

A New Hope for Preterm Pre-Eclampsia: Targeted sFlt-1 Removal and Emerging Therapies for Better Maternal and Fetal Outcomes

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ABSTRACT

Background: Preterm pre-eclampsia remains one of the most dangerous complications of pregnancy because clinicians must balance two competing risks: worsening maternal disease and iatrogenic prematurity for the fetus.

Objective: This review synthesizes recent evidence on preterm pre-eclampsia, angiogenic imbalance, sFlt-1/PlGF biomarkers, metformin, pravastatin, esomeprazole, and selective sFlt-1 removal.

Methods: The article is narrative review based on recent published literature, clinical trial reports, international guidelines and pediatric medication-administration evidence published mainly within 2021–2026.

Results: Preterm pre-eclampsia remains a major cause of maternal and neonatal morbidity because the only definitive cure is delivery, which often results in medically indicated preterm birth. Recent advances in angiogenic biology have created a realistic pathway toward disease-modifying therapy.

Conclusion: The most clinically valuable approach will not simply be to lower blood pressure, but to identify the biological driver of disease, select the right patient, intervene at the right time, and prolong pregnancy only when it is safe for the mother. If larger controlled trials confirm benefit, targeted sFlt-1 removal could become a landmark therapy that benefits both mother and child.

Keywords: metformin, maternal outcomes, fetal outcomes, pregnancy prolongation, neonatal morbidity

1. INTRODUCTION

Pre-eclampsia is a multisystem hypertensive disorder of pregnancy, usually occurring after 20 weeks of gestation, and is associated with maternal endothelial dysfunction, abnormal placentation, hypertension, proteinuria, organ injury, fetal growth restriction, and medically indicated preterm birth

[1]. The World Health Organization reports that pre-eclampsia affects approximately 3–8% of women who give birth worldwide, and hypertensive disorders were responsible for around 16% of global maternal deaths in 2023, equivalent to about 42,000 deaths [2]. Preterm pre-eclampsia is especially difficult because the disease occurs at a gestational age when fetal maturity is incomplete. When severe diseases develop 34 weeks before, clinicians often try expectant management under close hospital surveillance, but deterioration in maternal or fetal status may force early delivery [3]. ACOG guidance states that expectant management before 34 weeks can be considered only in carefully selected patients with stable maternal and fetal condition and appropriate resources for maternal and neonatal care. Until recently, most treatment strategies for pre-eclampsia were supportive rather than disease specific. Antihypertensives lower blood pressure but do not correct the placental disorder [4]. Magnesium sulfate reduces seizure risk but does not reverse endothelial injury. Corticosteroids improve fetal lung maturity but do not treat the maternal syndrome. Delivery removes the pathological placenta, but at the cost of prematurity when performed early. Therefore, a treatment that can safely slow disease progression and extend pregnancy could benefit both mother and child [5].

2. MATERIALS & METHODS

This narrative review synthesized recent literature published mainly from 2021 to 2026. The review prioritized clinical trials, systematic reviews, guideline updates, mechanistic reviews, and translational studies related to preterm pre-eclampsia, angiogenic biomarkers, sFlt-1 removal, metformin, proton-pump inhibitors, statins, and maternal-neonatal outcomes [6]. Different sources were also included because it reports pregnancy-induced hypertension-related maternal and fetal outcomes, including lactate dehydrogenase as a disease-severity marker.

3. PATHOPHYSIOLOGY OF PRETERM PRE-ECLAMPSIA

Preterm pre-eclampsia is strongly associated with abnormal placental development and an anti-angiogenic maternal circulation. The placenta releases excessive soluble fms-like tyrosine kinase-1, which binds and neutralizes pro-angiogenic factors such as placental growth factor and vascular endothelial growth factor [7]. This imbalance contributes to endothelial dysfunction, vasoconstriction, hypertension, glomerular injury, hepatic involvement, thrombocytopenia, and placental insufficiency. The 2023 *Nature Reviews Disease Primers* review describes pre-eclampsia as a life-threatening disease of pregnancy associated with maternal and neonatal morbidity, long-term maternal cardiovascular risk, and adverse offspring outcomes including preterm birth, perinatal death, neurodevelopmental disability, and later cardiometabolic disease [8]. The central biological logic of emerging therapy is therefore clear: if excess sFlt-1 drives endothelial injury, then reducing circulating sFlt-1 may reduce maternal disease activity and create time for fetal maturation.

4. CURRENT STANDARD MANAGEMENT AND ITS LIMITATIONS

Current management focuses on diagnosis, risk stratification, blood-pressure control, seizure prophylaxis, fetal surveillance, corticosteroids where appropriate, and timely delivery. However, these interventions do not remove the underlying placental anti-angiogenic burden.

