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[Nytta och risker med angiogena markörer vid klinisk handläggning av misstänkt prematur preeklampsi]

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1 Abstract

Background Pre-eclampsia is a clinical syndrome of pregnancy defined by maternal hypertension in combination with organ dysfunction and is associated with increased maternal and perinatal morbidity and mortality. Suspicion of preeclampsia may require hospitalisation and monitoring before the diagnosis can be confirmed or ruled out. Placental angiogenic markers, including placental growth factor (PlGF) and soluble Feline McDonough Sarcoma-like tyrosine kinase-1 (sFlt-1), in maternal blood have been associated with pre-eclampsia but the clinical value of these analyses remains unclear.

Question at issue Can the use of information on angiogenic markers (sFlt-1/PlGF ratio or PlGF alone) in the management of women with suspected pre-eclampsia between 20+0 and 36+6 weeks of gestation: 1) reduce maternal or offspring morbidity or mortality; 2) shorten time to diagnosis of pre-eclampsia; 3) reduce time to discharge or return to standard antenatal care; 4) decrease hospital admissions; or 5) improve quality of life?

Methods A systematic literature search was conducted in Medline, Embase, the Cochrane Library, and the Web of Science Core Collection. Two authors screened titles and abstracts. Full-text articles were assessed by at least two authors before final inclusion by consensus. Studies were critically appraised, results summarised by outcome, and meta-analyses performed when possible. Randomised controlled trials (RCTs) and stepped-wedge cluster randomised trials (SW-CRTs) were pooled in meta-analyses. Odds ratios (ORs) and risk differences (RDs) were calculated, and the certainty of evidence was assessed using GRADE.

Results Two RCTs, two SW-CRTs and one cohort study were included comprising 450, 3,238, and 683 women, respectively.

Maternal outcomes: Meta-analysis of two RCTs and two SW-CRTs showed no statistically significant effect of angiogenic marker testing on the frequency of pre-eclampsia diagnosis (OR 1.00, 95% confidence interval (CI) 0.85-1.17; GRADE ⊕⊕⊕O). Across the two SW-CRTs, no significant difference was observed in composite maternal morbidity (adjusted OR 0.66, 95% CI 0.20–2.18; GRADE ⊕⊕OO). One RCT reported no statistically significant difference in hospital admissions between the intervention and control groups (GRADE ⊕⊕OO). The effect of testing for angiogenic markers was uncertain for the remaining maternal outcomes including time to pre-eclampsia diagnosis (GRADE ⊕OOO).

Perinatal/neonatal outcomes:

No difference was found for the composite outcome neonatal morbidity (adjusted OR 1.55, 95% CI 0.94–2.55) based on the two SW-CRTs, low certainty of evidence (GRADE ⊕⊕OO). There was no difference observed in gestational age at delivery, risk of birth weight deviation, and admission to neonatal unit (GRADE ⊕⊕⊕O). Likewise, there was no difference in respiratory disease (GRADE ⊕⊕OO). For the remaining neonatal outcomes, the effect was uncertain.

Economic aspects The annual implementation costs (including testing of approximately 600 patients annually) in Region Västra Götaland (VGR) were estimated to approximately 240,000 SEK for PlGF and 475,000 SEK for sFlt-1/PlGF. Potential cost savings related to

clinical benefits or reduced healthcare utilisation could not be assessed, as no clear effects were identified.

Ethical aspects Improved risk stratification and clinical management of pre-eclampsia are needed. However, as no clear clinical or resource-related benefits of angiogenic marker-guided management were demonstrated, the current evidence base does not support a favourable benefit-risk balance for this strategy.

Conclusion Our literature review does not support a positive effect on maternal or perinatal outcomes, time to pre-eclampsia diagnosis or use of health care resources, for the management of women with suspicion of pre-eclampsia by testing with angiogenic markers compared with standard management. Further research is motivated based on low certainty of evidence for several outcomes.

2 Populärvetenskaplig sammanfattning – Plain language summary in Swedish

Frågeställning Kan blodprov med så kallade angiogena markörer hos kvinnor med icke fullgången graviditet och misstanke om preeklampsi (havandeskapsförgiftning) möjliggöra snabbare diagnos och tidigare behandling, och därigenom reducera dödlighet, sjuklighet eller vårdbehov hos moder och barn?

Bakgrund Preeklampsi är en graviditetskomplikation som inträffar i samband med 3–5% av alla graviditeter i Sverige och som kan orsaka allvarlig sjuklighet hos både moder och barn. Tillståndet kan vara svårt att upptäcka i tidigt skede och det krävs ofta upprepade kontroller för att en diagnos skall kunna ställas. Angiogena markörer är ämnen i blodet som speglar moderkakans funktion. Analys av angiogena markörer i blodprov skulle kunna förbättra riskbedömning och diagnostik vid misstänkt preeklampsi. Det är dock oklart om utfall för mor och barn kan påverkas genom att införa dessa tester i kliniskt arbete.

Metod Vi gjorde en systematisk genomgång av vetenskaplig litteratur och identifierade studier som var relevanta för frågeställningen. Studiernas kvalitet granskades och resultaten sammanställdes med vedertagna metoder för systematiska litteraturöversikter.

Resultat Vi identifierade fem studier som jämförde vård med och utan testning av angiogena markörer. Den samlade bedömningen visar att tillägg av analys av angiogena markörer i handläggningen av patienter med misstänkt preeklampsi sannolikt inte, eller möjligen bara i liten utsträckning, ändrar andelen patienter som diagnosticeras med preeklampsi. För tid från klinisk misstanke till ställd diagnos gav studierna olika resultat, och det är därför oklart om testningen påverkar detta. För övrig sjuklighet hos modern bedömdes effekten som möjligen ingen eller liten (medicinska komplikationer, behov av inläggning på sjukhus) eller osäker (dödlighet, graviditetskramper, blindhet orsakad av påverkan på hjärnan, näthinneavlossning, vätska i lungorna, njurskada, leverkapselblödning, behov av intensivvård och respiratorvård, antal slutenvårdsdygn samt antal återbesök). Sammanvägd analys visade att effekten för barnet sannolikt (graviditetslängd vid förlossning, risk för låg födselvikt och behov av inläggning på neonatalenhet) eller möjligen (sammanvägt mått på komplikationer och lungkomplikationer) var ingen eller liten. Effekten på dödlighet, hjärnblödning och tarminflammation hos barnet bedömdes som osäker.

Etiska aspekter Åtgärder som kan minska sjukdomsbördan vid preeklampsi är angelägna. Vår litteratursammanställning visade ingen tydlig klinisk nytta av att mäta angiogena markörer och stöd saknas därmed för en positiv nytta-risk-balans.

Ekonomi Den årliga kostnaden för att införa testerna i VGR uppskattas till cirka 240 000 SEK för PlGF och 475 000 SEK för sFlt-1/PlGF, inklusive analys av omkring 600 patienter per år. Eventuella besparingar i vården kunde inte bedömas eftersom studierna inte visade några tydliga kliniska effekter.

Slutsats Vår litteratursammanställning ger inget stöd för att tillägg av angiogena markörer i handläggningen av patienter med misstänkt preeklampsi skulle påverka tid till

diagnos eller kliniska utfallsmått för moder eller barn. Ytterligare forskning inom området är motiverad mot bakgrund av att bedömningen av flera utfallsmått är osäker.

The above summaries were written by representatives from HTA-centrum. The HTA report was approved by the regional board for quality assurance of activity-based HTA.

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DDS = Doctor of Dental Surgery
MD = Medical Doctor
PhD Doctor of Philosophy
RN = Registered Nurse
RM = Registered Midwife
SLT = Speech-Language Therapist

3 Summary of findings

Outcome	Number of studies[a] per study design, Number of participants	Odds ratio (95% CI)	Absolute Effect I=intervention C=control	Certainty of evidence* GRADE
Maternal outcomes				
Mortality	**2 SW-CRTs** n=3238 1 non-RCT n=683	No meta-analysis performed	I: 0.6/1000[7] C: 0/1000[7].	⊕OOO [1]
Maternal morbidity (composite outcome)	1 RCT, n=80 **2 SW-CRTs** n=3238 1 non-RCT n=683	aRR/OR[b] 0.66 (0.20 to 2.18), n.s.[7]	I: 81/1000[7] C: 94/1000[7]	Little or no difference ⊕⊕OO [3]
Diagnosis of pre-eclampsia	**2 RCTs** n=450 **2 SW-CRTs** n= 3238 1 non-RCT N=683	1.00 (0.85 to 1.17), n.s.[9]	I: 220/1000[9] C: 204/1000[9]	Little or no difference ⊕⊕⊕O [2]
Eclampsia	**1 RCT** n=80 **2 SW-CRTs** n=3238 1 non-RCT n=683	Peto OR: 0.13 (0.02 to 0.91), p=0.04	I: 0/1000[10] C: 2.4/1000[10]	⊕OOO [1]
Stroke	**1 RCT** n=80 **2 SW-CRTs** n=3238 1 non-RCT n=683	Peto OR 0.43 (0.04 to 4.19), n.s.	I: 0.6/1000[10] C: 1.2/1000[10]	⊕OOO [1]
Placental abruption	**1 RCT** n=80 **2 SW-CRTs** n=3238 1 non-RCT n=683	0.66 (0.31 to 1.41), n.s.	I: 6.7/1000[10] C: 10.1/1000[10]	⊕OOO [1]
Time to pre-eclampsia diagnosis	**1 RCT** n=370 **2 SW-CRTs**	No meta-analysis performed	RCT: I:7 vs C: 9.5 days n.s.	⊕OOO [4]

	n=3238		SW-CRT 1: I: 1.9 vs C: 4.1 days, p=0.027 SW-CRT 2: I:8 vs C:7 days n.s.	
Admission to hospital care	**1 RCT** n=370	N/A	Pre-eclampsia related admissions within 7 days of the test: I: 70/186 (37.6%) C: 65/184 (35.3%)	Little or no difference ⊕⊕OO [5]
Perinatal/neonatal outcomes				
Perinatal/neonatal mortality	**1 RCTs** n=80 **2 SW-CRTs** n=3238 1 non-RCT n=732	0.70 (0.34 to 1.40), n.s.	I: 8.6/1000[10] C: 12.4/1000[10]	⊕OOO [1]
Composite perinatal/neonatal outcome	2 RCTs n=450 **2 SW-CRTs** n=3238 1 non-RCT n=732	aRR/OR[b] 1.55 (0.94 to 2.55), n.s.[7]	I: 10.9/1000[7] C: 9.0/1000[7]	Little or no difference ⊕⊕OO [3]
Intra-ventricular haemorrhage	**2 SW-CRTs** n=3238 1 non-RCT, n=732	Any grade: 0.52 (0.24 to 1.14), n.s.[7]	I: 6.3/1000[7] C: 10.3/1000[7]	⊕OOO [1]
Necrotising enterocolitis	**2 SW-CRTs** n=3238 1 non-RCT n=732	1.10 (0.40 to 3.05), n.s.[7]	I: 6.9/1000[7] C: 5.5/1000[7]	⊕OOO [1]
Respiratory disease	**2 SW-CRTs** n=3238 1 non-RCT n=732	Respiratory distress syndrome 1.14 (0.89 to 1.45) n.s.[7]	I: 97/1000[7] C: 81/1000[7]	Little or no difference ⊕⊕OO [6]
Admission to neonatal unit	**2 RCTs** n=450 **2 SW-CRTs** n=3238 1 non-RCT n=732	1.03 (0.89 to 1.18), n.s.[9]	I: 343/1000[9] C: 334/1000[9]	Little or no difference ⊕⊕⊕O [2]

Gestational age at delivery	**1 RCT** n=370 **2 SW-CRTs** n= 3238 1 RCT n=80 1 non-RCT n=732	N/A	Risk difference: I vs C: -0.01 (-0.20 to 0.18) weeks, n.s.	Little or no difference ⊕⊕⊕O [2]
Small for gestational age (<10th or 5th centile)	2 RCTs n=450 2 SW-CRTs n=3238 1 non-RCT n=732 (meta-analysis based on 1 RCT and 1 SW-CRT)	Birth weight <10th centile 0.99 (0.76 to 1.28), n.s.[8]	I: 205/1000[8] C: 204/1000[8]	Little or no difference ⊕⊕⊕O [2]

Footnotes: aRR/OR, adjusted risk ratio/odds ratio; *CI*, confidence interval; *SW-CRT*, stepped-wedge cluster randomised trial; *RCT*, randomised controlled trial.

[a] Studies contributing to the meta-analysis or reporting relative or absolute effects are highlighted in bold.

[b]Adjusted for time and study site.

[1] Starting from ⊕⊕⊕⊕ downgraded one step for serious to very serious study limitations, and two steps for very serious imprecision

[2] Starting from ⊕⊕⊕⊕ downgraded one step for serious to very serious study limitations

[3] Starting from ⊕⊕⊕⊕ downgraded one step for serious to very serious study limitations, and one step for some limitations regarding directness and precision

[4] Starting from ⊕⊕⊕⊕ downgraded one step for serious to very serious study limitations, two steps for serious inconsistency, one step for serious imprecision, also some indirectness

[5] Starting from ⊕⊕⊕⊕ downgraded one step for serious to very serious study limitations, one step for serious imprecision, also some indirectness

[6] Starting from ⊕⊕⊕⊕ downgraded one step for serious to very serious study limitations, and one step for serious imprecision

[7] Meta-analysis based on the two SW-CRTs (Hayes Ryan, 2021a and Duhig, 2019a)

[8] Meta-analysis based on one RCT and one SW-CRT (Cerdeira, 2019 and Duhig, 2019a)

[9] Meta-analysis based on two RCTs (Cerdeira, 2019 and Sibiude, 2025) and two SW-CRTs (Duhig, 2019a and Hayes Ryan, 2021a)

[10] Meta-analysis based on one RCT (Sibiude, 2025) and two SW-CRTs (Duhig, 2019a and Hayes Ryan, 2021a)

* Certainty of evidence

High certainty ⊕⊕⊕⊕: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty ⊕⊕⊕O: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different to the estimate of the effect.

Low certainty ⊕⊕OO: Confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.

Very low certainty ⊕OOO: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

4 Abbreviations

ANC — Antenatal Care
AGNES — Antenatal Care Unit in Gothenburg providing subacute appointments for pregnant and postpartum women
ARR — Adjusted Risk Ratio
CI — Confidence Interval
FGR — Fetal Growth Restriction
HELLP — Hemolysis, Elevated liver enzymes, Low platelet count
ICU — Intensive Care Unit
NICE — National Institute for Health and Care Excellence
NICU — Neonatal Intensive Care Unit
NÄL — Norra Älvsborgs Sjukhus
OR — Odds Ratio
PE — Pre-eclampsia
PlGF — Placental Growth Factor
RCT — Randomised Controlled Trial
RCF — Relative Centrifugal Force
RR — Risk Ratio
sFlt-1 — Soluble Feline McDonough Sarcoma (fms)-like tyrosine kinase 1
SFOG — Svensk Förening för Obstetrik och Gynekologi
SkaS — Skaraborgs Sjukhus Skövde
SW-CRT — Stepped-wedge Cluster Randomised Trial
SÄS — Södra Älvsborgs Sjukhus
UK — United Kingdom
USA — United States of America
VGR — Region Västra Götaland [Västra Götalandsregionen]

5 Background

Disease/disorder of interest and its degree of severity

Pre-eclampsia is a pregnancy-specific disorder that occurs after 20 weeks of gestation and is characterised by maternal hypertension and organ dysfunction, including renal, hepatic, and neurological or haematological involvement, as well as fetal growth restriction (Chappell et al., 2021). It is associated with placental dysfunction and may be asymptomatic; therefore, in high-income countries, pre-eclampsia is often detected through routine antenatal screening.

If left untreated, pre-eclampsia may progress to eclampsia, HELLP (haemolysis, elevated liver enzymes and low platelets) syndrome, stroke, liver rupture, acute kidney failure or pulmonary oedema, all of which may be life-threatening (NICE 2022; Souza et al., 2013). Pre-eclampsia and eclampsia are major contributors to maternal mortality and morbidity globally. In Sweden, pre-eclampsia accounts for approximately one maternal death per 100,000 births annually (SFOG, 2019).

Delivery of the fetus and placenta is the only definitive treatment for pre-eclampsia, which poses a clinical challenge when the condition occurs preterm. Pre-eclampsia can be categorised by gestational age at onset. Women with early-onset disease (at <34 weeks of gestation) are more likely than women with late-onset disease (at ≥34weeks of gestation) to have end-organ involvement and associated fetal growth restriction. In most settings, conservative management is recommended until 37 weeks of gestation provided that maternal and fetal conditions are not deteriorating.

