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Review Article

Placental Gene Silencing of sFlt-1 and Soluble Endoglin as a Precision Therapeutic Strategy for Severe Early-Onset Preeclampsia

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ABSTRACT

Severe early-onset preeclampsia, defined by disease onset before 34 weeks of gestation, remains one of the most challenging obstetric complications because the only definitive treatment, placental delivery, often necessitates premature birth to safeguard maternal health. Advances in understanding its pathogenesis have identified placental ischemia and maladaptation as key drivers of excessive production of the antiangiogenic factors soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng). These circulating mediators disrupt vascular endothelial growth factor, placental growth factor, and transforming growth factor-β signaling, resulting in widespread maternal endothelial dysfunction, hypertension, proteinuria, and multiorgan injury. As the placenta is the principal source of these pathogenic factors and a transient organ, targeting their placental production represents a rational disease-modifying strategy rather than merely alleviating clinical manifestations. This review critically examines the biological and clinical rationale for placental silencing of sFlt-1 and sEng as a therapeutic approach for severe early-onset preeclampsia. We review the evidence that they are causal mediators and biomarkers, the limitations of current management strategies, and the mechanistic basis for correcting the antiangiogenic imbalance at its source. Emerging preclinical studies using rodent and nonhuman primate models show that decreased placental sFlt-1 expression lowers circulating antiangiogenic burden and ameliorates disease phenotypes while highlighting the potential and challenges of concomitant sEng targeting. However, no placental gene-silencing therapy has yet entered routine clinical practice, underscoring that current evidence remains predominantly preclinical. We also cover maternal-fetal safety, therapeutic timing, translational hurdles, and ethical considerations and conclude that placental gene-silencing therapies have moved from theoretical concepts to promising preclinical therapeutic candidates for precision medicine in pregnancy.

Introduction

The clinical problem of severe early-onset preeclampsia

Preeclampsia, a hypertensive disorder that complicates an estimated three to ten percent of pregnancies, remains a leading cause of maternal and perinatal morbidity and mortality worldwide [1, 2] The disorder is clinically heterogeneous, but its most dangerous form is severe early-onset disease, defined by presentation before 34 weeks of gestation [3] Early-onset preeclampsia is more strongly placental in origin, more closely tied to antiangiogenic imbalance, and associated with substantially worse maternal and fetal outcomes than the late-onset form, including a higher risk of eclampsia, the hemolysis-elevated-liver-enzymes-low-platelets (HELLP) syndrome, stroke,

fetal growth restriction, and stillbirth [4, 5]. It is in this early-onset population that the central dilemma of the disease is most acute and the need for new therapy most pressing [6]

The therapeutic vacuum and the case for a molecular approach

The bedrock of management of preeclampsia is the knowledge that the only cure is the delivery of the placenta and the accompanying fetus [7]. This is an acceptable solution in late-gestation disease; near term, delivering is a trivial (or even zero) neonatal penalty. In severe early-onset disease it is a slow-motion tragedy, because delivering a 26- or 28-week fetus delivers the maternal syndrome at the cost of the lifelong consequences of extreme prematurity [8] Clinicians are left to practice expectant management temporizing with antihypertensives, magnesium sulfate, and corticosteroids while watching for the signs of maternal deterioration that mandate delivery—buying days or weeks at considerable risk [9] No approved therapy modifies the underlying disease. This therapeutic vacuum, combined with a now-detailed understanding of the disease's molecular drivers, is precisely what motivates a targeted, mechanism-based approach: if the placental overproduction of antiangiogenic factors could be suppressed, pregnancy might be safely prolonged, converting an obstetric emergency into a more manageable condition [10].

Scope and thesis

This review develops the clinical case for correcting the antiangiogenic imbalance of preeclampsia at its placental source. Its thesis is that preeclampsia is an unusually favorable disease for a source-directed, gene-silencing strategy, its principal pathogenic mediators are known, are produced by a single, accessible, and ultimately disposable organ, and are amenable to selective suppression, and that the principal remaining obstacles are not conceptual but clinical and translational. We proceed from pathophysiology and target validation, through the limits of current management and the biological logic of silencing as a mechanism-based principle, to the preclinical evidence that lowering placental sFlt-1 ameliorates the disease, the clinical rationale for additionally targeting soluble endoglin, and the safety and ethical questions that govern any intervention in pregnancy. The review also identifies key knowledge gaps that must be addressed before placental gene-silencing therapies can be translated into human clinical trials.