Table 01: Current intervention and Main benefits

Current intervention	Main benefit	Main limitation
Antihypertensive therapy	Reduces severe blood pressure and stroke risk	Does not reverse placental disease
Magnesium sulfate	Reduces eclampsia risk	Does not prolong pregnancy directly
Corticosteroids	Improves fetal lung maturity	Does not treat pre-eclampsia itself

Expectant management	May gain time for fetal maturation	Requires high-level monitoring and carries maternal risk
Delivery	Definitive cure for maternal disease	Causes prematurity when performed early

This is why disease-modifying therapies are urgently needed. A successful therapy would ideally reduce maternal disease activity, improve endothelial function, preserve placental-fetal circulation, and safely extend pregnancy without exposing the fetus to toxic drug effects.

5. ANGIOGENIC BIOMARKERS: FROM DIAGNOSIS TO TREATMENT SELECTION

The sFlt-1/PlGF ratio has become increasingly important in pre-eclampsia risk stratification. A high ratio reflects anti-angiogenic imbalance and placental dysfunction. A 2022 review on clinical interpretation of the sFlt-1/PlGF ratio reported that the test has a very high negative predictive value for ruling out development of pre-eclampsia within 7 days among women with suspected disease [9]. In 2024, ACOG issued a Clinical Practice Update on biomarker prediction of pre-eclampsia with severe features. The update states that biomarker immunoassay can support risk assessment in certain hospitalized pregnant women with hypertensive disorders, but it should complement—not replace—clinical diagnosis. This is clinically important for the new treatment pathway. If sFlt-1 removal becomes validated, the sFlt-1/PlGF ratio may serve not only as a diagnostic or prognostic marker, but also as a therapeutic selection tool [10]. Women with very high sFlt-1-driven disease may be the subgroup most likely to benefit from targeted removal.

6. THE NEW TREATMENT: SELECTIVE REMOVAL OF SFLT-1

CONCEPT

Selective sFlt-1 removal is an extracorporeal apheresis technique. Blood or plasma is passed through a specialized adsorber column designed to bind sFlt-1, after which filtered, blood is returned to the patient. This differs from drug therapy because it does not introduce a new pharmacologic agent into the maternal circulation [11]. Instead, it removes a pathogenic circulating protein. The 2026 *Nature Medicine* News & Views article by Sugulle and Staff described this as a first-in-human trial involving selective removal of placental sFlt-1 in preterm pre-eclampsia and suggested it could mark the start of a new era of targeted therapy.

FIRST-IN-HUMAN PILOT TRIAL

The key pilot trial was published in *Nature Medicine* in 2026 by Thadhani and colleagues. The study developed an antibody-based adsorber containing high-affinity IgG1 antibodies against sFlt-1 and tested it in a single-arm, open-label trial in women with very preterm pre-eclampsia. The primary endpoints were safety and tolerability. In preclinical pregnant baboons, extracorporeal apheresis reduced circulating sFlt-1 by approximately 50% [12]. In women receiving single ascending doses, maternal and fetal vital signs and umbilical artery pulsatility indices remained stable before, during, and after apheresis. In the multiple-dose phase, each apheresis session reduced sFlt-1 levels by a mean of 16.7% and mean arterial pressure by 4.1 mmHg. Pregnancy continued from admission for a median of 10 days, with reported treatment-related adverse events including mild hypocalcemia, puncture-site skin hemorrhage, and false labor.

WHY THIS MATTERS

Even a few additional days of gestation can be clinically meaningful in very preterm pregnancy. At 26–32 weeks, each week gained may improve birth weight, reduce respiratory distress, reduce severe

neonatal morbidity, and allow completion of corticosteroid administration or transfer to a tertiary neonatal care unit [13]. Therefore, a therapy that safely prolongs pregnancy by reducing the biological driver of disease could benefit both maternal and neonatal outcomes.

7. COMPARISON WITH OTHER EMERGING TREATMENTS

Selective sFlt-1 removal is not the only emerging strategy. Other approaches include metformin, proton-pump inhibitors, statins, sulfasalazine, antioxidants, RNA-based placental therapies, and angiogenic factor restoration. However, most remain experimental or inconclusive.

METFORMIN

Metformin has received considerable attention because it is inexpensive, widely available, stable, and has a known pregnancy safety profile. The 2021 BMJ randomized, double-blind, placebo-controlled trial evaluated extended-release metformin in women with preterm pre-eclampsia between 26+0 and 31+6 weeks. The study suggested that metformin may prolong gestation, although larger trials were needed. The trial reported median time from randomization to delivery of 17.7 days in the metformin group and 10.1 days in the placebo group [14]. Among women who took the full dose, prolongation was greater, and no serious adverse events related to the trial drug were observed, although diarrhea was more common. A 2024 BMJ Open protocol for the PI3 trial notes that the previous PI2 trial suggested metformin XR may prolong gestation by about one week, but a larger trial is required to confirm or refute the finding.