As pre-eclampsia is a heterogeneous clinical syndrome, many women who are suspected of having the disease undergo repeated examinations before diagnosis. Reliable tests with the ability to support clinical assessment to confirm or rule out pre-eclampsia are therefore of clinical importance to enable timely diagnosis while avoiding unnecessary follow-up in low-risk women. Evidence suggests that angiogenic biomarker tests have greater value for ruling out than ruling in pre-eclampsia, with high negative predictive values at lower cut-offs, while positive predictive values for ruling in disease ranged from 46% to 100% depending on the test, cut-off, and predicted outcome (NICE, 2022). The rationale for angiogenic marker testing is that improved identification of women at low or high risk of developing pre-eclampsia may guide clinical management. A test indicating low risk may reduce the need for hospital admission, repeated investigations, and monitoring, whereas a result indicating high risk may prompt closer surveillance, earlier diagnosis, and timely intervention. Thus, any clinical benefit of testing is expected to occur indirectly by supporting clinical decision-making. In recent years, blood tests reflecting placental function, i.e., the angiogenic factors placental growth factor (PlGF) and soluble Feline McDonough Sarcoma (fms)-like tyrosine kinase 1 (sFlt-1), have been investigated in clinical trials in the assessment of suspected pre-eclampsia before 37 weeks of gestation and testing in clinical practice is currently recommended in some countries (NICE, 2022; Ziesler et al., 2016).

Prevalence and incidence

Pre-eclampsia affects approximately 3-5% of all pregnancies and in about 1% of cases the pre-eclampsia can be defined as preterm (before 37 weeks of gestation) (Chappell et al., 2021). The prevalence of suspected pre-eclampsia is unknown, as it is not defined as a distinct entity within the International Classification of Diseases (ICD).

In Sweden, there were approximately 97,500 births in 2025 (Statistics Sweden, 2026), with around 5,000 cases of pre-eclampsia diagnosed annually (SBU, 2023). In Region Västra Götaland, 930 women were diagnosed with pre-eclampsia in 2025 and approximately 140 preterm births related to pre-eclampsia or hypertensive disorders (Regional Health Care Analysis Unit VGR).

Globally, pre-eclampsia accounts for an estimated 42,000 maternal deaths annually (Chappell et al., 2021). In Sweden, maternal mortality related to pre-eclampsia, eclampsia, and HELLP syndrome is rare, with 10 reported cases over a 10-year period (Grunewald et al., 2019).

Present treatment

First-trimester assessment is based on maternal risk factors to identify women at high risk of pre-eclampsia, for whom prophylactic low-dose acetylsalicylic acid is recommended from 12 to 36 weeks of gestation or until disease onset (SFOG, 2019). There is no treatment to halt disease progression. Delivery of the placenta, and therefore the baby, is the only definitive treatment. At ≥37 weeks, induction of labour is recommended, while management before 37 weeks is individualised with close maternal and fetal monitoring. Treatment focuses on preventing complications, including antihypertensive therapy, magnesium sulfate for seizure prophylaxis, and fluid restriction in severe cases (SFOG, 2019).

The normal pathway through the healthcare system and current wait time for medical assessment/treatment

Most pregnant women in Sweden attend antenatal care, which includes routine blood pressure monitoring for early detection of gestational hypertension and pre-eclampsia. The standard programme comprises up to ten midwife visits throughout pregnancy. Women presenting with elevated blood pressure, with or without symptoms, undergo further assessment including urinary dipstick testing for proteinuria and blood tests to evaluate organ involvement. They are often referred for obstetric review, either in outpatient care or as inpatients depending on severity.

Women with moderately elevated blood pressure (140–159/90–109 mmHg) without symptoms of pre-eclampsia are assessed by an obstetrician within 24 hours, with a plan for reassessment within a few days, including repeated blood pressure measurements.

If a woman presents with severe symptoms of suspected pre-eclampsia, she is usually admitted to the hospital. The admission can last for 24 hours or until birth and postpartum.

Number of patients per year who undergo current treatment regimen 2024 and 2025, there were 16,713 and 16,578 births, respectively, in VGR with approximately 55% occurring at Sahlgrenska University Hospital. In 2024, 135 women were diagnosed with pre-eclampsia in hospital care in VGR, with an additional 630 cases recorded in antenatal care and 165 in primary care (Regional Health Care Analysis Unit, VGR).

As angiogenic marker testing is not currently used in VGR and no specific diagnostic code exists for suspected pre-eclampsia, a retrospective chart review was conducted to estimate the number of women with suspected pre-eclampsia (see economic aspects, page 38).

Present recommendations from medical societies or health authorities

The Swedish Society of Obstetrics and Gynecology (SFOG) does not currently recommend routine use of angiogenic markers (PlGF or sFlt-1) in women with suspected pre-eclampsia. However, testing has been implemented for suspected pre-eclampsia at Linköping University Hospital since 2021, where it has been used 145 times between 2021 and 2024. Linköping University Hospital has approximately 2,000 births annually. In contrast, UK guidelines recommend the use of PlGF and sFlt-1 testing in women with suspected preterm pre-eclampsia, as an adjunct to standard care, to support clinical decision-making and reduce unnecessary hospital admissions (NICE, 2022).

6 Health Technology at issue: Use of angiogenic markers in clinical management of suspected pre-eclampsia

This HTA report compares standard antenatal care plus blood-based testing of angiogenic factors (PlGF and sFlt-1) with standard antenatal care alone. The research question includes testing on any type of blood-based analytical platforms for PlGF and sFlt-1 but excludes urine-based tests. The relevant testing window is between 20+0 and 36+6 weeks of gestation; first or early second trimester testing was not considered within the scope of this report.

Several analytical platforms are available for biomarker assessment. In Region Västra Götaland, the technical platforms required for analysis of PlGF and sFlt-1 are already available at the larger hospitals (Sahlgrenska University Hospital, Södra Älvsborg Hospital and Skaraborg Hospital Skövde). However, implementation would require local set-up of the analyses, including validation procedures and procurement of reagents.

7 Focused question

Can the use of information on angiogenic markers (sFlt-1/PlGF ratio or PlGF alone) in the management of women with suspected pre-eclampsia between 20+0 and 36+6 weeks of gestation: 1) reduce maternal or offspring morbidity or mortality; 2) shorten time to diagnosis of pre-eclampsia; 3) reduce time to discharge or return to standard antenatal care; 4) decrease hospital admissions or 5) improve quality of life?

PICO	
P	Women with suspected pre-eclampsia between 20+0 to 36+6 weeks of gestation
I	Measurement of angiogenic markers sFlt-1/PlGF, or PlGF only, in addition to standard care
C	Standard care alone (with no or concealed measurement of angiogenic markers, sFlt-1/PlGF or PlGF)
O	**<u>Critical for decision-making</u>** **Maternal** • Maternal mortality • Composite maternal morbidity (as defined by the authors) **Neonatal** • Neonatal mortality • Stillbirth • Composite neonatal morbidity (as defined by the authors) **<u>Important for decision-making:</u>** **Maternal** • Diagnosis of pre-eclampsia • Maternal morbidity (assessed as individual outcomes* according to the core outcome set for pre-eclampsia in Duffy et al. (2020): eclampsia, stroke, cortical blindness, retinal detachment, pulmonary oedema, acute kidney injury, liver capsule haematoma or rupture, placental abruption, postpartum haemorrhage, admission to intensive care unit, and intubation and mechanical ventilation [not for childbirth]) • Time to pre-eclampsia diagnosis • Return to standard antenatal care • Admission to hospital care • Quality of life **Neonatal** • Neonatal morbidity (assessed as individual outcomes*: intracranial haemorrhage, necrotising enterocolitis, neonatal seizures, respiratory support, breathing difficulties, chronic lung disease, late-onset infection, admission to neonatal unit, gestational age at delivery, birth weight and

	small for gestational age (SGA), neonatal unit length of stay, neonatal resuscitation, preschool developmental delays)

* Most individual outcomes are encompassed within the composite outcomes. However, certain outcomes, such as eclampsia, are clinically critical but relatively rare; therefore, they were classified as important outcomes rather than included as standalone critical outcomes.

NICE HealthTech guidance (2022) is based on a systematic review by Frampton et al. (2021). The present report was based on relevant studies included in that review, complemented by an updated literature search for publications from 2021 onwards in English, Swedish, Norwegian or Danish. Study designs considered eligible were RCTs (irrespective number of patients) and cohort studies (with more than 500 patients in total) as well as systematic reviews published 2022 or later. Relevant studies included in the NICE HealthTech Guidance and published prior to 2021 were also eligible for inclusion.

If applicable, the following subgroup analyses were planned:

- Stratification for singleton or multifetal pregnancy
- Stratification for different test types (sFlt-1/PlGF, or only PlGF)
- Subgroup analysis of pregnancies 20+0 to 33+6 weeks of gestation (excluding pregnancies 34+0 to 36+6 weeks of gestation)
- Subgroup analysis of RCT without trustworthiness concerns according to published evaluation tools (INSPECT-SR (Wilkinson et al., 2025) or similar)

8 Method

Systematic literature search (Appendix 1)

During September 2025 and with an update in February 2026, two of the authors (TS, EMN), both medical librarians experienced in systematic review searching, performed literature searches in the following databases: Medline, Embase, the Cochrane Library and the Web of Science Core Collection. Search strategies were based on the strategies used in Frampton et al. (2021) (recently republished in an edited version by Shepherd et al., 2026). Additionally, a citation search of relevant reports was performed in Web of Science, and references in the NICE HealthTech Guidance (NICE, 2022) were also reviewed manually. Search strategies,eligibility criteria and a graphic presentation of the selection process are presented in Appendix 1. These authors conducted the literature searches, and independently of one another screened the obtained abstracts to decide eligibility for full-text retrieval. All abstracts were screened using the Rayyan tool (Ouzzani et al., 2016). Any disagreements were resolved by consensus. All full-text reports were read by at least two authors, independently of one another, and it was finally decided in a consensus meeting which reports should be included in the assessment.

Critical appraisal and certainty of evidence

For included studies, relevant data were extracted by one author and confirmed by at least one other author, with discrepancies resolved by consensus. The included articles were independently appraised regarding the domains of directness, risk of bias and precision. Depending on the study design different checklists were applied for RCTs or non-RCTs. These checklists were developed by HTA-centrum, Sahlgrenska University Hospital, based on checklists by the Swedish Agency for Health Technology Assessment and Assessment of Social Services. Consensus discussions were held to agree on the assessment of each study regarding directness, study limitations (risk of bias), and precision, in the categories + (no or minor problems), ? (some problems), and – (major problems). The assessments are summarised in Appendix 5. Systematic reviews were critically appraised using the AMSTAR 2 critical appraisal tool (Shea et al., 2017). Trustworthiness of included randomised controlled trials was assessed using the INSPECT SR tool (Wilkinson et al., 2025).

If two or more studies provided count data that could be pooled, random effects meta-analyses were performed to obtain odds ratios (OR), and risk difference (RD) including 95% confidence intervals (CI) and corresponding forest plots. We considered combination of OR based on crude values from RCTs and ORs adjusted for time and cluster from stepped-wedge cluster randomised trials (SW-CRTs) in the same meta-analysis as justified (Higgins, Eldridge and Li, 2024). In the identified SW-CRTs, adjusted ORs or risk ratios (RR) from both SW-CRTs were only available for the composite outcomes of maternal morbidity and neonatal morbidity and gestational age at delivery. For remaining outcomes, at least one SW-CRT did not report adjusted OR or RR. To generate pooled estimates using comparable effect measures across studies while recognizing differences in study design, we included crude data when adjusted ORs or RRs were unavailable for all SW-CRTs and conducted separate subgroup analyses for RCTs and SW-CRTs. Adjusted ORs were assumed to approximate adjusted RRs sufficiently for pooled analysis when the outcome was rare (commonly defined as an event rate of approximately <10%). The Peto OR method was used for meta-analyses of rare events when studies reported zero events in one treatment arm (Higgins, 2023). For continuous data, weighted mean differences were calculated using random effect model. Analyses were performed using Review Manager 5.4 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). For meta-analyses of adjusted OR/RR and mean differences, Stata version 19.5 (StataCorp LLC, College Station, TX, USA) was used. The certainty of evidence was assessed according to GRADE (Atkins et al., 2004), with reasons for downgrading described. Summary results per outcome and the associated certainty of evidence are presented in a Summary-of-findings table (pages 9-12).

This HTA was registered in the International prospective register of systematic reviews (PROSPERO) in January 2026 (CRD420251245859) prior to the start of data extraction. Compared with the registered protocol, neonatal mortality and stillbirth were not reported separately but integrated in the outcome peri/neonatal mortality instead.

Ongoing research

A search in clinicialtrials.gov (23 Jan 2026) using the search terms *(pre-eclampsia OR pre-eclamptic OR preeclampsia OR preeclamptic OR pre-clampsia OR pre-clamptic OR preclampsia OR preclamptic OR toxemia OR toxaemia OR gestosis OR hypertension OR hypertensive) AND (Placenta growth factor OR Placental growth factor OR PlGF OR Vascular Endothelial Growth Factor Receptor-1 OR VEGFR1 OR VEGFR 1 OR fms-like tyrosine kinase or FLT 1 or sFLT 1 or FLT1 or sFLT1 OR alere OR BRAHMS OR DELFIA OR elecsys OR kryptor OR perkinelmer OR quidel OR roche OR thermo OR thermofisher OR xpress)* identified 364 trials.

9 Results

Search results and study selection (Appendix 1)

The literature search identified 3,277 records after the removal of duplicates. DedupEndNote (Lobbestael, 2023) was used for deduplication. After reading the abstracts, 3,145 records were excluded. 124 reports were excluded after full-text reading, and five were finally included in the assessment (Appendix 2). In addition, three systematic reviews (SR), and one health economy study were commented upon.

Included studies

The five studies identified to meet the PICO were: two RCTs (Cerdeira et al., 2019 [INSPIRE]; Sibiude et al., 2025 [PRECOG]), two SW-CRTs (Duhig et al., 2019a [PARROT]; Hayes-Ryan et al., 2021a [PARROT Ireland]) and one cohort study (Sharp et al., 2018 [MAPPLE]). All studies were conducted in high-income countries that are comparable to Sweden; UK (Cerdeira et al., 2019; Duhig et al., 2019a), Ireland (Hayes-Ryan et al., 2021a), France (Sibiude et al., 2025), and in multiple countries (UK, Germany, Austria, and Australia) (Sharp et al., 2018). Four studies were multicentre and one RCT was conducted at a single tertiary hospital (Cerdeira et al., 2019). The cohort study compared clinical data from two different cohorts: MAPPLE (revealed testing group) and PELICAN (concealed testing group) (Sharp et al., 2018). The RCTs and SW-CRTs included only singleton pregnancies. The cohort study included both singleton and multifetal pregnancies (396 pregnancies/433 newborns in the revealed testing group and 287 pregnancies/299 newborns in the concealed testing group) and reported some results separately for singletons.

Population

All studies included women with suspected preterm pre-eclampsia based on standard clinical assessment (e.g. clinical signs, hypertension, proteinuria, abnormal blood tests, fetal growth restriction). Gestational age at inclusion ranged from 24+0 to 37+0 weeks (Cerdeira et al., 2019), 20+0 to 36+6 weeks (Duhig et al., 2019a; Hayes-Ryan et al., 2021a), 24+0 to 34+6 weeks (Sibiude et al., 2025), and before 35 weeks (Sharp et al., 2018).

Intervention

Across the included studies, testing involved either measurement of placental growth factor (PlGF) alone (Duhig et al., 2019a; Hayes-Ryan et al., 2021a; Sharp et al., 2018) or the soluble fms-like tyrosine kinase-1 to PlGF (sFlt-1/PlGF) ratio (Cerdeira et al., 2019, Sibiude et al., 2025). Duhig et al. (2019a) also evaluated outcomes stratified by PlGF level and Sibiude et al. (2025) by sFlt-1/PlGF ratio. In the intervention groups, test results were revealed to clinicians to be used to support clinical assessment and management (revealed testing group) but not as a sole indication for induction of birth or any other intervention. The comparator was standard clinical care without access to angiogenic biomarker test (concealed testing group). Repeated testing was not evaluated. In the studies included in this report, different analytical platforms and biomarker strategies were used. In one RCT (Cerdeira et al., 2019), the Roche e411 analyzer (Roche Diagnostics Limited, Burgess Hill, UK) was used to analyse the sFlt-1/PlGF ratio. A ratio at ≤38 indicated low risk and a ratio of >38 elevated risk of developing pre-eclampsia. Two studies (Duhig et al., 2019a; Hayes-Ryan et al., 2021a) used an automated Triage Meterpro (Quidel San Diego, CA, USA) to analyse PlGF level. Cut offs were: <12 pg/ml (highly abnormal) and 12-100 pg/ml (abnormal). Sharp et al. (2018), used the Triage System (Alere, San Diego, CA, USA), later bought by Quidel, and had the same cut off values for PlGF: PlGF <12 pg/ml (very low), 12-100 pg/ml (low), and >100 pg/ml (normal).

