxia.

The link between hypoxia and the onset of a placental adaptive response is suggested by some basic research studies. Moore et al. showed that nine hypoxia-induced factor (HIF)-related gene regions were specific of high-altitude Andeans and silenced in low-altitude individuals of the same geographic areas[10]; these genes were found to play a key role in oxygen-sensing and maternal physiological response to pregnancy. Besides this, the EGLN1 gene (also called PHD2), involved in the degradation of HIF-1alpha under normoxia or, contrariwise, in the preservation of HIF-under hypoxic conditions, was differently expressed in both Andeans and Tibetans versus low-altitude control populations.[11,12]

HIF-1alpha is a heterodimer that binds hypoxia-responsive elements (HREs) in the promoter region of hypoxia-sensitive genes. Low oxygen tension facilitates the binding between the finely tuned alfa-subunit and the constitutively expressed beta-subunit of the peptide; moreover, negative feedback activated by hypoxia inhibits HIF degradation operated by E3 ubiquitin and by Von–Hippel–Lindau (VHL) tumor suppressor protein. High levels of HIF were detected in syncytiotrophoblast, vascular endothelium, and mesenchymal tissue, together with decreased levels of factor inhibiting HIF (FIH), an asparagine-hydroxylase known to prevent HIF gene transcription via inhibition of transcription cofactors.[13] HIF-1alpha regulates even the expression of transforming growth factor-beta (TGF-beta), a protein that plays a key role in early placental development, and of VEGF, involved in angiogenesis. Indeed, in high-altitude placentae, TGF-beta is more than doubled, while VEGF significantly increases after

20 weeks of gestation.[13] VEGF may have paracrine effects within the placenta by binding its receptors Flt-1 (soluble Fms-like tyrosine kinase-1 [sFlt-1]) and sVEGFR-1 (soluble VEGF receptor-1); sFlt-1 displays antiangiogenic properties by reducing VEGF biological effects after binding. Namely, sFlt-1 is expressed and secreted from several different human tissues, such as endometrium, endothelial cells, and placental villi. During physiological pregnancy, sFlt-1 binds to VEGF and placental growth factor (PlGF) with high affinity, decreasing serum-free levels and proangiogenic activity of both. In high-altitude placentae, sFlt-1 was found in vascular and perivascular tissues: Nevo et al.[14] demonstrated an increased HIF-1-mediated sFlt-1 expression in in vivo and in vitro models of induced placental hypoxia, associated with increased vascularity of mature intermediate and terminal villi, reduced diffusional barrier, and increased density of terminal villi. Indeed, the excess of sFlt-1 may act to restrict excessive peripheral vascular development, as a sort of incomplete adaptation to high-altitude conditions. Even in preeclamptic pregnancies, the abnormal placentation following chronic hypoxia is characterized by increased sFlt-1 concentration, but sFlt-1 is expressed by trophoblast layers and leads to different histological features, including poorly branched villi and thickened exchange barriers.[15]

The onset of a second chorioangioma in the same pregnancy, some weeks after the first, is a very rare finding, never described before to the best of our knowledge. Recently, a case report described a "multiple chorioangioma syndrome," characterized by the presence of multiple vascular tumors, from very small early lesions (0.1–0.2 cm) to fully developed chorioangiomas[16]; however, in that case, chorioangiomas were found simultaneously while, in our case, the second chorioangioma appeared a few weeks after the first. Persistent hypoxia could have contributed to a long-lasting overproduction of angiogenic cytokines, in turn, able to cause the growth of the second chorioangioma.[3] It is impossible to clarify whether the infarction of the first chorioangioma could have caused vascular changes in placental flow, fetal blood stealing, and consequent hypoxia, in turn stimulating the release of pro-angiogenetic factors leading to the growth of another smaller tumor after a few weeks.

As concerns, the mechanism underlying the spontaneous thrombosis and the infarction of both chorioangiomas, the Virchow's triad (reduced blood flow, hypercoagulability, and vascular abnormality) could be the pathogenesis factor.[17,18] The sequestration of fetal platelets in the disorganized and tortuous chorioangioma vascular network may have led to turbulent responsible for endothelial injuries and blood stasis, promoting the formation of a clot. Furthermore, a rather large mass near the umbilical cord insertion may exert a compressive effect and consequently affect cord flow; indeed, in our case, the umbilical cord appeared hyperspiralized and linked to chorioangioma by a high-flow vessel, two conditions associated with a major risk of cord thrombosis. Placental modifications were likely due to impaired umbilical cord flow that could turn into cord thrombosis if the pregnancy had continued. On the other side, infarction of the chorioangiomas may have reduced adverse effects on fetal flows, preventing polyhydramnios and fetal anemia caused by hyperdynamic circulation.[19] In another case described by Chazotte et al.,[20] after the spontaneous infarction of a 5 cm chorioangioma in the placenta, fetal hydrops improved, and the patient delivered near term with good neonatal outcome.

