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Differential expression of VEGF, PlGF and their receptors in placentas from anti-Ro/SSA- and anti-La/SSB-positive pregnant women

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ABSTRACT

Members of the vascular endothelial growth factor (VEGF) family of growth factors and their receptors, including VEGF-A, placental growth factor (PlGF), VEGF receptor (VEGFR)-1, and VEGFR-2 with co-receptor neuropilin-1 (NRP-1), are known to play a crucial role in the normal development and maintenance of the morphofunctional features of the placenta, also contributing to the peculiar immune tolerance occurring during pregnancy. Indeed, an altered expression of VEGF family members and their receptors has been implicated in inadequate placentation and dysregulation of the immune tolerance in a variety of pregnancy complications, especially in maternal hypertensive disorders. Of note, a dysregulated immunological environment characterizes also pregnancies of women affected by different autoimmune diseases and displaying positivity for anti-Ro/SSA and anti-La/SSB autoantibodies. These women are at high risk of adverse pregnancies in which placental dysfunction seems to play a determinant role. Hence, the present study aimed to investigate the expression and localization of VEGF, PlGF, VEGFR-1, VEGFR-2, and NRP-1 in placentas from pregnancies of anti-Ro/SSA- and anti-La/SSB-positive women with autoimmune diseases by using immunohistochemistry. Our findings revealed a general decrease in the expression of VEGF members and their receptors in all the placental components of autoimmune disease cases compared to controls, although PlGF and VEGFR-2 showed more pronounced decrements. Collectively, our findings suggest that abnormalities in placental expression of VEGF family members and their receptors might be implicated in pathophysiological features of anti-Ro/SSA- and anti-La/SSB-positive pregnancies.

1. Introduction

The placenta is a temporary organ, unique to pregnancy at the maternal–fetal interface, which provides the fetus with the metabolic requirements necessary for development through the exchange of nutrients and wastes (Abu-Ghazaleh et al., 2023; Huang et al., 2021). To achieve this, the placenta maintains its own circulation and metabolism *via* angiogenesis, *i.e.* the formation and remodeling of blood vessels in a vascular network. The different steps of the angiogenic process – initiation, proliferation–invasion, and maturation–differentiation – are all critical for a normal development of the placenta and, therefore, a successful implantation of the embryo (Abu-Ghazaleh et al., 2023; Rana et al., 2022). In this context, the peculiar immunological environment that is established during pregnancy must be also considered. In fact, although pregnancy is a natural physiological phenomenon, the presence of the fetus represents a challenge to maternal immune tolerance. In a healthy pregnancy, maternal systems must accommodate the semi-allogenic fetus while simultaneously shielding it from rejection by the maternal immune response (Albonici et al., 2020; Qu and Khalil, 2020; Zielińska and Darmochwał-Kolarz, 2025). In normal conditions, a balance between pro-inflammatory and anti-inflammatory responses supports trophoblast invasion and placental development. In particular, the early stages of pregnancy are characterized by the correct balance between inflammation and immune tolerance, which contributes to the remodeling of the endometrial tissue and to angiogenesis, thus favoring the correct embryo implantation. In addition to the establishment of such a peculiar microenvironment, the trophoblast is capable of invading the surrounding maternal tissues by sharing the same behavior

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of invasive tumors. Afterward, an immunosuppressive phase is activated preventing excessive inflammation and avoiding fetal immuno-mediated rejection (Albonici et al., 2020; Qu and Khalil, 2020; Torres-Torres et al., 2024). The complex placentation process and the unique immunological environment, in which it occurs, are sustained by several soluble molecules such as cytokines, chemokines, hormones, prostaglandins, and growth factors (Albonici et al., 2020; Bolatai et al., 2022; Castellanos Gutierrez et al., 2022; Cyprian et al., 2019; Kametas et al., 2022; Laakkonen et al., 2019; Modzelewski et al., 2023; Naidoo et al., 2022; Ruyani and Sumarsono, 2023; Velegrakis et al., 2023). Moreover, the placenta has its own immune system and produces a broad range of biologically active components with a variety of functions including immunoregulation (Seymen, 2021; Ye et al., 2023).

The numerous mediators that contribute to the placentation process through different stages of pregnancy include the vascular endothelial growth factors (VEGF) family members and their receptors. In particular, VEGF-A (commonly referred to as VEGF), placental growth factor (PlGF), VEGF receptor (VEGFR)-1/Flt-1, and VEGFR-2/Flk-1/KDR and its co-receptor neuropilin-1 (NRP-1) seem to play a crucial role in remodeling of the uterine vessels, angiogenesis, and trophoblast invasion, proliferation, and differentiation, as well as in the regulation and maintenance of the immune tolerance during pregnancy (Albonici et al., 2020; Bolatai et al., 2022; Kametas et al., 2022; Laakkonen et al., 2019; Modzelewski et al., 2023; Naidoo et al., 2022; Ruyani and Sumarsono, 2023; Velegrakis et al., 2023). Indeed, it is well known that an altered expression of these growth factors and their receptors and an imbalance in their interplay are implicated in inadequate placentation and dysregulation of the immune tolerance found in a variety of pregnancy complications, especially in maternal hypertensive disorders (Abu-Ghazaleh et al., 2023; Albonici et al., 2020; Bolatai et al., 2022; Chau et al., 2017; Chen and Zheng, 2014; Kametas et al., 2022; Karumanchi, 2016; Liu et al., 2021; Marini et al., 2007, 2008; Modzelewski et al., 2023; Naidoo et al., 2022; Qu and Khalil, 2020; Rana et al., 2022; Sgambati et al., 2004; Torres-Torres et al., 2024; Velegrakis et al., 2023; Zielińska and Darmochwał-Kolarz, 2025).

To our knowledge, the expression of VEGF family members in placentas from pregnancies with autoimmune abnormalities has been poorly investigated (Ibba-Manneschi et al., 2010). Of note, pregnancies with autoimmune abnormalities are characterized by a dysregulated immunological environment, which may affect embryo implantation, placental function, and fetal development (Castellanos Gutierrez et al., 2022, 2023; Manolis et al., 2020; Ye et al., 2023). The presence of circulating autoantibodies is a hallmark of autoimmune diseases (ADs). Indeed, serum autoantibody detection has a central role in the diagnosis and classification of ADs, and many of these autoantibodies are detectable even years before clinical manifestations (Fayyaz et al., 2016; Shen and Suresh, 2017). Moreover, it is becoming increasingly evident that autoantibodies may also play a pivotal role in the pathophysiology of different ADs by mediating both systemic inflammation and tissue injury (Shen and Suresh, 2017). In particular, antinuclear antibodies directed against the autoantigens Ro/SSA and La/SSB are amongst the most common autoantibodies found in ADs (Fayyaz et al., 2016). Both the anti-Ro/SSA and anti-La/SSB antigen-antibody systems can be present in a variety of ADs including mainly Sjögren's disease (SjD), previously referred to as Sjögren's syndrome (Tsironis et al., 2026), systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA) (Fernández-Buhigas, 2022; Nagliya et al., 2024), which are all chronic inflammatory disorders involving multiple organs or systems (Fernández-Buhigas, 2022; Longhino et al., 2023; Nagliya et al., 2024; Siegel and Sammaritano, 2024; Stefanski et al., 2017; Yang et al., 2023). SjD can be present alone (*i.e.*, primary SjD) or in association with other ADs, most commonly RA or SLE (Fernández-Buhigas, 2022; Nagliya et al., 2024; Stefanski et al., 2017). Pregnant women with ADs are at high risk of both adverse maternal and fetal outcomes such as pre-eclampsia, miscarriage, stillbirth, preterm birth, low birthweight, and small for gestational age infants (Dao and Bermas, 2022; Grygiel-Górniak et al., 2023; Nagliya et al., 2024; Singh et al., 2023; Tarter and Bermas, 2024). In addition, the infants of mothers with ADs sometimes develop several complications, such as congenital neonatal lupus erythematosus and complete heart block, because of autoantibodies transferred from the mother through the placenta (Dao and Bermas, 2022; De Carolis et al., 2020; Evers et al., 2019; Fernández-Buhigas, 2022; Madhusudan et al., 2016; Makadia et al., 2023; Manolis et al., 2020; Nagliya et al., 2024; Shao et al., 2024; Takahashi et al., 2020). Of note, ~ 50% of the mothers are asymptomatic despite carrying those autoantibodies, and almost half of them ultimately progress to develop some ADs (Fayyaz et al., 2016; Liszewska and Woźniacka, 2022). Therefore, because of the fundamental role of placenta in regulating maternal–fetal interactions, placental dysfunctions may play a crucial role in leading to adverse pregnancy outcomes (Castellanos Gutierrez et al., 2022, 2023).