Directness, study limitations and precision

Two trials (Duhig et al., 2019a; Hayes-Ryan et al., 2021a) were considered to have no or minor problems with directness. In Duhig et al. (2019a), directness regarding ethnicity was unclear, frequency of aspirin use was higher than in Sweden, and no information was provided about non-participants. Cerdeira et al. (2019) had some concerns with directness because inclusion started at 24+0 weeks rather than 20+0 weeks, potentially excluding cases of early severe pre-eclampsia and the trial was confined to a single center. Sibiude et al. (2025) had major concerns with directness because only hospitalised patients were included and the number of screened patients was not given. Sharp et al. (2018) also had major concerns with directness due to inclusion of both suspected pre-eclampsia and intrauterine growth restriction before 35 weeks, and no information was provided about non-participants. The study-specific definitions of suspected preeclampsia are provided in Appendix 2.

All the included studies had some or high risk of bias. The RCT of Cerdeira et al. (2019) had some problems: the study protocol was published after study start, the trial was not blinded, not all outcomes defined in the protocol were reported, and the funder had reviewed the study protocol. The RCT of Sibiude et al. (2025) had some problems: the study was not blinded, the funder reviewed the study protocol, there was a long delay to publication (the study was conducted between 2018 and 2020 and published 2025), and there were errors in tables. Attempts were made to contact the authors to clarify the tables, however this was unfortunately unsuccessful. Two studies had some or major problems due to the stepped wedge cluster randomised trial design, with few clusters and lack of clarity on randomisation and no blinding of clinicians or participants (Duhig et al., 2019a; Hayes-Ryan et al., 2021a). Sharp et al. (2018) had

major problems including: absence of protocol, inclusion of two different cohorts, unclear reporting of loss to follow-up, lack of blinding and industry funding. Two studies did not reach prespecified sample size (Hayes-Ryan et al., 2021a, Sibiude et al., 2025).

Across the studies, precision varied for different outcomes. Duhig et al. (2019a) and Hayes-Ryan et al. (2021a) had no or minor problems with precision for their main outcomes (time to diagnosis of pre-eclampsia and composite maternal and neonatal outcomes, respectively). It is noted that one of these studies with stepped-wedge design recruited substantially more patients (Duhig et al., 2019a) and the other substantially less patients (Hayes Ryan et al., 2021a) than planned. Cerdeira et al. (2019) had some concerns for their main outcome (pre-eclampsia related admissions to hospital) due to unclear assumptions in sample size calculation. Sibiude et al. (2025) had large confidence intervals and Sharp et al. (2018) lacked power calculation.

Results per outcome

Outcomes critical for decision-making:

Maternal

Maternal mortality (Appendix 4.1)

Maternal mortality (follow-up to 12 weeks postpartum or not defined) in the revealed testing group compared with the concealed testing group was reported in two SW-CRTs with unclear or high risk of bias (Duhig et al., 2019a; Hayes-Ryan et al., 2021a) and one cohort study with high risk of bias (Sharp et al., 2018). Across the SW-CRTs, 1,590 participants were included in the revealed testing group and 1,648 in the concealed testing group. In SW-CRTs, one indirect late maternal mortality occurred in the revealed testing group of 10 weeks postpartum due to acute complications of a known underlying cardiac condition (crude event rate 0.06%). No maternal deaths were reported in the cohort study (396 participants in the revealed testing group and 287 in the concealed testing group).

Conclusion: It is uncertain whether add-on use of angiogenic markers affects maternal mortality compared to standard care without angiogenic markers. (GRADE ⊕OOO)

Composite maternal morbidity (Appendix 4.2, Figure 1, Supplementary Figures 1 and 2)

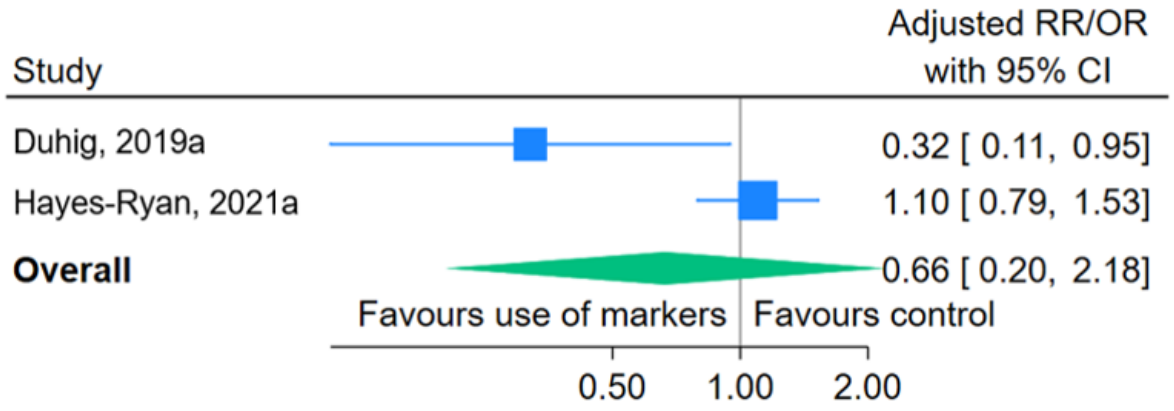
A composite outcome for maternal morbidity (see Appendix 4.2 for definition in each study) in the revealed testing group compared with the concealed testing group was reported in two SW-CRTs (Duhig et al., 2019a; Hayes-Ryan et al., 2021a) and one RCT (Sibiude et al., 2025) with unclear or high risk of bias and one cohort study with high risk of bias (Sharp et al., 2018). Due to differences in definition of the composite outcome variable, only two SW-CRTs with similar definitions (as defined by the fullPIERS-[Pre-eclampsia Integrated Estimate of RiSk] consensus (von Dadelszen et al., 2011)) were included in meta-analysis (Duhig et al., 2019a; Hayes-Ryan et al., 2021a). In Hayes-

Ryan et al. (2021a), the composite maternal outcome was a post hoc analysis conducted to facilitate comparison with Duhig et al. (2019a). Across the two SW-CRTs, 1,590 participants were included in the revealed testing group and 1,648 in the concealed testing group. The crude event rate across these trials was 8.1% in the revealed testing group and 9.4% in the concealed testing group. Meta-analysis of the SW-CRTs showed no significant difference between the two groups (adjusted OR/RR 0.66, 95% CI 0.20 to 2.18, Figure 1). The pooled weighted RD was -0.01 percentage points (95% CI -0.03 to 0.01).

In the trial by Sibiude et al. (2025), the rate of composite maternal morbidity was 42.5% in the revealed testing group and 52.5% in the concealed testing group (p=0.37).

In the cohort study (Sharp et al., 2018), the rate of composite maternal morbidity was 11.9% in the revealed testing group and 10.1% in the concealed testing group (RR 1.17 95% CI0.76-1.82).

Figure 1. Outcome composite maternal morbidity



Conclusion: The add-on use of angiogenic markers may result in little or no difference in maternal morbidity compared to standard care without angiogenic markers (GRADE ⊕⊕OO).

Neonatal

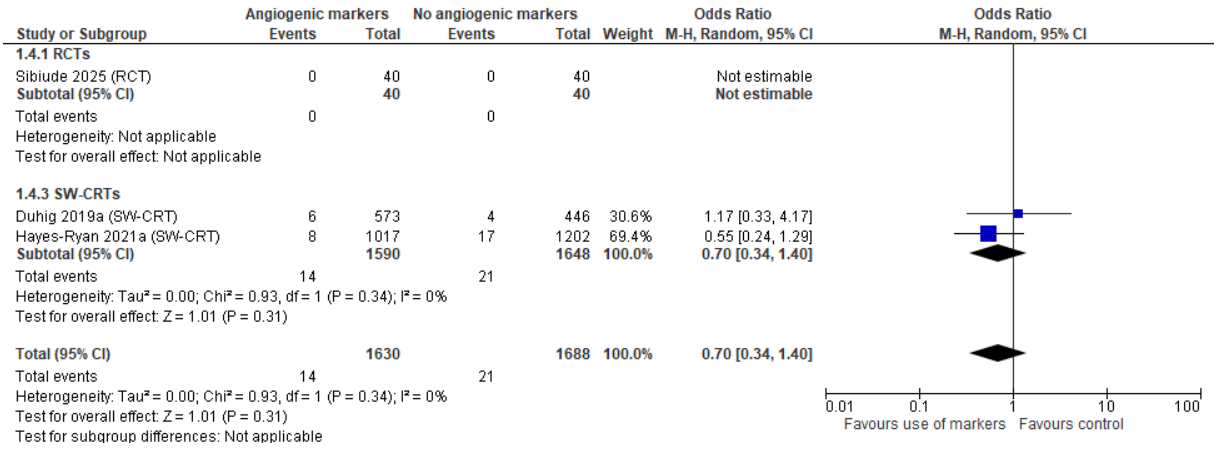
Perinatal/neonatal mortality (Appendix 4.3, Figure 2, Supplementary Figure 3)

Perinatal/neonatal mortality (stillbirth and neonatal mortality within 7 or 28 days, before hospital discharge, or not further specified) in the revealed testing group compared with the concealed testing group was reported in two SW-CRTs (Duhig et al., 2019a; Hayes-Ryan et al., 2021a) and in one RCT (Sibiude et al., 2025) with unclear or high risk of bias and in one cohort study (including multiple pregnancies) with high risk of bias (Sharp et al., 2018). Across the SW-CRTs and the RCT, 1,630 participants were included in the revealed testing group and 1,688 in the concealed testing group. The crude event rate across the trials was 8.6/1,000 births in the revealed testing group and 12.4/1,000 births in the concealed testing group. Meta-analysis of the trials showed no significant difference in perinatal/neonatal mortality between groups, OR 0.70 (95% CI 0.34 to

1.40; p=0.31). The pooled weighted RD was –0.00 percentage points (95% CI –0.01 to 0.00).

In the cohort study (Sharp et al., 2018), the perinatal mortality rate was 4.6 per 1,000 births in the revealed testing group and 30.1 per 1,000 births in the concealed testing group (RR 0.16, 95% CI 0.03 to 0.74).

Figure 2. Outcome perinatal/neonatal mortality



Conclusion: It is uncertain whether the add-on use of angiogenic markers affects perinatal/neonatal mortality compared to standard care without angiogenic markers (GRADE ⊕OOO).

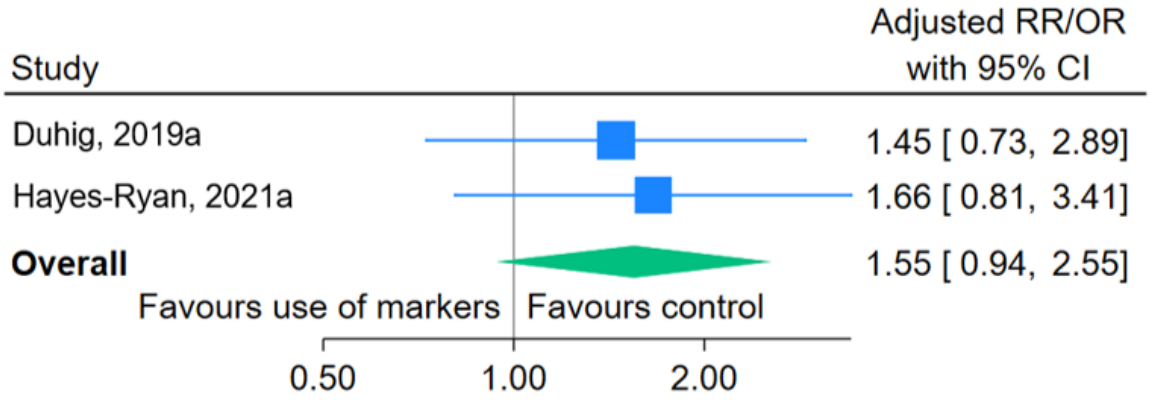
Composite perinatal/neonatal outcome (Appendix 4.4, Figure 3, Supplementary Figures 4 and 5)

A composite outcome variable for perinatal/neonatal mortality and morbidity (see Appendix 4.4 for definition in each study) in the revealed testing group compared with the concealed testing group was reported in two SW-CRTs (Duhig et al., 2019a; Hayes-Ryan et al., 2021a) and in one RCT (Sibiude et al., 2025) with unclear or high risk of bias and in one cohort study with high risk of bias (Sharp et al., 2018). Due to differences in the definition of the composite outcome variables, only the two SW-CRTs with similar definition were included in meta-analysis (Duhig et al., 2019a; Hayes-Ryan et al., 2021a). In both SW-CRTs, the composite neonatal outcome was analysed post hoc. Across these trials 1,590 participants were included in the revealed testing group and 1,648 in the concealed testing group. The crude event rate across the SW-CRTs was 10.9% in the revealed testing group and 9.0% in the concealed testing group. Meta-analysis of the SW-CRTs showed no significant difference in composite neonatal outcome between groups, OR 1.16 (95% CI 0.92 to 1.46; p=0.22) and adjusted OR/RR 1.55 (95% CI 0.94 to 2.55) (Figure 3). The pooled weighted RD was 0.01 percentage points (95% CI -0.01 to 0.03). Sibiude et al. (2025) reported a rate of composite neonatal

morbidity of 35.0% in the revealed testing group and 42.5% in the concealed testing group (p=0.49).

In the cohort study (Sharp et al., 2018), the composite perinatal/neonatal mortality and morbidity rate was 30.3% in the revealed testing group and 20.1% in the concealed testing group (RR 1.51, 95% CI 1.15 to 1.98).

Figure 3. Outcome composite neonatal morbidity



Conclusion: The add-on use of angiogenic biomarkers may result in little or no difference in composite neonatal morbidity compared to standard care without angiogenic markers (GRADE ⊕⊕OO).

Outcomes important for decision-making:

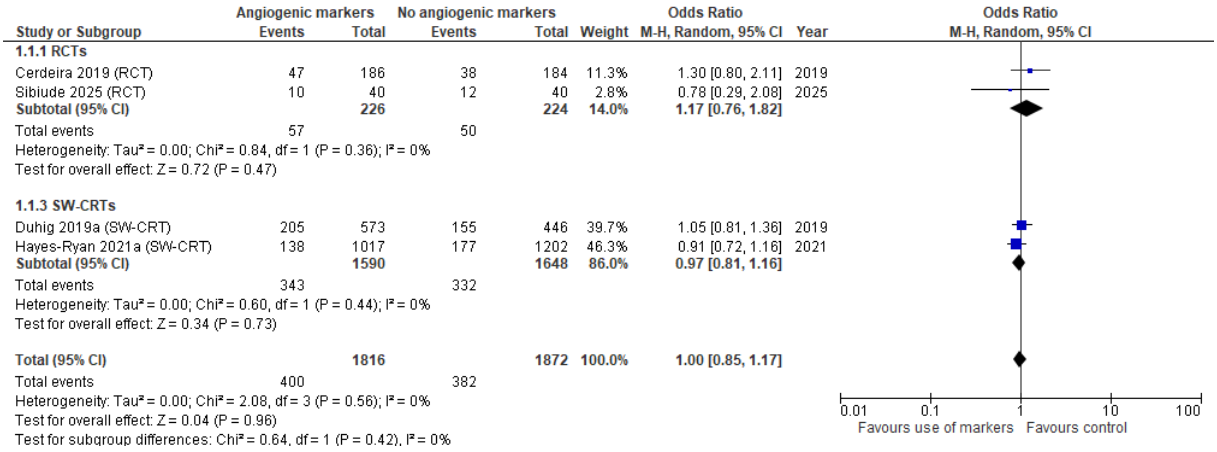
Maternal

Diagnosis of pre-eclampsia (Appendix 4.5, Figure 4, Supplementary Figure 6)

A diagnosis of pre-eclampsia in the revealed testing group compared with concealed testing group was reported in two RCTs (Cerdeira et al., 2019; Sibiude et al., 2025) and in two SW-CRTs (Duhig et al., 2019a; Hayes-Ryan et al., 2021a) with unclear or high risk of bias and in one cohort study with high risk of bias (Sharp et al., 2018). Across the RCTs and SW-CRTs, 1,816 participants were included in the revealed testing group and 1,872 in the concealed testing group. The crude event rate across trials was 22.0% in the revealed testing group and 20.4% in the concealed testing group. Meta-analysis of the trials showed no significant difference in diagnosis of pre-eclampsia between groups, OR 1.00 (95% CI 0.85 to 1.17; p=0.96). The pooled weighted RD was -0.0 percentage points (95% CI -0.03 to 0.02).

