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New Insights in the Pathophysiology of Antiphospholipid Syndrome

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Abstract

The antiphospholipid syndrome (APS) is an autoimmune disorder characterized by an elevated risk for arterial and venous thrombosis and pregnancy-related morbidity. Since the discovery of the disease in 1980s, numerous studies in cell culture systems, in animal models, and in patient populations have been reported, leading to a deeper understanding of the pathogenesis of APS. These studies have determined that circulating autoantibodies, collectively called antiphospholipid antibodies (aPL), the majority of which recognize cell surface proteins attached to the plasma membrane phospholipids, play a causal role in the development of the disease. The binding of aPL to the cell surface antigens triggers interaction of the complex with transmembrane receptors to initiate intracellular signaling in critical cell types, including platelets, monocytes, endothelial cells, and trophoblasts. Subsequent alteration of various cell functions results in inflammation, thrombus formation, and pregnancy complications. Apolipo-protein E receptor 2 (apoER2), a lipoprotein receptor family member, has been implicated as a mediator for aPL actions in platelets and endothelial cells. Nitric oxide (NO) is a signaling molecule known to exert potent antithrombotic, anti-inflammatory, and anti-atherogenic effects. NO insufficiency and oxidative stress have been linked to APS pathogenesis. This review will focus on the recent findings on how apoER2 and dysregulation of NO production contribute to aPL-mediated pathologies in APS.

Keywords

antiphospholipid syndrome; endothelium; trophoblast; apoE receptor 2; nitric oxide synthase

The antiphospholipid syndrome (APS) is a systemic autoimmune disease and the patients have persistently elevated levels of autoantibodies termed antiphospholipid antibodies (aPL).^{1–3} APS patients are at high risk for both thrombosis and nonthrombotic vascular occlusion, resulting in an increased incidence of cardiovascular morbidity and mortality.^{4,5} They also suffer from elevated risk for pregnancy-related complications, including premature births, fetal loss, intrauterine growth restriction (IUGR), and preeclampsia.^{6–8} A recent report in which the investigators follow 10 years of disease process in 1,000 APS patients in 13 European countries has shown that thrombotic events appeared in 16.6% during first 5 years and 14.4% during the second 5 years⁸ and that the most common disorders were strokes,

transient ischemic attacks, deep vein thrombosis, and pulmonary embolism. The most prevalent obstetric complications were early pregnancy loss (16.5%), IUGR (26.3% of total live birth), and prematurity (48.2%). Death occurred in 9.3% of the subjects, with the most frequent cause of death being severe thrombosis (36.5%). A recent meta-analysis of existing literature shows that aPL positivity accounts for 13.5% of stroke, 11% of myocardial infarction, 9.5% of deep vein thrombosis, and 6% of pregnancy morbidity.⁹ These works clearly indicate that APS patients still develop significant morbidity and mortality despite current treatments, and that a deeper understanding of the disease pathogenesis is urgently needed.

Accumulating evidence from studies in animal models, in vitro experiments, and humans has revealed that aPL promote cellular dysfunction, which leads to thrombosis, nonthrombotic vascular occlusion, and pregnancy complications.^{1,10,11} APL are composed of heterogeneous sets of antibodies that recognize plasma or cell surface antigens, which include the antibodies against proteins related to coagulation such as tissue factor (TF), annexins, and $\beta 2$ glycoprotein I^{1,10–12} ($\beta 2$ GPI). Particularly, the presence of high titer anti- $\beta 2$ GPI antibodies is closely associated with both thrombosis and pregnancy complications.^{1,12} $\beta 2$ GPI is an abundant plasma protein with five distinct domain structures (domain I–V), which binds to the phospholipid in the plasma membrane through domain V. Upon binding to the cell membrane, $\beta 2$ GPI undergoes a conformational change, which exposes the antigenic domains to anti- $\beta 2$ GPI antibodies.^{13,14} The interaction of aPL with $\beta 2$ GPI on the surface of target cells in turn engages transmembrane receptors to initiate intracellular signaling events to alter the behavior of the cell. The aPL target cell types relevant to the disease development are platelets, monocytes/leukocytes, endothelial cells, and trophoblasts. Involvement of multiple receptors on the surface of these cells has been demonstrated, which include family members of toll-like receptors (TLR-2 and TLR-4) and low-density lipoprotein (LDL) receptors (apoER2), and several distinctive signaling pathways were identified to be modulated by aPL– $\beta 2$ GPI interactions with these receptors.^{15–18} Nitric oxide (NO) is a key signaling molecule for the maintenance of normal vascular function. NO produced by endothelial nitric oxide synthase (eNOS) stimulates vascular relaxation, prevents endothelial inflammation, attenuates platelet activation, and reduces smooth muscle cell proliferation and migration.^{19,20} On the other hand, oxidative stress enhances dysregulation of eNOS system, which produces superoxide species instead of NO, contributing to vascular dysfunction.¹⁹ In APS, insufficient bioavailable NO and enhanced oxidative stress have been reported.^{21–24}

