American Journal of Medical Genetics Part A

WILEY

AMERICAN JOURNAL OF medical genetics PART A

RESEARCH LETTER OPEN ACCESS

Coffin-Siris Syndrome and Unusual Angiogenic Profiles in Pregnancy: A Case Study Emphasizing Caution in Interpreting a Very Low sFlt-1/PlGF Ratio

Valentina Giardini[1] | Arianna Pelucchi[1] | Cecilia Daolio[2] | Marco Casati[3] | Patrizia Vergani[4] | Martina Lattuada[5] | Anna Locatelli[1]

[1]Department of Obstetrics, IRCCS San Gerardo Dei Tintori Foundation, University of Milano-Bicocca, Monza, Italy | [2]Pediatrics, IRCCS San Gerardo Dei Tintori Foundation, Monza, Italy | [3]Laboratory Medicine, IRCCS San Gerardo Dei Tintori Foundation, Monza, Italy | [4]Department of Obstetrics, MBBM Foundation Onlus, University of Milano-Bicocca, Monza, Italy | [5]School of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy

Correspondence: Valentina Giardini (valentinagiardini1985@gmail.com) | Anna Locatelli (anna.locatelli@unimib.it)

Received: 30 August 2024 | **Revised:** 15 October 2024 | **Accepted:** 2 November 2024

Funding: The authors received no specific funding for this work.

Nowadays, angiogenic assessment during pregnancy is a relevant component of obstetric care, especially for screening, diagnosing, and monitoring placental dysfunction disorders such as preeclampsia (preE) and fetal growth restriction (FGR). The markers available in clinical practice include placental growth factor (PlGF) and soluble fms-like tyrosine kinase 1 (sFlt-1). PlGF is a proangiogenic factor from the vascular endothelial growth factor (VEGF) family, mainly expressed in the placenta that stimulates blood vessel growth and dilation by releasing nitric oxide and prostacyclin. In contrast, sFlt1, a soluble VEGF receptor, acts as an anti-angiogenic factor by antagonizing these effects. This leads to increased production of procoagulant and vasoconstrictor substances, resulting in endothelial dysfunction (Stepan et al. 2023), as illustrated in Figure 1. Recent studies have primarily focused on defining reference cut-offs for the sFlt-1/PlGF ratio, particularly in the management of preE, identifying four categories of obstetric risk relative to the 34th week of gestation: low (< 38), intermediate (38–85/38–110), high (> 85/> 110), and very high (> 655/> 201) (Herraiz, Llurba, and Verlohren 2018). While it is widely recognized that a high sFlt-1/PlGF ratio is a strong predictor of adverse maternal-fetal-neonatal outcomes (Graupner and Enzensberger 2021), less attention has been given to cases where this ratio is low or very low. Furthermore, significant uncertainties persist regarding the optimal use of these markers and their role in various obstetric conditions (Rana, Burke, and Karumanchi 2022). A correlation has been established between the natural aging process of the placenta and the levels of angiogenesis markers in maternal blood: toward the end of a normal gestation, PlGF levels typically decrease while sFlt-1 levels rise (Chiarello et al. 2018). In cases of placental dysfunction, however, PlGF is lower and sFlt-1 is elevated beyond the norms expected for the gestational age (Rana, Burke, and Karumanchi 2022). Elevated sFlt-1 in maternal serum is linked to the clinical syndrome of preE (Maynard et al. 2003). High sFlt-1 levels have also been observed in other conditions characterized by endothelial dysfunction, such as sepsis, heart disease, acute pancreatitis, and COVID-19, all of which are associated with poor outcomes (Giardini et al. 2020). Low PlGF concentrations are particularly associated with FGR, while the effects of excessive PlGF production are not well understood (Shinar et al. 2021). Here, we report a case of a pregnant woman with FGR and a very low sFlt-1/PlGF ratio at term, characterized by notably high PlGF levels. Genetic analysis of the baby revealed Coffin-Siris syndrome (CSS). A 19-year-old primigravida from Bangladesh, at 38.4 weeks of gestation, was admitted to the hospital due to reduced fetal movements and FGR. The ultrasound biometric assessment showed a slowdown in fetal growth compared to previous check-ups, with abdominal circumference below the 1st percentile according to Hadlock et al. (1984) and an estimated fetal weight of 2605 g, corresponding to the 5th percentile according to Hadlock, Harrist, and Martinez-Poyer (1991). At Doppler examination, the uterine arteries, umbilical artery, and middle cerebral artery showed normal results. The pregnancy had progressed normally until then. Her medical history included a past Hepatitis B (HBV) infection with positive HBsAg and an enucleation of a benign cyst in the