Pathophysiology: From Placental Ischemia to Maternal Endothelial Dysfunction

The two-stage model and defective spiral-artery remodeling

The prevailing framework for preeclampsia is a two-stage model. In the first stage, defective placentation—inadequate invasion of the maternal spiral arteries by extravillous trophoblast and their incomplete remodeling from high-resistance into low-resistance vessels—leads to a poorly perfused, intermittently ischemic placenta [11, 12]. In the second stage, this ischemic and oxidatively stressed placenta releases soluble factors into the maternal circulation that produce the systemic maternal syndrome [13] The factors that translate placental ischemia into maternal disease are, principally, the antiangiogenic proteins sFlt-1 and soluble endoglin, whose overproduction tips the maternal vasculature from an angiogenic-balanced state into endothelial dysfunction. Early-onset preeclampsia maps most cleanly onto this model, with the deepest placental abnormalities and the highest antiangiogenic burden [14, 15].

sFlt-1 (sVEGFR-1): the dominant antiangiogenic driver

Molecular biology and the placental splice isoforms

Soluble fms-like tyrosine kinase 1 (sFlt-1 or sVEGF-R1): A truncated, secreted form of the membrane receptor FLT1. Alternative splicing and intronic polyadenylation of the FLT1 transcript generates isoforms that retain the extracellular ligand-binding domain, but lack the transmembrane and intracellular tyrosine-kinase domains [16] Importantly, the placenta produces specific soluble isoforms, chiefly the primate-enriched e15a variant and the i13 intron-retention variant that account for most circulating sFlt-1 in preeclampsia, distinct from the full-length, membrane-bound FLT1 that performs essential physiological signaling [17]. This important molecular distinction makes selective therapeutic intervention theoretically feasible because it can focus on suppression of the pathogenic soluble isoforms while preserving the full-length receptor essential for function [15]

Mechanism: VEGF/PlGF sequestration and endothelial injury

Mechanistically, sFlt-1 functions as a circulating decoy. It then sequesters both proangiogenic ligands VEGF and placental growth factor (PlGF) that bind with high affinity to cripple endothelial receptor engagement and lower the free, bioavailable concentrations of both [14] Since VEGF signaling is central to maintaining appropriate endothelium (especially for fenestrated endothelium of the renal glomerulus, the liver, and the brain), functional withdrawal of VEGF signaling produces exactly those lesions of preeclampsia: glomerular endotheliosis and proteinuria, hepatic dysfunction, and cerebral disturbance [18]. Experimentally, sFlt-1 causal sufficiency was confirmed when its overexpression in pregnant rats reproduced a hypertensive and proteinuric phenotype consistent with a preeclampsia-like syndrome and, clinically, through the observation that anti-VEGF cancer therapies produced analogous proteinuric hypertension phenotypes [19]

Soluble endoglin: the synergistic second hit

Endoglin biology and ectodomain shedding

Endoglin is a co-receptor for transforming growth factor-β (TGF-β), and is highly expressed on vascular endothelium and on the syncytiotrophoblast of the placenta [20] Endoglin is upregulated in preeclampsia and its extracellular domain is released to the maternal circulation as soluble endoglin (sEng) [21] The strongest association with sFlt-1 escalation occurs in circulating sEng, which doubles from baseline starting two to three months prior to clinical onset and correlates closely with disease severity, peaking in the HELLP variant. Thus, sEng is both a biomarker as well as a mediator like sFlt-1 as illustrated in Figure 1 [22]

eNOS, endothelial nitric oxide synthase; NO, nitric oxide; sEng, soluble endoglin; sFlt-1, soluble fms-like tyrosine kinase-1; TGFβ, transforming growth factor-beta; VEGF, vascular endothelial growth factor.

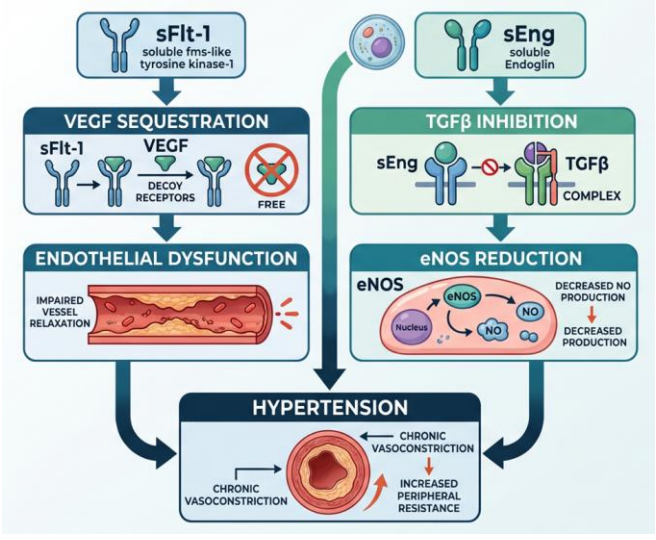

Figure 1: Synergistic Pathways of sFlt-1 and Soluble Endoglin in the Pathogenesis of Preeclampsia-Associated Hypertension.

