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Mini review

sFLT-1-based experimental models of preeclampsia: biological relevance, limitations, and implications for model selection

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Abstract: Preeclampsia is a pregnancy-associated disorder characterized by hypertension and multisystem maternal complications. Soluble fms-like tyrosine kinase-1 (sFLT-1) is widely used to establish experimental animal models, since elevated circulating sFLT-1 reproducibly induces endothelial dysfunction, hypertension, proteinuria, and glomerular injury. These findings indicate that angiogenic imbalance can generate the maternal syndrome of the disease. However, preeclampsia originates from abnormal placentation, whereas sFLT-1 primarily mediates the maternal systemic response. To clarify the biological meaning of these models, published sFLT-1 animal models were evaluated from four aspects: species differences, source of expression, placenta specificity, and isoform variation. The analysis showed that systemic sFLT-1 overexpression models reliably reproduce maternal vascular and renal manifestations but lack primary placental pathology. In contrast, placenta-restricted expression improves physiological relevance but still bypasses upstream mechanisms of trophoblast invasion failure. Therefore, sFLT-1 models do not represent the entire disease process and instead correspond to a specific pathological stage. These models are suitable for studying endothelial injury, renal pathology, and angiogenic-targeted interventions but are limited in investigating disease initiation, immune maladaptation, and clinical heterogeneity. Recognizing these boundaries can improve model selection and interpretation in experimental preeclampsia research.

Keywords: preeclampsia; animal model; sFLT-1; angiogenic imbalance; endothelial dysfunction; placentation

1. Introduction

Preeclampsia (PE) is a multisystem disorder unique to pregnancy, defined by new-onset hypertension after 20 weeks of gestation accompanied by maternal organ injury [1]. It affects approximately 2%–6% of pregnancies worldwide and remains a major contributor to maternal and perinatal morbidity and mortality, frequently associated with preterm birth and fetal growth restriction [2]. Despite extensive investigation, the initiating mechanisms of the disease are still incompletely understood. Preeclampsia is a pregnancy-specific vascular syndrome, distinct from generic gestational hypertension, characterized by abnormal placentation, systemic endothelial dysfunction, and long-term maternal cardiovascular risks [3,4].

PE is commonly described as a two-stage disorder. The first stage occurs in the placenta and is characterized by impaired trophoblast invasion and inadequate remodeling of the uterine spiral arteries. The first stage is also influenced by placental hypoxia and dysregulated angiogenic signaling, which have been demonstrated in early studies localizing VEGF and Flt-1 in the human placenta and showing release of soluble VEGF antagonists consistent with sFLT-1 [5,6]. The second stage represents the maternal syndrome, including hypertension, proteinuria, endothelial dysfunction, and systemic inflammation [7]. Maternal manifestations are primarily driven by circulating factors released from a dysfunctional placenta rather than direct structural abnormalities [8].

Among these factors, soluble fms-like tyrosine kinase-1 (sFLT-1) has been studied extensively. sFLT-1 is an anti-angiogenic splice variant of vascular endothelial growth factor receptor-1 (VEGFR-1) that binds vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), thereby reducing their bioavailability and disrupting endothelial homeostasis [9,10]. Experimental elevation of circulating sFLT-1 in animals induces hypertension, proteinuria, and glomerular endotheliosis, supporting a causal relationship between angiogenic imbalance and the maternal manifestations of PE [11].

However, PE is a multifactorial disorder. Additional pathways, including soluble endoglin (sEng), oxidative stress, inflammation, coagulation disturbances, and maternal cardiovascular susceptibility, contribute to disease heterogeneity and severity, particularly in early-onset PE. Consequently, although sFLT-1 is a key mediator of maternal endothelial dysfunction, it does not fully account for the initiating placental abnormalities.

However, a central question remains unresolved: whether increased sFLT-1 represents the disease itself or only reproduces the maternal syndrome secondary to placental dysfunction. PE is widely regarded as a disorder originating from abnormal placentation, whereas many experimental models induce symptoms through systemic sFLT-1 overexpression without reproducing the initial placental pathology. This discrepancy raises concerns regarding the biological validity and translational interpretation of sFLT-1-based animal models.

Because spontaneous PE does not occur in experimental animals, a variety of surgical, pharmacological, and genetic approaches have been used to generate inducible models. Rodents are most commonly employed due to their hemochorial placentation and experimental accessibility. Nevertheless, important interspecies differences exist: mice exhibit relatively shallow trophoblast

invasion, whereas rats demonstrate deeper uterine invasion and spiral artery remodeling patterns more similar to those of humans [12,13]. Such differences may influence the extent to which placental pathology and maternal symptoms are reproduced.

Therefore, rather than simply cataloging modeling techniques, it is necessary to determine which biological components of PE are actually represented in these systems. In this review, we critically evaluate rodent models based on sFLT-1, focusing on their biological relevance, mechanistic implications, and limitations. Particular attention is given to whether these models recapitulate the full disease process or primarily represent the maternal endothelial syndrome of preeclampsia.

