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Pravastatin to prevent recurrent fetal death in massive perivillous fibrin deposition of the placenta (MPFD)

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Abstract

Massive perivillous fibrin deposition of the placenta (MPFD) or maternal floor infarction (MFI) is a serious condition associated with recurrent complications including fetal death and severe fetal growth restriction. There is no method to evaluate the risk of adverse outcome in subsequent pregnancies, or effective prevention. Recent observations suggest that MFI is characterized by an imbalance in angiogenic/anti-angiogenic factors in early pregnancy; therefore, determination of these biomarkers may identify the patient at risk for recurrence. We report the case of a pregnant woman with a history of four consecutive pregnancy losses, the last of which was affected by MFI. Abnormalities of the anti-angiogenic factor, sVEGFR-1, and soluble endoglin (sEng) were detected early in the index pregnancy, and treatment with pravastatin corrected the abnormalities. Treatment resulted in a live birth infant at 34 weeks of gestation who had normal biometric

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Declaration of interest

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parameters and developmental milestones at the age of 2. This is the first reported successful use of pravastatin to reverse an angiogenic/anti-angiogenic imbalance and prevent fetal death.

Keywords

Angiogenic factors; maternal floor infarction; placental growth factor; preeclampsia; proton pump inhibitor; soluble endoglin; soluble vascular endothelial growth factor receptor-1

Introduction

Massive perivillous fibrin deposition of the placenta (MPFD) or maternal floor infarction (MFI) is characterized by the extensive deposition of fibrinoid materials surrounding chorionic villi, hampering gas and nutrient exchange in the intervillous space [1]. First described by Benirschke and Driscoll in 1967 [2], this condition is associated with recurrent serious adverse pregnancy outcomes [3–5] including miscarriage [1,6–8], fetal growth restriction [1,6,7,9–15], and fetal death [6,7,10,13,14,16–18]. We have reported that MFI is characterized by an imbalance of angiogenic/anti-angiogenic factors favoring anti-angiogenesis [increased concentration of soluble vascular endothelial growth factor receptor (sVEGFR)-1 and soluble endoglin (sEng)]. The elevation in maternal plasma concentrations of these two anti-angiogenic factors is detectable, both at the time of diagnosis and at the beginning of the second trimester. The severe magnitude of the abnormality, as well as the early onset, is characteristic of MFI. We proposed that serial determinations of angiogenic and anti-angiogenic factors could be used to monitor future pregnancies and identify patients at risk for adverse pregnancy outcome [19]. In addition, we have been interested in therapeutic interventions, given that the administration of aspirin, heparin, and intravenous immunoglobulin has not led to a consistent prevention of this recurrent condition [20–22]. Statins can reverse an anti-angiogenic state, and can prevent preeclampsia in an animal model [23–26]. We report for the first time the use of pravastatin to reverse an angiogenic/anti-angiogenic imbalance and prevent fetal death in a mother with a history of four recurrent pregnancy losses and MFI.

Case report

A 38-year-old woman with a history of four early pregnancy losses presented for consultation at Hutzel Women's Hospital at 15 weeks and 4 d of gestation. Her first and third pregnancies ended in spontaneous abortion between 9 and 10 weeks of gestation. Her second pregnancy was complicated by anhydramnios, placental sonographic abnormalities, elevated alpha feto-protein (AFP) (4.7 MoM), and fetal demise at 18 weeks of gestation. The amniotic fluid concentration of acetylcholine esterase at 18 weeks was normal, as was the fetal karyotype (46XX). Due to the history of three consecutive pregnancy losses, treatment with heparin at 5 weeks and, preconceptionally, aspirin were initiated and continued during the patient's fourth pregnancy. Vaginal progesterone suppositories were administered starting at 8 weeks of gestation. Her maternal plasma pregnancy-associated plasma protein-A (PAPP-A) concentration was low (0.1 percentile) at 12 weeks, and maternal serum AFP was elevated (9.26 MoM) in the second trimester. Ultrasound examination at 16 weeks revealed a thick placenta with numerous large placental lakes. The patient had a fetal demise

at 20 weeks of gestation associated with anhydramnios and severe early-onset fetal growth restriction, which was treated by dilation and evacuation. Fetal autopsy revealed bilateral club feet without other anatomical anomalies. Cytogenetic study of the fetal skin and placenta showed a normal karyotype. Histopathologic examination of the placenta revealed MPFD or MFI, and failure of physiologic transformation in the decidual segment of the spiral arteries (Figure 1a and b).