ESOMEPRAZOLE AND SULFASALAZINE

Esomeprazole and sulfasalazine have been studied because they may reduce sFlt-1 secretion and endothelial dysfunction in experimental models. However, clinical efficacy remains uncertain. A 2022 BMC Medicine pipeline review reported that esomeprazole had potential for prevention, while sulfasalazine was considered a high-potential early-phase treatment candidate, but stronger trial evidence was still needed [15].

PRAVASTATIN AND OTHER STATINS

Statins are biologically attractive because they may improve angiogenic balance, reduce endothelial dysfunction, and increase placental growth factor. However, pravastatin trials in established early-onset pre-eclampsia have not yet shown clear clinical benefit [16]. The 2022 pipeline review reported that a 2020 early-onset pre-eclampsia trial found no effect of pravastatin on maternal plasma sFlt-1 or pregnancy duration, possibly because the study was underpowered.

RNA AND PLACENTAL-TARGETED THERAPIES

Advanced platforms, including RNA interference and placental-targeted mRNA or nanoparticle delivery, are being explored to modify placental pathways directly. These are scientifically exciting but remain far from routine clinical use because fetal exposure, placental specificity, immunogenicity, long-term safety, and ethical concerns must be addressed.

8. POTENTIAL MATERNAL BENEFITS OF TARGETED SFLT-1 REMOVAL

The maternal benefits of sFlt-1 removal may include:

- Reduction of anti-angiogenic burden: Direct removal of the pathogenic protein could reduce endothelial injury.
- Blood-pressure improvement: The pilot trial showed a mean arterial pressure reduction after apheresis, correlated with sFlt-1 reduction.

- Delay in disease progression: If repeated sessions stabilize disease, delivery may be safely deferred [17].
- Reduced severe maternal complications: This remains hypothetical until controlled trials measure outcomes such as eclampsia, HELLP syndrome, pulmonary edema, stroke, renal injury, and ICU admission [18].
- Reduced need for extreme emergency delivery: Stabilization may allow planned delivery in a controlled setting.

However, this therapy must never be interpreted as a reason to delay delivery when maternal deterioration is present. It should be evaluated as an adjunct to expert maternal-fetal care, not as a replacement for established safety thresholds [19].

9. POTENTIAL FETAL AND NEONATAL BENEFITS

The fetal benefit is mainly indirect: pregnancy prolongation. In very preterm gestations, additional time in utero may allow fetal lung maturation, weight gain, improved thermoregulation, improved feeding readiness, and reduced neonatal intensive care complications.

Table 02: Potential neonatal benefits may include

Potential benefit	Clinical reasoning
Higher gestational age at birth	Reduces prematurity-related morbidity
Increased birth weight	May improve neonatal resilience
Completion of antenatal corticosteroids	Reduces respiratory distress syndrome
Time for magnesium sulfate neuroprotection	May reduce cerebral palsy risk in very preterm birth
Transfer to tertiary center	Improves access to neonatal intensive care
Avoidance of crash delivery	May reduce birth trauma and instability

The 2026 pilot trial reported that neonatal birth weights generally remained stable or increased among pregnancies with the longest extensions, but it was not powered to prove neonatal benefit.

10. SAFETY CONSIDERATIONS

Safety is the central issue because any pre-eclampsia treatment affects two patients: mother and fetus. Although apheresis avoids direct fetal drug exposure, it still carries procedural risks.

Table 03: Possible concerns include

Safety concern	Explanation
Vascular access complications	Bruising, bleeding, infection, thrombosis
Hypocalcemia	Citrate anticoagulation during apheresis may lower calcium
Hemodynamic instability	Fluid shifts may affect maternal or uteroplacental circulation
Fetal monitoring concerns	Uteroplacental perfusion must remain stable
Rebound sFlt-1	Placenta may continue producing sFlt-1 after treatment
Resource intensity	Requires trained staff, equipment, and tertiary-care setting
Delayed delivery risk	Treatment must not mask clinical deterioration

The pilot trial's adverse events were mild, but the sample size was small. Therefore, rare maternal or fetal harms cannot yet be excluded.

11. CLINICAL IMPLEMENTATION FRAMEWORK

Before targeted sFlt-1 removal can be considered for routine use, it should pass through a careful implementation pathway.