2. Candidate factors contributing to preeclampsia

Preeclampsia is a multifactorial disorder involving impaired trophoblast invasion, abnormal spiral artery remodeling, placental hypoxia, oxidative stress, maternal immune maladaptation, inflammatory cytokines, and maternal cardiovascular susceptibility [14,15]. Among circulating mediators, soluble fms-like tyrosine kinase-1 (sFLT-1) has been most extensively studied because it reliably induces maternal hypertension, proteinuria, and endothelial dysfunction in experimental models and serves as a clinically useful biomarker (sFLT-1/PlGF ratio) [16]. Other factors, such as soluble endoglin (sEng), also contribute to disease heterogeneity [17]. For example, soluble endoglin (sEng) exacerbates vascular injury and hypertension; inflammatory cytokines such as TNF-α and IL-6 promote systemic inflammation and endothelial activation; vasoactive peptides like angiotensin II and endothelin-1 directly raise blood pressure; and oxidative stress aggravates proteinuria and endothelial damage [17–19].

Genetic and molecular evidence further supports this multifactorial nature. Fetal FLT1-adjacent risk loci (e.g., rs4769613) are associated with preeclampsia susceptibility [20], and alternative splicing of FLT1 produces multiple sFLT-1 isoforms whose relative abundance is altered in the disease [21]. Importantly, some patients do not exhibit marked sFLT-1 elevation, and naturally low sFLT-1 expression or FLT1 variants do not fully prevent preeclampsia, as other pathogenic pathways (e.g., excessive sEng or immune maladaptation) can still induce the maternal syndrome (summarized in Table 1) [22]. To date, no loss-of-function FLT1 mutation has been demonstrated to confer complete protection against preeclampsia in humans.

sFLT-1 remains a central focus of research because it is a well-characterized downstream mediator linking placental dysfunction to maternal endothelial injury, allowing standardized manipulation in experimental models and presenting translational relevance as a clinical biomarker [16].

Table 1. Candidate factors in preeclampsia pathogenesis and their links to sFLT-1.

Candidate factor	Source/mechanism	Pathophysiological effect	Relation to sFLT-1	Ref.
sFLT-1	Placental trophoblast	Endothelial dysfunction, hypertension, proteinuria	Central mediator	[4,16]
sEng	Placenta	Vascular injury, hypertension	Synergistic	[17]
Oxidative stress	Placental hypoxia/ischemia-reperfusion	Trophoblast injury, endothelial activation	Promotes sFLT-1 upregulation	[4,15]
Inflammatory cytokines (TNF-α, IL-6)	Placenta/maternal immune system	Systemic inflammation, endothelial activation	Amplifies sFLT-1 effects	[15,17]
Immune maladaptation	Maternal–fetal interface dysfunction	Shallow trophoblast invasion, defective placentation	Upstream of sFLT-1 rise	[14,15]
Coagulation/complement disturbances	Placental vascular dysregulation	Placental ischemia, endothelial damage	Parallel contributor	[14,15]
Maternal cardiovascular susceptibility	Pre-existing maternal vascular risk	Exaggerated maternal syndrome	Modifies response to sFLT-1	[14,15]
Genetic/epigenetic factors	FLT1, VEGFA, ENG, other related genes	Disease susceptibility and heterogeneity	Upstream/modifying factor	[20,22]

3. What biological features should a preeclampsia model reproduce?

Before evaluating individual animal models, it is necessary to clarify what it means to reproduce preeclampsia. The maternal manifestations of the disease arise as systemic responses triggered by early placental dysfunction, including impaired trophoblast invasion and dysregulated angiogenic signaling. Accordingly, the presence of hypertension or proteinuria alone does not demonstrate that the disease itself has been replicated [1,14]. Many experimental systems reliably elevate maternal blood pressure during pregnancy, yet such phenotypes primarily reflect maternal endothelial injury rather than the complete pathophysiological process of PE [23]. In this sense, maternal symptoms represent downstream consequences rather than sufficient evidence of disease reproduction.

From a pathophysiological perspective, a biologically informative model should reproduce multiple stages of the disease. First, abnormalities in placental development should be present, such as reduced trophoblast invasion or impaired spiral artery remodeling [7]. These changes should lead to altered placental perfusion and the release of anti-angiogenic or inflammatory mediators into the maternal circulation [23]. Subsequently, maternal clinical features—gestational hypertension, proteinuria, and glomerular endotheliosis—emerge as secondary effects, collectively forming the

maternal syndrome of PE [13]. An additional hallmark of the human condition is improvement after delivery or placental removal, which should also be observed when possible [24]. A model displaying only elevated blood pressure without placental involvement is therefore unlikely to represent disease initiation.

Based on these considerations, the validity of preeclampsia models can be discussed at three levels. Face validity refers to the reproduction of observable clinical features. Construct validity refers to whether the underlying mechanism—placental dysfunction—has been replicated. Predictive validity concerns whether the model responds to interventions in a manner consistent with the human disease, such as improvement after delivery or restoration of angiogenic balance. Models that possess only face validity may be useful for studying maternal vascular injury but are limited for investigating disease onset.