Based on these premises, we performed a preliminary morphological study, employing immunohistochemistry, to investigate for the first time the expression of VEGF, PlGF, VEGFR-1, VEGFR-2, and NRP-1 in placentas from pregnancies of anti-Ro/SSA- and anti-La/SSB-positive women diagnosed with primary SjD or SjD associated with RA and/or SLE.

2. Materials and Methods

2.1. Study cases

Study cases consisted of six anti-Ro/SSA- and anti-La/SSB-positive pregnant women recruited at the Rehabilitation Clinical Hospital Cluj-Napoca, Rheumatology Division, Cluj-Napoca, Romania. Three patients had primary SjD (AD cases 1, 2, and 3), one SjD in association with SLE (AD case 4), one SjD in association with RA (AD case 5), and one SjD in association with both RA and SLE (AD case 6). All women were monitored for disease activity and pregnancy planning in low disease activity status and had therapeutic schemes compatible with pregnancy according to the 2023 guidelines (Flint et al., 2016; Russell et al., 2023). Patients were treated throughout the entire pregnancy as follows: five patients received hydroxychloroquine 400 mg/day (in association with low dose corticosteroids for three patients), and one patient received sulfasalazine 2000 mg/day in monotherapy. Prior to the pregnancy and throughout the first 12 pregnancy weeks, all women took folic acid 5 mg/day. Visits were scheduled up to 3–6 months pre-pregnancy, at first, second, and third trimester of pregnancy, and postpartum in the first 3 months. At each visit, clinical examination was performed and laboratory data were collected. As standard of care for women with ADs who are considered risk pregnancies, pregnant women had a monthly visit in the Obstetrics and Gynecology Department. At delivery, the maternal age was between 26 and 37 years, and the gestational age was between 38 and 42 weeks. There were five singleton pregnancies and one twin pregnancy (*i.e.*, pregnancy with two placentas; case 6), three natural deliveries and three caesarean sections (including the twin pregnancy of case 6). All seven full-term infants showed no pathology. As per the personal patients' request, placental samples were recovered from the Pathological Anatomy Department connected with the Obstetrics and Gynecology Department where the delivery took place. In addition, placental samples from three healthy uncomplicated pregnancies, matched with pathological cases for maternal age and gestational age at delivery (between 38 and 41 weeks), were retrieved as control group. No control had known or suspected ADs and/or connective tissue diseases. Placental samples of control cases were obtained after receiving the approval of the Institutional Review Board as described elsewhere (protocol no. 0005381/I) (Perna et al., 2023). All enrolled women provided written informed consent. The maternal and neonatal clinical details of study cases are shown in Table 1.

Table 1
Maternal and neonatal clinical details.

	Control 1	Control 2	Control 3	AD case 1	AD case 2	AD case 3	AD case 4	AD case 5	AD case 6
Maternal age (years)	32	29	35	29	26	31	31	31	37
Gestation at delivery (weeks)	38	40	41	38	40	39	41	42	38
Spontaneous delivery	+	+	+	+	−	−	+	+	−
Caesarean section	−	−	−	−	+	+	−	−	+
Type of AD:									
Primary SjD	−	−	−	+	+	+	−	−	−
SjD + RA	−	−	−	−	−	−	−	+	−
SjD + SLE	−	−	−	−	−	−	+	−	−
SjD + RA + SLE[§]	−	−	−	−	−	−	−	−	+
Anti-Ro/SSA	−	−	−	+	+	+	+	+	+
Anti-La/SSB	−	−	−	+	+	+	+	+	+
Salivary gland US assessment (abnormalities suggestive for SjD)	−	−	−	+	+	+	+	+	+
APGAR score 1 min	9	9	9	9	9	9	9	9	9
APGAR score 5 min	10	10	10	10	10	10	9	10	9
Birth weight (g)	3340	3360	3530	2940	3450	2850	3670	3700	2500/ 2400*
BMI	21	22	24	25	21	22	22	25	20

+ , present; −, absent; AD, autoimmune disease; RA, rheumatoid arthritis; SjD, Sjögren's disease; SLE, systemic lupus erythematosus; US, ultrasound; [§]SLE immunological features, but not anti-dsDNA antibodies and internal organ involvement; *twins.

2.2. Placental tissue collection

At delivery, a random sampling procedure was used to obtain 10 blocks of full-thickness tissue specimens (area = 1 cm^2) per placenta. Placental samples were fixed in 10% neutral buffered formalin solution for 12 h and processed in a standard manner for the preparation of paraffin blocks; 5-μm thick tissue sections were cut.

2.3. Immunohistochemistry

Immunohistochemistry was performed according to previously published protocols (Rosa et al., 2018; Rosa et al., 2023). Tissue sections (5-μm thick) were deparaffinized and subjected to heat-mediated antigen retrieval in sodium citrate buffer (10 mM, pH 6.0; Sigma-Aldrich, St. Louis, MO, USA) followed by inactivation of endogenous peroxidases in 3% hydrogen peroxide solution for 15 min at room temperature. Tissue slides then underwent blockade of non-specific antibody binding sites with Ultra V block (catalog no. TA-125-UB; Lab Vision, Fremont, CA, USA) for 10 min at room temperature, and subsequently incubated overnight at 4 °C with primary antibodies against VEGF (mouse anti-VEGF-A, catalog no. 555036, BD Pharmingen, San Diego, CA, USA; 1:50 dilution), PlGF (rabbit anti-PlGF, catalog no. ab9542, Abcam, Cambridge, UK; 1:50 dilution), VEGFR-1 (rabbit anti-VEGFR-1, catalog no. bs-0170R, Bioss, Woburn, MA, USA; 1:200 dilution), VEGFR-2 (rabbit anti-VEGFR-2, catalog no. ab39638, Abcam; 1:200 dilution), and NRP-1 (rabbit anti-NRP-1, catalog no. ab81321, Abcam; 1:100 dilution). Negative controls were performed by overnight incubation of serial sections with isotype-matched and concentration-matched irrelevant IgG (Sigma-Aldrich). Antigen-antibody complexes were revealed by sequentially applying to tissue sections biotinylated secondary antibodies (catalog no. TP-125-BN; Lab Vision) and streptavidin peroxidase reagent (catalog no. TS-125-HR; Lab Vision), both for 10 min at room temperature, followed by 3-amino-9-ethylcarbazole chromogenic solution (catalog no. TA-125-SA; Lab Vision). After counterstaining with Mayer's hematoxylin (Bio-Optica, Milan, Italy), tissue slides were mounted with VectaMount AQ aqueous mounting medium (catalog no. H-5501; Vector Laboratories, Burlingame, CA, USA) and observed under a Leica DM4000 B microscope equipped with a Leica DFC310 FX 1.4-megapixel digital color camera and the LAS V3.8 software (Leica Microsystems, Mannheim, Germany).