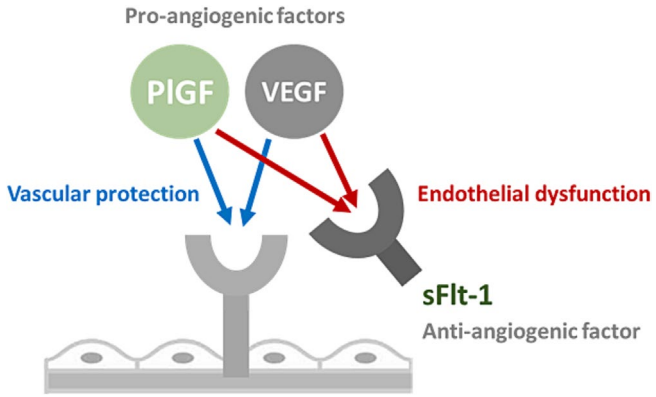

FIGURE 1 | Angiogenic factor interactions.

right breast. Her partner, also from Bangladesh and non-consanguineous, was in good health. Both reported a family history of isolated preauricular tags. During the hospital stay, blood pressure values were normal, as were the routine laboratory tests. Given the fetal growth concerns, angiogenic markers were also measured to rule out a placental cause. The sFlt-1/PlGF ratio was found to be very low, equal to 0.67, due to high PlGF levels, equal to 2615 pg/mL, more than four times above the 90th percentile for an uncomplicated singleton term pregnancy (620 pg/mL) (Verlohren et al. 2014). Conversely, sFlt-1 levels were within normal limits for the gestational age (1757 pg/mL). The low ratio was also confirmed by a second maternal blood sample (PlGF 1872 pg/mL, sFlt-1 1887 pg/mL, sFlt-1/PlGF 1.01). No drug was taken during the pregnancy or hospital stay. At 39.3 weeks of gestation, considering the ultrasound findings and gestational age, the labor was medically induced. At 39.5 weeks, a cesarean section was performed due to failed induction. The baby, a male, weighed 2640 g, which was the 4th percentile according to INTERGROWTH-21st (Villar et al. 2014), with an Apgar score of 9/10 and an umbilical artery pH of 7.18. At birth, he presented with a right preauricular tag and facial asymmetry, which raised concerns for the oculo-auriculo-vertebral spectrum. However, further evaluations, including spine X-rays, auditory tests, and an ophthalmological examination, were normal. An echocardiogram revealed a small, non-significant left-to-right shunt at the level of the foramen ovale. Given the maternal history, active and passive prophylaxis for HBV was administered. Cytomegalovirus tests were negative. Blood glucose monitoring and the Guthrie test were negative. On the 3rd day of life, noisy breathing and brief desaturation episodes during feeding were observed, leading to a transfer to an intensive care setting where these episodes gradually decreased without the need for respiratory support. The polysomnography was normal. A bronchoscopy performed 15 days after birth showed severe laryngomalacia, which was confirmed by a computed tomography scan. A few hours after discharge at 21 days, the baby experienced an episode of regurgitation, followed by apnea, cyanosis, and generalized hypertonia. A magnetic resonance of the brain revealed a hypoplastic corpus callosum. The patient was discharged after 10 days, but experienced several hospitalizations due to issues such as apnea, regurgitation, and poor appetite. Further follow-up investigations revealed mild hearing loss, a persistent left superior vena cava, and neurological evaluations showed psychomotor delay. Given the complex clinical presentation, the infant and his parents underwent Whole-Exome Sequencing (WES trio). Genetic investigations identified a de novo p.Arg521Trp heterozygous variant in the protein encoded by the *SMARCA4* gene in the infant, which is likely pathogenic. This variant may be associated with the clinical manifestations, allowing for a diagnosis of CSS, a rare genetic condition with highly variable clinical presentations. Key features include intellectual disability, dysmorphic facial features, ectodermal issues like hypertrichosis, sparse