This framework is particularly important for interpreting sFLT-1-based models. While elevated circulating sFLT-1 can induce endothelial dysfunction, hypertension, and renal injury in experimental systems, whether sFLT-1 overexpression reproduces any elements of the initiating placental pathology of PE remains uncertain [25,26]. As sFLT-1 acts downstream of multiple upstream placental and maternal factors, these models are best interpreted according to the stage of disease they represent rather than as complete equivalents of preeclampsia [27].

4. Biological role and pathological position of sFLT-1 in human preeclampsia

Preeclampsia is strongly associated with an imbalance between pro-angiogenic and anti-angiogenic signaling in the maternal circulation. Among the candidate mediators, soluble fms-like tyrosine kinase-1 (sFLT-1) is widely considered a key link between placental dysfunction and systemic maternal manifestations. As introduced above, sFLT-1 acts as a circulating decoy receptor neutralizing VEGF and PlGF [15].

During normal pregnancy, tightly regulated angiogenesis supports placental vascular development and maternal vascular adaptation. In preeclampsia, placental hypoxia, oxidative stress, endoplasmic reticulum (ER) stress, and inflammatory signaling stimulate trophoblast transcriptional programs and alternative splicing, leading to overproduction of soluble FLT-1 isoforms (sFLT-1), resulting in elevated circulating concentrations weeks before clinical symptoms appear and correlating with disease severity and early-onset PE [28]. Consistent with this observation, the sFLT-1/PlGF ratio has been adopted as a clinical tool for risk stratification and diagnostic support [16].

The principal target of sFLT-1 is the maternal vascular endothelium. By antagonizing VEGF and PlGF signaling, sFLT-1 reduces nitric oxide availability, increases peripheral vascular resistance, and promotes vasoconstriction. In the kidney, VEGF signaling maintains glomerular endothelial fenestrations; inhibition of this pathway results in endothelial swelling, proteinuria, and reduced filtration function, changes that closely resemble glomerular endotheliosis in preeclampsia. Experimental administration of sFLT-1 to pregnant animals induces hypertension and proteinuria, further supporting its role in generating the maternal syndrome, while studies also show that systemic sFLT-1 overexpression reproduces maternal symptoms without replicating initiating placental pathology [24].

Despite this evidence, sFLT-1 elevation alone is unlikely to represent the initiating event of PE. Early defective trophoblast invasion and inadequate spiral artery remodeling occur upstream of marked sFLT-1 elevation, indicating that sFLT-1 primarily acts downstream of placental dysfunction. After delivery and placental removal, maternal sFLT-1 concentrations rapidly decline in parallel with clinical improvement, indicating that the placenta remains the primary source of pathogenic signaling [15,24,29].

Taken together, these observations support the interpretation that sFLT-1 primarily mediates and amplifies the maternal endothelial syndrome of PE rather than serving as the primary cause of disease. Systemic sFLT-1 overexpression reproduces maternal features but does not recapitulate initiating placental pathology, highlighting the stage-specific relevance of sFLT-1-based animal models and emphasizing the upstream molecular signals that induce sFLT-1 production. Accordingly, sFLT-1-based animal models are best viewed as representing specific stages of the disease process rather than reproducing preeclampsia in its entirety. Defining the biological position of sFLT-1 in human disease helps clarify both the applicability and the limitations of these experimental systems.

5. Systemic sFLT-1 overexpression models

Elevating circulating sFLT-1 experimentally is one of the earliest and most widely used strategies to model preeclampsia (PE). By using adenoviral vectors, continuous recombinant protein infusion, or plasmid expression, sFLT-1 levels can be artificially increased in pregnant animals, thus inducing an imbalance in angiogenesis. These models are mainly employed to study maternal clinical features of PE [15].

In pregnant rodent models, elevated circulating sFLT-1 induces hypertension, proteinuria, and glomerular endotheliosis, which closely resemble the maternal symptoms observed in PE. The proposed mechanisms underlying these maternal features are illustrated in Figure 1. Similar vascular and renal changes are also observed in non-pregnant animals, suggesting that sFLT-1 elevation alone is sufficient to induce systemic endothelial injury. Mechanistically, placental or ectopic stress signals trigger transcriptional upregulation and alternative splicing of FLT1, producing soluble isoforms that act as decoy receptors to neutralize VEGF and PlGF, thereby reducing nitric oxide bioavailability and promoting vasoconstriction and glomerular endothelial damage [3]. This supports the role of angiogenesis imbalance in the development of the maternal syndrome [30,31].