In the current (5th) pregnancy, the patient was enrolled in a longitudinal research protocol which was approved by the Institutional Review Boards of Wayne State University, Detroit, Michigan, and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NIH/ DHHS). A workup for thrombophilia (including protein-C deficiency, protein-S deficiency, homocysteinemia, antithrombin III deficiency, prothrombin gene mutations, factor V Leiden mutation, and anti-phospholipid syndrome) was negative. The paternal genotype analysis revealed the presence of the HLA-A25 antigen, and an antibody to this antigen was identified in the maternal serum. The patient had been receiving aspirin and heparin, and was given intravenous immunoglobulin (IVIG), based on the evidence that MFI represents maternal anti-fetal rejection in some cases [27].

The patient received subcutaneous 5000 units of heparin twice a day, one 81 mg aspirin tablet daily, and IVIG 1 mg/kg every 4 weeks from the beginning of the current pregnancy. At 12 weeks and 2 d gestation, maternal serum PAPP-A concentration was low (1st percentile). At 15 weeks, an ultrasound evaluation showed normal fetal anatomy with appropriate fetal growth (66th centile). However, bilateral uterine artery notching [mean uterine artery pulsatility index 2.23 (95th percentile)] was noted. At 13, 15 and 17 weeks of gestation, plasma concentrations of sVEGFR-1 and sEng were extremely high (96th–98th percentile; Table 1, Figure 2a and c), whereas those of placental growth factor (PlGF) were within normal limits (59th–62nd percentile; Table 1, Figure 2b). The PlGF/sVEGFR-1 ratio concentrations were low at 4th, 6th and 10th percentiles, respectively (Table 1, Figure 2d).

The patient was informed of these findings, of the poor prognosis associated with extremely high plasma sVEGFR-1 concentrations, and of the likelihood that this pregnancy, like the previous one, could be affected by MFI [19]. After being counseled extensively about the potential adverse events and issues of safety about pravastatin administration during pregnancy, and informed that there was evidence from animal experiments that pravastatin could reverse an angiogenic/ anti-angiogenic factor imbalance, the patient was offered and opted to receive pravastatin 20 mg once daily as an innovative therapy at 17 weeks and 4 d of gestation. At 21 weeks of gestation, plasma concentration of sVEGFR-1 decreased to the normal range (56th percentile) while that of PlGF increased to 93rd percentile. Plasma soluble endoglin (sEng) remained high, at the 94th percentile.

Ultrasonographic evaluation of the fetus at 24 weeks of gestation revealed a fetal weight appropriate for gestational age (66th percentile). While on pravastatin, the plasma concentrations of sVEGFR-1 started to increase again from 80th percentile at 25 weeks to 99th percentile at 33 weeks of gestation, whereas those of PlGF decreased from 79th percentile at 25 weeks to 46th percentile at 33 weeks. During this period, the plasma concentrations of sEng remained unchanged and were at 85th–94th percentile. The patient

developed preterm prelabor rupture of membranes and was induced at 34 weeks of gestation. A male neonate weighing 2220 g, APGAR scores 8 and 8 at 1 and 5 min, respectively, was delivered vaginally and discharged home without major complications in 7 d. His weight, height and developmental milestones at age 2 are normal.

Histopathological examination of the placenta revealed fibrinoid deposition in the intervillous space (approximately 20%), distal villous hypoplasia (consistent with maternal vascular underperfusion) [28] and persistent muscularization of the spiral arteries in the basal plate (Figure 3).

Discussion

MFI is a placental pathologic diagnosis [1,2] associated with recurrent serious pregnancy complications [3–5] including miscarriage [1,6–8], fetal growth restriction [1,6,7,9–15] and fetal death [6,7,10,13,14,16–18]. Although this condition has been described for almost four decades, the precise mechanisms leading to MFI are unknown. Proposed etiologies include an autoimmune phenomenon (such as anti-phospholipid [9,13,14] or anti-urokinase antibodies [9]) and proposed cytotoxicity caused by the proliferation of X-cells, now called extravillous trophoblasts. The latter are a source of major basic protein similar to that of eosinophil granules [15] and are considered to have the potential to damage surrounding tissues. Little progress has been made in the understanding of MFI.