In this review, we will provide an overview on the role of apoER2 in the pathogenesis of APS and the cell signaling pathways downstream of apoER2 in various target cells. We will also discuss how dysregulation of NO system contributes to the vascular complications of APS.

ApoER2 in the Pathogenesis of the Antiphospholipid Syndrome

ApoER2

ApoER2, also known as LRP8, belongs to a family of low-density lipoprotein receptors, which include LDL receptor, megalin, LRP1, apoER2, and very low density lipoprotein

receptor (VLDLR). These receptors share common structural features, which consist of a large extracellular domain with ligand-binding motifs, a single transmembrane domain, and a cytoplasmic tail with multiple adaptor-binding sites.²⁵ Unlike other members of the family, which play a major role in maintaining lipid homeostasis by mediating internalization of cholesterol associated with lipoproteins, apoER2 does not contribute to the lipid metabolism; instead, it serves as a signaling receptor.^{26,27} When human apoER2 cDNA was initially cloned, high expression of mRNA was detected in the brain and in the placenta.²⁸ Subsequently, a critical role of the receptor was discovered in neuronal migration during brain development as the receptor for Reelin.^{29–31} In the neuronal cells, Reelin binding to apoER2 initiates recruitment of its adaptor Dab-1 to the cytoplasmic NPXY motif, which in turn activates a series of kinases to regulate cellular function required for normal brain development.^{30–33}

Subsequently it became apparent that apoER2 is also expressed in cells in the circulation as well as in the vascular walls.^{34–36} These include platelets, monocytes/macrophages, endothelial cells, and smooth muscle cells.^{15,34–41} ApoER2 has various splice variants, and each cell type expresses distinctive sets of the variants. In platelets, at least three different variants are expressed, all of which result in alterations in the extracellular domain.^{35,36} In human umbilical vein endothelial cells, microvascular endothelial cells, and arterial smooth muscle cells, four splice variants have been reported, which result in changes in both extracellular and cytoplasmic domain of the receptor.³⁴ Studies in both cultured cells and mouse models have revealed that apoER2 in the vascular cells plays a variety of roles in regulation of coagulation, neointima hyperplasia, and atherosclerosis. Similar to the other members of the LDL receptor, apoER2 binds to several distinctive sets of ligands. As mentioned above, Reelin binding to the receptor in the neuron is required for normal brain development and neuronal survival in the adult brain.^{29,32} Recent work from our group showed that apoER2 mediates Reelin signaling in endothelial cells and macrophages to promote vascular inflammation and atherosclerosis.⁴² The receptor in the endothelium also binds to apolipoprotein E (apoE). We have shown that, upon binding of apoE3, a common apoE allele associated with cardioprotective phenotype in human, apoER2 stimulates eNOS and cell migration.⁴¹ Another study in endothelial cells showed that apoER2 is required for antiapoptotic actions of activated protein C (APC), a serine protease in the circulation, which is known to protect endothelial cell barrier disruption.³⁹ In vivo, apoER2-deficient mice showed impaired endothelial cell repair and exaggerated neointima hyperplasia.⁴¹ On the other hand, hetero- or homozygous apoER2 knockout mice were less prone to thrombus formation.⁴³ Furthermore, apoER2-deficient mice in the background of hypercholesterolemia developed atherosclerosis with more complex lesions and extensive lesion necrosis compared with the mice expressing apoER2.⁴⁴ In humans, genome-wide association studies indicated that polymorphisms of apoER2 gene are linked to premature coronary artery diseases and myocardial infarction in humans.^{45–48} In sum, apoER2 in the vascular wall exerts pro- or antiatherogenic function depending on the ligand and the cell types.