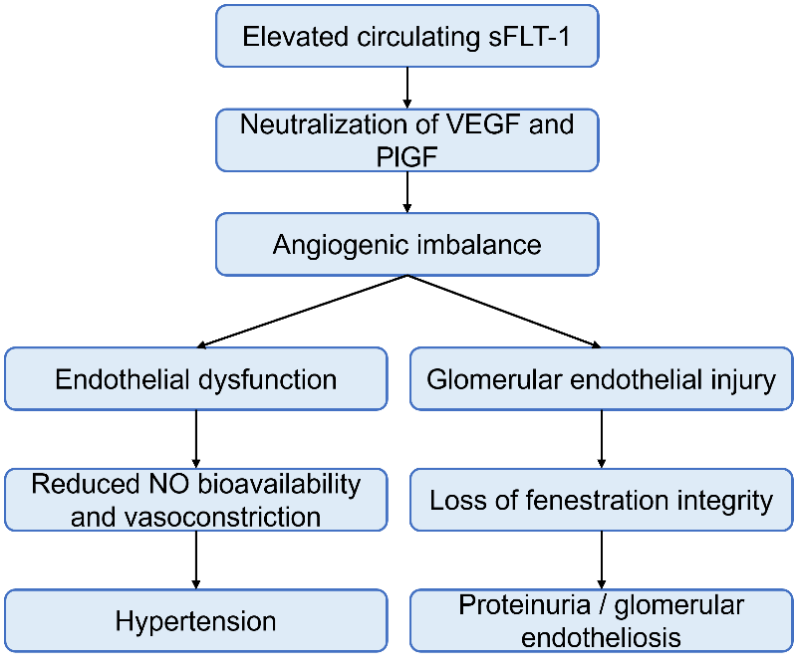

Figure 1. Proposed mechanisms by which elevated circulating sFLT-1 induces hypertension, proteinuria, and glomerular endotheliosis in pregnant rodent models.

However, according to the previously described evaluation framework, these models primarily demonstrate face validity rather than construct validity. Although they consistently reproduce maternal hypertension and renal damage, they generally do not exhibit initiating placental abnormalities such as defective trophoblast invasion or impaired spiral artery remodeling. Observed placental changes are typically secondary to maternal circulatory alterations rather than primary pathological events [14].

Another important consideration is the source of gene expression. After intravenous adenoviral injection, sFLT-1 is primarily expressed in the liver or other ectopic tissues, rather than the placenta, meaning that circulating sFLT-1 originates from ectopic expression. Additionally, viral vectors themselves can induce liver inflammation, elevated transaminases, and hematological changes, some resembling features of HELLP syndrome, which may confound interpretation [32,33].

Despite these limitations, systemic sFLT-1 models provide valuable insight into PE pathophysiology: they demonstrate that sFLT-1 functions as a downstream mediator linking placental abnormalities with maternal disease, and that maternal symptoms can be experimentally induced even in the absence of primary placental pathology [24].

Consequently, systemic sFLT-1 overexpression models are best understood as representing the maternal syndrome of preeclampsia rather than the complete disease. They are suitable for studying vascular injury mechanisms, renal pathology, and anti-angiogenic therapeutic interventions, but are not appropriate for investigating the initiating mechanisms of placental formation defects [15,20].

6. Placenta-specific sFLT-1 expression models

Given that preeclampsia is considered to originate from placental dysfunction, researchers have increasingly sought to enhance the biological relevance of models by restricting sFLT-1 expression to placental tissues. Strategies such as blastocyst-stage lentiviral transduction and transgenic systems limiting sFLT-1 expression to the trophoblast lineage have been employed [33,34]. Unlike systemic overexpression models, these approaches aim to more closely mimic the site and timing of pathogenic factor release during human pregnancy, rather than simply increasing sFLT-1 levels in the maternal circulation.

Studies have shown that trophoblast-derived sFLT-1 is sufficient to induce maternal hypertension, proteinuria, and fetal growth restriction [35]. Notably, maternal blood pressure rapidly returns to normal after delivery, resembling the clinical course of preeclampsia. Structural and functional changes in the placenta, such as reduced vascularization in the labyrinth zone, impaired nutrient transport, and enhanced hypoxia-related signaling, have also been observed. These findings suggest that placenta-specific sFLT-1 models reproduce both maternal and placental phenotypes to some extent, but do not fully replicate initiating placental pathology in human PE [17,36].

Despite these advances, placenta-specific sFLT-1 models still have significant limitations. In some lentiviral systems, sFLT-1 expression occurs at pre-implantation or early placental development stages, which is not consistent with the disease progression seen in humans [37]. Early expression may interfere with normal placental development rather than simulate the pathological process of an already dysfunctional placenta [37,38]. Moreover, the expression of human sFLT-1 in mouse trophoblast cells does not fully replicate species-specific regulatory mechanisms, and the promoter activity may differ from that of endogenous genes [33,39]. Some transgenic models also exhibit developmental compensation, potentially altering the severity of the disease phenotype [40].

Furthermore, these models do not reproduce upstream placental mechanisms. In human

preeclampsia, abnormal trophoblast invasion, immune maladaptation, and failed spiral artery remodeling typically occur before the rise in anti-angiogenic factors. In placenta-specific sFLT-1 models, sFLT-1 is set as the initiating event, bypassing these primary placental pathologies. Therefore, the observed placental changes are more likely consequences of angiogenic imbalance rather than causative events [14,29].