In the cohort study (Sharp et al., 2018), the rate of pre-eclampsia diagnosis was 48.7% in the revealed testing group and 61.3% in the concealed testing group (RR 0.86; 95% CI 0.75 to 0.99).

Figure 4. Outcome diagnosis of pre-eclampsia



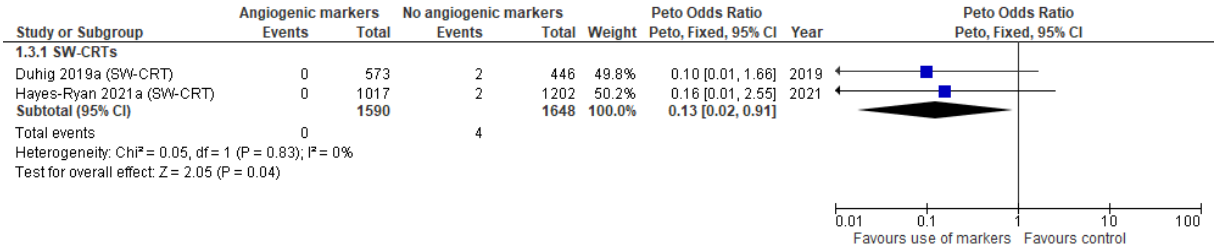
Conclusion: The add-on use of angiogenic markers probably results in no or little difference in diagnosis of pre-eclampsia compared to standard care without angiogenic markers (GRADE ⊕⊕⊕O).

Eclampsia (Appendix 4.6, Figure 5, Supplementary Figure 7)

Eclampsia in the revealed testing group compared with the concealed testing group was reported in two SW-CRTs (Duhig et al., 2019a; Hayes-Ryan et al., 2021a) and one RCT (Sibiude et al., 2025) with unclear or high risk of bias and one cohort study with high risk of bias (Sharp et al., 2018). Across the SW-CRTs and the RCT, 1,630 participants were included in the revealed testing group and 1,688 in the concealed testing group. The crude event rate across trials was 0% in the revealed testing group and 0.24% in the concealed testing group. Meta-analysis of the SW-CRTs showed a significantly lower rate of eclampsia in the revealed testing group, Peto OR 0.13 (95% CI 0.02 to 0.91; p=0.04) corresponding to a pooled weighted RD of -0.00 percentage points (95% CI -0.01 to 0.00).

In the cohort study (Sharp et al., 2018), the rate of eclampsia was 0% in the revealed testing group and 0.35% in the concealed testing group, no statistics were reported.

Figure 5. Outcome eclampsia



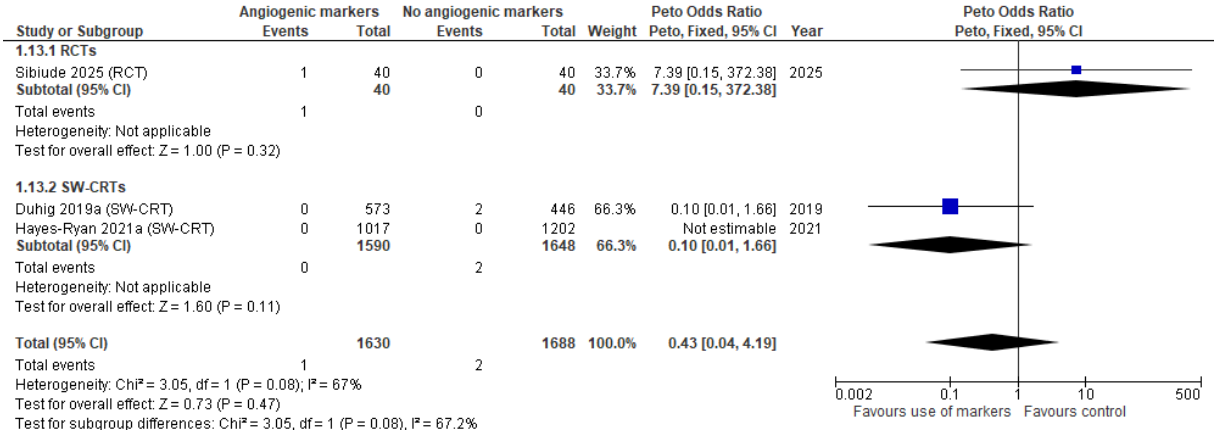
Conclusion: It is uncertain whether the add-on use of angiogenic markers reduces the risk of eclampsia compared to standard care without angiogenic markers (GRADE ⊕OOO).

Stroke (Appendix 4.7, Figure 6, Supplementary figure 8)

Stroke in the revealed testing group compared with the concealed testing group was reported in two SW-CRTs (Duhig et al., 2019a; Hayes-Ryan et al., 2021a) and one RCT (Sibiude et al., 2025) with unclear or high risk of bias and one cohort study with high risk of bias (Sharp et al., 2018). Across the SW-CRTs and the RCT, 1,630 participants were included in the revealed testing group and 1,688 in the concealed testing group. The crude event rate across trials was 0.06% in the revealed testing group and 0.12% in the concealed testing group. Meta-analysis of the SW-CRTs showed no significant difference in stroke between groups, Peto OR 0.43 (95% CI 0.04 to 4.19; p=0.47). The pooled weighted RD was 0 percentage points (95% CI 0 to 0).

In the cohort study (Sharp et al., 2018), the rate of stroke was 0% in both groups.

Figure 6. Outcome stroke



Conclusion: It is uncertain whether the add-on use of angiogenic markers reduces the risk of stroke compared to standard care without angiogenic markers (GRADE ⊕OOO).

Cortical blindness (Appendix 4.8)

Cortical blindness in the revealed testing group compared with the concealed testing group was reported in two SW-CRTs with unclear or high risk of bias (Duhig et al., 2019a; Hayes-Ryan et al., 2021a), and in one cohort study with high risk of bias (Sharp et al., 2018). Across the SW-CRTs, 1,590 participants were included in the revealed testing group and 1,648 in the concealed testing group, respectively. No trial reported any cortical blindness. The cohort study (Sharp et al., 2018) reported no cortical blindness.

Retinal detachment (Appendix 4.9)

Retinal detachment in the revealed testing group compared with the concealed testing group was reported in one cohort study (396 vs 287 participants) with high risk of bias (Sharp et al., 2018). No retinal detachment was reported.

Pulmonary oedema (Appendix 4.10)

Pulmonary oedema in the revealed testing group compared with the concealed testing group was reported in one SW-CRT (573 vs 446 participants) with unclear or high risk of bias (Duhig et al., 2019a) and in one cohort study (396 vs 287 participants) with high risk of bias (Sharp et al., 2018). Incidence was 0.35% vs 0% in the SW-CRT and 0.51% vs 0.70% in the cohort study for the revealed testing group and the concealed testing group, respectively. No statistical analysis was reported.

Acute kidney injury (Appendix 4.11)

Acute kidney injury (defined as creatinine >150 µmol/L) in the revealed testing group compared with the concealed testing group was reported in one SW-CRT (573 vs 446 participants) with unclear or high risk of bias (Duhig et al., 2019a) and in one cohort study (396 vs 287 participants) with high risk of bias (Sharp et al., 2018). Incidence of acute kidney injury was 1.22% vs 1.35% in the SW-CRT and 1.77% vs 0.70% in the cohort study; no statistics were reported. One SW-CRT reported kidney and liver compromise combined (1,017 vs 1,202 participants); the incidence was 6.39% vs 6.82% (RR 1.08; 95% CI 0.62 to 1.88, p=0.79) (Hayes-Ryan et al., 2021a).

Liver capsule haematoma or rupture (Appendix 4.12)

Severe hepatic complications in pregnancy (liver capsule haematoma, rupture, or acute fatty liver) in the revealed testing group compared with the concealed testing group was reported in one SW-CRT (573 vs 446 participants) with unclear or high risk of bias (Duhig et al., 2019a) and in one cohort study (396 vs 287 participants) with high risk of bias (Sharp et al., 2018). Incidence of severe hepatic complications was 0% in both groups in the SW-CRT and 0.25% vs 0% in the cohort study. One SW-CRT reported kidney and

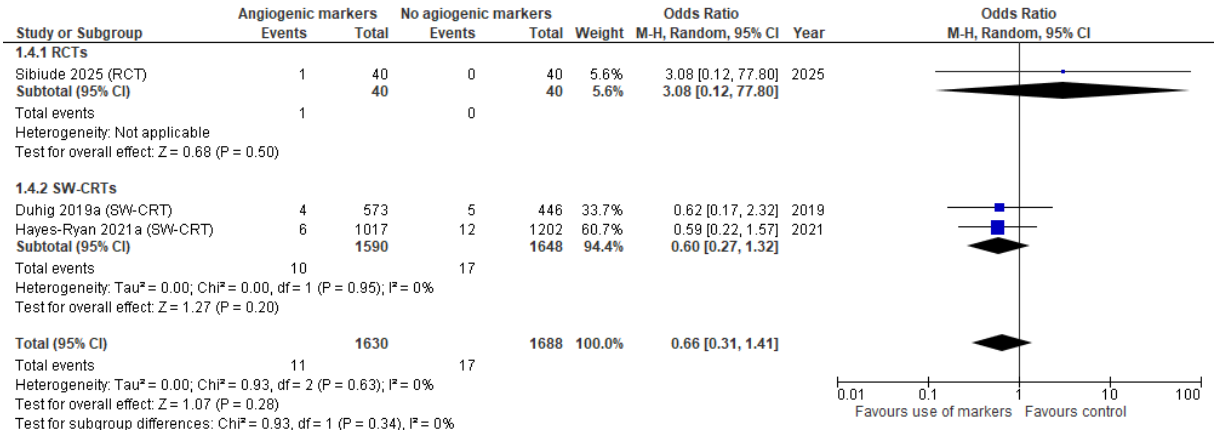
liver compromise combined (1,017 vs 1,202 participants); the incidence was 6.39% vs 6.82% (RR 1.08; 95% CI 0.62 to 1.88, p=0.79) (Hayes-Ryan et al., 2021a).

Placental abruption (Appendix 4.13, Figure 7, Supplementary Figure 9)

Placental abruption in the revealed testing group compared with the concealed testing group was reported in two SW-CRTs (Duhig et al., 2019a; Hayes-Ryan et al., 2021a) and one RCT (Sibiude et al., 2025) with unclear or high risk of bias and one cohort study with high risk of bias (Sharp et al., 2018). Across the SW-CRTs and the RCT, 1,630 participants were included in the revealed testing group and 1,688 in the concealed testing group, respectively. The crude event rate across trials was 0.67% in the revealed testing group and 1.01% in the concealed testing group. Meta-analysis of the trials showed no significant difference in placental abruption between groups, OR 0.66 (95% CI 0.31 to 1.41; p=0.28). The pooled weighted RD was -0.00 percentage points (95% CI -0.01 to 0.00).

In the cohort study (Sharp et al., 2018), the rate of placental abruption was 0.25% in the revealed testing group and 1.39% in the concealed testing group (396 vs 287 participants, no statistical analysis was reported).

Figure 7. Outcome placental abruption



Conclusion: It is uncertain whether the add-on use of angiogenic markers reduces the risk of placental abruption compared to standard care without angiogenic markers (GRADE ⊕OOO).

Postpartum haemorrhage (Appendix 4.14)

Postpartum haemorrhage in the revealed testing group compared with the concealed testing group was reported in one RCT (Cerdeira et al., 2019) and one SW-CRT (Duhig et al., 2019a) with unclear or high risk of bias. Across the trials, 759 participants were included in the revealed testing group and 630 in the concealed testing group. The RCT

reported postpartum haemorrhage as median (IQR) blood loss: 400 (300 to 525) ml in the revealed testing group (186 participants) and 500 (300 to 600) ml in the concealed testing group (184 participants) (p=0.027) (Cerdeira et al., 2019). The SW-CRT reported major postpartum haemorrhage (not further defined) in 8.6% in the revealed testing group (573 participants) and 10.8% in the concealed testing group (446 participants); no statistical analysis was reported (Duhig et al., 2019a).

Admission to intensive care unit (Appendix 4.15)

Admission to intensive care unit in the revealed testing group compared with the concealed testing group was reported in one SW-CRT (Hayes-Ryan et al., 2021a). Incidence was 0% in the revealed testing group (1,017 participants) compared with 0.08% in the concealed testing group (1,202 participants); no statistical analysis was reported.

Intubation and mechanical ventilation (Appendix 4.16)

Intubation and mechanical ventilation in the revealed testing group compared with the concealed testing group were reported in one SW-CRT (573 vs 446 participants) with unclear or high risk of bias (Duhig et al., 2019a) and in one cohort study (396 vs 287 participants) with high risk of bias (Sharp et al., 2018). The incidence in the revealed testing group vs the concealed testing group was 0% vs 0.22% in the SW-CRT and 0% vs 0.35% in the cohort study. No statistical analysis was reported.

Time to pre-eclampsia diagnosis (Appendix 4.17)

Time to pre-eclampsia diagnosis in the revealed testing group compared with the concealed testing group was reported in one RCT (Cerdeira et al., 2019) and two SW-CRTs (Duhig et al., 2019a; Hayes-Ryan et al., 2021a) with unclear or high risk of bias. Across the trials, 1,776 participants were included in the revealed testing group and 1,832 in the concealed testing group. In patients with a final diagnosis of pre-eclampsia, the median (IQR) time to diagnose in revealed testing group vs concealed testing group was 7 (0-29) days vs 9.5 (0-32) days (p=0.64) in Cerdeira et al. (2019), 1.9 (0.5-9.2) days vs 4.1 (0.8-14.7) days (time ratio 0.36; 95% CI 0.15-0.87, p=0.027) in Duhig et al. (2019a), and 8 (1-23) days vs 7 (1-25) days (geometric mean difference 0.92; 95% CI 0.56-1.49, p=0.73) in Hayes-Ryan et al. (2021a), respectively. Owing to serious inconsistency, the certainty of evidence was downgraded by two levels.

Conclusion: It is uncertain whether the add-on use of angiogenic markers affects time to diagnosis of pre-eclampsia compared to standard care without angiogenic markers (GRADE ⊕OOO).

Admission to hospital care (Appendix 4.18)

Admission to inpatient hospital care in the revealed testing group compared with the concealed testing group was reported in one RCT with unclear risk of bias (Cerdeira et al., 2019). The number of pre-eclampsia related admissions within 24 hours of the test was 32.3% (60/186) in the revealed testing group and 26.1% (48/184) in the concealed testing group (RR 1.24, 95% CI 0.89 to 1.70). Similarly, there was no difference in pre-eclampsia related admissions within 7 days of the test: 37.6% (70/186) in the revealed testing group vs 35.3% (65/184) in the concealed testing group (RR 1.06, 95% CI 0.81 to 1.39).

Conclusion: The add-on use of angiogenic markers may result in little or no difference in rate of admission to hospital care compared to standard care without angiogenic markers (GRADE ⊕⊕OO).

Inpatient nights (Appendix 4.19)

Inpatient nights (outcome not included in PICO) were reported in the revealed testing group compared with the concealed testing group in two SW-CRTs (Duhig et al., 2019a; Hayes-Ryan et al., 2021a) and one RCT (Sibiude et al., 2025) with unclear or high risk of bias and one cohort study with high risk of bias (Sharp et al., 2018). In Duhig et al. (2019a), women in the revealed testing group spent a mean (SE) of 7.43 (0.36) nights in inpatient care vs 7.26 (0.38) in the concealed testing group (mean difference -0.06; 95% CI -0.22 to 0.09). Hayes-Ryan et al. (2021a) reported total inpatient nights (median, IQR) stratified by PlGF level in the revealed testing group. In the revealed testing group, women with PlGF <12 pg/ml spent 9.5 (6, 15) nights, women with PlGF 12-100 pg/ml spent 6 (4, 10) nights, and women with PlGF >100 spent 5 (3, 7) nights. Median (IQR) inpatient nights in the concealed testing group were 5 (3, 9). No statistics were provided. Sibiude et al. (2025) reported hospitalisation ≥24 hours (primary outcome), ≥36 hours, ≥48 hours, and the median duration of hospitalisation. Hospitalisation for ≥24 hours was 75% in the revealed testing group and 80% in the concealed testing group (RR 0.9; 95% CI 0.7 to 1.2, p=0.59). Groups did not differ in hospitalisation duration for other cut-off values.