It was initially reported in 2003 that apoER2', a variant of apoER2 expressed in platelets, can interact with dimerized β 2GPI in platelets.⁴⁹ Because anti- β 2GPI antibodies- β 2GPI complex formation plays a central role in pathogenesis of APS, a series of studies ensued in

in vitro experiment, in cell culture, and in mouse models to elucidate the role of apoER2 in aPL actions.^{15,17,50–53}

ApoER2 in APS Thrombosis

Requirement for apoER2 in aPL-induced thrombosis has been demonstrated in mouse models of APS.^{15,17} Our group has shown that aPL administration enhances thrombus formation in the mesenteric arterioles in wild-type mice, whereas it does not do so in apoER2 knockout mice.¹⁵ The other researchers have also demonstrated that apoER2 knockout mice are protected from aPL- or dimerized β 2GPI-induced thrombosis in femoral vein.¹⁷ The latter study used soluble form of the apoER2-binding domain 1 (sBD1), a peptide mimicking the first ligand-binding domain which blocks interactions with β 2GPI, to further demonstrate that aPL– β 2GPI interaction with apoER2 mediates aPL actions in vivo.

The pathogenic aPL promote thrombosis through their actions in multiple target cell types, which include platelets, endothelial cells, and monocytes/macrophages. As noted above, all of these cell types express multiple splice variants of apoER2.^{35,36} In isolated platelets, aPL induce activation and aggregation of platelets, and the effect of aPL is dependent on the presence of β 2GPI, apoER2, and glycoprotein Ib α . Anti- β 2GPI antibodies binding to β 2GPI on the surface of platelets induces dimerization of β 2GPI, which in turn, through domain V, associates with the ligand-binding domain 1 of apoER.^{49,53} It has been further shown that engagement of apoER2 causes stimulation of the cellular activation via the phosphorylation of the cytoplasmic tail of the receptor, dissociation from its adaptor protein Dab-1, and alteration of subcellular localization.⁵² Interestingly, aPL engagement of glycoprotein Ib α occurs independent of the apoER2 pathway, and activation of both pathways is required for platelet activation by aPL.⁵² How these two pathways intertwine is currently unknown.

In endothelial cells, our group found that monoclonal anti- β 2GPI antibodies or polyclonal human aPL attenuate activity of eNOS through dephosphorylation of Ser1177, the critical phosphorylation site for the activity of the enzyme, leading impaired production of NO, which causes attenuated cell migration and increased adhesion to monocytes in culture¹⁵ (see “ApoER2 and NO Dysregulation in APS Vascular Phenotypes” Section). These aPL actions were abrogated with apoER2 knockdown in cultured endothelial cells. In wild-type mice, administration of aPL causes decreased eNOS-mediated vascular relaxation, impaired carotid artery reendothelialization after thermal injury, and increased leukocyte adhesion to the vascular endothelial layer.^{15,54} In contrast, apoER2 knockout mice were protected from these effects by aPL.

ApoER2 in monocytes or macrophages has been shown to modulate intracellular signaling pathways to exert anti-inflammatory and anti-atherogenic effect when bound by activated protein C or apoE, or pro-atherogenic effect when bound by Reelin.^{40,42,44,55} Dysregulation of cellular function of monocytes has been implicated in the procoagulant activity of aPL.^{56,57} Monocytes isolated from APS patients showed differential expression patterns of the genes related to inflammation compared with those from SLE or control subjects.^{58–60} A recent study showed that aPL induces upregulation of TF in peritoneal macrophages in wild-type mice, whereas TF expression was attenuated in peritoneal macrophages isolated from aPL-treated apoER2-deficient mice.¹⁷ Furthermore, the upregulation of TF in the wild-type

mice was abrogated by coadministration of sBD1. However, whether the effect of aPL on macrophages is directly mediated by macrophage apoER2 or indirectly regulated by the receptor-mediated actions in other cell types such as endothelial cells is not known. On the other hand, in cultured monocytic cell lines and in human peripheral blood mononuclear cells, it has been demonstrated that anti- β 2GPI antibodies upregulate TF and TNF- α expression in a TLR-dependent manner.^{56,57} Thus, apoER2 in platelets and endothelial cells plays an essential role in aPL-induced thrombosis, but it is currently unclear whether the receptor in monocytes or macrophages is directly involved in aPL actions (Fig. 1).