Overall, placenta-specific models improve physiological relevance by restoring the tissue-specific source of sFLT-1 and reproducing postpartum symptom resolution. However, they primarily reflect disease progression rather than the initiating mechanisms of placental dysfunction. These models are best suited for studying the effects of angiogenic imbalance on maternal and fetal-placental interactions, but remain limited for investigating the earliest stages of placental development abnormalities. The positions of systemic and placenta-specific models within the disease timeline are summarized in Figure 2, and a detailed comparison of their features, strengths, and limitations is provided in Table 2.

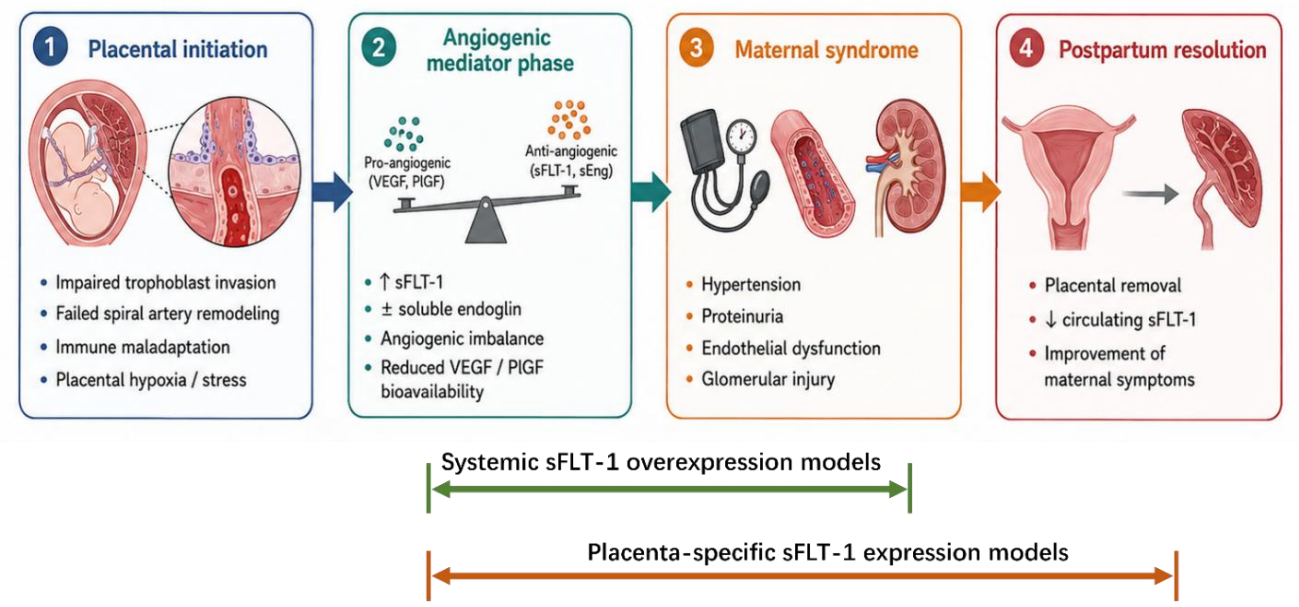

Figure 2. Conceptual timeline of preeclampsia pathogenesis and the stage-specific relevance of sFLT-1-based animal models. Systemic sFLT-1 overexpression models primarily correspond to stages 2 and 3. Placenta-specific sFLT-1 expression models correspond to stages 2, 3, and 4. Neither model reproduces stage 1.

Table 2. Features, strengths, and limitations of systemic and placenta-specific sFLT-1 models.

Feature	Systemic sFLT-1 overexpression models	Placenta-specific sFLT-1 expression models
Source of sFLT-1	Ectopic/systemic	Placental/trophoblast-restricted expression
Main biological stage represented	Maternal syndrome of PE	Maternal syndrome of PE + secondary placental changes due to sFLT-1; primary initiation defects not reproduced
Maternal hypertension/proteinuria	Robustly reproduced	Reproduced
Placental pathology	Secondary changes or absent	Secondary placental changes; primary placental initiation defects bypassed
Trophoblast invasion defect	Not reproduced	Not reproduced
Spiral artery remodeling failure	Generally absent	Not reproduced
Fetal growth restriction	Rarely observed	Frequently observed
Postpartum resolution	Not observed	Observed
Strengths	Strong face validity for maternal syndrome; useful for studying maternal endothelial injury, hypertension, and renal pathology	Restores placental source of sFLT-1; improves physiological relevance; reproduces postpartum maternal symptom resolution
Limitations	Poor construct validity for placental initiation; does not replicate early trophoblast/spiral artery defects	Still bypasses upstream placental mechanisms; does not reproduce maternal–fetal immune maladaptation or early invasion defects
Best use	Maternal endothelial injury, renal pathology, anti-angiogenic intervention studies	Maternal–placental interaction, placental-source angiogenic imbalance, fetal growth restriction studies

7. Species differences and selection of rodent models: mice vs. rats

The choice of animal species plays a critical role in determining the interpretative scope of preeclampsia (PE) models. While both humans and rodents possess hemochorial placentation, significant differences exist in trophoblast invasion depth and uterine vascular remodeling. These differences not only affect the maternal phenotype but also determine whether the model can simultaneously replicate placental pathology.