2.4. Evaluation of the immunohistochemical staining

For each control and AD placental tissue sections (5 sections for each specimen), 10 random 600625-μm^2 optical square fields (40 × objective) were examined and scored for location of immunopositivity. The staining intensity was evaluated in a semiquantitative manner as +++ , ++, + , ±, and − for strong, moderate, weak, very weak, and negative staining, respectively. Trophoblast, vessels, and stromal cells of the intermediate and terminal chorionic villi were examined. This semiquantitative scoring system has been previously used and validated to assess immunohistochemical staining in placental tissues (Marini et al., 2011; Perna et al., 2023; Sgambati et al., 2007) The sections were examined and scored blindly by two independent investigators (M.M. and E.S.). Slides were coded so that the two examiners were blinded to the experimental groups. In case of interobserver disagreement, the specimens were re-reviewed by both observers and the disagreement resolved.

3. Results

3.1. Immunohistochemical findings

Placental tissue sections incubated with irrelevant IgG as negative controls were unreactive, which confirmed the specificity of immunohistochemistry results (Figs. 1A,B, 2A,B, 3A,B, 4A,B, and 5A,B).

3.2. VEGF immunostaining

In placental samples from the control cases, the villous trophoblast and vessels showed strong VEGF immunostaining, while stromal cells were moderately immunostained (Fig. 1C,D). The trophoblast and vessels of placental samples from AD cases 1, 2, and 3 were weakly immunostained, and stromal cells very weakly immunostained (Fig. 1E-J). The trophoblast of AD cases 4, 5, and 6 showed moderate immunostaining, while vessels from moderate to weak or very weak (Fig. 1K-P). Stromal cells were not immunostained in AD case 4, and weakly immunostained in AD cases 5 and 6 (Fig. 1K-P).

3.3. PlGF immunostaining

The villous trophoblast and vessels of control placental tissue samples showed strong PlGF immunostaining, while stromal cells were weakly immunostained (Fig. 2C,D). PlGF immunoreactivity of the

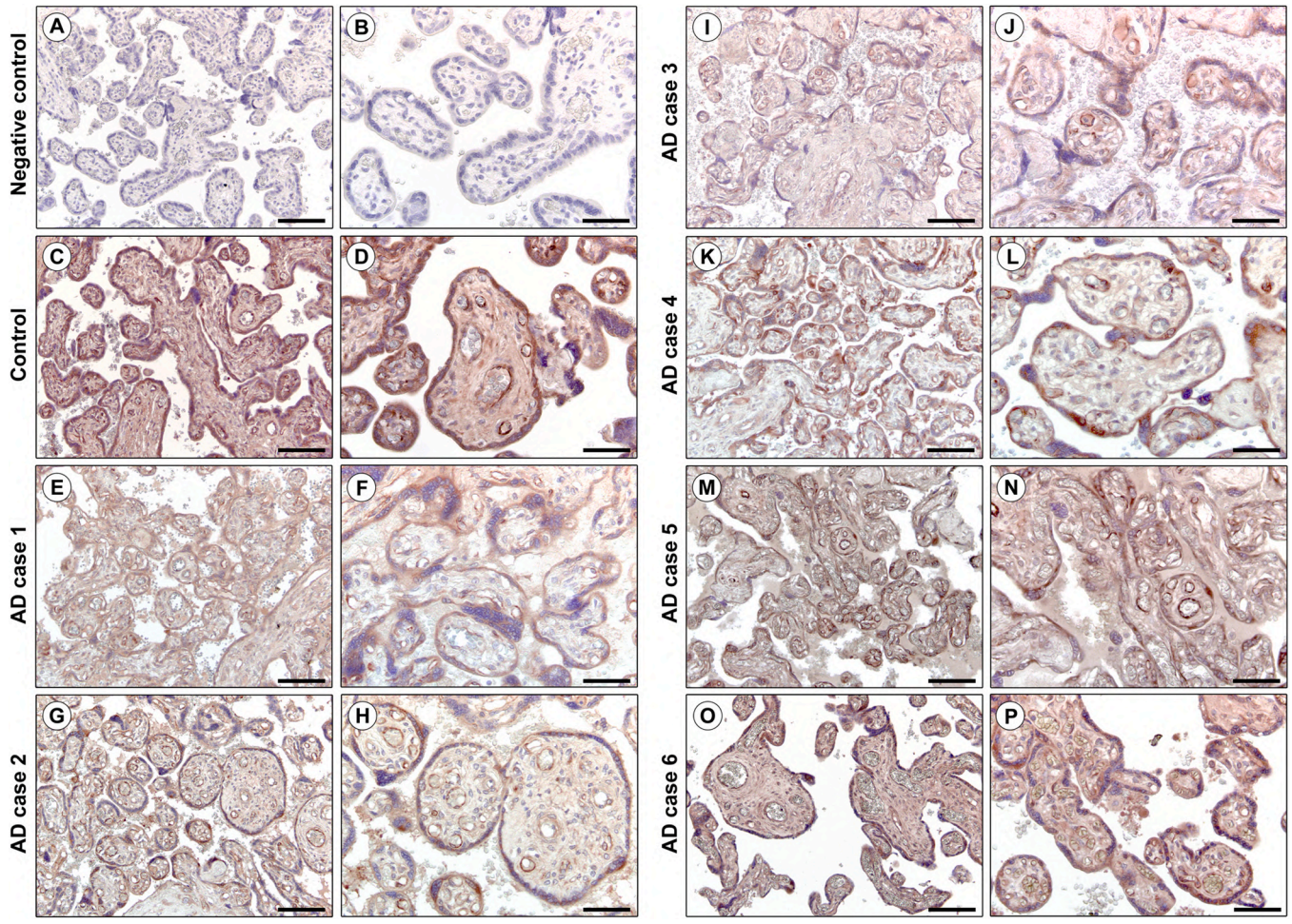

Fig. 1. Vascular endothelial growth factor (VEGF) immunostaining in tissue sections of control placentas and placentas from autoimmune disease (AD)-affected pregnant women carrying anti-Ro/SSA- and anti-La/SSB autoantibodies. Representative micrographs of placental sections incubated with irrelevant IgG as negative controls (A, B). Representative micrographs of placental tissue from a control sample (C, D), AD case 1 (E, F), AD case 2 (G, H), AD case 3 (I, J), AD case 4 (K, L), AD case 5 (M, N), and AD case 6 (O, P). (A, B) No immunoreactivity is observed in all the placental components. (C, D) In control placentas, the trophoblast and vessels show strong VEGF immunostaining, while stromal cells are moderately immunostained. (E-J) Placental trophoblast and the vessels are weakly immunostained, and the stromal cells show very weak immunostaining in AD cases 1, 2, and 3. Moderate VEGF immunostaining is detected in the trophoblast of AD cases 4, 5, and 6 (K-P). The vessels are moderately immunoreactive in AD case 4 (K, L), from moderately to weakly or very weakly in AD case 5 (M, N), and weakly in AD case 6 (O, P). No VEGF immunostaining is detected in the stromal cells in AD case 4 (K, L), whereas in AD cases 5 and 6 the stromal cells show weak immunostaining (M-P). Scale bar: 100 μm (A, C, E, G, I, K, M, O); 50 μm (B, D, F, H, J, L, N, P).

trophoblast was from moderate to weak or very weak in all AD cases (Fig. 2E-P). A PlGF immunostaining from moderate to weak or very weak was observed in all villous vessels of AD cases 1, 4, and 6, and in a few vessels of AD cases 2, 3, and 5 (Fig. 2E-P). Indeed, the majority of vessels of AD cases 2, 3, and 5 were not immunoreactive (Fig. 2G-J,M,N). Stromal cells lacked immunostaining in AD cases 1, 2, and 3, while they were very weakly immunostained in AD cases 4, 5, and 6 (Fig. 2E-P).