TGF-β and eNOS disruption, and the sFlt-1–sEng synergy

The action of soluble endoglin is through antagonizing TGF-β signaling at the endothelial surface, inhibiting TGF-β–driven activation of endothelial nitric oxide synthase (eNOS) and, thus, compromising nitric oxide-dependent vasodilation and vascular homeostasis [23]. The pathogenic significance of sEng and sFlt-1 is mainly the result of synergy: when sEng and sFlt-1 are co-administered to pregnant rats, they induce a much more severe HELLP-like syndrome with hypertension, proteinuria, and the laboratory signature of microangiopathy than either factor alone [24] This synergy is considered the main pathophysiological argument of this review as it suggests that suppression of sFlt-1 alone might not be sufficient in the most severe form of the disease and sEng could provide an additive or synergistic effect when combined [25]

The maternal endothelial phenotype

The common result of excess sFlt-1 and sEng is systemic endothelial dysfunction. The maternal vasculature shifts to a vasoconstricted, pro-thrombotic, hyperpermeable state: nitric oxide bioavailability decreases, endothelin 1 increases and also the response to vasopressors, vascular permeability increases and also the disruption of a glomerular filtration barrier [26] In this regard, preeclampsia is best viewed not as a blood pressure disease, but rather as a disease of the maternal endothelium, for which hypertension and proteinuria are considered as downstream biomarkers of a systemic insult to the endothelium [27]. This is clinically relevant framing because it identifies the antiangiogenic factors as the rational targets not the blood pressure and predicts that lowering such factors should improve the endothelial phenotype broadly rather than as a single sign [28]

The sFlt-1/PlGF ratio: biomarker and target validation

The clinical translation of this biology is the sFlt-1/PlGF ratio, which integrates the antiangiogenic and proangiogenic arms into a single index. The ratio rises before clinical onset, tracks severity, and has been validated as a predictive tool [14] in the multicenter PROGNOSIS study, a low ratio reliably ruled out the development of preeclampsia within one week, and a high ratio identified women at substantial short-term risk [29] Beyond its diagnostic utility, the ratio constitutes powerful target validation—its tight correlation with disease onset and severity is exactly the dose–response relationship one would want before committing to a therapy that lowers sFlt-1, and it provides a ready pharmacodynamic biomarker against which the effect of any such therapy could be titrated [29]

The Limits of Current Management

Delivery as the only cure, and the prematurity trade-off

As noted, delivery of the placenta remains the only definitive treatment, and in severe early-onset disease this creates an irreducible conflict between maternal and fetal interests [30] Every week of prolongation gained reduces neonatal morbidity substantially in the periviable and very-preterm range, but every week also exposes the mother to the risk of catastrophic complications. Expectant management is the art of navigating this conflict, and a disease-modifying therapy that lowered the antiangiogenic burden would, in effect, widen the safe window for prolongation the single most valuable outcome a new treatment could offer [31]

Symptomatic therapy

Current management is symptomatic. Antihypertensive agents (labetalol, nifedipine, methyldopa) that improve maternal blood pressure and decrease the risk of maternal stroke exert no effect on the underlying placental disorder [32] Magnesium sulfate is used to prevent and treat eclamptic seizures. Antenatal corticosteroids promote fetal pulmonary maturity in the setting of anticipated preterm birth. None of these approaches inhibits placental production of sFlt-1 or sEng, and none targets the pathophysiological process that drives the maternal syndrome [33, 34]

Disease-modifying attempts and their modest returns

Approaches targeting directly the antiangiogenic axis proved only partially effective. Extracorporeal apheresis with dextran sulfate columns can physically deplete circulating sFlt-1 and has prolonged pregnancy in small pilot studies—proof of concept for the idea that lowering sFlt-1 is helpful but is invasive, repetitive, and impractical for widespread use [35]. The logic of retarding placental sFlt-1 and sEng secretion prompted trials of repurposed agents, including pravastatin, the proton-pump inhibitor esomeprazole , and metformin, all of which had at least some reasonable preclinical promise and measurable biomarker effects, but disappointing (or borderline) results in randomized trials [36] A metformin trial in preterm preeclampsia suggested a modest, though not statistically significant, and esomeprazole did not prolong pregnancy in its randomized trial [37]. In conclusion one needs a focused, direct and repeatable approach to suppressing the production of these antiangiogenic factors as indirect and incomplete reduction with repurposed agents have so far not yet produced any clinically transformative endpoint [37] A comprehensive summary of current therapeutic approaches including standard management and repurposed agents along with their respective mechanisms, advantages, limitations, and specific examples, is provided in Table 1

Table 1: Current and investigational therapies in preeclampsia relative to the placental antiangiogenic (sFlt-1/sEng) axis: mechanisms, advantages, and limitations.