Outpatient visits (Appendix 4.20)

Outpatient visits (outcome not included in PICO) were reported in the revealed testing group compared with the concealed testing group in two SW-CRTs with unclear or high risk of bias (Duhig et al., 2019a; Hayes-Ryan et al., 2021a) and in one cohort study with high risk of bias (Sharp et al., 2018). The revealed testing group had a mean (SE) of 6.14 (0.53) outpatient visits vs 9.44 (0.81) in the concealed testing group (adjusted mean difference -0.04; 95% CI -0.23 to 0.16) in Duhig et al (2019a). Hayes-Ryan et al. (2021a) reported GP visits, antenatal care visits, emergency out-of-hour visits, fetal ultrasounds stratified by PlGF level in the revealed testing group and in the concealed testing group, but with no statistics. The cohort study reported outpatient visits stratified by PlGF level only in the revealed testing group.

Quality of life

Outcome maternal quality of life was not reported in any study.

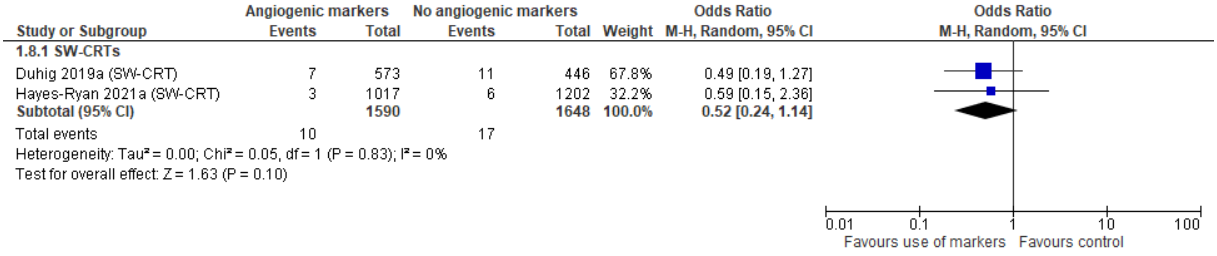
Neonatal

Intraventricular haemorrhage (Appendix 4.21, Figure 8, Supplementary Figure 10)

Intraventricular haemorrhage in the revealed testing group compared with the concealed testing group was reported in two SW-CRTs (any grade of intraventricular haemorrhage) with unclear or high risk of bias (Duhig et al., 2019a; Hayes-Ryan et al., 2021a) and one cohort study (intraventricular haemorrhage grade 3-4) with high risk of bias (Sharp et al., 2018). Across the SW-CRTs 1,590 participants were included in the revealed testing group and 1,648 in the concealed testing group. The crude event rate was 0.6% in the revealed testing group and 1.0% in the concealed testing group. Meta-analysis of the SW-CRTs showed no significant difference in intraventricular haemorrhage between groups, OR 0.52 (95% CI 0.24 to 1.14; p=0.10). The pooled weighted RD was -0.01 percentage points (95% CI -0.02 to 0.01).

In the cohort study (Sharp et al., 2018), the rate of intraventricular haemorrhage was 0.9% in the revealed testing group and 0% in the concealed testing group; no statistical analysis was reported.

Figure 8. Outcome intraventricular haemorrhage



Conclusion: It is uncertain whether the add-on use of angiogenic markers reduces the risk of intraventricular haemorrhage compared to standard care without angiogenic markers (GRADE ⊕OOO).

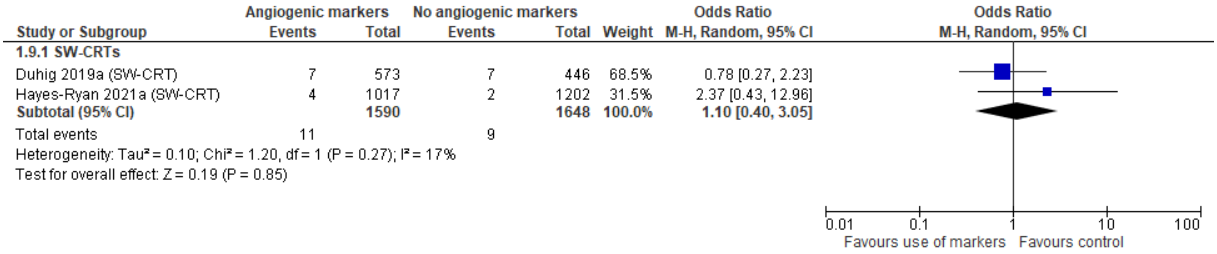
Necrotising enterocolitis (Appendix 4.22, Figure 9, Supplementary Figure 11)

Necrotising enterocolitis in the revealed testing group compared with the concealed testing group was reported in two SW-CRTs with unclear or high risk of bias (Duhig et al., 2019a; Hayes-Ryan et al., 2021a) and one cohort study with high risk of bias (Sharp et al., 2018). Across the RCTs, 1,590 participants were included in the revealed testing group and 1,648 in the concealed testing group. The crude event rate was 0.7% in the revealed testing group and 0.5% in the concealed testing group. Meta-analysis of the SW-CRTs showed no significant difference in necrotising enterocolitis between groups, OR

1.10 (95% CI 0.40 to 3.05; p=0.85). The pooled weighted RD was 0.00 percentage points (95% CI -0.01 to 0.01).

In the cohort study (Sharp et al., 2018), the rate of necrotising enterocolitis was 1.6% in the revealed testing group and 1.3% in the concealed testing group; no statistical analysis was reported.

Figure 9. Outcome necrotising enterocolitis



Conclusion: It is uncertain whether the add-on use of angiogenic markers reduces the risk of necrotising enterocolitis compared to standard care without angiogenic markers (GRADE ⊕OOO).

Neonatal seizures (Appendix 4.23)

Neonatal seizures in the revealed testing group compared with the concealed testing group were reported in one SW-CRT with unclear or high risk of bias (Duhig et al., 2019a). Neonatal seizures were reported in 0% of the revealed testing group (573 participants) and in 0.45% of the concealed testing group (446 participants); no statistical analysis was reported.

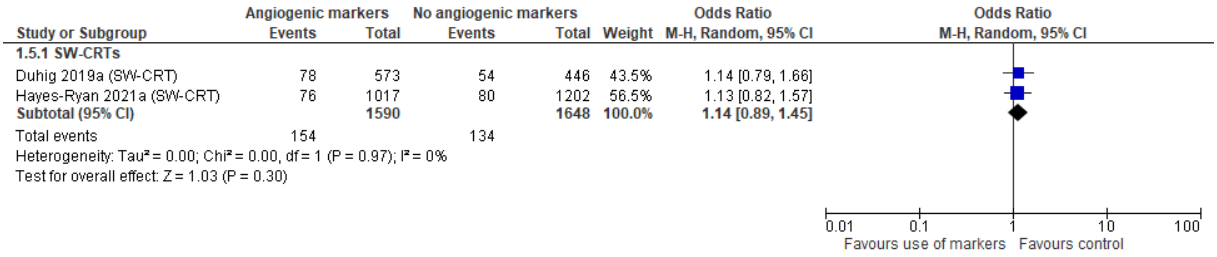
Respiratory diseases (respiratory distress syndrome and bronchopulmonary dysplasia) (Appendix 4.24, Figure 10, Supplementary Figure 12)

Respiratory distress syndrome in the revealed testing group compared with the concealed testing group was reported in two SW-CRTs with unclear or high risk of bias (Duhig et al., 2019a; Hayes-Ryan et al., 2021a) and one cohort study with high risk of bias (Sharp et al., 2018). Across the SW-CRTs 1,590 participants were included in the revealed testing group and 1,648 in the concealed testing group. The crude event rate was 9.7% in the revealed testing group and 8.1% in the concealed testing group. Meta-analysis of the SW-CRTs showed no significant difference in respiratory distress syndrome between groups, OR 1.14 (95% CI 0.89 to 1.45; p=0.30). The pooled weighted RD was 0.01 percentage points (95% CI –0.01 to 0.03). The rate of bronchopulmonary dysplasia was 1% in both groups in Duhig et al. (2019a); no statistical analysis was reported.

In the cohort study (Sharp et al., 2018), the respiratory distress syndrome rate was 29.6% in the revealed testing group and 15.4% in the concealed testing group, no statistical analysis was reported. The bronchopulmonary dysplasia rate was 6.7% in the

revealed testing group and 2.0% in the concealed testing group; no statistical analysis was reported.

Figure 10. Outcome respiratory distress syndrome



Conclusion: The add-on use of angiogenic markers may result in little or no difference in respiratory distress syndrome compared to standard care without markers (GRADE ⊕⊕OO).

Confirmed neonatal infection (Appendix 4.25)

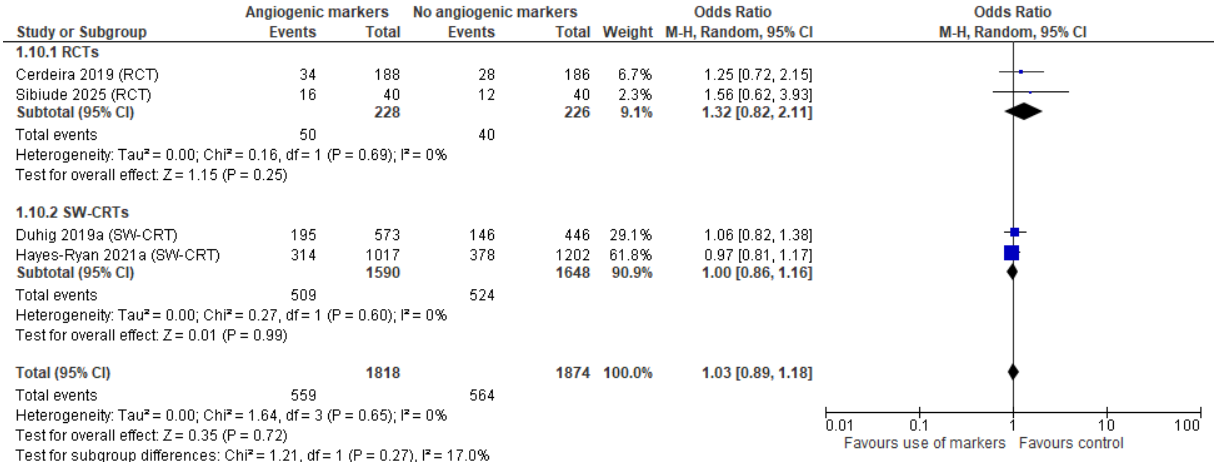
Confirmed neonatal infection in the revealed testing group compared with the concealed testing group was reported in one SW-CRT with unclear or high risk of bias (Hayes-Ryan et al., 2021a). Confirmed neonatal infection occurred in 1.08% in the revealed testing group (1,017 participants) and 0.92% in the concealed testing group (1,202 participants); no statistical analysis was reported. Late onset infection was not reported.

Admission to neonatal care unit (Appendix 4.26, Figure 11, Supplementary Figure 13)

Admission to a neonatal care unit in the revealed testing group compared with the concealed testing group was reported in two RCTs (Cerdeira et al., 2019; Sibiude et al., 2025) and two SW-CRTs (Duhig et al., 2019a; Hayes-Ryan et al., 2021a) with unclear or high risk of bias and one cohort study with high risk of bias (Sharp et al., 2018). Across the RCTs and SW-CRTs, 1,818 participants were included in the revealed testing group and 1,874 in the concealed testing group. The crude event rate across the trials in the revealed testing group was 30.7% and 30.1% in the concealed testing group. Meta-analysis of the trials showed no significant difference in admittance to neonatal care unit between groups, OR 1.03 (95% CI 0.89 to 1.18; p=0.72). The pooled weighted RD was 0.01 percentage points (95% CI -0.02 to 0.04).

In the cohort study (Sharp et al., 2018), the rate of admission to a neonatal unit was 43.9% in the revealed testing group and 39.1% in the concealed testing group (RR 1.14; 95% CI 0.95 to 1.37).

Figure 11. Outcome admission to neonatal care unit



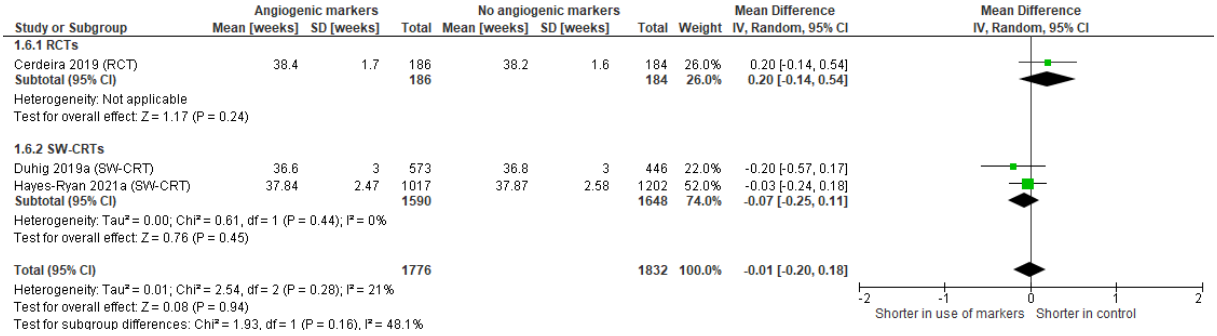
Conclusion: The add-on use of angiogenic markers probably results in little or no difference in admission to a neonatal care unit compared to standard care without markers (GRADE ⊕⊕⊕O).

Gestational age at delivery (Appendix 4.27, Figure 12)

Gestational age in the revealed testing group compared with the concealed testing group was reported in one RCT (Cerdeira et al., 2019) and two SW-CRTs (Duhig et al., 2019a; Hayes-Ryan et al., 2021a) with unclear or high risk of bias and one cohort study with high risk of bias (Sharp et al., 2018). Across the trials 1,776 participants were included in the revealed testing group and 1,832 in the concealed testing group. Meta-analysis of the studies showed no significant difference in gestational age, mean difference -0.01 (95% CI -0.20 to 0.18; p=0.94) weeks. No difference in preterm birth was reported by Duhig et al. (2019a) for birth before 37 weeks (OR 1.00, 95% CI 0.61 to 1.63) or by Hayes-Ryan et al. (2021a) for birth at 32–36 weeks, 28–31 weeks, or <28 weeks (RR 0.92, 95% CI 0.60 to 1.42; RR 0.88, 95% CI 0.25 to 3.10; and RR 3.03, 95% CI 0.73 to 12.48, respectively).

The cohort study (Sharp et al., 2018) showed a significant lower median (quartiles) gestational age at delivery 34.9 (32.0 to 37.1) weeks in the revealed testing group vs 36.7 (33.6 to 38.6) weeks in the concealed testing group; median difference -1.4 (95% CI -0.9 to -2.0).

Figure 12. Outcome gestational age at delivery (weeks)



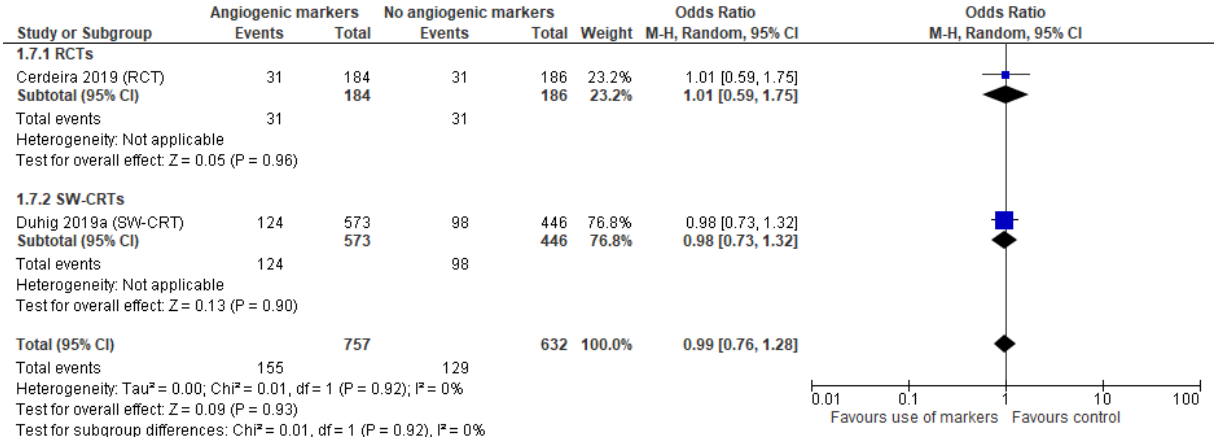
Conclusion: The add-on use of angiogenic markers probably results in little or no difference in gestational age at delivery compared to standard care without markers (GRADE ⊕⊕⊕O).