In human pregnancy, the extravillous trophoblasts migrate into the decidua and, to some extent, the myometrium, remodeling the spiral arteries from high-resistance small arteries into low-resistance,

perfusion-efficient channels. Impaired remodeling of these vessels is considered a key initiating event in early-onset PE [14,41]. In contrast, among commonly used experimental animals, rats exhibit more extensive trophoblast invasion, and the structural changes in their uterine arteries are more similar to those in humans. In mice, however, trophoblast invasion is limited to the decidual layer, with less extensive vascular remodeling [15, 41–43].

As such, the rat model offers greater value in studies focused on placental formation and the regulation of uterine-placental perfusion. Studies have shown that rat placental vascular remodeling is more pronounced, and the structural changes in uterine arteries are clearer, making it easier to identify and quantify trophoblast-related abnormalities [44,45].

Mice, on the other hand, offer significant advantages in genetic manipulation. The availability of advanced transgenic and conditional expression systems makes mice ideal for investigating molecular signaling pathways, angiogenesis regulation, maternal vascular responses, and immune responses. However, due to their shallower trophoblast invasion, mice are less capable of fully replicating the placental vascular remodeling failure seen in human PE [46].

This species difference is particularly crucial when interpreting sFLT-1 models. In both species, systemic elevation of sFLT-1 induces hypertension and proteinuria, indicating a conserved maternal endothelial response. However, sFLT-1 models primarily reproduce "maternal syndrome features" rather than the initiating placental abnormalities. The ability of these models to replicate placental pathology depends on species-specific placental structure. Therefore, mouse models are more suited for studying maternal endothelial injury and vascular responses, whereas rat models are better suited for evaluating placental vascular remodeling and uterine-placental perfusion abnormalities.

8. Functional differences between truncated and full-length sFLT-1 and their impact on model phenotypes

sFLT-1 is not a single protein but a set of soluble receptor isoforms generated by alternative splicing of the FLT-1 gene [47]. The two most commonly studied isoforms in experimental research are truncated sFLT-1 and the more complete soluble receptor form. The molecular structures of these variants are illustrated in Figure 3. Both retain the ligand-binding immunoglobulin (Ig) domains (typically IgD1-3 or IgD1-6), but truncated sFLT-1 lacks additional structural regions that stabilize receptor conformation. The secretion of sFLT-1 occurs via the classical constitutive secretory pathway: after translation, the soluble protein is packaged into vesicles and released without requiring specific proteolytic cleavage, although alternative splicing directly produces a transcript lacking the transmembrane domain [48].