Current therapy	Mechanism	Advantages	Limitations	Examples (agents / key trials)
Antihypertensive – combined α-/β-adrenergic blocker	Blocks α1- and β-adrenoceptors, lowering peripheral vascular resistance and maternal blood pressure; provides symptomatic control of severe hypertension.	Rapid, reliable BP control (oral and IV); extensive pregnancy-safety record; lowers risk of maternal stroke and severe hypertension; guideline first-line agent.	Purely symptomatic; no effect on placental antiangiogenic pathology or circulating sFlt-1/sEng; does not modify disease course or prolong gestation.	Labetalol (first-line); BP targets informed by the CHIPS trial [38]
Antihypertensive – dihydropyridine calcium-channel blocker	Inhibits L-type Ca2+ channels in vascular smooth muscle, producing vasodilation and reduced blood pressure.	Effective oral agent for severe hypertension; well tolerated; additional tocolytic activity.	Symptomatic only; does not lower sFlt-1 or correct the underlying angiogenic imbalance; no disease-modifying effect.	Nifedipine (immediate- or extended-release). [39]
Anticonvulsant / seizure prophylaxis	NMDA-receptor antagonism, cerebral vasodilation and membrane stabilization; prevents and treats eclamptic seizures (not primarily antihypertensive).	Approximately halves the risk of eclampsia; fetal neuroprotection at early gestations; inexpensive and widely available.	Prevents seizures but does not modify placental disease or lower sFlt-1/sEng; narrow therapeutic index (toxicity, respiratory depression) requiring monitoring; no disease-modifying prolongation of gestation.	Magnesium sulfate; Magpie Trial [40]
Extracorporeal removal of circulating sFlt-1 (investigational)	Negatively charged dextran sulfate cellulose columns—or, more recently, anti-sFlt-1 monoclonal-antibody columns—adsorb and remove circulating sFlt-1 from maternal plasma, reducing the antiangiogenic burden at its downstream target.	Directly lowers circulating sFlt-1; reduces proteinuria and stabilizes blood pressure; pilot data suggest pregnancy prolongation without major maternal/fetal harm; avoids fetal drug exposure.	Invasive, resource-intensive and repetitive; modest sFlt-1 reduction (~18% with dextran sulfate); requires specialized apheresis access; evidence limited to small pilot/uncontrolled studies; impractical for widespread use.	Dextran sulfate apheresis [41-43]
Repurposed HMG-CoA reductase inhibitor (statin)	Upregulates heme oxygenase-1, reduces placental sFlt-1 secretion, and improves endothelial/nitric-oxide function through pleiotropic, antioxidant effects.	Oral, inexpensive, reassuring pregnancy-safety data; strong biological rationale; possible benefit when used for prevention in high-risk women.	In the StAmP trial, did not significantly lower maternal plasma sFlt-1 or prolong pregnancy once early-onset preeclampsia was established; therapeutic (vs preventive) benefit unproven.	Pravastatin; StAmP Trial [44]
Repurposed biguanide	Inhibits mitochondrial electron-transport-chain complex I, reducing placental/endothelial sFlt-1 and sEng secretion; improves endothelial function and promotes angiogenesis.	Oral, low-cost, well-established pregnancy safety; the PI2 trial showed a modest gestational prolongation.	Prolongation modest (~1 week) and not robust across analyses; inconsistent effect on circulating sFlt-1/PlGF; gastrointestinal intolerance.	Metformin XR; PI2 Trial [45]

Repurposed proton-pump inhibitor	Induces heme oxygenase-1 and decreases sFlt-1 and sEng secretion, mitigating endothelial dysfunction and oxidative stress (preclinical rationale).	Oral, inexpensive, excellent pregnancy-safety profile; potent preclinical effects on the angiogenic axis.	In the PIE trial, 40 mg daily did not prolong gestation or lower sFlt-1 in early-onset preeclampsia—a negative primary outcome.	Esomeprazole; PIE Trial [46]

Abbreviations: BP, blood pressure; sFlt-1, soluble fms-like tyrosine kinase-1; sEng, soluble endoglin; PlGF, placental growth factor; NMDA, N-methyl-D-aspartate; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; IV, intravenous; XR, extended-release.

The profile of an ideal therapeutic

These limitations allow one to define the properties of an ideal therapeutic for preeclampsia. It would suppress the overproduction of sFlt-1 and sEng by the placenta itself, directly and potently; it would act at the source rather than soaking up circulating protein [47]; it would persist long enough to extend pregnancy by weeks from only a handful of administrations; and it would achieve all of this without harming fetal well-being or greatly impairing the placental functions required to sustain the pregnancy. A source-directed, selective gene-silencing approach is attractive precisely because, in principle, it satisfies each of these criteria [48].

Silencing as a Mechanism-Based Therapeutic Principle

RNA interference is a natural, sequence-specific gene-regulatory process. A short double-stranded RNA, once its guide strand is loaded into the RNA-induced silencing complex, directs the recognition and cleavage of the complementary messenger RNA [49] thereby lowering the production of the encoded protein [49]. Two features make this an appealing basis for treating a disease such as preeclampsia. First, the effect is programmable by sequence, so a single defined transcript can be targeted with high specificity well suited to a disorder driven by the overexpression of known proteins from a known organ [50] Second, because suppression occurs at the level of the messenger RNA, secreted decoy molecules such as sFlt-1 which are typically challenging difficult targets for conventional small molecules or antibodies become tractable [51] For most of the field's history, the limiting factor was not the silencing concept but the ability of such agents to act stably in the body and to reach the relevant tissue. Advances in the chemistry of these molecules have made them durable enough to function in vivo and to support infrequent administration [52] and clinically validated approaches have, to date, acted overwhelmingly on the liver [53] Reaching organs outside the liver has therefore been the central obstacle to extending the approach to other diseases. The placenta is one such extrahepatic organ—and, as the next section argues, an unusually apt one [54] The sequential pathway of this mechanism—from siRNA introduction and RISC assembly to targeted mRNA cleavage and the subsequent reduction of sFlt-1 is illustrated in Figure 2.