Birth weight deviation (small for gestational age) (Appendix 4.28, Figure 13, Supplementary Figure 14)

Birth weight deviation (<3th , <5th, or <10th centile) in the revealed testing group compared with the concealed testing group was reported in two RCTs (Cerdeira et al., 2019; Sibiude et al., 2025) and in two SW-CRTs (Duhig et al., 2019a; Hayes-Ryan et al., 2021a) with unclear or high risk of bias and in one cohort study with high risk of bias (Sharp et al., 2018). One RCT (Cerdeira et al., 2019) and one SW-CRT (Duhig et al., 2019a) with similar definition (<10th centile) were included in meta-analysis. Across these trials, 757 participants were included in the revealed testing group and 632 in the concealed testing group. The crude event rate across the two trials was 20.5% in the revealed testing group and 20.4% in the concealed testing group. Meta-analysis of the two trials showed no significant difference in birth weight deviation between groups, OR 0.99 (95% CI 0.76 to 1.28; p=0.93). The pooled weighted RD was -0.00 percentage points (95% CI -0.04 to 0.04). In the SW-CRT by Hayes-Ryan et al. (2021a) no significant difference between groups in birth weight <5th centile (28.12% vs 20.19%, RR 1.06; 95% CI 0.96 to 1.16, p=0.26) was reported. Sibiude et al. (2025) also reported no difference in birth weight <3rd centile (12.5% vs 12.8%, p=1.0).

In the cohort study (Sharp et al., 2018), the rate of birthweight <10th centile was 42.2% in the revealed testing group and 48.3% in the concealed testing group (RR 0.87; 95% CI 0.74 to 1.02). Corresponding results for birthweight <3rd centile was 28.9% vs 36.1% (RR 0.80; 95% CI 0.65 to 0.99).

Figure 13. Outcome birth weight deviation (<10th centile)



Conclusion: The add-on use of angiogenic markers probably results in little or no difference in birth weight deviation (<10th centile) compared to standard care without angiogenic markers (GRADE ⊕⊕⊕O).

Neonatal outcomes not reported

Neonatal outcomes not reported were neonatal resuscitation, neonatal unit length of stay and preschool developmental delays.

Subgroup analyses

Prespecified subgroup analyses could not be performed due to sparse data for the following: singleton and multifetal pregnancies, different test types (sFlt-1/PlGF ratio or PlGF alone), and gestational age between 20+0 and 33+6 weeks. No concerns regarding the trustworthiness of the included RCTs or SW-CRTs were identified based on established evaluation tools.

10 Ethical aspects

The current literature review does not support a positive benefit-risk balance for management of women with suspicion of pre-eclampsia by adding testing with angiogenic markers compared with standard management, since no clear clinical or resource-related benefits were demonstrated.

According to **the human dignity principle**, all women should have equal access to appropriate diagnostic assessment. However, the lack of compelling evidence for a clinical effect or saving of health care resources argue against routine implementation. Respect for autonomy requires transparent communication about both potential benefits and the low certainty of evidence. Maternal and fetal interests may sometimes be in conflict, especially when decisions about preterm birth are considered. In these situations, it is important to recognise that the fetus does not have autonomy before birth.

According to **the need and solidarity principle**, resources should be directed to those with the greatest medical need. The overarching aim of introducing angiogenic markers in the management of women with suspected preterm pre-eclampsia is to support diagnosis and risk stratification and improve critical clinical outcomes for both mother and baby and/or save resources for the healthcare system by avoiding unnecessary diagnostic procedures, hospital admissions and interventions. However, no clear clinical benefits were demonstrated in the present HTA. In addition, resource-related benefits to support cost-effectiveness could not be shown in the analyses.

The cost-effectiveness principle - at present, there is insufficient evidence to support clinical benefits or resource savings.

11 Organisational aspects

The method for measuring PlGF and/or sFlt-1 to PlGF ratio is currently not available for clinical use at any of the hospitals in Region Västra Götaland, but there is technical infrastructure in place that would allow analysis within 1.5 to 2 hours with round-the-clock availability. Nevertheless, implementation would require procurement of reagents, establishment of local analysis protocols and the incorporation of testing in the clinical care pathway.

12 Economic aspects

We have refrained from a full health economic evaluation given the absence of clear evidence for effects on clinical outcomes and/or resource utilisation. Instead, a budget impact analysis was conducted.

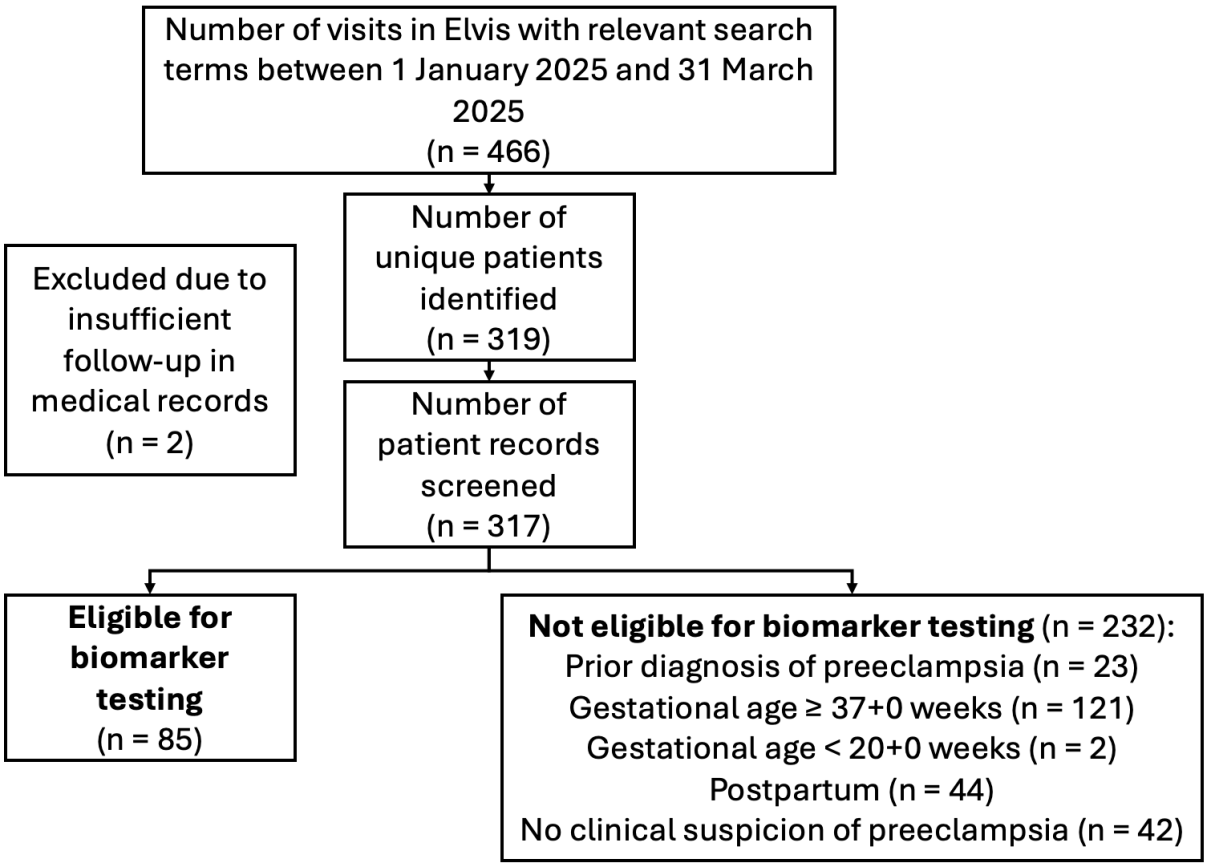
How often would testing for angiogenic markers be needed?

A retrospective chart review was conducted to estimate how often testing with angiogenic biomarkers would have been indicated in routine care in VGR Region. This approach was chosen to estimate the potential target population and to generate a clinically relevant basis for future studies, particularly for planning prospective evaluations and assessing the feasibility of implementing angiogenic biomarker testing in routine care.

The review covered the period from 1 January to 31 March 2025 and included women presenting to the Emergency Department for Pregnancy and Recently Delivered at Östra Sjukhuset, Gothenburg. Identification of the target population could not rely on registry-based diagnostic codes alone since there is no specific code for suspected pre-eclampsia. Instead, we applied a structured search strategy using predefined clinical search terms in the electronic medical record system "Elvis".

The search terms pre-eclampsia (preeklampsi), chest pain (bröstsmärta), acute abdominal pain (akut buk), headache (huvudvärk), neurology (neurologi), kidney (njure), and circulatory symptoms (cirkulation) were applied in the electronic medical record system Elvis. A total of 319 unique patients were identified, of whom 317 medical

records were screened. In eighty-five patients, we considered that testing for angiogenic biomarkers would have been indicated. Extrapolated to a full year, this would correspond to approximately 340 women in need of angiogenic biomarker testing at Sahlgrenska University hospital or 598 women in the entire VGR Region. Reasons for exclusion or ineligibility for testing are presented in Flowchart 1.



Flowchart 1. Flowchart of patient identification, screening, and eligibility for angiogenic biomarker testing, January to March, 2025.

Present costs of currently used technologies

The current management strategy for suspected pre-eclampsia varies depending on the severity of symptoms. It may involve hospital admission for observation and initiation or adjustment of antihypertensive treatment. One hospital admission/night for suspected pre-eclampsia is estimated to cost 22,832 SEK.

Alternatively, care can be intensified in the outpatient setting, for example through home blood pressure monitoring or more frequent antenatal visits at a midwife-led clinic. An outpatient visit for assessment of suspected pre-eclampsia is estimated to cost 1,982 SEK per visit.

Budget impact analysis

For calculation of annual costs for introduction of biomarker testing on a regional level, we collected data from regulatory bioanalysis specialists at the Department of Clinical Chemistry, Sahlgrenska University Hospital and used estimates of volume from the electronic medical record system (Elvis) mentioned above.

The total cost of conducting these tests consists of two components: the cost of the test itself and the cost of setting up the analysis laboratory. The former includes the costs of reagents, staff time, and maintenance. The approximated cost per PlGF test is 389 SEK, while the cost per combined sFlt-1 and PlGF test is 778 SEK.

The setup of two analyses incurs a cost of 150,000 SEK per year. This cost is considered a capital input as this cost has longer effects in terms of service provisioning. Assuming a 20-year lifetime of the laboratory setup and a discount rate of 3%, the annual equivalent cost is estimated at 10,082 SEK (150,000 SEK divided by annuity factor 14.8775).

Table 1. Annual costs of biomarker tests in VGR, year 2025

Inputs	Costs (SEK)	
	PlGF	sFlt-1 and PlGF
Cost of tests (e.g. regents, staff-time & maintenance)	232,618	465,237
Costs of analysis setup (incl. training)	10,082	10,082
Total cost	**242,700**	**475,319**
Cost per patient	**406**	**795**

This implies that the total cost of PlGF testing would be 243,000 SEK per year, while the total cost of combined sFlt-1 and PlGF testing would be 475,000 SEK per year. The corresponding cost per patient is 406 SEK for PlGF testing and 795 SEK for combined sFlt-1 and PlGF testing.

No potential downstream cost savings associated with testing were calculated due to uncertainty of the clinical effectiveness.

Available economic evaluations or cost advantages/disadvantages

Duhig et. al. (2019b) performed a cost-effectiveness analysis based on the PARROT UK trial (Duhig, 2019a). Resource use, costs, and maternal adverse outcomes were analysed using adjusted statistical models and Monte Carlo simulation from the perspective of the National Health Service (NHS), the publicly funded healthcare system in the UK. This simulation suggested that PlGF-guided care was less costly and more effective than usual care, with an estimated saving of £149 per woman tested (including test costs). The estimated savings were primarily driven by fewer outpatient visits and a reduction in

maternal adverse events; however, these effects were not confirmed in our analysis. We critically appraised the publication of Duhig et. al. (2019b) using a tool for health economic studies from Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU, 2025) and found major methodological limitations; also, information regarding healthcare resource consumption was not transparent in relation to the description in the clinical paper (Duhig et al, 2019a).

13 Discussion

Summary of main results

This HTA analysis assessed whether adding angiogenic marker testing to standard clinical management (i.e., as an add-on test with test results revealed to the physician) for women with suspected preterm pre-eclampsia could reduce maternal or neonatal mortality and morbidity, shorten time to diagnosis, decrease hospital admissions or influence quality of life.

We found that use of angiogenic markers probably results in no or little difference in the incidence of pre-eclampsia, infants born small for gestational age, gestational age at birth, or admission to neonatal care unit. Use of angiogenic markers may also result in little or no difference in composite maternal morbidity, composite neonatal morbidity, respiratory disease, or admission to hospital. For other outcomes, including maternal and perinatal/neonatal mortality, and time to diagnosis, the certainty of evidence for conclusion was very low. Based on these results, a formal health economic evaluation was not done in this HTA.

In summary, no clear benefits of testing angiogenic markers in women with suspected preterm pre-eclampsia have been found for either the mother or the child.

Overall completeness and applicability of evidence

To our knowledge, this HTA report represents the most up-to-date assessment of the use of angiogenic markers in addition to standard clinical assessment for women with suspected preterm pre-eclampsia in high-income settings. A comprehensive literature search identified five studies meeting our PICO criteria: two conventional individual RCTs (450 participants), two SW-CRTs (3 238 participants), and one cohort study (683 participants).

We chose to conduct and base our conclusions on de novo meta-analyses combining conventional RCTs and SW-CRTs in the same meta-analysis. This approach is in line with recommendations in the Cochrane Handbook (Higgins, Eldridge and Li, 2024) and has the advantage that a single effect estimate is produced. However, this also means that specific limitations related to the SW-CRT design affect grading. Both SW-CRTs were pragmatically designed to evaluate the implementation of an intervention at cluster (hospital) level. Cluster design has a strong external validity in general, but internal validity may be a weakness. A key limitation with the SW-CRT design is the risk of time-related confounding, as the sequential roll-out makes it difficult to separate intervention effects from temporal changes in clinical practice or patient populations. Most of our meta-analyses relied on unadjusted crude event rates because adjusted effect estimates

were reported only for the primary and a limited number of secondary outcomes in Duhig et al. (2019a). In addition, the small number of clusters (11 and 7, respectively) introduces a risk of baseline imbalances, which was further increased by constraints in the randomisation process related to cluster size. In one SW-CRT, incomplete reporting of allocation concealment suggests a potential risk of selection bias (Duhig et al., 2019a). In contrast, conventional RCTs with individual randomisation generally provide stronger internal validity, better balance between groups, and a more straightforward interpretation of causal effects. The lack of blinding present in both the conventional RCTs and the SW-CRTs increases the risk of performance and detection bias. Overall, the risk of bias was judged to be moderate for the conventional RCTs and between moderate and, in comparison with an individually randomised study, as moderate to high for the SW-CRTs. Two studies did not reach their recruitment targets (Hayes-Ryan et al, 2021a, Sibiude et al., 2025), and most were underpowered to assess rare but serious outcomes such as maternal or perinatal/neonatal mortality and severe maternal or neonatal morbidity, resulting in substantial statistical imprecision. Of note, the SW-CRT by Duhig et al. (2019a) aimed for a sample size of 504 patients which was exceeded as 1035 women were included. The MAPPLE cohort study by Sharp et al. (2018) suggested that PlGF-guided management may improve outcomes (i.e., lower perinatal mortality); however, the strength of evidence was limited by the non-randomised design, the use of a historical control group from a previous study (Chappell et al., 2013), and the modest sample size.