3.4. VEGFR-1 immunostaining

The trophoblast of placental specimens from controls displayed strong VEGFR-1 immunostaining, whereas villous vessels and stromal cells were moderately immunostained (Fig. 3C,D). In the trophoblast, VEGFR-1 immunostaining varied from moderate to weak or very weak in all AD cases (Fig. 3E-P). Placental vessels showed weak or very weak staining in AD cases 1 4, 5, and 6, while no immunostaining was observed in AD cases 2 and 3 (Fig. 3E-P). Stromal cells were very weakly immunostained for VEGFR-1 in AD cases 1, 3, 4, 5 and 6, while no immunostaining could be detected in stromal cells of AD case 2 (Fig. 3E-P).

3.5. VEGFR-2 immunostaining

In control placental samples, both the villous trophoblast and vessels exhibited strong VEGFR-2 immunostaining, while stromal cells were moderately immunostained (Fig. 4C,D). The trophoblast displayed moderate VEGFR-2 immunostaining in all AD cases (Fig. 4E-P). Moreover, in all AD cases, immunostaining for VEGFR-2 was moderate or weak in placental vessels, and weak or very weak in the stromal cells (Fig. 4E-P).

3.6. NRP-1 immunostaining

In control placental samples, NRP-1 immunostaining was strong in the trophoblast and moderate in the vessels (Fig. 5C,D). Weak NRP-1 immunostaining was observed in some stromal cells, while a subset of stromal cells displaying thin and long cytoplasmic extensions were strongly immunoreactive (Fig. 5C,D). In all AD cases, the trophoblast exhibited moderate or weak immunostaining for NRP-1, while the vessels and stromal cells were weakly and very weakly immunostained, respectively (Fig. 5E-P).

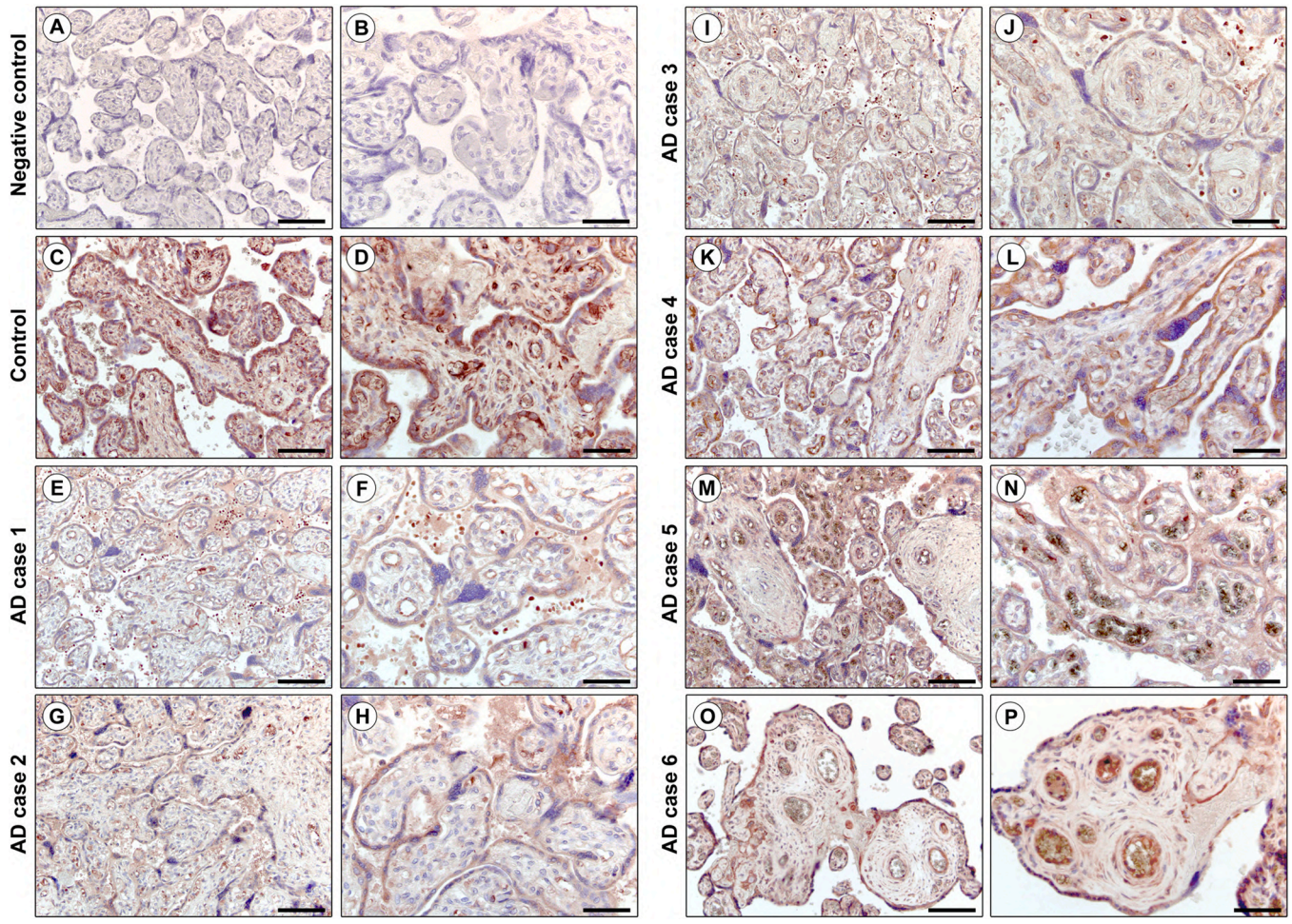

Fig. 2. Placental growth factor (PlGF) immunostaining in tissue sections of control placentas and placentas from autoimmune disease (AD)-affected pregnant women carrying anti-Ro/SSA- and anti-La/SSB autoantibodies. Representative micrographs of placental sections incubated with irrelevant IgG as negative controls (A, B). Representative micrographs of placental tissue from a control sample (C, D), AD case 1 (E, F), AD case 2 (G, H), AD case 3 (I, J), AD case 4 (K, L), AD case 5 (M, N), and AD case 6 (O, P). (A, B) No immunostaining is detected in all the placental components. (C, D) In control placentas, the trophoblast and vessels display strong PlGF immunoreactivity, whereas stromal cells are weakly immunostained. PlGF immunostaining of the placental trophoblast is moderate in AD case 4 (K, L), weak in AD cases 1, 2, 5, and 6 (E-H, M-P), and very weak in AD case 3 (I, J). In all placental vessels, PlGF immunostaining is weak in AD case 1 (E, F) and moderate in AD case 4 (K, L). Some vessels of AD cases 2, 3, and 5 show weak immunostaining, while the majority of vessels is not immunostained (G-J, M, N). In AD case 6, a few vessels are moderately immunostained, while other vessels show weak or very weak immunostaining (O, P). Villous stromal cells do not show PlGF immunostaining in AD cases 1, 2, and 3 (E-J), while they are very weakly immunostained in AD cases 4, 5, and 6 (K-P). Scale bar: 100 μm (A, C, E, G, I, K, M, O); 50 μm (B, D, F, H, J, L, N, P).