In the case we observed, the histological analysis described a placenta consisting of 40% normal mature morphology and 60% immature areas, occupied by villi with hyperspiralized capillary vessels (Figure 7).

This condition is actually known as "chorangiosis,"[21] defined when more than 10 capillaries per terminal villus are seen in at least 10 villi in several regions of the placenta. Chorangiosis is considered an aberrant terminal villous growth pattern, leading to hypercapillarization of an otherwise well-perfused placenta, and is possibly triggered by an excess of growth factors, hypoxia (linked to smoking, high-altitude, anemia), increased capillary pressure (partial cord occlusion), or excess cytokine production.[22] The coexistence of chorioangioma and chorangiosis in the same placenta was already described in the placenta of high-altitude residents, and similarly to chorioangioma, chorangiosis may arise in predisposed individuals.[23] Indeed, the placentae of high-altitude individuals can increase gas exchange capacity beyond the normal range to preserve fetal growth; via the development of vascular hyperplasia in terminal chorionic villi, exchange surfaces can widen, increasing oxygen transit between maternal and fetal circulation.[24]

In our rare case of two placental vascular tumors in the same pregnancy, a somehow predisposed placenta generated a chorioangioma, whose infarction caused by tumor vessel tortuosity created a secondary hypoxic environment triggering the growth of a new chorioangioma a few weeks later. Normal fetal growth was likely ensured because the placenta successfully increased its exchange surface through chorangiosis to overcome chorioangioma blood stealing and obstructed umbilical flow. Although molecular pathways involving HIF-1alpha, VEGF, and TGF can explain neo-angiogenesis and growth of possible microscopic chorioangiomas already present

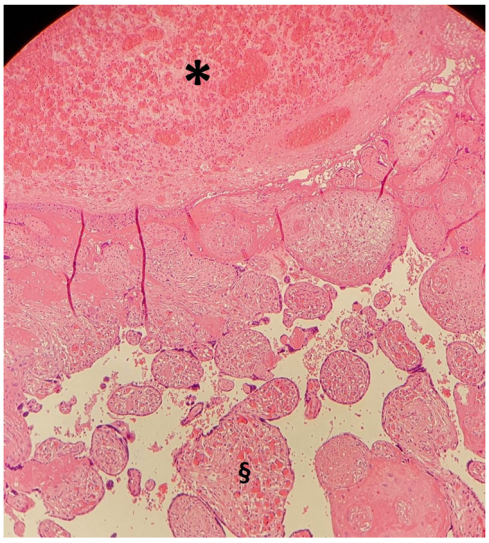

FIGURE 7 Chorioangioma and chorangiosis. Comparison between chorioangioma (*) and chorangiosis (§)