Step 1: Patient selection

Ideal candidates in future trials may include women with:

- singleton pregnancy;
- very preterm pre-eclampsia, especially before 34 weeks;
- high sFlt-1 or high sFlt-1/PlGF ratio;
- stable maternal status at enrollment;
- fetal status compatible with expectant management;
- access to tertiary maternal-fetal and neonatal care.

Step 2: Exclusion of unsafe cases

Therapy should not delay delivery in cases of:

- uncontrolled severe hypertension;
- eclampsia;
- pulmonary edema;
- severe renal or liver deterioration;
- HELLP syndrome with worsening labs;
- placental abruption;
- non reassuring fetal status;
- absent neonatal survival expectation;
- maternal refusal or inability to consent.

Step 3: Biomarker-guided monitoring

A future protocol should include serial:

- sFlt-1;
- PlGF;
- sFlt-1/PlGF ratio;
- blood pressure;
- platelet count;
- liver enzymes;
- creatinine;
- urine protein;
- fetal growth and Doppler studies;
- neonatal outcomes after birth.

Step 4: Delivery endpoints

The goal should be safe prolongation, not indefinite pregnancy extension. Delivery must occur when maternal or fetal risk exceeds the benefit of continuing pregnancy.

12. VALUE-ADDED PROPOSED MODEL

Table 04: A future precision-treatment model for preterm pre-eclampsia may look like this:

Disease stage	Biomarker profile	Preferred approach
Suspected pre-eclampsia	Low sFlt-1/PlGF	Outpatient or reduced-intensity monitoring if clinically safe

Confirmed preterm disease, stable	Moderate-high sFlt-1/PlGF	Inpatient surveillance, antihypertensives, corticosteroids
Very preterm disease, high sFlt-1, stable	Very high sFlt-1/PlGF	Consider trial-based sFlt-1 removal or metformin protocol
Severe maternal/fetal deterioration	Any biomarker level	Stabilization and delivery
Postpartum phase	Declining placental biomarkers	Maternal cardiovascular follow-up

This model recognizes that not every patient with pre-eclampsia will benefit from the same therapy. The best future approach is likely to be biomarker-guided, gestational-age-specific, and resource-sensitive.

13. ETHICAL AND HEALTH-SYSTEM CONSIDERATIONS

Targeted sFlt-1 removal raises important ethical questions. In high-income settings, advanced apheresis technology may be available in tertiary centers. In low- and middle-income settings, where pre-eclampsia mortality is often higher, access may be limited. If the treatment is expensive or infrastructure-dependent, it could widen global disparities unless simplified, scaled, and evaluated in diverse healthcare systems. There is also an ethical balance between maternal safety and fetal benefit. Pregnancy prolongation is valuable only if maternal risk remains acceptable. Any future trial must have strict stopping rules, independent safety monitoring, and clear maternal-priority decision-making.

14. CONCLUSION

Preterm pre-eclampsia remains a major cause of maternal and neonatal morbidity because the only definitive cure is delivery, which often results in medically indicated preterm birth. Recent advances in angiogenic biology have created a realistic pathway toward disease-modifying therapy. The 2026 first-in-human pilot trial of selective sFlt-1 removal by antibody-based apheresis is one of the most important translational developments in preterm pre-eclampsia treatment. It showed that targeted depletion of circulating sFlt-1 is technically feasible, appeared safe and well tolerated in a small group, and may help stabilize maternal disease long enough to prolong pregnancy. Metformin also remains a promising low-cost candidate, while esomeprazole, statins, sulfasalazine, and RNA-based approaches require further evidence. The future of preterm pre-eclampsia treatment is likely to be biomarker-guided and individualized. The most clinically valuable approach will not simply be to lower blood pressure, but to identify the biological driver of disease, select the right patient, intervene at the right time, and prolong pregnancy only when it is safe for the mother. If larger controlled trials confirm benefit, targeted sFlt-1 removal could become a landmark therapy that benefits both mother and child.

AUTHOR CONTRIBUTION STATEMENT

Ahmad Firdaus & Nur Aisyah Rahman: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work, Drafting the work or reviewing it critically for important intellectual content; AND Final approval of the version to be published, and Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Data Availability: The datasets and information used in this study are publicly available from the sources cited within the article. No proprietary or restricted data were used.

Trial Registration: Trial registration is not applicable to this study, as it does not involve clinical trials, human participants, or experimental interventions.

Generative AI Disclosure: Generative artificial intelligence tools were not used for generating research data, conducting analyses, or producing scientific conclusions in this study. The authors take full responsibility for the content and accuracy of the manuscript.

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SUPPLEMENTAL MATERIAL

No supplementary files, datasets, figures, or additional materials are associated with this study. Any information necessary to understand and evaluate the work is included in the main article.