hair, and hypoplastic nails of the fifth fingers or toes and congenital anomalies. Craniofacial characteristics include microcephaly, coarse features such as thick eyebrows, a broad nasal tip, and a wide mouth with a thin vermilion border on the upper lip and a thick one on the lower lip. Most pregnancies are uneventful, but neonatal issues often include hypotonia, growth deficits, feeding difficulties, and infections. Developmental milestones are delayed, with most children sitting by 12 months, walking by 30 months, and speaking first words around 2 years. Intellectual disability is present in most cases, typically ranging from moderate to severe. Many individuals also experience behavioral problems. Common congenital abnormalities involve the brain, heart, and genitourinary system, with some children also facing respiratory, ocular, and hearing issues (Schrier Vergano et al. 2013). CSS has a heterogeneous genetic etiology, as it can be caused by heterozygous mutations in one of the genes encoding the protein subunits of the BAF (mammalian SWI/SNF) complex. The most frequently involved genes are *ARID1B*, *ARID1A*, *ARID2*, *SMARCA4*, *SMARCB1*, *SMARCC2*, *SMARCD1*, *SMARCE1*, *SOX4*, *SOX11*, and *DPF2*. This multiprotein complex is involved in chromatin remodeling and the regulation of gene expression during development, explaining the significant phenotypic variability associated with the syndrome (van der Sluijs et al. 2022). Furthermore, recent research highlights the significant tumor-suppressive roles of the BAF complex, with approximately 20% of human cancers exhibiting pathogenic alterations in its subunits (Mardinian et al. 2021). In our case, the germline *SMARCA4* variant is responsible for CSS, which is typically sporadic, but can also be inherited in an autosomal dominant manner. *SMARCA4*, also known as transcriptional activator *BRG1* (brahma-related gene 1), is correlated with embryonic vascular development, especially it is an essential regulator for neurogenesis in the vertebrate nervous system (Seo, Richardson, and Kroll 2005), in addition to being a tumor suppressor. Nonetheless, the specific function of *BRG1* in angiogenesis and the underlying molecular mechanisms are still not fully understood. A study shows that BRG1 plays an important role in angiogenesis in colorectal cancer and it can regulate the expression of VEGF-A (Lan et al. 2017), an angiogenic growth factor essential for placental vascular development like PlGF. This connection could therefore explain the high levels of PlGF found at the end of pregnancy. To our knowledge, this is the first instance connecting a fetal genetic disorder with an angiogenic prenatal maternal profile. While this report may offer new insights into the role of angiogenic markers, especially elevated PlGF levels, we acknowledge the need for further studies to establish a definitive association between the genetic condition and PIGF levels. Additionally, it emphasizes the importance of incorporating angiogenic markers into routine clinical practice, especially in case of FGR. The accurate interpretation of these profiles will be the next significant challenge for obstetrics. They indeed allowed us to conclude that the fetal growth disorder was not related to a classic placental dysfunction, which is typically characterized