Why the Placenta Is a Biologically Apt Target

A transient organ producing the pathogenic factors

Three features make the placenta a remarkably favorable target. First, it is the source: the pathogenic sFlt-1 and sEng of preeclampsia are produced overwhelmingly by the placenta, and circulating sFlt-1 falls precipitously after delivery, confirming the organ as the factory [14]. Acting on the placenta therefore addresses the disease at its origin rather than at its periphery [54]. Second, the placenta is transient and ultimately disposable it is shed at the end of pregnancy so concerns about permanent consequences of gene suppression in the target organ are inherently bounded in time [55] Third, the placenta receives a large fraction of maternal cardiac output and presents an enormous surface area of trophoblast to the maternal blood, making it physically accessible to an agent given into the maternal circulation [56]

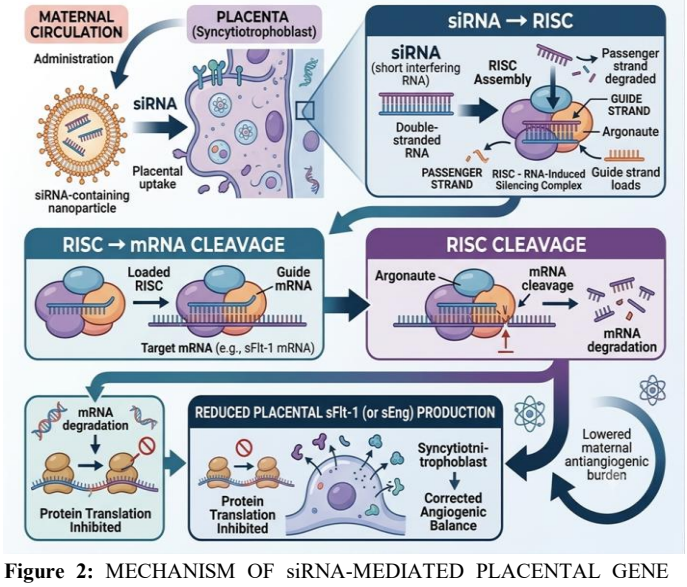

Figure 2: MECHANISM OF siRNA-MEDIATED PLACENTAL GENE SILENCING. siRNA: short interfering RNA, RISC: RNA-Induced Silencing Complex, sFlt-1: soluble fms-like tyrosine kinase 1, sEng: soluble endoglin, mRNA: messenger RNA, dsRNA: double-stranded RNA, Argonaute: A key protein component of the RISC complex responsible for cleavage.

The syncytiotrophoblast interface

The maternal-facing surface of the placenta is the syncytiotrophoblast, a continuous multinucleated layer bathed directly in maternal blood within the intervillous space. It is both the principal producer of sFlt-1 and sEng and the first cell layer a circulating agent encounters [57]. An agent that accumulates in and is taken up by the syncytiotrophoblast is therefore positioned to suppress the relevant transcripts in the very cells overproducing them. Demonstrating productive accumulation in this layer the placental

labyrinth in rodents has been a key benchmark in the preclinical work discussed below [58]

The dual mandate: reach the placenta, protect the fetus

What distinguishes the placenta as a target is that it is a barrier to be protected and behind that barrier is a fetus. It follows then that the therapeutic mandate is to do both: by reaching and acting on syncytiotrophoblast as well as by not entering the fetal circulation to levels that would suppress fetal genes or disrupt development [59]. The need for both maternal–placental efficacy and exclusion from the fetus governs every aspect of the strategy and is the only aspect making placental silencing fundamentally different from gene silencing in all other organs [60].

Evidence That Lowering Placental sFlt-1 Ameliorates Disease

Isoform selectivity: the molecular basis for a safe target

Isoform selectivity determines the feasibility of a safe sFlt-1–directed therapy. The soluble isoforms that are pathogenic and placentally dominant (in particular e15a and i13) can, in principle, be blocked while leaving full-length, membrane-bound FLT1, which carries out important signaling around the circulation intact [61]. In the fundamental work, agents were designed to specifically suppress the soluble sFLT1 isoforms responsible for placental overexpression while leaving the full-length FLT1 protein intact. It is fundamentally the conceptual key that undergirds the entire approach: deleting just the pathological decoy out from circulation to keep the healthy receptor in place that would, if lost, be pathologically detrimental [62].