ApoER2 in Nonthrombotic Vascular Phenotypes Related to APS

In addition to thrombosis, APS patients have elevated risk for nonthrombotic vascular occlusion. A series of studies indicated that APS patients have increased carotid artery intima-media thickness^{61–64} and greater stenosis of the celiac, intracranial, mesenteric, and renal arteries compared with non-APS individuals.^{65–71} These nonthrombotic phenotypes along with the propensity to thrombosis contribute to the risk for cardiovascular complications such as atherosclerosis.

Dysfunction of endothelial cells and vascular smooth muscle cells (VSMC) plays a central role in the development of neointima hyperplasia.^{72–76} We have recently found that, when medial hypertrophy and neointima formation are invoked in mice by carotid artery endothelial denudation, administration of aPL induces exaggerated neointima formation compared with control human IgG.⁵⁴ We further demonstrated that the neointima hyperplasia induced by aPL was related to impaired reendothelialization after injury. In contrast to the wild-type animals, apoER2-deficient mice were protected from the adverse effects of aPL on re-endothelialization. In addition to the importance of endothelial cell monolayer disruption to neointima development, aberrant VSMC growth and migration can contribute to neointima hyperplasia.^{73,74} Our finding in primary mouse smooth muscle cells indicates that aPL do not affect basal or platelet-derived growth factor-stimulated VSMC proliferation or migration.⁵⁴ These results indicate that aPL cause neointima hyperplasia invoked by endothelial injury, and that this is related to marked attenuation of endothelial monolayer repair mediated by apoER2. In addition to endothelial cells and smooth muscle cells, increase in monocyte recruitment into vascular injury sites can promote neointima hyperplasia.⁷⁷ Monocyte infiltration aggravates neointima growth through upregulation of chemokines and adhesion molecules in the injured vessels.⁷⁷ Similarly, activation of platelets and their interaction with vascular endothelial cells contribute to atherosclerosis by inducing secretion of chemokines, which further triggers atherogenic recruitment of vascular cells.^{78,79} As described above, both platelets and monocytes express apoER2, and aPL alter functions of these cell types; however, the role of the receptor in these additional cell types in aPL-induced neointima hyperplasia is currently unknown.

ApoER2 in APS Pregnancy Complications

A recent comprehensive review of the literature found that there is a significant association between aPL and overall pregnancy-related morbidity, pregnancy loss, late pregnancy loss, and severe preeclampsia.⁹ The underlying mechanism by which aPL affect the pregnancy complications is not completely understood. A causal role of aPL in adverse fetal outcome

has been demonstrated in mouse models of APS pregnancy, in which elevations of aPL in pregnant mice, induced by injections of β 2GPI or human polyclonal aPL or monoclonal β 2GPI antibodies, result in increased fetal loss and IUGR.^{80,81} It was initially assumed that pregnancy complications in APS patients would be due to placental insufficiency stemming from thrombotic events. However, histological studies have revealed that intravascular or inter-villous thrombi are rarely found in the placentas of APS patients.⁸² Instead, APS is often characterized by impaired placentation, with reduced vascular and decidual trophoblast invasion and less spiral artery transformation.^{82–84} Numerous studies using primary trophoblasts, trophoblast-derived cell lines, or placental explants have demonstrated that aPL induce decreased cell proliferation and migration, increased apoptosis, and attenuated differentiation by altering the expression or activation of key proteins such as matrix metalloproteinases, interleukins, and chorionic gonadotropin.⁸⁵ An abundant expression of apoER2 was found in the placenta, and we have recently shown that both human and mouse trophoblasts express apoER2.^{28,86} We further demonstrated for the first time that apoER2 is required for aPL-induced trophoblast dysfunction in culture and fetal loss and IUGR in mice.⁸⁶ In cultured trophoblasts, we found that the receptor is required for aPL inhibition epidermal growth factor-induced Akt phosphorylation, cell migration, and proliferation. In mice, pregnant apoER2-deficient mice injected with human aPL showed attenuated fetal loss and IUGR compared with the wild-type mice (Fig. 1).