by low PlGF levels. It was only after birth that we recognized these elevated values might be associated with the suspected syndromic condition. Additionally, this case underscores the importance of analyzing both markers, not just the sFlt-1/PlGF ratio, and comparing them with values from an uncomplicated pregnancy at the same gestational age and term (Giardini et al. 2024). Furthermore, it highlights that a very low sFlt-1/PlGF ratio warrants attention and that elevated PlGF levels can be associated with neonatal complications. Caution is advised when interpreting the angiogenic profile during pharmacological therapies, uncontrolled diabetes mellitus or gestational diabetes, and infections, as these conditions may impact placental angiogenesis (Herraiz, Llurba, and Verlohren 2018). For example, some studies have shown that maternal serum PlGF levels can be elevated in pregnant women with gestational diabetes (Gorkem, Togrul, and Arslan 2020). While this was not the case here, it highlights the importance of considering the context. In conclusion, our data suggest that an abnormal angiogenic profile during pregnancy may also indicate a genetic fetal disorder. To the light of these considerations, we think that additional research is warranted to explore placental angiogenesis. In the meantime, it is crucial to educate obstetricians and neonatologists on interpreting these markers as integrated tools for surveillance to be contextualized within the overall clinical, ultrasound, and laboratory picture.

Author Contributions

Study concept, interpretation of data: V.G. Data collection: V.G. and A.P. Drafting of the paper: V.G. Critical revision: A.L., C.D., M.C., P.V., and M.L. All authors have read and agreed to the published version of the manuscript.

Acknowledgments

Open access publishing facilitated by Universita degli Studi di Milano-Bicocca, as part of the Wiley - CRUI-CARE agreement.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

Chiarello, D. I., C. Abad, D. Rojas, et al. 2018. "Oxidative Stress: Normal Pregnancy Versus Preeclampsia." *Biochimica et Biophysica Acta - Molecular Basis of Disease* 1866: 165354.

Giardini, V., A. Carrer, M. Casati, E. Contro, P. Vergani, and C. Gambacorti-Passerini. 2020. "Increased sFLT-1/PlGF Ratio in COVID-19: A Novel Link to Angiotensin II-Mediated Endothelial Dysfunction." *American Journal of Hematology* 95, no. 8: E188–E191. https://doi.org/10.1002/ajh.25882.

Giardini, V., M. Casati, P. Vergani, and A. Locatelli. 2024. "Letter to the Editor: Caution: Not all sFlt-1/PlGF Ratios Are the Same." *Pregnancy Hypertension* 37: 101149. https://doi.org/10.1016/j.preghy.2024.101149.

Gorkem, U., C. Togrul, and E. Arslan. 2020. "Relationship Between Elevated Serum Level of Placental Growth Factor and Status of Gestational Diabetes Mellitus." *Journal of Maternal-Fetal and Neonatal Medicine* 33, no. 24: 4159–4163. https://doi.org/10.1080/14767058.2019.1598361.

Graupner, O., and C. Enzensberger. 2021. "Prediction of Adverse Pregnancy Outcome Related to Placental Dysfunction Using the sFlt-1/PlGF Ratio: A Narrative Review." *Geburtshilfe und Frauenheilkunde* 81, no. 8: 948–954. https://doi.org/10.1055/a-1403-2576.

Hadlock, F. P., R. L. Deter, R. B. Harrist, and S. K. Park. 1984. "Estimating Fetal Age: Computer-Assisted Analysis of Multiple Fetal Growth Parameters." *Radiology* 152, no. 2: 497–501. https://doi.org/10.1148/radiology.152.2.6739822.

Hadlock, F. P., R. B. Harrist, and J. Martinez-Poyer. 1991. "In Utero Analysis of Fetal Growth: A Sonographic Weight Standard." *Radiology* 181, no. 1: 129–133. https://doi.org/10.1148/radiology.181.1.1887021.

Herraiz, I., E. Llurba, and S. Verlohren. 2018. "Galindo A; Spanish Group for the Study of Angiogenic Markers in Preeclampsia. Update on the Diagnosis and Prognosis of Preeclampsia With the Aid of the sFlt-1/PlGF Ratio in Singleton Pregnancies." *Fetal Diagnosis and Therapy* 43, no. 2: 81–89. https://doi.org/10.1159/000477903.