Reaching the placenta after systemic administration

A study found systemic accumulation of an agent given to the pregnant animal through the placenta, with mainly hepatic clearance and limited placental transfer to the fetus consistent with the dual mandate defined above [63]. The clinical reasoning here not technical: the pathology is accessible from the maternal circulation, and the agent is managed to mitigate fetal exposure. Further efforts optimized the approach to enhance potency and safety, further suggesting the capability to iteratively increase placental selectivity to generate a candidate for clinical evaluation [64].

Proof of concept across species

Across species, the translatability of the therapeutic effect has been shown. siRNAs targeting the three mRNA isoforms of sFLT1 responsible for its overexpression without reducing full-length FLT1 yielded up to 50% lower circulating sFLT1 in maternal plasma and ameliorated the preeclampsia-like phenotype in pregnant mice [65]. Notably, in a baboon model of preeclampsia a nonhuman primate whose placental biology is closer to humans than that of rodents and which more faithfully mirrors human sFLT1 splice isoforms a single bolus of these siRNAs inhibited placental sFLT1 overproduction and alleviated the clinical features of preeclampsia [65] This primate finding is important because sFlt1-e15a, the dominant pathogenic isoform, is primate-specific and essentially absent in rodents [66, 67]; baboon efficacy is therefore a more accurate predictor of human relevance than murine efficacy alone. Together, these data define a causal mechanism in which lowering placental sFLT1 reduces the circulating antiangiogenic burden and thereby improves the disease phenotype in a species capable of human-like placentation—the central preclinical proof of concept upon which this therapeutic strategy is based [65] A comprehensive summary of these pivotal preclinical studies detailing the animal models, therapeutic targets, delivery vehicles, and specific physiological outcomes is provided in Table 2.

Targeted Action and the Feasibility of Treating More Than One Mediator

Two additional lines of pre-clinical evidence relate directly to the clinical goal of this review.

Placental targeting

Firstly, several approaches have demonstrated that treatment can be intentionally focused on the placenta without exposure of maternal organs and the fetus, e.g placenta-homing strategies have combined placenta-targeted delivery of gene-modulating cargo to the placenta in pregnant mice effecting transient placental gene expression changes without disruption of normal development [68]. This further emphasizes the central safety imperative of local action within the maternal–placental compartment.

Dual silencing

Secondly and applying to the dual-target argument, more than one placental mediator can do be downregulated simultaneously. In a mouse model of preeclampsia, synchronized suppression of two independent placental transcripts sFLT1 along with the oxidative-stress regulator Nrf2 benefited both maternal and fetal outcomes [71]. This sets the premise that two signaling payloads can function in coordination in the placenta, a necessity for accomplishing simultaneous targeting of sFlt-1s and soluble endoglin.

Current evidence

Similar strategies based on the same class of carrier utilized for the messenger-RNA vaccines conduction have also been directed to the placenta and, when applied to restore proangiogenic signaling, reversed hypertension and improved outcomes in animal models of preeclampsia [72], with further optimization of placental delivery subsequently described [72]. While it is important to note that these studies restored a proangiogenic factor, not a pathogenic one, and so do not show that selective silencing of pathological factors can be achieved, collectively confirm the placental accessibility and potential selectivity of actions during pregnancy [73]

Extending the Strategy to Soluble Endoglin and Dual Silencing

The rationale for co-targeting soluble endoglin

The pathophysiological case for suppressing soluble endoglin alongside sFlt-1 rests on the synergy described earlier: the two factors act through distinct but convergent pathways VEGF/PlGF sequestration and TGF-β/eNOS antagonism and together produce a more severe, HELLP-like endothelial injury than either alone [74]. In severe early-onset disease, where both factors are markedly elevated and the most dangerous variants occur, lowering sFlt-1 while leaving sEng untouched may leave a substantial component of the antiangiogenic insult intact. Co-suppressing both mediators is therefore the logical clinical extension, aimed at the full antiangiogenic burden rather than half of it [14]

The feasibility of dual suppression

Encouragingly, the feasibility of acting on two distinct placental transcripts at once has already been demonstrated, albeit with a different second target, as described above [75]. There is no fundamental barrier to directing the second payload against endoglin instead, or to combining an sFlt-1 and an sEng–directed agent within a single

treatment. The selectivity principles established for sFlt-1 isoform consideration, durable action, and confinement to the placenta—could in principle be applied to an endoglin-directed agent in the same way [62].