We have recently reported the results of a retrospective, longitudinal case–control study of patients with MFI [19], and found that patients who subsequently had an MFI had an early and severe abnormal angiogenic/anti-angiogenic profile – specifically, the concentrations of sVEGFR-1 were extremely elevated in early pregnancy. Derangement in the concentrations of PlGF and sEng occurred after the abnormalities in sVEGFR-1 had been detected. This profile of abnormalities is different from that reported in longitudinal studies in patients who subsequently developed early- or late-onset preeclampsia [29–42], small for gestational age [35,43–45], spontaneous preterm labor and delivery [46] or fetal death [47,48]. Moreover, we have also found evidence of maternal antifetal rejection in patients with MFI, as these patients tend to have sensitization against fetal anti-HLA antigens, plasma cell deciduitis, evidence of complement activation on umbilical vein endothelium and elevations of the chemokine CXCL-10 in maternal blood [27].

The role of intravenous immunoglobulin (IVIG) and recurrent pregnancy loss

IVIG was added to the aspirin and heparin regimen because we detected an antibody against a paternal antigen (HLA-A25) in the maternal serum in the previous pregnancy, suggesting that an antibody-mediated maternal anti-fetal rejection mechanism may be operative [49–53]. IVIG is thought to be effective for treating diseases mediated by autoantibodies or immune complexes [54,55]. Moreover, among HLA-sensitized patients who undergo live-donor renal transplantation, desensitization with plasma pheresis and IVIG may overcome HLA incompatibility and improve survival [56].

Evidence from a meta-analysis [21] and the most recent randomized controlled trial [21,22], however, concluded that there is no significant benefit from IVIG in patients with recurrent

miscarriages [21,22]. The beneficial effects of IVIG in preventing recurrent pregnancy loss, like those of heparin and aspirin, appear to be confined to patients who have evidence of anti-phospholipid syndrome or increased NK cell activity [57–59]. Yet, IVIG has been recommended for treatment of recurrent pregnancy losses in cases with poor prognosis [60], those who failed heparin and aspirin therapy [61] or in those with a history of MFI [20].

The patient described herein had taken heparin, aspirin and IVIG from the first trimester, yet still had abnormal plasma concentrations of PAPP-A (1st percentile) and sVEGFR-1 (above the 95th percentiles), suggesting that these interventions had not been effective in reversing the pathologic processes.

Angiogenic/anti-angiogenic factors for the identification of patients at risk for recurrent maternal floor infarction

In the present case, maternal plasma concentrations of sVEGFR-1 were above the 95th percentile starting at 13 weeks of gestation. This observation was consistent with our previous findings that an early elevation of sVEGFR-1 in the second trimester, especially from 14 to 16 weeks of gestation, without a change in PlGF, appears to be suggestive of MFI [19]. We also found that the plasma concentrations of sEng were above the 95th percentile from 13 weeks of gestation (instead of after 17–19 weeks of gestation in our previous study) [19]. The concomitant elevation of sVEGFR-1 and sEng suggested a serious derangement. Further studies are required to evaluate the diagnostic performance of angiogenic/anti-angiogenic factors for the identification of patients at risk for recurrent MFI.

Pravastatin reverses an angiogenic/anti-angiogenic imbalance in animal experiments

Pravastatin, a 3-hydroxy-3-methyl-glutaryl-coenzyme-A reductase inhibitor, is a cholesterol-lowering agent [62]. This agent has been used to lower blood cholesterol and reduce the risk of acute coronary syndrome, stroke and death due to atherosclerotic vascular disease in non-pregnant patients [63]. In animal models of preeclampsia, pravastatin has been shown to ameliorate high blood pressure, improve vascular function as assessed by *in vitro* carotid artery vascular reactivity [23], decrease circulating sVEGFR-1 and sEng as well as increase PlGF and VEGF concentrations [24,25,64]. The precise mechanisms of how pravastatin reverses the angiogenic/anti-angiogenic imbalance is unknown. Animal studies reported increased serum concentrations of PlGF, as well as a decrease in sVEGFR-1 and mRNA expression of hypoxic inducible factor-1α by trophoblasts in response to pravastatin [24,25]. Pravastatin also stimulates VEGF synthesis in endothelial and vascular smooth muscle cells [65] and improves endothelial cell function (without significant changes in cholesterol concentration) through increased bioavailability of endothelial nitric oxide synthase [23,26], up-regulation of heme-oxygenase-1 enzyme [66,67] (which reduces oxidative stress [64,68] and improves placental angiogenesis [69,70]), reduction of inflammation [71], and inhibition of complement [72], as well as activation of tissue factor [73,74].