Incidence of pre-eclampsia was included as an outcome in the HTA-analysis to detect a potential influence of the addition of angiogenic markers on clinical recognition and diagnosis of pre-eclampsia. Our meta-analysis showed that management with angiogenic markers had little or no difference for the incidence of pre-eclampsia.

A limitation of the pooled estimates is that some meta-analyses combined studies evaluating different angiogenic biomarker tests (PlGF alone and sFlt-1/PlGF ratio). Although these tests are based on related pathophysiological mechanisms, they differ in analytical characteristics, diagnostic thresholds, and clinical performance.

None of the included studies reported on the following predefined outcomes in our PICO: maternal health-related quality of life, neonatal resuscitation, or preschool developmental delays, which were all predefined outcomes in our PICO. Termination of pregnancy before fetal viability was not included as a predefined outcome in our PICO and was therefore outside the scope of this assessment.

Prespecified subgroup analyses for singleton and multifetal pregnancies were not feasible, as only the cohort study (Sharp et al., 2018) included multifetal pregnancies. There were also insufficient data to perform subgroup analyses by type of angiogenic test (sFlt-1/PlGF ratio or PlGF alone) or by restricting testing to an earlier gestational age (20+0 to 33+6 weeks).

Agreements and disagreements with other studies and reviews

This HTA report was undertaken in response to the updated NICE HealthTech Guidance on PlGF-based testing to help diagnose suspected pre-eclampsia published in 2022 (NICE, 2022). The NICE HealthTech Guidance was based on a systematic review by

Frampton et al. (2016; updated 2021) recently also published in an edited version (Shepherd et al., 2026). We built on these findings by reviewing and adapting the original literature search strategy and critically appraising the studies included in Frampton et al. (2021). In addition, we conducted an updated literature search using the same strategy, covering the period from 2021 to February 2026. In contrast to our analysis, Frampton et al. (2021) refrained from meta-analyses based on the argument that the available studies did not report sufficiently comparable outcomes. Instead, they provided a structured narrative synthesis, consistent with their original review. Much of the evidence was based on the two large SW-CRTs, PARROT UK (Duhig et al., 2019a) and PARROT Ireland (Hayes-Ryan et al., 2021a). The PARROT UK trial suggested that PlGF-based testing in addition to standard clinical assessment improves maternal outcomes, with significantly fewer adverse events in the revealed group (4% vs 5%). In contrast, the PARROT Ireland trial found no significant effect (10.4% vs 10.9%), possibly due to differences in study populations (i.e. different rates of pregnancies with suspected fetal growth restriction and incidence of pre-eclampsia). None of the studies showed any difference in perinatal adverse outcomes between groups. However, the evidence remains uncertain due to the rarity of mortality and severe morbidity. Overall, the NICE HealthTech Guidance concluded that there was some evidence that PlGF testing may help with clinical decision making and improve clinical outcomes, although uncertainty remains. An important point in the NICE HealthTech Guidance was that angiogenic tests should not be used to determine the timing of birth. The NICE HealthTech Guidance concluded that the use of PlGF or sFlt-1/PlGF ratio testing is cost-effective and dominates standard assessment (i.e. results in lower costs and more quality-adjusted life-years) when used to rule in or rule out preterm pre-eclampsia. The model used a decision tree to compare PLGF-based testing with standard care in women with suspected preterm pre-eclampsia over pregnancy and the neonatal period. Evidence was from three studies (the PARROT-UK, INSPIRE and PreOS studies) linking test accuracy to clinical decisions and outcomes. Overall, the NICE HealthTech Guidance suggested that testing was cost-saving and improved outcomes, although this suggestion remains dependent on modelling assumptions.

Our literature search also identified an HTA from Canada (Ontario Health Technology Assessment, 2023) evaluating the clinical utility and cost-effectiveness of angiogenic biomarkers in women with suspected preterm pre-eclampsia. This report included the same studies as Frampton et al. (2021) and an additional cohort study by Hughes et al. (2023), which was a single-arm study and therefore not relevant to this report. Similar to the NICE HealthTech Guidance but unlike our HTA, the Ontario HTA graded the evidence without pooling the results in meta-analyses and instead based their conclusions on individual studies. The Ontario HTA concluded that PlGF-based testing likely improves prediction of pre-eclampsia, and may also reduce time to pre-eclampsia diagnosis, severe adverse maternal outcomes, and length of stay at neonatal intensive care unit, although the evidence is low. For other clinical outcomes such as maternal admission to hospital and perinatal adverse outcomes, they found little or no difference. Like our findings, the Ontario HTA economic evaluation concluded that it was not possible to assess the cost-effectiveness of PlGF-based testing due to uncertainty around key clinical outcomes; however, they did include a budget impact analysis. They estimated that publicly funding PlGF-based testing in the Ontario HTA would cost an additional €1.24 million over 5 years, increasing from €0.18 million in year 1 to €0.31 million in year 5.

The differing conclusions between the NICE HealthTech Guidance, the Ontario HTA, and our HTA may be explained by differences in focus and evidence appraisal and the decision to use meta-analyses as support for evidence synthesis. While the NICE HealthTech Guidance and the Ontario HTA emphasized the potential value of PlGF-based testing for clinical decision-making, our HTA focused on whether testing translates into improvements in clinically important maternal and neonatal outcomes. As evidence for such benefits was limited, our conclusions were more cautious.

Implications for research

In our HTA, uncertainty in clinical effectiveness resulted in insufficient evidence to support the use of PlGF or sFlt-1/PlGF ratio testing in addition to standard of care as a rule-in or rule-out strategy for pre-eclampsia in a Swedish context. As existing evidence is derived from similar, but not identical, healthcare systems, further research in a Swedish or Nordic context is warranted. A conventional RCT with randomisation at the individual patient level is the most robust design but the recruitment process is demanding. Therefore, despite the afore-mentioned limitations, a well-designed SW-CRT, building on the experience from the PARROT trials and addressing the remaining knowledge gaps identified in the current review may be a feasible alternative. To be able to provide more conclusive results than previous trials, a future multicenter SW-CRT needs to include a larger number of sites and a larger total number of participants. Furthermore, increased focus on the ability of the test to rule out a diagnosis of pre-eclampsia and thereby reduce need for additional monitoring would be valuable. Potential settings for coordinating future research on this topic include the Swedish Network for National Clinical Studies in Obstetrics and Gynecology (SNAKS) and/or the Nordic Alliance for Clinical Trials in Obstetrics and Gynecology (NORD-ACT). These networks provide unique opportunities to conduct high-quality clinical research, including the use of comprehensive national health data and quality registers available in the Nordic countries, enabling the recruitment of larger patient populations through a greater number of participating clusters, thereby strengthening statistical power and generalisability.

Only one cohort study included multifetal pregnancies, precluding stratified analyses by plurality. As PlGF and sFlt-1 levels may differ in multifetal pregnancies due to greater placental mass, further research is needed to determine appropriate cut-offs.

This HTA found no clear clinical benefit of PlGF-based testing. It is also important to point out that the concept with one-time testing that was the scope of this systematic review was not associated with harm, mitigating initial concerns that abnormal results might lead to unnecessary preterm birth. In contrast, evidence from the PARROT-2 study suggests that repeat PlGF-based testing may increase iatrogenic preterm birth before 34 weeks, likely due to earlier diagnosis and intervention, and increase the rate of caesarean birth, without clear maternal benefit (Hurrell et al., 2025). These findings do not support routine repeat testing for all patients, although certain subgroups may still benefit and warrant further studies.

Furthermore, the optimal type of angiogenic test (sFlt-1/PlGF ratio versus PlGF alone) to be added to standard of care for the management of patients with suspected pre-eclampsia requires additional investigation.

14 Future perspectives

Scientific knowledge gaps

The available data were insufficient, and our meta-analyses indicate that there is currently inadequate evidence to determine whether angiogenic markers when used in addition to standard of care can contribute as reliable rule-in or rule-out tests for preterm pre-eclampsia, or whether they shorten the time to diagnosis. These findings highlight the need for further research. Additional studies, particularly in a Swedish context, would be of considerable value.

Ongoing research

A search in clinicaltrials.gov on the 23th of January 2026 identified 364 studies. One study was considered relevant according to the PICO of this report: *sFlt-1/PlGF Ratio: Impact on the Management of Patients With Suspected Pre-eclampsia (PROSPE)*, NCT05228002*.* The trial was completed on 3 March 2025 but has not been published. The study evaluates the impact of using the sFlt-1/PlGF ratio in the clinical management of pregnant women with suspected pre-eclampsia. Specifically, it investigates whether incorporating this biomarker into routine care can improve clinical decision-making and reduce unnecessary hospitalisations within the French healthcare system. The planned sample size was 160 participants; however, only 43 participants were ultimately recruited according to the clinical trial registration.

15 Participants in the project

The question was nominated by

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Declaration of interests

Lina Bergman has performed studies where PlGF reagents were donated by Roche, Perkin Elmer and Thermo Fischer. She has also served as a course leader for a Swedish course on pre-eclampsia that received sponsorship from Thermo Fischer and Roche.
Dr Bergman has consulted for DiaMedica and Arraka therapeutics, companies invested in finding new treatments for pre-eclampsia. She is also a board member of intervention

trials in pre-eclampsia in which the trial drug has been donated by Merck. Due to above-mentioned conflicts of interest, Dr Bergman did not take part in the grading of evidence.

No other conflicts of interest were reported.

Project time

The HTA was accomplished during the period of 2025-09-10 to 2026-09-02.
Literature searches were conducted 2025-09-30 and updated 2026-02-13.

Components of this Health Technology Assessment

- ✓ Description of methods
- ✓ PICO
- ✓ Full literature search
- ✓ Flowchart
- ✓ Selection based on relevance
- ✓ Quality assessment
- ✓ Data tabulation
- ✓ Evidence synthesis
- ✓ Meta-analysis
- ✓ Certainty of evidence by GRADE
- ✓ Summary
- ✓ Economical aspects
- ✓ Organisational aspects
- ✓ Ethical aspects
- ✓ Ongoing studies
- ✓ Excluded articles
- ✓ Participation of experts
- ✓ External review
- ✓ Knowledge gaps identified
- ✓ Conflict of interest reported

Appendix 1: PICO, study selection, search strategies, and references

Question(s) at issue:
Can the use of angiogenic markers (sFlt-1/PlGF ratio or PlGF alone) in the management of women with suspected pre-eclampsia between 20+0 and 36+6 weeks gestation: 1) reduce maternal or offspring morbidity or mortality; 2) shorten time to diagnosis of pre-eclampsia; 3) reduce time to discharge or return to standard antenatal care; 4) decrease hospital admissions or 5) improve quality of life?

PICO: (*P=Patient I=Intervention C=Comparison O=Outcome*)

PICO	
P	Women with suspected preeclampsia between 20+0 to 36+6 weeks gestation
I	Measurement of angiogenic markers sFlt-1/PlGF, or PlGF only, in addition to standard care
C	Standard care alone (with no or concealed measurement of angiogenic markers, sFlt-1/PlGF or PlGF)
O	**Critical for decision-making:** **Maternal** • Maternal mortality • Composite maternal morbidity (as defined by the authors) **Neonatal** • Neonatal mortality • Stillbirth • Composite neonatal morbidity (as defined by the authors) **Important for decision-making:** **Maternal** • Diagnosis of pre-eclampsia • Maternal morbidity (assessed as individual outcomes* according to the core outcome set for pre-eclampsia in Duffy et al. (2020): eclampsia, stroke, cortical blindness, retinal detachment, pulmonary oedema, acute kidney injury, liver capsule haematoma or rupture, placental abruption, postpartum haemorrhage, admission to intensive care unit, and intubation and mechanical ventilation [not for childbirth]) • Time to pre-eclampsia diagnosis • Return to standard antenatal care • Admission to hospital care • Quality of life

	Neonatal • Neonatal morbidity (assessed as individual outcomes*: intracranial haemorrhage, necrotising enterocolitis, neonatal seizures, respiratory support, breathing difficulties, chronic lung disease, late-onset infection, admission to neonatal unit, gestational age at delivery, birth weight and small for gestational age (SGA), neonatal unit length of stay, neonatal resuscitation, preschool developmental delays)

* Most individual outcomes are encompassed within the composite outcomes. However, certain outcomes, such as eclampsia, are clinically critical but relatively rare; therefore, they were classified as important outcomes rather than included as standalone critical outcomes.

Eligibility criteria

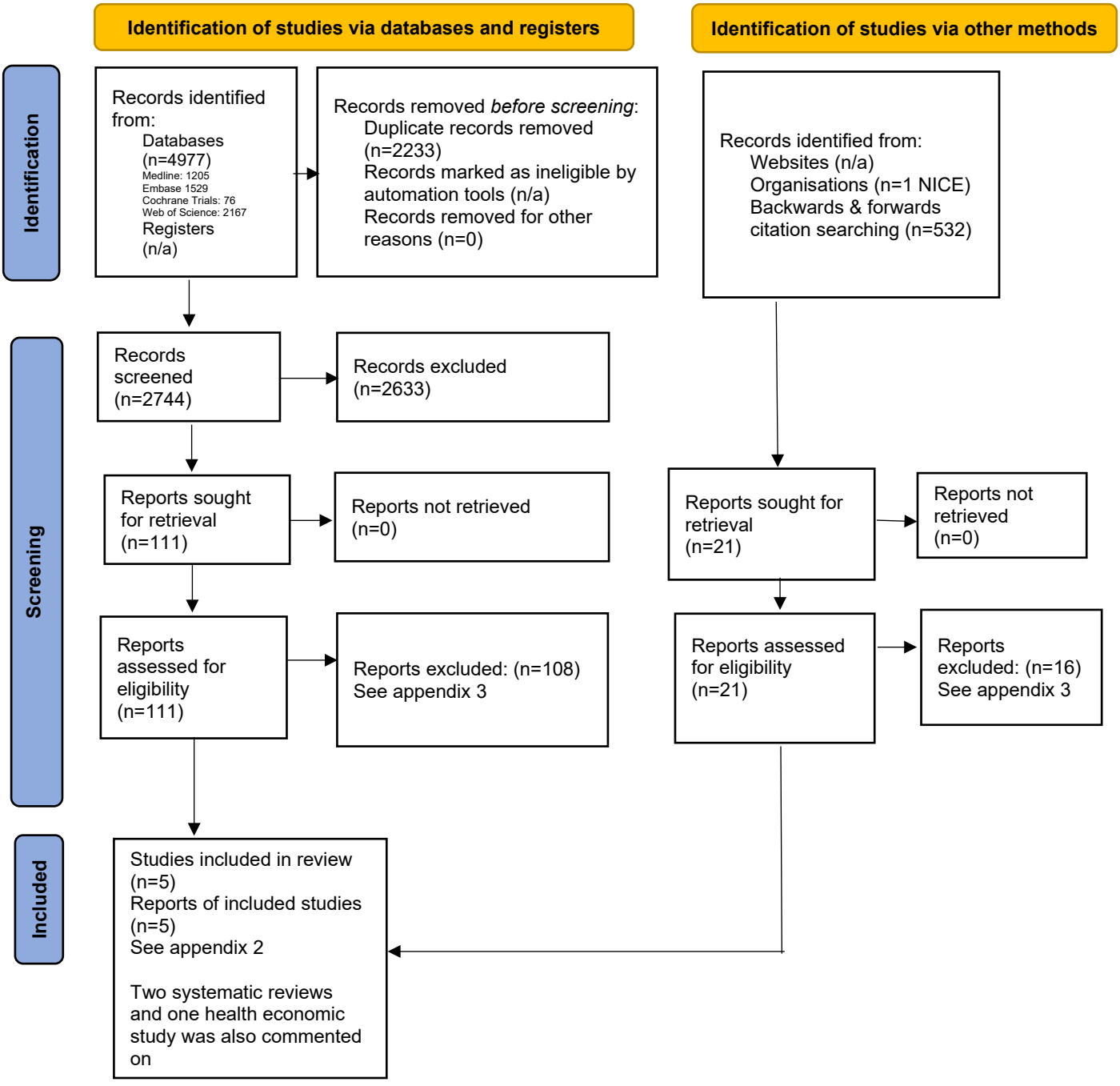
Study design:
Systematic reviews published 2022 or later
Randomised controlled trials (any number of patients)
Cohort studies if ≥ 500 patients

Language:
English, Danish, Norwegian, Swedish

Publication date: 2021- for original articles, 2022- for systematic reviews

Selection process – flow diagram

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources



From: Page et al., 2021

Summary of Search Strategy Modifications to the NICE Protocol

Search strategies were based on those in the NICE guideline (Frampton et al., 2021). The search strategies for both EMBASE and MEDLINE via Ovid were revised to improve specificity and relevance.