Challenges specific to endoglin silencing

The biological rationale for targeting soluble endoglin together with sFlt-1 is based on the mechanism summarized previously: both factors function through completely distinct yet converging downstream pathways: VEGF/PlGF sequestration and TGF-β/eNOS antagonism [76]. Together they result in a more severe HELLP-like endothelial cell injury than either factor alone [24]. In severe early-onset disease, when both factors are significantly elevated and the most pathological variants are present, manipulating sFlt-1 to reduce expression at the expense of sEng-perhaps by vehicle stabilization-may spare a major portion of the antiangiogenic insult. Thus, co-suppressing both mediators is a rational clinical extension to just targeting half the antiangiogenic burden [77]

Safety, Fetal Considerations, and Translational Hurdles

Fetal exposure and the placental barrier

Fetal exposure is the most crucial safety issue for any agent given in pregnancy. The objective is to confine action to the syncytiotrophoblast on the maternal-facing side of the placenta while minimizing passage of the agent into the fetal circulation, so as to avoid suppressing fetal genes or otherwise perturbing development [56]. The preclinical biodistribution noted above is encouraging placental uptake with hepatic clearance and limited fetal transfer, and the placental confinement achievable with placenta-directed approaches but verifiable evidence of minimal fetal exposure across gestational ages and in species with human-like placentation remains an essential prerequisite for clinical translation. The placental barrier is at once the obstacle and the protector, and a quantitative characterization of transfer is non-negotiable [78, 79]

Immunogenicity in the pregnant host

Pregnancy is an immunologically distinctive state, and innate immune sensing of nucleic acids is of particular concern, because inappropriate inflammation at the maternal–fetal interface is associated with adverse outcomes. Because inadequately designed agents can activate innate immune pathways [80] approaches that minimize such activation address a safety requirement as much as an efficacy one. Where a carrier is used, the potential immunogenicity of the carrier and any targeting component must likewise be evaluated specifically in the pregnant context, in which an inflammatory response can have direct fetal consequences [81]. Off-target gene silencing is a general concern for any RNA-interference strategy: partial complementarity between the siRNA seed region and unintended transcripts leads to microRNA-like repression of genes other than sFLT1 [82]. Importantly, this risk is heightened in the context of the pregnant host, where inadvertent silencing of critical placental or fetal transcripts could disturb trophoblast function or fetal development, over and above reducing efficacy. Seed-mediated off-target activity is substantial and sequence-dependent, but largely predictable and thus can be controlled [83] This liability is reduced by rational sequence selection that screens candidates against the transcriptome, screening of the seed region to minimize spurious base-pairing, and isoform-selective design already utilized to spare full-length FLT1. The preclinical evidence of minimal off-target signatures together with on-target potency is an indispensable preclinical safety criterion before any placental sFLT1-silencing therapeutic reaches the clinic.

The therapeutic window: silence enough, but not too much

The degree of suppression is a subtle but crucial issue. Preeclampsia reflects an excess of antiangiogenic activity, yet VEGF and TGF-β signaling are themselves essential to placental and fetal vascular development [84]. The aim is therefore not to eliminate these factors but to restore a normal balance. Excessively lowering sFlt-1 could permit unopposed VEGF activity with its own vascular effects, and excessive suppression of endoglin could disrupt physiological TGF-β signaling [85]. The therapeutic goal is thus a partial, titratable reduction that brings the antiangiogenic burden down to a safe level something for which the sFlt-1/PlGF ratio provides a convenient pharmacodynamic guide, allowing dosing to be calibrated to a defined target reduction rather than to maximal suppression [62]

Dosing and the ethics of trials in pregnancy

Substantial translational hurdles separate the biology from the clinic. A therapy must be deliverable in a regimen appropriate to the weeks of prolongation required, and its effect must be controllable and reversible enough to be safe [86]. The regulatory and ethical challenges are the most daunting of all: pregnant women have historically been excluded from drug development, and evaluating a novel intervention in a setting where two patients mother and fetus are simultaneously at risk demands exceptional preclinical safety data, trial designs that will likely enroll the sickest patients with the fewest alternatives, and sustained engagement with the ethical questions that maternal–fetal therapeutics raise [87]. The history of repurposed-agent trials in preeclampsia illustrates how difficult it is to prove benefit even with well-tolerated agents, and the bar for a first-in-class silencing therapy will be higher still. Far from reasons for pessimism, these are the parameters that define the work still to be done [88]

Future Directions

Several clinical priorities will shape the field's progress. The first is the rigorous, quantitative characterization of fetal exposure and long-term offspring safety for lead candidates in species with human-like placentation, since this is the gating question for any clinical trial. The second is the development and validation of an endoglin-directed strategy that respects the physiological roles of membrane endoglin, whether through placental restriction, targeting, or calibrated partial knockdown, so that the dual-target promise can be realized. The third is the clinical ambition of correcting both mediators at once a single approach capable of lowering sFlt-1 and soluble endoglin with placental specificity. The fourth is the integration of the sFlt-1/PlGF ratio and emerging placental biomarkers into trial design as pharmacodynamic and patient-selection tools, enabling dosing to a defined target and enrollment of the women most likely to benefit. Underlying all of these is the need for trial frameworks and regulatory pathways that can responsibly evaluate disease-modifying therapeutics in pregnancy at all. Ultimately, the speed of development in this area will be determined by coincident advances of computational and molecular technologies. Today, artificial-intelligence and machine-learning models more commonly fuse clinical, biochemical, and imaging datasets to predict preeclampsia