The beneficial effects of pravastatin are not limited to mothers who take this medication. Recent animal experiments in offspring born to mothers with preeclampsia (generated by an adenovirus encoding sVEGFR-1 gene) who received pravastatin therapy during pregnancy reported improvement in blood pressure [75–77], post-weaning weight, concentrations of

cholesterol and glucose [78,79], brain volume (especially in male fetuses) [80,81], and improved vestibular function, balance, and coordination [82]. One study raised a concern that pravastatin treatment might blunt a peripheral vasoconstrictor response to hypoxia, a fetal defense mechanism for the redistribution of blood flow to essential vascular beds, such as those that perfuse the brain and heart [83].

Pravastatin reverses an angiogenic/anti-angiogenic imbalance: evidence in humans

The patient decided to take pravastatin as an “innovative therapy” after extensive counseling about potential benefits, side effects and the possibility of unknown effects on the fetus. After having taken pravastatin for 2 weeks, plasma sVEGFR-1 concentrations started to decrease from the 96th percentile to the 93rd percentile, and further decreased to the 56th percentile after 4 weeks of treatment. In contrast, plasma concentrations of PlGF started to increase from the 62nd percentile to the 76th percentile after 2 weeks, and rose to the 93rd percentile after 4 weeks of treatment. The dramatic changes in plasma concentrations of anti-angiogenic and angiogenic factors suggested that pravastatin could reverse an anti-angiogenic state in humans.

The patient continued taking pravastatin, yet, plasma sVEGFR-1 concentrations became abnormal again in the third trimester, probably due to the increase in the size of the placenta, which is a major source of this anti-angiogenic protein [84–89]. Pravastatin treatment has been shown to reduce plasma concentrations of sEng and placental mRNA expression of transforming growth factor-β3 in animal experiments [25]. Yet, plasma sEng concentrations in the index case remained high throughout pregnancy.

Safety of pravastatin

Statins are considered category X drugs. The concern is that inhibition of cholesterol synthesis during embryonic development can interfere with sonic hedgehog signal transduction [90]. Congenital anomalies reported in patients taking statins included isolated anomalies such as central nervous system or limb defects and the VACTERL association (especially for lipophillic statins) [91]. However, abnormal pregnancy outcomes have not been reported following exposure to pravastatin or fluvastatin [91]. Furthermore, higher doses than those commonly prescribed in humans were used in the animal studies in which congenital anomalies were associated with exposure to statins [92], and post-marketing surveillance of Lovastatin and Simvastatin has not found any adverse pregnancy outcomes in patients with an early exposure to these drugs [93,94]. A recent systematic review and meta-analysis concluded that statins are unlikely to be teratogenic in humans [92]. Moreover, this agent has been reported to be an effective therapy in patients with early onset preeclampsia and anti-phospholipid syndrome [95].

Pharmacokinetics of pravastatin

Pravastatin, unlike other statins (i.e. atorvastatin, fluvastatin, lovastatin, and simvastatin) that are lipophilic, is water soluble [96] and, therefore, moderately crosses the placenta [97,98]. In an experimental model using a dually perfused term human placental lobule, 14% of the pravastatin was retained by the placental tissue, 68% remained in the maternal circuit, and only 18% was transferred to the fetal circuit [99]. Given that this drug has an

elimination half-life of 2 h and 50% protein binding, the transfer of pravastatin from the maternal to the fetal compartment may be more limited than that observed in the perfusion experiments [98]. A randomized trial is currently being conducted in the United States to determine the pharmacokinetic parameters and collect preliminary safety data for pravastatin when used as a prophylactic daily treatment in pregnant women at high risk of preeclampsia (http://clinicaltrials.gov/show/NCT01717586).