Lan, J., H. Li, X. Luo, J. Hu, and G. Wang. 2017. "BRG1 Promotes VEGF-A Expression and Angiogenesis in Human Colorectal Cancer Cells." *Experimental Cell Research* 360, no. 2: 236–242. https://doi.org/10.1016/j.yexcr.2017.09.013.

Mardinian, K., J. J. Adashek, G. P. Botta, S. Kato, and R. Kurzrock. 2021. "SMARCA4: Implications of an Altered Chromatin-Remodeling Gene for Cancer Development and Therapy." *Molecular Cancer Therapeutics* 20, no. 12: 2341–2351. https://doi.org/10.1158/1535-7163.MCT-21-0433.

Maynard, S. E., J.-Y. Min, J. Merchan, et al. 2003. "Excess Placental Soluble Fms-Like Tyrosine Kinase 1 (sFlt1) May Contribute to Endothelial Dysfunction, Hypertension, and Proteinuria in Preeclampsia." *Journal of Clinical Investigation* 111: 649–658.

Rana, S., S. D. Burke, and S. A. Karumanchi. 2022. "Imbalances in Circulating Angiogenic Factors in the Pathophysiology of Preeclampsia and Related Disorders." *American Journal of Obstetrics and Gynecology* 226, no. 2S: S1019–S1034. https://doi.org/10.1016/j.ajog.2020.10.022.

Schrier Vergano, S., G. Santen, D. Wieczorek, et al. 2013. "Coffin-Siris Syndrome." In *GeneReviews®*, edited by M. P. Adam, J. Feldman, G. M. Mirzaa, et al. Seattle, WA: University of Washington. https://www.ncbi.nlm.nih.gov/books/NBK131811.

Seo, S., G. A. Richardson, and K. L. Kroll. 2005. "The SWI/SNF Chromatin Remodeling Protein Brg1 Is Required for Vertebrate Neurogenesis and Mediates Transactivation of Ngn and NeuroD." *Development* 132: 105–115.

Shinar, S., M. Tigert, S. Agrawal, W. A. Parks, and J. C. Kingdom. 2021. "Placental Growth Factor as a Diagnostic Tool for Placental Mediated Fetal Growth Restriction." *Pregnancy Hypertension* 25: 123–128.

Stepan, H., A. Galindo, M. Hund, et al. 2023. "Clinical Utility of sFlt-1 and PlGF in Screening, Prediction, Diagnosis and Monitoring of Pre-Eclampsia and Fetal Growth Restriction." *Ultrasound in Obstetrics & Gynecology* 61, no. 2: 168–180. https://doi.org/10.1002/uog.26032.

van der Sluijs, P. J., M. Joosten, C. Alby, et al. 2022. "Discovering a New Part of the Phenotypic Spectrum of Coffin-Siris Syndrome in a Fetal Cohort." *Genetics in Medicine* 24, no. 8: 1753–1760. https://doi.org/10.1016/j.gim.2022.04.010.

Verlohren, S., I. Herraiz, O. Lapaire, et al. 2014. "New Gestational Phase-Specific Cutoff Values for the Use of the Soluble Fms-Like Tyrosine Kinase-1/Placental Growth Factor Ratio as a Diagnostic Test for Preeclampsia." *Hypertension* 63, no. 2: 346–352. https://doi.org/10.1161/HYPERTENSIONAHA.113.01787.

Villar, J., L. Cheikh Ismail, C. G. Victora, et al. 2014. "International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st). International Standards for Newborn Weight, Length, and Head Circumference by Gestational Age and Sex: The Newborn Cross-Sectional Study of the INTERGROWTH-21st Project." *Lancet* 384, no. 9946: 857–868. https://doi.org/10.1016/S0140-6736(14)60932-6.