3.7. Semiquantitative analysis

As shown in Table 2, a consistent reduction in the immunostaining intensity was observed for all VEGF family members and their receptors across the three placental compartments (*i.e.*, trophoblast, vessels, and stromal cells) in all AD cases compared to controls, with PlGF and VEGFR-1 showing the most pronounced decrements, particularly in placental vessels and stromal cells.

Results of semiquantitative analysis of the intensity of VEGF, PlGF, VEGFR-1, VEGFR-2, and NRP-1 immunostaining in the different placental tissue components of control specimens and each AD case are summarized in Table 2. No differences in immunostaining for each marker were observed amongst the three control placentas, as well as amongst the two placental tissue samples from the twin pregnancy of AD case 6.

4. Discussion

For the first time, in this study we performed an investigation of the expression of the growth factors VEGF and PlGF, receptors VEGFR-1 and VEGFR-2, and co-receptor NRP-1 in placentas from pregnancies of anti-Ro/SSA- and anti-La/SSB-positive women with different ADs including primary SjD or SjD associated with RA and/or SLE.

Despite some variability, our findings highlighted similar changes in the expression of VEGF family members and their receptors in different placental components (*i.e.*, villous trophoblast, vessels and stromal cells) from all AD cases compared to healthy control placentas. Indeed, we detected a general decrease in the placental expression of VEGF, PlGF, VEGFR-1, VEGFR-2 and co-receptor NRP-1 in AD cases with respect to controls. In particular, PlGF and VEGFR-1 expression showed a more severe reduction in AD placental tissue compared to the other VEGF family members, though with some differences. In fact, PlGF expression was more reduced or completely lacking especially in the placental vessels, whereas VEGFR-1 was less expressed in all the placental components from AD cases. Moreover, another interesting finding concerns NRP-1, which was found to be strongly expressed in a subset of stromal cells exhibiting thin and long cytoplasmic extensions in control placentas and underwent a drastic decrease in all AD cases. Of note, the evidence that the aforementioned changes were consistently detectable in the placental tissue regardless of the type of AD suggests that they

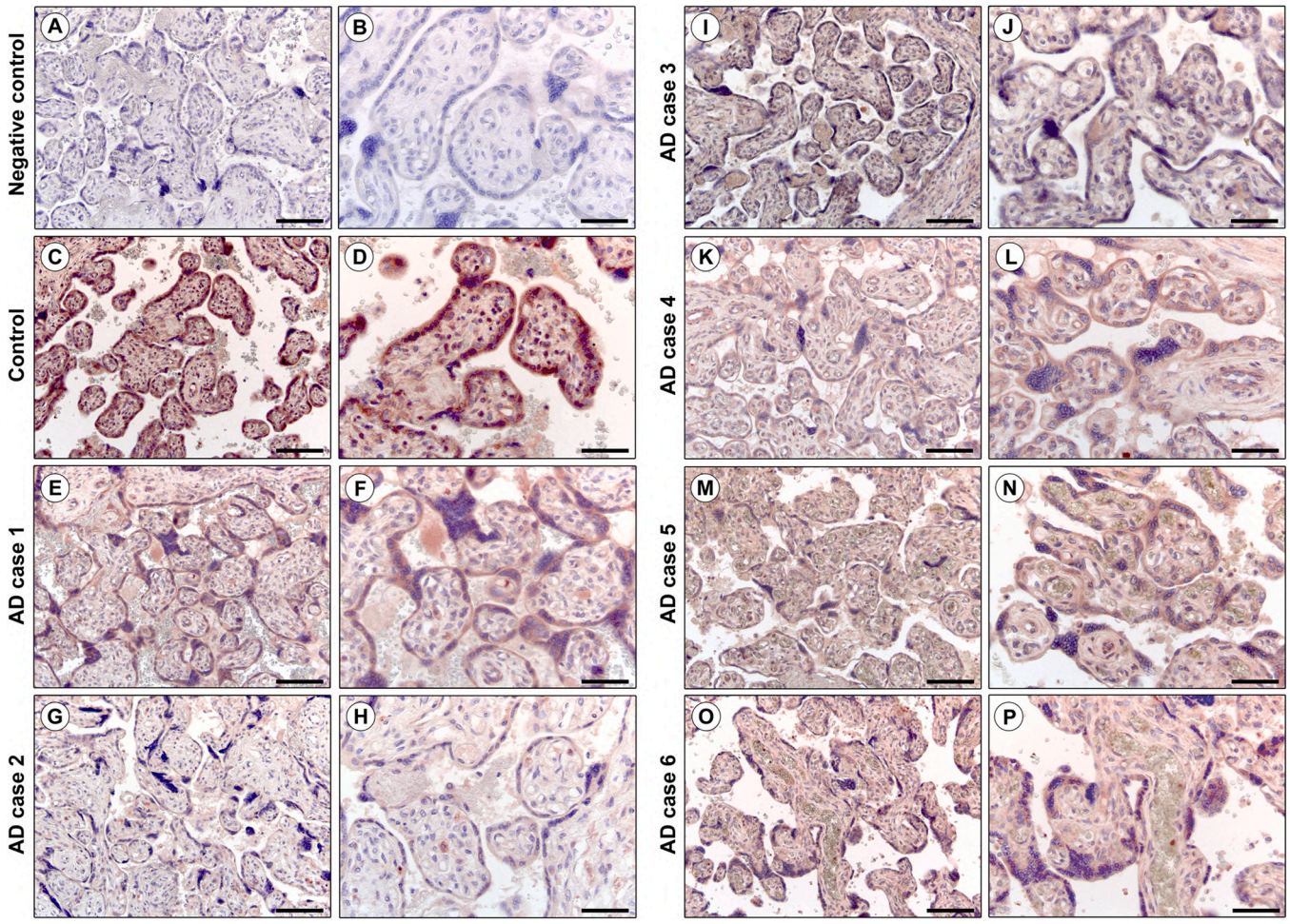

Fig. 3. Vascular endothelial growth factor receptor (VEGFR)-1 immunostaining in tissue sections of control placentas and placentas from autoimmune disease (AD)-affected pregnant women carrying anti-Ro/SSA- and anti-La/SSB autoantibodies. Representative micrographs of placental sections incubated with irrelevant IgG as negative controls (A, B). Representative micrographs of placental tissue from a control sample (C, D), AD case 1 (E, F), AD case 2 (G, H), AD case 3 (I, J), AD case 4 (K, L), AD case 5 (M, N), and AD case 6 (O, P). (A, B) No immunostaining is observed in all the placental components. (C, D) In control placentas, the trophoblast shows strong VEGFR-1 immunostaining, whereas vessels and stromal cells are moderately immunostained. In the placental trophoblast, VEGFR-1 immunostaining is moderate in AD case 1 (E, F), very weak in AD cases 2 and 3 (G-J) and weak in AD cases 4, 5, and 6 (K-P). Placental vessels show weak immunostaining in AD cases 1 and 4 (E, F, K, L) and very weak in AD cases 5 and 6 (M-P), while no immunostaining is observed in AD cases 2 and 3 (G-J). Placental stromal cells are very weakly immunostained for VEGFR-1 in AD cases 1, 3, 4, 5, and 6 (E, F, I-P), while no immunostaining is detected in stromal cells of AD case 2 (G, H). Scale bar: 100 μm (A, C, E, G, I, K, M, O); 50 μm (B, D, F, H, J, L, N, P).

may be related to a common autoimmune background, namely the presence of anti-Ro/SSA- and anti-La/SSB autoantibodies. Nevertheless, a further important consideration concerns the potential influence of the treatments received by the patients on the placental expression of VEGF family members. Indeed, hydroxychloroquine, which was administered to five out of six patients, has been reported to exert immunomodulatory effects that could theoretically affect angiogenic factor expression, although direct evidence on placental VEGF family members is currently lacking. Similarly, low-dose corticosteroids and sulfasalazine may interfere with inflammatory and angiogenic pathways. Since all AD cases in the present study were under treatment, it is not possible to dissociate the effects of the autoimmune background from those of the pharmacological treatments. Therefore, future studies including treatment-naïve patients or patients stratified by treatment regimen will be necessary to clarify this aspect.