Conclusion

Our findings suggest that pravastatin can reverse an angiogenic imbalance without correcting the underlying cause of the disease because the patient's placenta had pathological findings similar to, but less severe than, those found in her previous pregnancy, which ended in a fetal demise. It appears that pravastatin acts more distally along the pathophysiological pathway that culminates in fetal death to reverse an angiogenic imbalance and to prevent fetal death or delay the need for delivery until viability. This is the first case report of the successful use of pravastatin to reverse an angiogenic/anti-angiogenic imbalance and prevent fetal death in a patient with MFI. Whether other interventions can reverse the anti-angiogenic state associated with massive perivillous fibrin deposition of the placenta remains to be established. Recent observations suggest that proton pump inhibitors (such as esomeprazole, rabeprazole, lansoprazole) can decrease sVEGFR-1 and sEng, and quench endothelial dysfunction [100,101]

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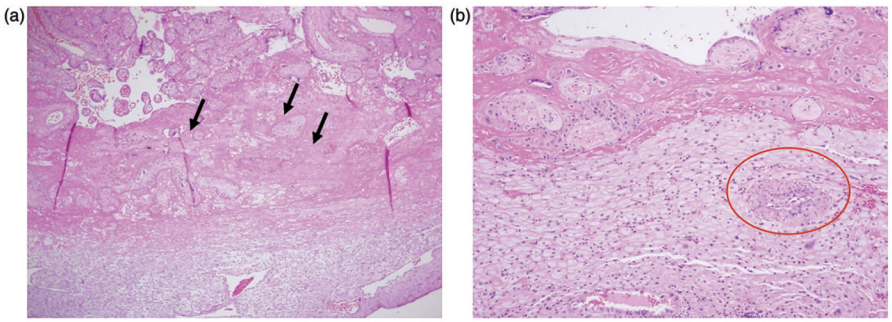

Figure 1.

Histopathological examination of the placenta from a previous pregnancy showed fibrinoid deposition (arrow) in the intervillous space surrounding more than 50% of the villi in some full-thickness sections (H&E; 40×) (a) and absence of physiologic transformation of a spiral artery, i.e. persistent muscularization (circle) in the basal plate (H&E, 100×) (b).

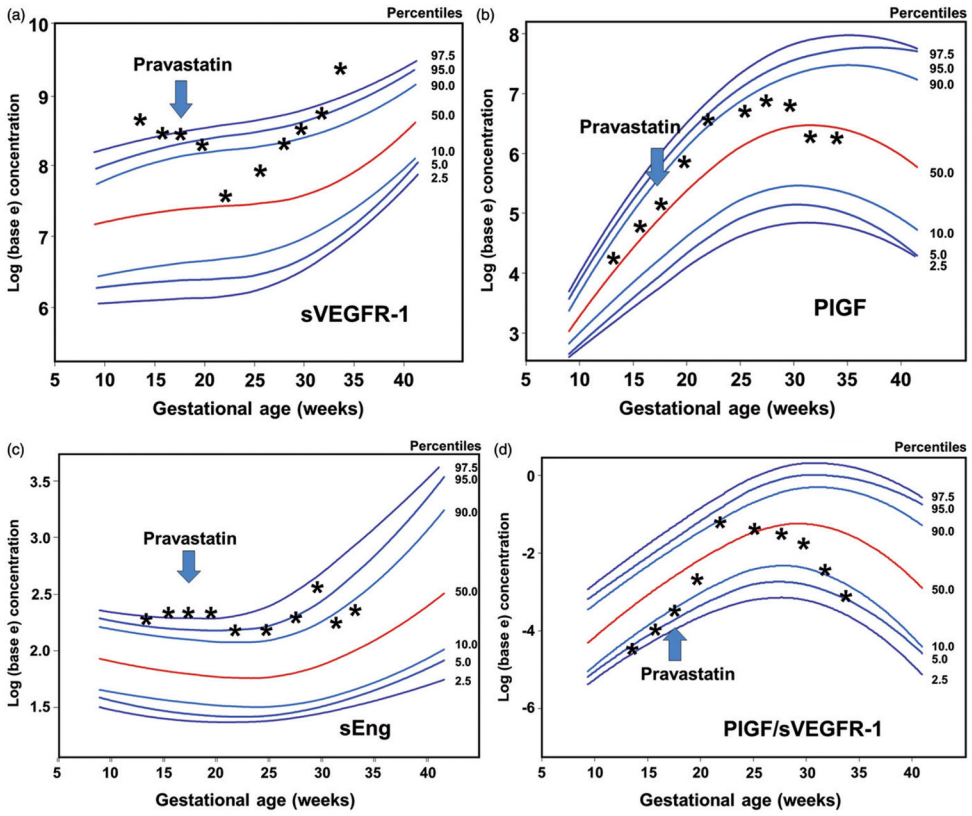

Figure 2.