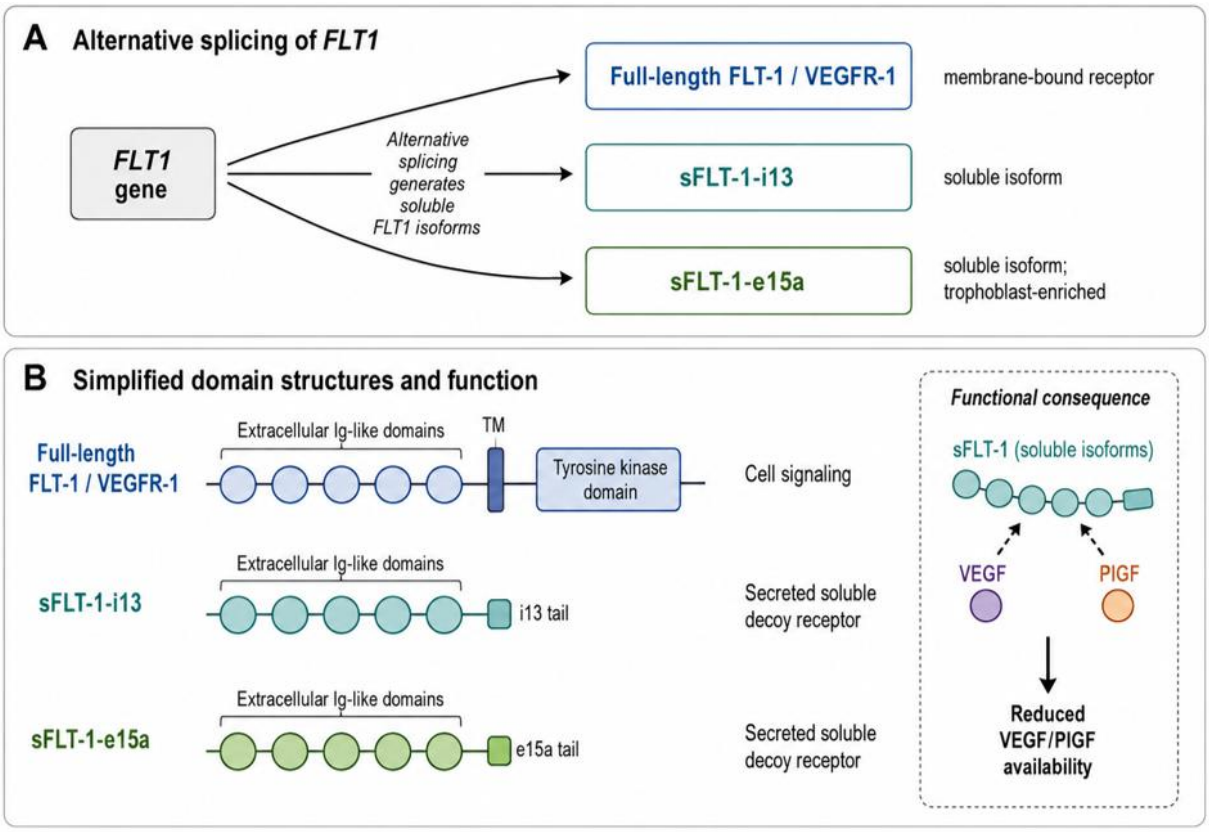

Figure 3. Simplified structure and generation of sFLT-1 isoforms.

Truncated sFLT-1 includes the N-terminal immunoglobulin-like domain essential for VEGF binding but lacks other structural regions that maintain receptor conformation stability. As a result, truncated sFLT-1 has a wider distribution in the circulation and more readily binds and neutralizes VEGF and PlGF. When overexpressed experimentally, even at relatively low levels, truncated sFLT-1 often rapidly induces a strong anti-angiogenic state, accompanied by hypertension and proteinuria [15]. Truncated sFLT-1 primarily impacts the maternal syndrome of PE, reflecting its downstream mediator role, with limited influence on initiating placental pathology [49].

In contrast, full-length sFLT-1 contains additional structural segments that promote receptor dimerization and alter ligand binding dynamics. This isoform is structurally more stable, but its effective bioavailability is lower, requiring higher expression levels to induce similar maternal phenotypes [29,48]. Differences in renal pathology observed across studies may stem from these kinetic differences: truncated sFLT-1 more readily causes acute endothelial injury, while full-length sFLT-1 produces a slower and more variable response. Full-length sFLT-1 may affect the placental–fetal unit to some extent, but still represents a downstream effect rather than the initiating placental abnormality.

Regarding the receptor system, sFLT-1 itself is a soluble decoy receptor and does not transduce signals. Instead, it binds to its ligands VEGF-A, VEGF-B, and PlGF, thereby preventing them from interacting with their membrane-bound signaling receptors. The principal membrane receptors for these ligands are VEGFR-1 (Flt-1, full-length) and VEGFR-2 (KDR/Flk-1). In addition, neuropilin-1 (NRP1) acts as a co-receptor that enhances VEGF binding to VEGFR-2. Therefore, sFLT-1 modulates the activation of multiple receptors (VEGFR-1, VEGFR-2, NRP1) by sequestering their common

ligands [15,50]. This multi-receptor antagonism explains the broad endothelial and renal effects of elevated sFLT-1.

These molecular differences are particularly important when interpreting experimental results. Some studies report severe hypertension without fetal growth restriction, while others show placental structural changes. These discrepancies may not be due to differences in modeling techniques but rather reflect the distinct biological effects of each isoform. The highly diffusible truncated form primarily impacts the maternal vascular system, whereas the sustained expression of full-length sFLT-1 may predominantly affect the placental–fetal unit [35].

It is also important to note that multiple isoforms of sFLT-1 exist in human preeclampsia, and their relative abundance changes dynamically during pregnancy [51,52]. Therefore, models based solely on one isoform may not reproduce the full temporal progression from placental initiation to maternal syndrome, highlighting their limitation in fully representing human PE. Experimental conclusions should be interpreted in the context of the specific isoform used, and models should not be regarded as functionally equivalent without considering these molecular differences.

Overall, the choice of sFLT-1 isoform influences phenotype severity, affected organs, and the interpretative scope of the model. Differences observed across studies reflect biological heterogeneity rather than merely technical error, underscoring the importance of considering isoform-specific effects when interpreting experimental results.

9. Applicability and limitations of sFLT-1 animal models

By integrating evidence from placental biology, species differences, expression sources, and isoform structure, a more precise positioning of sFLT-1 models can be made. These models do not replicate the entire preeclampsia (PE) disease process, but rather simulate the pathological stage driven by an imbalance in angiogenesis [51,53]. In other words, sFLT-1 acts as a downstream mediator, and the maternal hypertension and renal injury observed represent secondary effects rather than initiating events. Ignoring this distinction can lead to misinterpretation, where maternal hypertension and renal injury may be mistakenly viewed as the primary cause of the disease, rather than its downstream effects [54,55].