The observed variations in protein expression may lead to a perturbed interplay amongst the various VEGF family members, in turn affecting the placental morphofunctionality. In fact, VEGF and PlGF have different binding affinity to their receptors, which determines a peculiar interplay between factors under physiological conditions. Specifically, VEGF binds with greater affinity to VEGFR-1 than to VEGFR-2, while PlGF binds with high affinity exclusively to VEGFR-1. Of note, VEGFR-1 is a weak promoter of angiogenesis and, by depleting the pool of available VEGF for the stronger promoter of angiogenesis VEGFR-2, exerts an antiangiogenic effect. Owing to the binding to VEGFR-1 but not VEGFR-2, PlGF competes with VEGF for VEGFR-1 binding and, therefore, increases the availability of VEGF to VEGFR-2 (Huang et al. 2021; Modzelewski et al., 2023). In addition, the co-receptor NRP-1 plays a crucial role in increasing the binding of VEGF and VEGFR-2 by up to 6-folds (Naidoo et al., 2022; Ruyani and Sumarsono, 2023).

It is well known that during placentation VEGF and VEGFRs are critically required for all steps of placental vascular formation and development, which supports their pivotal role in vasculogenesis. In such a context, PlGF seems to play a synergistic role with VEGF for the formation of the vascular network during the development of the villous tree. VEGF and VEGFR-2 expression is higher in early pregnancy and declines as pregnancy advances, whereas the expression of PlGF and VEGFR-1 increases towards term. Hence, the predominance of VEGF/VEGFR-2 promotes an establishment of richly branched, low-resistance capillary beds within immature placental villi during the first two trimesters of pregnancy. On the contrary, the presence of poorly

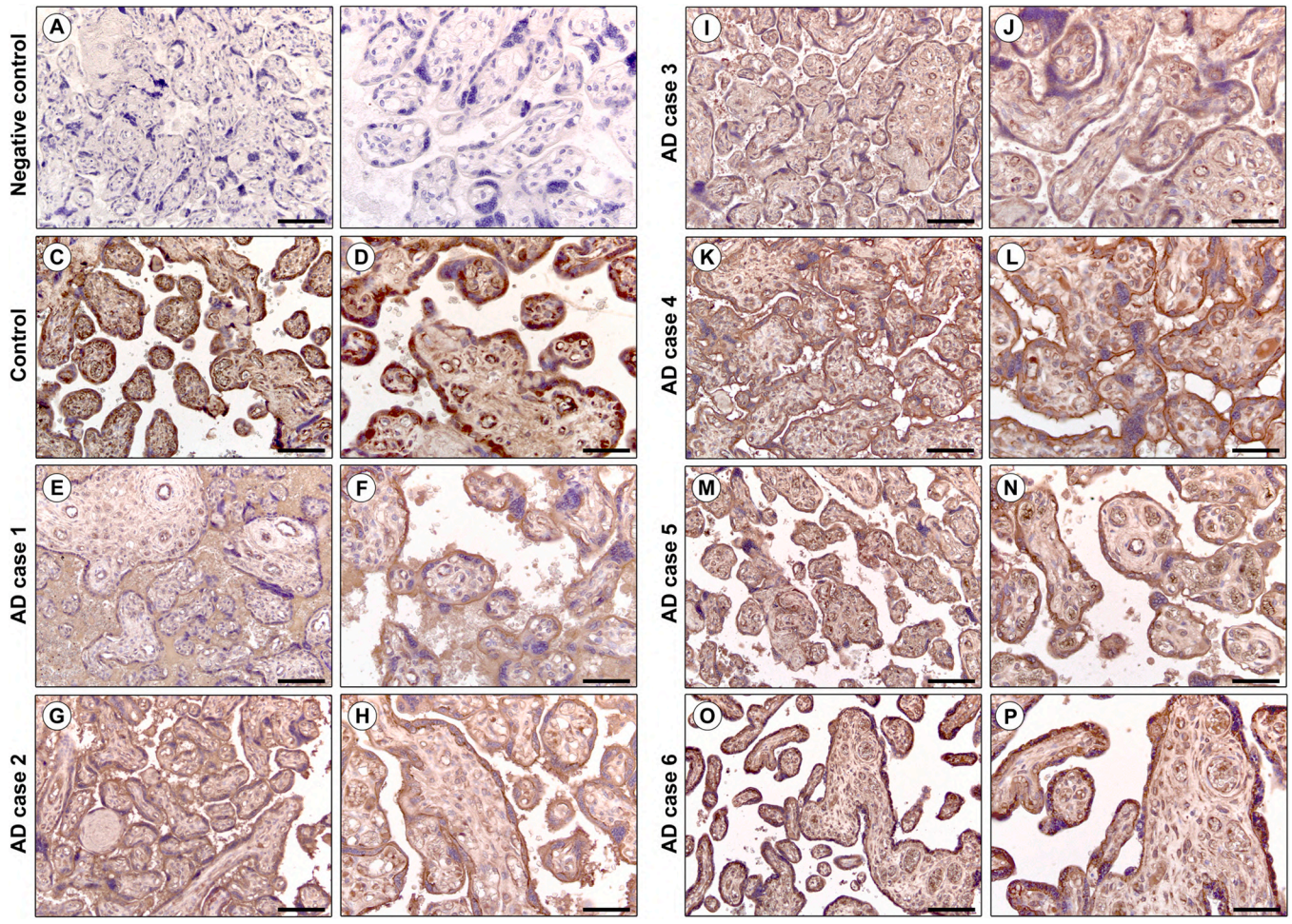

Fig. 4. Vascular endothelial growth factor receptor (VEGFR)-2 immunostaining in tissue sections of control placentas and placentas from autoimmune disease (AD)-affected pregnant women carrying anti-Ro/SSA- and anti-La/SSB autoantibodies. Representative micrographs of placental sections incubated with irrelevant IgG as negative controls (A, B). Representative micrographs of placental tissue from a control sample (C, D), AD case 1 (E, F), AD case 2 (G, H), AD case 3 (I, J), AD case 4 (K, L), AD case 5 (M, N), and AD case 6 (O, P). (A, B) No immunostaining is detectable in all the placental components. (C, D) In control placentas, the trophoblast and vessels exhibit strong VEGFR-2 immunostaining, while stromal cells are moderately immunostained. (E-P) Moderate VEGFR-2 immunostaining is observed in the trophoblast of all AD cases. In placental vessels, VEGFR-2 immunostaining is moderate in AD cases 1, 2, 3, and 4 (E-L), and weak in AD cases 5 and 6 (M-P). Stromal cells show weak VEGFR-2 immunostaining in cases 2, 3, 4, 5, and 6 (G-P), and very weak in AD case 1 (E, F). Scale bar: 100 μm (A, C, E, G, I, K, M, O); 50 μm (B, D, F, H, J, L, N, P).