Maternal plasma concentrations (log base e) of soluble vascular endothelial growth factor receptor-1 (sVEGFR-1) (a), placental growth factor (PlGF) (b), soluble endoglin (sEng) (c) and the ratio of PlGF/sVEGFR-1 (d) throughout pregnancy plotted against reference ranges at 2.5th 5th, 10th, 50th, 90th, 95th, and 97.5th percentile of uncomplicated pregnancies.

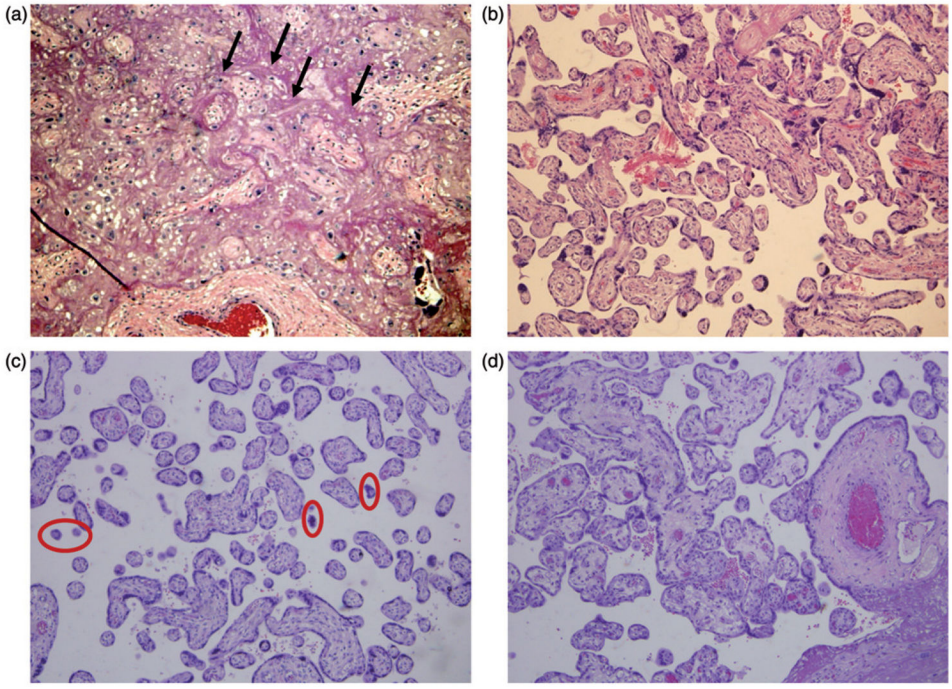

Figure 3.

Histopathological examination of the placenta from the current pregnancy reveals fibrinoid deposition (arrow) in the intervillous space, involving 20% of the villi (a) and areas with normal intervillous space (b) (H&E, 100×). Small and poorly developed villi (circle) or distal villous hypoplasia (H&E, 100×) are shown in (c). (d) Displays well-developed villi at 34 weeks of gestation (H&E, 100×).

Table 1

Plasma concentrations (percentile for gestational age) of angiogenic and anti-angiogenic factors.

Gestational age (weeks + d)	sVEGFR-1 (pg/mL) (percentile)	PlGF (pg/mL) (percentile)	sEng (ng/mL) (percentile)	PlGF/s VEGFR-1 (percentile)
13^{+3}	5664 (98th)	60 (59th)	9.8 (96th)	0.01 (4th)
15^{+4}	4897 (98th)	100 (60th)	11.8 (98th)	0.02 (6th)
17^{+4}	4480 (96th)	157 (62th)	11.3 (98th)	0.03 (10th)
19^{+5}	4148 (93th)	306 (76th)	13.1 (98th)	0.07 (23th)
21^{+6}	1889 (56th)	644 (93th)	8.7 (94th)	0.34 (90th)
25^{+3}	2854 (80th)	768 (79th)	8.8 (94 th)	0.27 (51th)
27^{+4}	3881 (90th)	869 (74th)	9.9 (95th)	0.22 (34th)
29^{+4}	4684 (93th)	821 (65th)	12.7 (97th)	0.18 (25th)
31^{+4}	6370 (97th)	536 (44th)	9.6 (85th)	0.08 (10th)
33^{+5}	11202 (99th)	528 (46th)	12.7 (85th)	0.04 (6th)

sVEGFR-1, soluble vascular endothelial growth factors receptor-1; PlGF, placental growth factor; sEng, soluble endoglin.

Percentile distribution was based on a published reference range [20].