From a research perspective, sFLT-1 models offer valuable insight into maternal syndrome. Experimental elevation of circulating sFLT-1 consistently induces endothelial dysfunction, hypertension, proteinuria, and glomerular injury, making these models useful for studying vascular tone regulation, oxidative stress responses, and endothelial–kidney interactions [7,23]. These models are particularly suited to studying maternal endothelial injury and the downstream consequences of angiogenic imbalance. Furthermore, when sFLT-1 is expressed specifically in the placenta, fetal growth restriction, altered placental transport, and abnormal maternal–fetal signaling can be observed, bringing the model closer to mimicking the pathological progression of the disease [9,23]. However, even placenta-specific expression does not fully reproduce initiating placental defects such as abnormal trophoblast invasion or failed spiral artery remodeling.

However, these models do not replicate the upstream mechanisms of preeclampsia. Impaired trophoblast invasion, immune maladaptation at the maternal–fetal interface, and failed spiral artery remodeling typically occur prior to the rise in anti-angiogenic factors. In sFLT-1 models, these processes are artificially bypassed, making them unsuitable for studying the disease's initiating mechanisms [39,55,56]. Additionally, PE presents with significant clinical heterogeneity, with

differences in placental involvement and metabolic-immune backgrounds across subtypes. A single anti-angiogenic mechanism cannot fully account for this complexity [10,57]. They bypass early placental and immune events, limiting their use for studying disease initiation or preventive strategies.

Therefore, a more appropriate conceptual distinction is that sFLT-1 models should be understood as *models of the angiogenic imbalance mechanism*, rather than *models of preeclampsia pathogenesis*. The pathological pathways of preeclampsia can be divided into sFLT-1-dependent and sFLT-1-independent categories (Table 3). They are ideal for investigating maternal syndrome and therapeutic interventions targeting angiogenic pathways, but are limited in studying the initiation of placental abnormalities, maternal immune tolerance, or disease prevention mechanisms. It is important to emphasize that while sFLT-1 rodent models provide mechanistic insight and proof-of-concept, definitive validation of preeclampsia mechanisms ultimately relies on human studies, including longitudinal biomarker analysis, prospective cohort studies, and postpartum resolution of disease.

Table 3. Classification of sFLT-1-dependent and sFLT-1-independent pathological pathways in preeclampsia.

Pathway category	Key mediators/mechanisms	Pathophysiological effects	Representative clinical features
sFLT-1-dependent	sFLT-1 (soluble FLT-1 isoforms) → sequestration of VEGF and PlGF	Endothelial dysfunction, reduced nitric oxide bioavailability, vasoconstriction, glomerular endotheliosis	Hypertension, proteinuria, renal injury
sFLT-1-independent (upstream placental pathways)	Immune maladaptation, shallow trophoblast invasion, failed spiral artery remodeling	Poor placentation, placental hypoperfusion, placental stress	Placental dysfunction, fetal growth restriction, increased risk of maternal syndrome
sFLT-1-independent/parallel pathways	Soluble endoglin (sEng) → inhibition of TGF-β signaling; inflammatory cytokines (TNF-α, IL-6); oxidative stress; coagulation/complement disturbances	Endothelial activation, vascular injury, placental ischemia, systemic inflammation	Hypertension, proteinuria, systemic inflammation, fetal growth restriction

10. Conclusion

This study emphasizes the critical role of sFLT-1 in preeclampsia, linking placental dysfunction to maternal systemic symptoms. Elevated sFLT-1 induces endothelial dysfunction, hypertension, and renal pathology, supporting its involvement in the maternal syndrome of PE. However, preeclampsia fundamentally originates from placental abnormalities, with trophoblast invasion defects and spiral

artery remodeling failure preceding the rise in anti-angiogenic factors. Therefore, sFLT-1 is more likely a mediator of the disease rather than its primary cause.

As downstream mediators, sFLT-1 models reproduce maternal symptoms without recapitulating the initiating placental pathology. sFLT-1 models are valuable for studying vascular dysfunction, renal injury, and therapeutic interventions targeting angiogenesis, but they do not replicate the initial placental abnormalities that drive the disease. These models are best understood as representing the maternal syndrome of PE, rather than a complete disease model.

Future research should combine sFLT-1 models with those addressing placental development defects and immune dysfunction to better reflect the full complexity of preeclampsia.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

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We would like to thank you for following the instructions above very closely in advance. It will definitely save us lot of time and expedite the process of your paper's publication.

The authors are requested to identify the organizations, institutions or people who provided financial support for conducting the research and/or preparing the article when you submit your article.

Conflict of interest

The authors declare no conflict of interest.

Author contributions

Mi Zhang and Weihua Zhao conceived the study. Mi Zhang performed the literature search, data collection, and drafted the manuscript. Caijing Wu and Jialing Liu contributed to literature screening and data organization. Yu Wang, Peiying Ye, Qixuan Yue, Huijie Xu and Xingzheng Gu participated in data interpretation and manuscript revision. Yihua Zhu and Jie Tang contributed to critical revision of the manuscript and provided academic guidance. Guanglei Li supervised the study and revised the manuscript for important intellectual content. Weihua Zhao was responsible for overall project design, coordination, and final approval of the manuscript. All authors read and approved the final version of the manuscript.

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