earlier while also identifying precision biomarkers that improve risk stratification and patient selection [89] Similarly, single-cell RNA sequencing has elucidated how the cellular heterogeneity of the maternal–fetal interface creates pro- and anti-angiogenic neuro-immune and vascular populations [90] that drive the antiangiogenic imbalance, while spatial transcriptomics captures where pathogenic transcripts including those for sFLT1 are produced within this normally well-coordinated tissue structure, the placenta [91]. High-resolution atlases like these can identify novel placental targets and delineate the cell populations that a silencing therapeutic must target. CRISPR-based transcriptional repression (CRISPRi) provides an additional, programmable pathway for sequence-specific silencing of pathogenic placental genes beyond RNA interference [92] Combining these technologies to select patients with predictive analytics, define targets with single-cell and spatial maps, and to intervene using next-generation silencing platforms represents the translational window through which an eventual precision therapy for preeclampsia will be constructed.

Table 2: Preclinical in vivo proof-of-concept studies for placental modulation of the antiangiogenic axis in preeclampsia, across species.

Study	Animal model	Target	Delivery	Key outcome
Turanov et al., 2018 [65]	Mouse	sFLT1	Chemically stabilized, cholesterol-conjugated siRNA; systemic	Circulating sFLT1 ↓ ~50%; preeclampsia-like phenotype ameliorated
Turanov et al., 2018 [65]	Baboon (nonhuman primate)	sFLT1	Single-dose siRNA; systemic	Placental sFLT1 ↓; proteinuria ↓; blood pressure stabilized; clinical signs alleviated
Davis et al., 2022 [51]	Mouse	sFLT1	Chemically optimized siRNA; systemic	More potent and safer placental sFLT1 silencing (lead-candidate optimization)
Beards et al., 2017 [68]	Mouse	Placental growth-restrictive miRNAs	Placental-homing peptide–miRNA-inhibitor conjugate	Placenta-selective delivery; intrinsic placental growth signaling enhanced without disrupting development
Li et al., 2020 [69]	Mouse	sFlt1 + Nrf2 (dual)	CSA-targeted lipid-polymer nanoparticle (siRNA)	Simultaneous knockdown of both transcripts; angiogenic factors ↑; maternal and fetal outcomes improved (dual-target proof of concept)
Swingle et al., 2025 [70]	Mouse	VEGF (mRNA; restoration, not silencing)	Placenta-tropic ionizable LNP; single systemic dose	Maternal hypertension resolved to term; placental function and fetal health improved (delivery-platform proof of concept)

Abbreviations: CSA, chondroitin sulfate A; LNP, lipid nanoparticle; miRNA, microRNA; mRNA, messenger RNA; Nrf2, nuclear factor erythroid 2-related factor 2; sFLT1/sFlt-1, soluble fms-like tyrosine kinase-1; siRNA, small interfering RNA; VEGF, vascular endothelial growth factor. ↓ decreased; ↑ increased.

Conclusion

Severe early-onset preeclampsia is a disease whose molecular cause is understood, whose pathogenic mediators are known and measurable, and whose only definitive treatment—ending the pregnancy—is often a defeat dressed as a cure. Source-directed silencing of the placental antiangiogenic factors offers, for the first time, a credible means of treating the placenta rather than removing it. The pathogenic factors sFlt-1 and soluble endoglin are produced by an accessible, transient organ; sFlt-1 in particular can be suppressed through its pathogenic isoforms while sparing its essential full-length counterpart; and experimental approaches have already achieved selective placental silencing and clinical improvement in a nonhuman-primate model of the disease, while related placenta-directed approaches have demonstrated the ability to act on more than one target at once. The extension to soluble endoglin is biologically compelling but technically harder, constrained by the absence of a clean pathogenic isoform and the physiological importance of membrane endoglin. And every advance must clear the singular bar of safety in a setting where two patients are treated through one—demanding minimal fetal exposure, immune quiescence, titratable rather than maximal effect, and an ethical and regulatory path suited to pregnancy. The field has moved decisively from concept to preclinical proof; whether it can cross into the clinic will depend less on the elegance of the silencing than on the rigor with which these remaining clinical problems are solved. If they are, a single class of intervention could transform the management of a disease that has, for too long, offered mothers and their physicians only the choice between two harms.

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Conflict of Interest

The author declares no conflicts of interest related to this work.

Data availability

No datasets were generated or analyzed during the preparation of this review.

Declaration of AI Use

AI was used to design Figures 1 and 2; both were subsequently reviewed, edited, and verified by the authors for scientific accuracy

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A.S.A. contributed to conception and study design, analysis and interpretation of the literature, drafting of the manuscript, and final approval of the manuscript. L.G.S. contributed to literature search and data acquisition, analysis and interpretation of the literature, drafting of the manuscript, critical revision and proofreading, and final approval of the manuscript. Both authors read and approved the final version of the manuscript, meet the ICMJE criteria for authorship, and agree to be accountable for all aspects of the work.

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