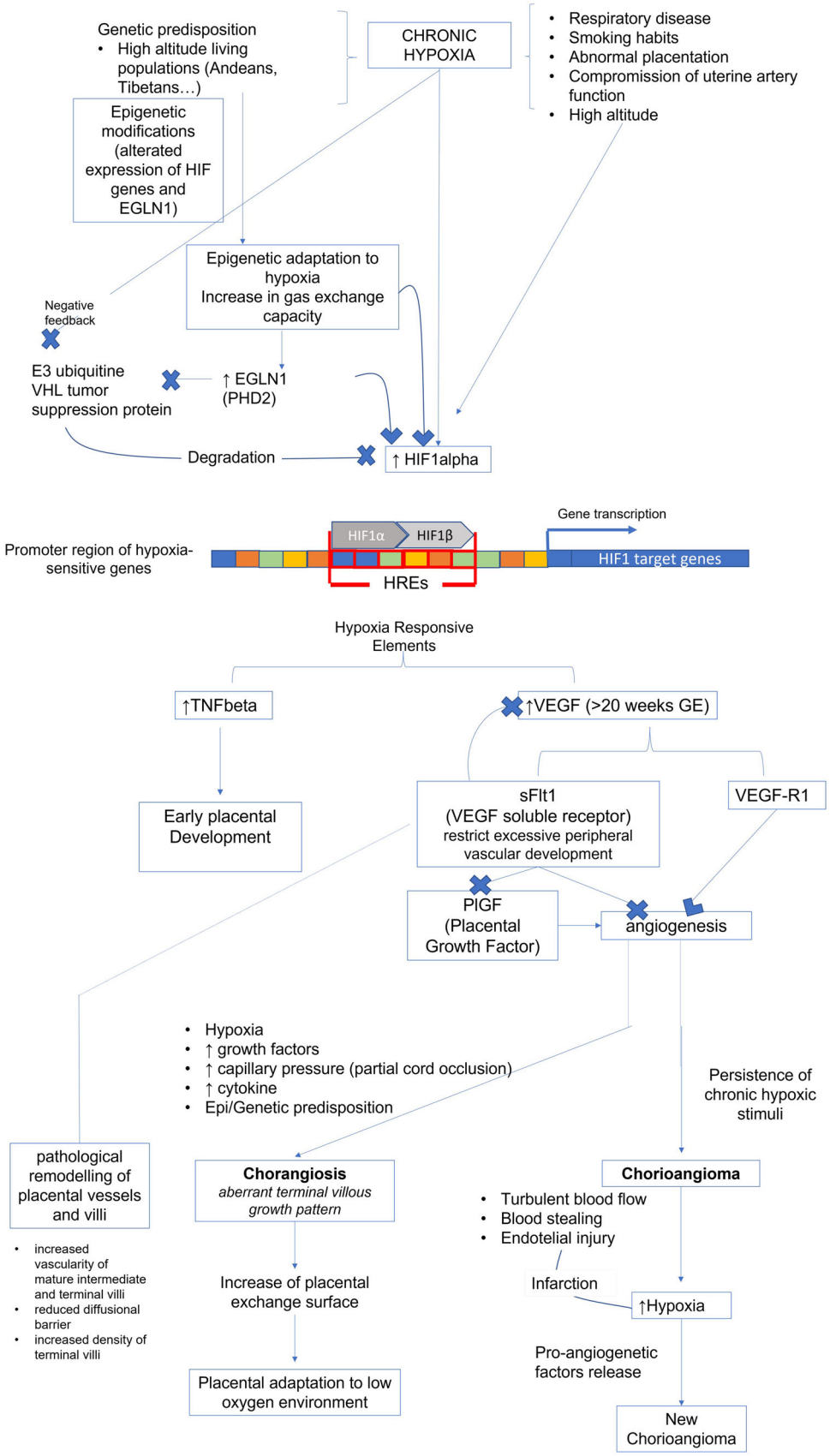

FIGURE 8 Schematic flowchart of hypothesis on chorioangioma and chorangiosis etiopathogenesis. EGLN1, Egl-9 family hypoxia-inducible factor 1; HIF, hypoxia-induced factors; PlGF, placental growth factor; sFlt1, soluble Fms-like tyrosine kinase 1; TNFbeta, tumor necrosis factor beta; VEGF, vascular-endothelial growth factor; VEGF-R1, vascular-endothelial growth factor receptor 1; VHL, Von–Hippel–Lindau

inside the placenta, the action of sFlit-1 may explain pathological remodeling of placental vessels and villi, similarly to what happens in pre-eclampsia or high-altitude models (Figure 8).

4 | CONCLUSIONS

The onset of chorioangioma appeared to be related to overexpression of HIF1alpha, induced by chronic hypoxic stimuli; the consequent overregulation of angiogenesis mediated by VEGF and the abnormal placental development, related to the increase of TNF-beta, are counterposed to the inhibiting action of sFlt1 with a subsequent pathological remodeling of placental vessels and villi. In some predisposed populations, the epigenetic modifications seemed to allow the placenta to increase the oxygen exchanges, granting a normal fetal growth. The risks of a pregnancy complicated by chorioangioma are related to the procoagulant environment, with a higher risk of cord thrombosis, the hyperdynamic flow due to shunt effect with hyperfiltration, polyhydramnios, fetal heart failure and hydrops, fetal blood stealing with fetal anemia, thrombocytopenia and disseminated intravascular coagulation and failure in placental function with growth restriction and fetal death. According to these findings, in case of a diagnosis of placental chorioangioma, a correct management should include serial ultrasound scans of the placenta and the fetus, Doppler flowmetry of umbilical cord and middle cerebral artery, and amniotic liquid measurement. An attentive clinical approach may allow detecting the eventual onset of a new vascular mass and preventing serious complications like umbilical cord thrombosis. Further research is required to investigate the mechanisms underlying chorioangioma onset and to define guidelines for a proper management.

ACKNOWLEDGMENT

The authors received no funding from an external source.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

ETHICS STATEMENT

All authors have read and approved the final version of the manuscript. Informed consent has been obtained from the patient. No personal information that could identify the patient is included.

AUTHOR CONTRIBUTIONS

Conceptualization: Chiara Germano, Eleonora Pilloni, Alessandro Rolfo, and Giovanni Botta. *Data curation*: Chiara Germano, Ilenia Cotrino, Eleonora Pilloni, and Giovanni Botta. *Investigation*: Chiara Germano, Eleonora Pilloni, and Alessandro Rolfo. *Methodology*: Chiara Germano, Eleonora Pilloni, and Alessandro Rolfo. *Supervision and validation*: Alberto Revelli and Bianca Masturzo. *Visualization*: Bianca Masturzo, Paolo Cortese, and Rossella Attini. *Writing—original draft preparation*: Chiara Germano and Alessandro Rolfo. *Writing—review and editing*: Chiara Germano and Giulia Parpinel. Dr. Chiara Germano had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are entirely available within the article.

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How to cite this article: Germano C, Pilloni E, Rolfo A, et al. Consecutive chorioangiomas in the same pregnancy: a clinical case and review of literature. *Health Sci. Rep*. 2022;5:e566. doi:10.1002/hsr2.566