Endothelial cell dysfunction in the placenta also influences pregnancy outcome through insufficient development of endometrial angiogenesis.^{87,88} It has been reported in cultured endometrial endothelial cells and in a mouse angiogenesis model that aPL impair endothelial cell migration and neovascularization.⁸⁹ The inhibitory action of aPL was associated with decreased expression of VEGF (vascular endothelial growth factor) and matrix metalloproteinases, and it was abrogated by the synthetic peptide TIFI (including the key amino acid sequence [Thr-Ile-Phe-Ile] within the peptide), a competitive blocker of aPL binding to endothelium.^{89,90} Our work showed in aortic or carotid artery endothelium that aPL inhibit endothelial cell migration, which is dependent on the presence of apoER2.⁵⁴ Requirement for apoER2 in aPL-induced pregnancy loss has been shown in the mice with global apoER2 deletion, and further studies are warranted to determine whether apoER2 in trophoblast, endothelium, or platelets (or in all three cell types) is required for aPL-induced pregnancy morbidity. Interestingly, in humans, polymorphisms in apoER2 gene have been associated with fetal growth restriction,⁹¹ although the role of the polymorphism in the pregnancy phenotypes in APS has not been explored.

ApoER2 and NO Dysregulation in APS Vascular Phenotypes

NO is a short-lived gaseous molecule that exerts a variety of biological actions in multiple tissues and cell types. NO is produced by nitric oxide synthase (NOS) by converting L-arginine to L-citrulline and NO. There are three types of NOS: neuronal NOS (nNOS or NOS1), inducible NOS (iNOS or NOS2), and eNOS (NOS3).⁹² eNOS is the critical NOS responsible for the maintenance of healthy vasculature. NO produced by eNOS exerts antiatherogenic and antithrombotic effects by preventing monocyte/leukocyte interactions with endothelium and platelet activation. These functions of NO are achieved by the activation of soluble guanylyl cyclase and cyclic guanosine monophosphate-dependent

signaling and by modulation of s-nitrosylation of proteins. For normal enzymatic function, eNOS needs to be dimerized and the presence of the cofactor tetrahydrobiopterin (BH₄) is required. Insufficient provision of BH₄, which occurs in the condition associated with cardiovascular risk factors such as hypertension and dyslipidemia, results in uncoupling of eNOS, which, instead of beneficial NO, produces superoxides, a potent contributor of oxidative stress.^{19,92,93} Thus, both diminished activation of eNOS and increased uncoupling of eNOS play a critical role in the development of cardiovascular diseases.

In APS patients, there is evidence of decreased bioavailable NO or increased oxidative stress.^{21,22,24,94} A recent study showed that average plasma NO²⁻ (nitrite), a maker for bioavailable NO, was lower and nitrotyrosine, an indicator of oxidative stress, was elevated in APS patients.²² Furthermore, in the thrombotic primary APS, the titer of aPL and the number of vascular occlusions negatively predicted the levels of plasma nitrite. Our study showed that aPL inhibit eNOS activation by multiple agonists in cultured endothelial cells through attenuation of the stimulatory phosphorylation of the enzyme at Ser1177 in a phosphatase PP2A (protein phosphatase 2A) dependent manner.¹⁵ Decreased NO production by aPL treatment resulted in increased monocyte adhesion to endothelial cells, which was prevented by addition of NO donor S-nitroso-N-acetyl-penicillamine (SNAP).¹⁵ In mice, we found that eNOS-mediated vascular relaxation by acetylcholine was suppressed by injection of aPL, and that aPL-induced increase in leukocyte adhesion to vascular endothelium and in thrombus formation was not observed in mice lacking eNOS.¹⁵ Administration of molsidomine, a potent NO donor in vivo, prevented impaired reendothelialization and exaggerated neointima hyperplasia induced by aPL.⁵⁴ In addition to the endothelium, platelets have been shown to express eNOS, providing an additional source of vascular NO which plays an important role in regulating platelet activation.⁹⁵⁻⁹⁸ Whether aPL inhibit eNOS activation in platelets and whether it is mediated by apoER2 have not been tested. These studies collectively suggest that aPL inhibition of eNOS and resulting attenuation of NO production from endothelial cells contributes to thrombotic as well as nonthrombotic manifestation of aPL, and that impaired NO may provide a potential therapeutic target in APS.