branched terminal capillary loops in the last trimester seems to be controlled by the predominance of PlGF/VEGFR-1, which favors the maturation of the placental vascular system (Chau et al., 2017; Chen and Zheng, 2014; Ibba-Manneschi et al., 2010). As far as NRP-1 is concerned, its expression occurs across all three trimesters of pregnancy, although the highest expression arises in the first trimester, thus contributing to the formation of new blood vessels early in pregnancy to facilitate implantation and placentation (Naidoo et al., 2022). Moreover, although the role of these factors and their receptor is mainly described in relation to placental vascular network development, they are also implied in the regulation of trophoblast invasion, proliferation, and differentiation (Albonici et al., 2020; Bolatai et al., 2022; Kametas et al., 2022; Laakkonen et al., 2019; Modzelewski et al., 2023; Naidoo et al., 2022; Ruyani and Sumarsono, 2023; Velegrakis et al., 2023). On the other hand, VEGF and PlGF with their receptors are expressed in all the placental components, such as the trophoblast, vascular endothelial cells, and stromal cells, which suggests their contribution to the development, maturation, and physiology of the entire villous tree (Albonici et al., 2020; Chau et al., 2017; Chen and Zheng, 2014; Laakkonen et al., 2019; Marini et al., 2008; Naidoo et al., 2022; Sgambati et al., 2004, 2007; Velegrakis et al., 2023). Another important point to consider is that these factors and their receptors also play an important role in the regulation and maintenance of the immune tolerance during pregnancy. Concerning VEGF, it is known in general as an active player in shaping the immune microenvironment (Bolatai et al., 2022). In pregnancies, the decidual expression and release of VEGF has been linked to the function of macrophages in the endometrium, promoting the shift from the M1 to M2 phenotype and, then, favoring the remodeling of the uterine wall during early pregnancy (Laakkonen et al. 2019; Rana et al., 2022). Besides VEGF, PlGF seems to play the highest impact on the immune response by acting on both innate and adaptive immune cells, supporting the early events of implantation and placental development (Albonici et al., 2020; Modzelewski et al., 2023). Overall, it appears that immune-mediated mechanisms can regulate the cell response to angiogenic growth factors and, in turn, angiogenic growth factors can modulate the behavior of immune cells (Albonici et al., 2020). Interestingly, an alteration of the immune response, associated with an imbalance in VEGF and PlGF expression, has been related to pathological pregnancies, such as implantation failure and development of hypertensive disorders (Albonici et al., 2020; Laakkonen et al., 2019; Modzelewski et al., 2023).

On these bases, it is conceivable that a differential decrease in the placental expression of VEGF, PlGF, and their receptors may be related to the peculiar and complex immunological dysregulation underlying ADs. In particular, the presence of anti-Ro/SSA- and anti-La/SSB

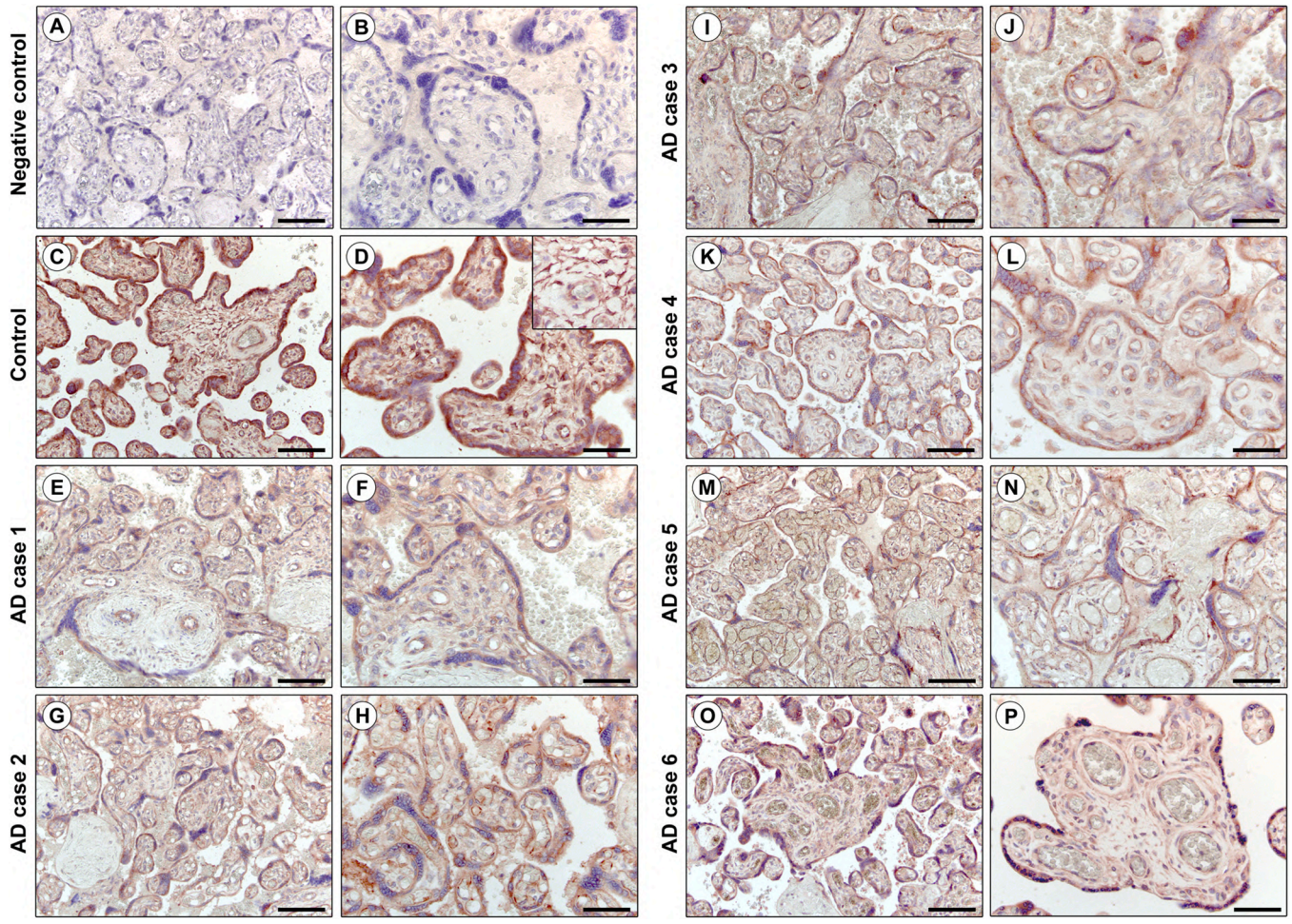

Fig. 5. Neuropilin-1 (NRP-1) immunostaining in tissue sections of control placentas and placentas from autoimmune disease (AD)-affected pregnant women carrying anti-Ro/SSA- and anti-La/SSB autoantibodies. Representative micrographs of placental sections incubated with irrelevant IgG as negative controls (A, B). Representative micrographs of placental tissue from a control sample (C, D), AD case 1 (E, F), AD case 2 (G, H), AD case 3 (I, J), AD case 4 (K, L), AD case 5 (M, N), and AD case 6 (O, P). (A, B) No immunostaining is revealed in all the placental components. (C, D) NRP-1 immunostaining is strong in the trophoblast and moderate in the vessels of control placentas. Weak NRP-1 immunostaining is detected in some control placental stromal cells, while other stromal cells displaying thin and long cytoplasmic extensions are strongly immunoreactive (C, D, inset in D). The trophoblast displays weak NRP-1 immunostaining in AD cases 1, 2, and 5 (E-H, M, N), while moderate in AD cases 3, 4, and 6 (I-L, O, P). (E-P) Weak NRP-1 immunostaining is found in placental vessels and very weak in stromal cells of all AD cases. Scale bar: 100 μm (A, C, E, G, I, K, M, O); 50 μm (B, D, F, H, J, L, N, P).