Conclusion

Accumulative evidence has revealed the molecular mechanisms by which aPL disrupt normal cellular function leading to vascular and obstetric phenotypes of APS. Interventions based on the mechanisms have started to emerge. These include small peptides that block β 2GPI interaction with target cells⁹⁹⁻¹⁰¹ and a monoclonal antibody that displaces pathological aPL binding to β 2GPI.¹⁰² With respect to apoER2, a small peptide, termed A1-A1, has been engineered from two identical ligand-binding domains of the receptor. Both sBD1 and A1-A1 have been shown to attenuate aPL-induced thrombosis in mice.^{17,103} Although these mechanism-based interventions have been effective in preclinical animal models, none of them are yet to be tested in human.¹⁰¹ To translate these novel approaches into successful therapies for APS, we need to address many questions that remain unanswered. First, requirement for apoER2 in aPL-induced thrombosis and fetal loss/IUGR has been demonstrated in the global knockout mice of the receptor. Because apoER2 is expressed in multiple cell types pertinent to the phenotypes, the relative contribution of

apoER2 signaling in different cell types is not known. It is critical to determine the role of the receptor in distinctive cell types using mouse strains with cell-type-specific deletion of the receptor. Second, several studies both in vivo and in cultured cells have established the involvement of toll-like receptors and downstream signaling in APS pathogenesis.^{16,18,104} In endothelial cells, aPL- β 2GPI complex in conjunction with annexin II activates TLR4-MyD88-TRAK pathway, leading to NF κ B activation, inflammation, and TF expression. In monocytes, TLR4 mediates aPL activation of p38 kinase, leading to inflammatory reaction. In platelets, it has been shown that both apoER and glycoprotein Iba are required for aPL induction of platelet activation.^{51,52} Currently, it is unknown how engagement of the multiple receptors by aPL interacts each other. Interestingly, in neurons as well as in endothelial cells, apoER2 is known to act as a coreceptor for VLDLR, N-methyl-D-aspartate receptor, and APC receptor.^{25,39} Further researches are warranted to elucidate the relationship between apoER2 and other surface receptors in aPL actions. Lastly, we demonstrated that aPL- β 2GPI-apoER2 tandem impairs eNOS phosphorylation in a PP2A-dependent manner.¹⁵ In contrast, we found that apoE3 binding to apoER2 stimulates eNOS phosphorylation and activation.⁴¹ Thus, further investigation is needed to elucidate how β 2GPI binding to apoER2 exerts signaling cascade to activate PP2A and how different ligand-apoER2 complex exerts distinctive signaling pathway.

In conclusion, aPL binding to β 2GPI engages apoER2 to modulate intracellular signaling in endothelial cells, platelets, and trophoblasts, resulting in enhanced thrombosis and adverse fetal outcome in mice. ApoER2 activation in the endothelium causes impaired eNOS activation, and subsequent NO insufficiency may contribute to the aPL-induced thrombosis and nonthrombotic vascular occlusion. Thus, apoER2 and its downstream effector molecules as well as provision of NO may provide a new mode of therapeutic interventions to combat APS.

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Fig. 1.

Role of apoER2 signaling in antiphospholipid antibody (aPL) actions in platelets, endothelial cells, and trophoblasts. APL binding to the cell surface $\beta 2\text{GPI}$ triggers dimerization of the protein, which in turn associates with the first ligand-binding domain of apoER2. In platelets, the aPL- $\beta 2\text{GPI}$ complex binding causes phosphorylation of tyrosine residues of the receptor and dissociation from the adaptor molecule Dab-1, leading to the activation of downstream signaling pathway. In endothelial cells, engagement of apoER2 inactivates eNOS by decreasing the serine phosphorylation of the enzyme (peNOS $\downarrow$). In trophoblasts, apoER2 mediates aPL-induced attenuation of Akt kinase by dephosphorylating the critical serine residue of the kinase (pAkt $\downarrow$). These intracellular signaling pathways initiated by aPL- $\beta 2\text{GPI}$ engagement of apoER2 result in various cellular dysfunction, contributing thrombus formation, neointima hyperplasia, fetal loss, and intrauterine growth restriction (IUGR).