autoantibodies in the maternal circulation could contribute to a dysregulation of the unique immunological environment required during placentation, including an imbalance in the placental expression of VEGF family members that, in turn, could further alter immunoregulation processes at the maternal–fetal interface. Of note, we should consider that the decrement in the placental expression of VEGF, PlGF, VEGFR-1, and NRP-1 could be also in part due to an increase in the soluble forms of VEGFR-1 and NRP-1, which are known to play an important role in the growth factor interplay during pregnancy. As previously reported in some pregnancy complications, a raise in the levels of soluble VEGFR-1 and soluble NRP-1, which bind to PlGF and VEGF, respectively, may prevent growth factor binding to membrane receptors, thus interfering with their functions (Albonici et al., 2020; Chau et al., 2017; Chen and Zheng, 2014; Laakkonen et al., 2019; Modzelewski et al., 2023; Naidoo et al., 2022; Porter et al., 2021; Rana et al., 2022; Zielińska and Darmochwał-Kolarz, 2025). In addition, the finding of strong NRP-1 expression in a subset of stromal cells displaying thin and long cytoplasmic extensions in control placentas, but not in AD cases, also deserves discussion. Based on their distinctive morphology, characterized by thin and long cytoplasmic extensions, it could be tentatively hypothesized that these cells might represent dendritic cells, although definitive identification would require additional immunophenotypic characterization using specific markers such as CD11c or CD209/DC-SIGN. Notably, NRP-1 has been reported to be expressed in dendritic cells and to play a role in immune tolerance during pregnancy (Albonici et al., 2020; Modzelewski et al., 2023; Velagala et al., 2025). It is known that NRP-1 is also expressed in immune cells, especially in dendritic cells, and seems to play a role in immune tolerance during pregnancy (Albonici et al., 2020; Modzelewski et al., 2023; Velagala et al., 2025). Therefore, the severe decrement in the expression of NRP-1, particularly in villous stromal cells, observed in all the AD cases might contribute to dysregulation of the immune surveillance at the maternal–fetal interface.

Interestingly, all the AD cases examined in the present study did not display relevant placental histopathological signs and successfully ended pregnancy without maternal and fetal/neonatal complications. The observed altered expression of VEGF/PlGF/receptors, despite the absence of histopathological changes and clinical symptoms, may suggest a state of “compensated” placental dysfunction that could potentially progress to clinical manifestations under additional physiological or environmental stressors. In fact, we cannot exclude that an altered expression of VEGF family members in association with other yet unidentified factors could be a trigger for altered placental morpho-functionality, possibly leading to complicated pregnancies and adverse

Table 2
VEGF, PlGF, VEGFR-1, VEGFR-2, and NRP-1 immunostaining intensity in control placentas and placentas from autoimmune disease-affected pregnant women carrying anti-Ro/SSA- and anti-La/SSB autoantibodies.

	VEGF			PlGF			VEGFR-1			VEGFR-2			NRP-1		
	TB	Vessels	Stromal cells	TB	Vessels	Stromal cells	TB	Vessels	Stromal cells	TB	Vessels	Stromal cells	TB	Vessels	Stromal cells
Controls	+ ++	+++	++	+ ++	+++	+	+ ++	++	++	+ ++	+++	++	+ ++	++	+*
AD case 1	+	+	±	+	+	−	++	+	±	++	++	±	+	+	±
AD case 2	+	+	±	+	+**	−	±	−	−	++	++	+	+	+	±
AD case 3	+	+	±	±	+**	−	±	−	±	++	++	+	++	+	±
AD case 4	++	++	−	++	++	±	+	+	±	++	++	+	++	+	±
AD case 5	++	++§	+	+	+**	±	+	±	±	++	+	+	+	+	±
AD case 6	++	+	+	+	++§	±	+	±	±	++	+	+	++	+	±

AD, autoimmune disease; NRP-1, neuropilin-1; PlGF, placental growth factor; TB, trophoblast; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor; −, no immunostaining; ±, very weak immunostaining; + , weak immunostaining; ++, moderate immunostaining; +++ , strong immunostaining; *, +++ some stromal cells; **, − some vessels; §, +/± some vessels.
AD case 1, primary Sjögren's disease (SjD); AD case 2, primary SjD; AD case 3, primary SjD; AD case 4, SjD associated with systemic lupus erythematosus (SLE); AD case 5, SjD associated with rheumatoid arthritis (RA); AD case 6, SjD associated with both RA and SLE.

maternal and/or fetal/neonatal outcomes. In this regard, in a previous study we found an aberrant expression of peculiar carbohydrate molecules, namely sialic acids, which could even contribute to placental dysfunction in pregnancies of mothers carrying anti-Ro/SSA- and anti-La/SSB antibodies (Manetti et al., 2024).

In conclusion, our preliminary findings demonstrated a common trend in the dysregulation of the expression of VEGF, PlGF and their receptors in all placental components from anti-Ro/SSA- and anti-La/SSB-positive pregnancies regardless of the type of ADs. Therefore, it is tempting to speculate that such autoimmune-related alterations in the expression of VEGF family members could contribute to placental dysfunction in these pregnancies. Of course, the small number of cases enrolled represents a major limitation of the present study, which prevents any formal statistical power analysis and limits the generalizability of the findings. This is inherent to the rarity of the condition and the challenges associated with prospective recruitment of anti-Ro/SSA- and anti-La/SSB-positive pregnant women. Furthermore, although the semiquantitative scoring system employed has been previously validated for placental immunohistochemistry, we acknowledge that it carries intrinsic limitations in terms of objectivity compared to quantitative image analysis approaches, which should be considered in future larger-scale investigations. Anyway, we are confident that our pilot observations provide the basis for further investigations of the expression of these growth factors and receptors in placentas from pregnancies with autoimmune abnormalities in larger case series. For instance, additional insights into the implication of VEGF members in AD pregnancies could be achieved from an analysis of placentas displaying severe histopathological signs, such as those from complicated pregnancies, miscarriage, and preterm deliveries, as well as placentas from asymptomatic anti-Ro/SSA- and anti-La/SSB-positive women, *i.e.* without any manifest AD. Moreover, because of their proven implication in complicated pregnancies, additional members of the VEGF family, such as the soluble forms of VEGFR-1 and NRP-1 are worthy of investigation. In perspective, an in-depth elucidation of the role of altered expression of the different VEGF family growth factors, receptors and co-receptors in placentas from pregnancies with autoimmune abnormalities could also provide new insights to develop novel preventive and/or therapeutic approaches.

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Consent statement/Ethical approval

Institutional Review Board approved the research design (Protocol no. 0005381/i).

CRediT authorship contribution statement

Mihaela Micu: Writing – review & editing, Visualization, Investigation. **Irene Rosa:** Writing – review & editing, Visualization, Investigation. **Mirko Manetti:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Resources, Investigation, Conceptualization. **Eleonora Sgambati:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Resources, Investigation, Conceptualization.

Declaration of Competing Interest

The authors declare no conflict of interests.

Data availability

Data will be made available on request.

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