Search strategies

Database: MEDLINE (OvidSP)
Date: 30 Sep 2025
No. of results: 1,085
Search updated: 13 Feb 2026, 120 results

#	Searches	Results
1	Pre-Eclampsia/	38927
2	(preeclamp* or pre eclamp* or preclamp* or pre clamp*).ab,kf,ti.	46806
3	((eclampt* or gestational or gravidum or maternal or pregnan*) adj5 tox?emi*).ab,kf,ti.	5278
4	(?edema adj3 hypertension adj3 proteinuria).ab,kf,ti.	229
5	gestosis.ab,kf,ti.	1247
6	Hypertension, Pregnancy-Induced/	5819
7	(pregnan* adj3 hypertens*).ab,kf,ti.	17994
8	(gestation* adj3 hypertens*).ab,kf,ti.	6974
9	((maternal or maternity) adj3 hypertens*).ab,kf,ti.	2435
10	Pregnant People/	17064
11	Pregnancy/	1049956
12	Pregnancy Trimester, Second/ or Pregnancy Trimester, Third/	29018
13	Pregnancy Complications/ or Pregnancy Complications, Cardiovascular/	118484
14	10 or 11 or 12 or 13	1050901
15	Hypertension/	270811
16	hypertens*.ab,kf,ti.	572210
17	15 or 16	627108
18	14 and 17	36016
19	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 18	82581
20	Placenta Growth Factor/	2722
21	Vascular Endothelial Growth Factor Receptor-1/	5093
22	(Placenta* growth factor* or PlGF).ab,kf,ti.	4602
23	(VEGFR1 or VEGFR 1).ab,kf,ti.	3394
24	(fms-like tyrosine kinase* or FLT 1 or sFLT 1 or FLT1 or sFLT1).ab,kf,ti.	7353
25	(angiogenic adj3 (marker* or biomarker* or bio-marker*)).ab,kf,ti.	1721
26	(alere* or BRAHMS* or DELFIA* or elecsys* or kryptor* or perkinelmer* or quidel* or roche* or thermo or thermofisher* or xpress*).ab,kf,ti.	40251
27	20 or 21 or 22 or 23 or 24 or 25 or 26	55196
28	19 and 27	3322
29	animals/ not (animals/ and humans/)	5345252
30	(animal or animals or rat or rats or mouse or mice or rodent or rodents or dog or dogs or cat or cats or cow or cows or hamster or hamsters or koalas or rabbit or rabbits or swine or murine or porcine or horses or horse or goats or goat or cadaver or cadaveric).ti.	2286543

31	29 or 30	5836135
32	28 not 31	2994
33	limit 32 to (danish or english or norwegian or swedish)	2931
34	**limit 33 to yr="2021 -Current"**	**1085**

Database: Embase 1974 to 2025 September 29 (OvidSP)
Date: 30 Sep 2025
No. of results: 1,373
Search updated: 13 Feb 2026 (1974 to 2026 February 11), 156 results

#	Searches	Results
1	preeclampsia/ or "eclampsia and preeclampsia"/	86982
2	(preeclamp* or pre eclamp* or preclamp* or pre clamp*).ti,ab,kf.	74032
3	((eclampt* or gestational or gravidum or maternal or pregnan*) adj5 tox?emi*).ab,kf,ti.	2177
4	(?edema adj3 hypertension adj3 proteinuria).ab,kf,ti.	378
5	gestosis.ab,kf,ti.	1326
6	maternal hypertension/	33117
7	(pregnan* adj3 hypertens*).ab,kf,ti.	27632
8	(gestation* adj3 hypertens*).ab,kf,ti.	11804
9	((maternal or maternity) adj3 hypertens*).ab,kf,ti.	3914
10	pregnancy/	763311
11	pregnancy complication/	75775
12	cardiovascular pregnancy complication/	93
13	pregnancy disorder/	10406
14	exp pregnant person/	143044
15	second trimester pregnancy/ or third trimester pregnancy/	66824
16	10 or 11 or 12 or 13 or 14 or 15	897859
17	Essential hypertension/ or hypertension/	916423
18	hypertens*.ab,kf,ti.	916069
19	17 or 18	1266789
20	16 and 19	53927
21	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 20	139359
22	placental growth factor/	8305
23	vasculotropin receptor 1/	12950
24	(Placenta* growth factor* or PlGF).ab,kf,ti.	7570
25	(VEGFR1 or VEGFR 1).ab,kf,ti.	5909
26	(fms-like tyrosine kinase* or FLT 1 or sFLT 1 or FLT1 or sFLT1).ab,kf,ti.	11369
27	(angiogenic adj3 (marker* or biomarker* or bio-marker*)).ab,kf,ti.	2786
28	(alere* or BRAHMS* or DELFIA* or elecsys* or kryptor* or perkinelmer* or quidel* or roche* or thermo or thermofisher* or xpress*).ab,kf,ti.	86087
29	22 or 23 or 24 or 25 or 26 or 27 or 28	114983
30	21 and 29	6426
31	animal/ not (animal/ and human/)	1267024

32	(animal or animals or rat or rats or mouse or mice or rodent or rodents or dog or dogs or cat or cats or cow or cows or hamster or hamsters or koalas or rabbit or rabbits or swine or murine or porcine or horses or horse or goats or goat or cadaver or cadaveric).ti.	2485812
33	31 or 32	3441212
34	30 not 33	5889
35	limit 34 to (danish or english or norwegian or swedish)	5725
36	limit 35 to yr="2021 -Current"	1905
37	**limit 36 to (embase or medline)**	**1373**

Database: The Cochrane Library, Reviews and Trials only
Date: 1 Oct 2025
No. of results: 61
Cochrane reviews: 0
Trials: 61
Search updated: 13 Feb 2026, 15 results
Cochrane reviews: 0
Trials: 15

ID	Search	Hits
#1	MeSH descriptor: [Pre-Eclampsia] explode all trees	1579
#2	(preeclamp* or pre eclamp* or preclamp* or pre clamp*):ti,ab,kw (Word variations have been searched)	5661
#3	(((eclampt* or gestational or gravidum or maternal or pregnan*) near/4 tox?emi*)):ti,ab,kw (Word variations have been searched)	71
#4	((?edema near/2 hypertension near/2 proteinuria)):ti,ab,kw (Word variations have been searched)	8
#5	(gestosis):ti,ab,kw (Word variations have been searched)	27
#6	MeSH descriptor: [Hypertension, Pregnancy-Induced] this term only	419
#7	((pregnan* near/2 hypertens*)):ti,ab,kw (Word variations have been searched)	1907
#8	((gestation* near/2 hypertens*)):ti,ab,kw (Word variations have been searched)	819
#9	(((maternal or maternity) near/2 hypertens*)):ti,ab,kw (Word variations have been searched)	996
#10	MeSH descriptor: [Pregnant People] this term only	1069
#11	MeSH descriptor: [Pregnancy] this term only	33290
#12	MeSH descriptor: [Pregnancy Trimester, Second] this term only	814
#13	MeSH descriptor: [Pregnancy Trimester, Third] this term only	803
#14	MeSH descriptor: [Pregnancy Complications] this term only	2528
#15	MeSH descriptor: [Pregnancy Complications, Cardiovascular] this term only	412
#16	#10 OR #11 OR #12 OR #13 OR #14 OR #15	33526
#17	MeSH descriptor: [Hypertension] this term only	23814
#18	(hypertens*):ti,ab,kw (Word variations have been searched)	83264
#19	#17 OR #18	83264
#20	#16 AND #19	1580
#21	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #20	7526
#22	MeSH descriptor: [Placenta Growth Factor] this term only	113
#23	MeSH descriptor: [Vascular Endothelial Growth Factor Receptor-1] this term only	114
#24	(((Placenta* growth factor*) or PlGF)):ti,ab,kw (Word variations have been searched)	682
#25	(VEGFR1 or "VEGFR 1"):ti,ab,kw (Word variations have been searched)	373

#26	((fms-like tyrosine kinase*) or "FLT 1" or "sFLT 1" or FLT1 or sFLT1):ti,ab,kw (Word variations have been searched)	469
#27	((angiogenic near/2 (marker* or biomarker* or bio-marker*))):ti,ab,kw (Word variations have been searched)	143
#28	(alere* or BRAHMS* or DELFIA* or elecsys* or kryptor* or perkinelmer* or quidel* or roche* or thermo or thermofisher* or xpress*):ti,ab,kw (Word variations have been searched)	6455
#29	#22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28	7864
#30	#21 AND #29	370
#31	(clinicaltrials OR trialsearch):so	591573
#32	(conference proceeding):pt	266041
#33	#31 OR #32	857614
#34	#30 NOT #33	179
Limit Cochrane Reviews to publication 2022- **Limit Cochrane Trials to publication year 2021**		**0** **61**

Database: Web of Science Core Collection
Entitlements: -WOS.SCI: 1970 to 2025, - WOS.AHCI: 1975 to 2025, - WOS.BHCI: 2005 to 2025, - WOS.BSCI: 2005 to 2025, - WOS.ESCI: 2020 to 2025, - WOS.ISTP: 1990 to 2025, - WOS.SSCI: 1970 to 2025, - WOS.ISSHP: 1990 to 2025
Date: 1 Oct 2025
No. of results: 1,986
Search updated: 13 Feb 2026, 181 results

#	Search Query	Results
1	preeclamp* or "pre eclamp*" or "pre-eclamp*" or preclamp* or "pre clamp*" or "pre-clamp*" (Topic)	58765
2	TS=((eclampt* or gestational or gravidum or maternal or pregnan*) NEAR/4 tox$emi*)	1153
3	TS=((?edema NEAR/2 hypertension NEAR/2 proteinuria))	36
4	TS=(gestosis)	608
5	TS=((pregnan* NEAR/2 hypertens*))	18954
6	TS=((gestation* NEAR/2 hypertens*))	7536
7	TS=(((maternal or maternity) NEAR/2 hypertens*))	2470
8	#7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1	72074
9	TS=(((Placenta* growth factor*) or PlGF))	20380
10	TS=(VEGFR1 or "VEGFR 1")	3599
11	TS=((fms-like tyrosine kinase*) or "FLT 1" or "sFLT 1" or FLT1 or sFLT1)	8695
12	TS=((angiogenic NEAR/2 (marker* or biomarker* or bio-marker*)))	1891
13	TS=(alere* or BRAHMS* or DELFIA* or elecsys* or kryptor* or perkinelmer* or quidel* or roche* or thermo or thermofisher* or xpress*)	158907
14	#9 OR #10 OR #11 OR #12 OR #13	189170
15	#14 AND #8	7186
16	TI=(animal OR animals OR rat OR rats OR mouse OR mice OR rodent OR rodents OR dog OR dogs OR cat OR cats OR cow OR cows OR hamster OR hamsters OR koalas OR rabbit OR rabbits OR swine OR murine OR porcine OR horses or horse OR goats OR goat OR cadaver OR cadaveric)	2874134
17	#15 not #16	6667
18	#15 not #16 and Article or Review Article (Document Types)	6118
19	#15 not #16 Timespan: 2021-01-01 to 2025-10-01	2000
20	**#15 not #16 and English (Languages) Timespan: 2021-01-01 to 2025-10-01**	**1986**

Citation searching

A backwards citation search in Web of Science [17 Nov 2026] resulted in 525 records after deduplication. Systematic reviews and guidelines assessed for eligibility in this report / Relevant systematic reviews / Reports included in this report were used as seed references. A manual citation search of Frampton et al. (2021) was also done to identify articles corresponding to our PICO.

Articles used in backwards citation searching:

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Yang M, Bai Y, Li M, Lin X, Duan X, Zhang X. Predictive value of the soluble fms-like tyrosine kinase 1 to placental growth factor ratio for preeclampsia in twin pregnancies: a systematic review and meta-analysis. Am J Obstet Gynecol MFM. 2024 Mar;6(3):101290. doi: 10.1016/j.ajogmf.2024.101290.

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Project: Clinical benefits and risks of angiogenic marker-guided management of women with suspected preterm pre-eclampsia

Appendix 2. Included studies

Author Year Country	Study Design	Study Period	Inclusion criteria	Type of test used	Supplier	Study Groups; Intervention (I) vs control (C)	Mean Age (years)	Nulliparous, number (%)	Outcome variables
Cerdeira 2019 UK	RCT	June 2015 to April 2017	≥18 years Suspected PE[a] between gw 24+0 - 37+0 Singleton pregnancy	SFlt-1/PlGF ratio ≤38 low risk >38 elevated risk	Roche e411 analyzer (Roche Diagnostics Limited, Burgess Hill, UK)	I: n=186 C: n=184	I: 30.9 C: 31.1	I: 86 (46.2) C: 94 (51.1)	**Primary outcome:** PE-related inpatient admission within 24 hours of the test, within 7 days, or by delivery. Secondary outcomes: incidence of PE within 7 days and by the time of delivery; birth weight; Special Care Baby Unit admission; Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) score at delivery; platelet count, renal, and hepatic function measured using blood tests at time of first clinical assessment (ie, study enrollment/baseline) and time of delivery.
Hayes Ryan 2021a Ireland	Stepped wedge CRT	29 June 2017 to 26 April 2019	Suspected PE[b] between gw 20+0-36+6 Singelton pregnancy	PlGF Abnormal <100 pg/ml and highly abnormal <12 pg/ml	An automated Triage Meterpro (Quidel San Diego, CA, USA)	I: n=1017 C: n=1202	I: 31.8 C: 31.9	I: 373 (36.7) C: 487 (40.5)	**Co-primary outcomes:** Maternal morbidity composite (Confirmed placental abruption, intensive care admission, central nervous system compromise [eclampsia, Glasgow Coma Scale <13, cerebral haemorrhage or infarct, cortical blindness, retinal detachment, transient ischaemic attack, reversible ischaemic neurological deficit], cardiorespiratory compromise [myocardial ischaemia or infarction, blood oxygen saturation <90%, intubation (other than for caesarean section), pulmonary oedema, need for positive inotrope support], haematological compromise (transfusion of any blood product, platelet count <100x10^9/L)], liver compromise [hepatic dysfunction (ALT or AST >70 IU/L), haematoma, rupture], kidney compromise [acute renal insufficiency (creatinine >150 mikromol/L), hemodialysis], severe hypertension (systolic blood pressure ≥160 mm Hg on at least one occasion in either antenatal or postnatal period) and

Appendix 2. Included studies

Author Year Country	Study Design	Study Period	Inclusion criteria	Type of test used	Supplier	Study Groups; Intervention (I) vs control (C)	Mean Age (years)	Nullipar ous, number (%)	Outcome variables
									neonatal morbidity composite (perinatal death or death before hospital discharge, neonatal intensive care unit admission for ≥48 hours, birthweight ≤ 5th customised centile, apgar score <7 at 5 minutes, umbilical artery acidosis at birth (cord pH <7.2), admission to neonatal unit, respiratory distress syndrome, intraventricular haemorrhage, necrotising enterocolitis). Secondary outcomes: each component of the composite primary outcome. Post hoc analyses include three additional outcomes: time from enrollment until pre-eclampsia diagnosis, maternal and neonatal composite outcomes (same as PARROT UK trial; Duhig, 2019).
Duhig 2019a UK	Stepped wedge CRT	June 13 2016 to October 27 2017	≥18 years Suspected PE[c] between gw 20+0 - 36+6 Live singleton fetus	PlGF cut offs <12 pg/mL or 12-100 pg/mL	Triage instrument (Quidel Cardiovascular INC, San Diego, CA)	I: n=576 C: n=447	I: 31.9 C: 31.5	I: 317 (55) C: 211 (47)	**Primary outcome:** Time in days from trial entry to a documented diagnosis of PE. Secondary maternal composite outcomes: maternal death, eclampsia, a Glasgow Coma Scale score of less than 13, stroke, transient ischaemic attack, cortical blindness or retinal detachment, posterior reversible encephalopathy, a requirement for positive inotropic support, a requirement for parenteral infusion of a third-line antihypertensive, myocardial ischaemia or infarction, blood oxygen saturations of less than 90%, 50% FiO2 (or higher) for more than 1 h, a requirement for intubation (other than for caesarean section), pulmonary oedema, a requirement for transfusion of blood products, a platelet count of less than 50×10^9 platelets per L, hepatic dysfunction, haematoma or hepatic rupture, severe acute kidney injury

Appendix 2. Included studies

Author Year Country	Study Design	Study Period	Inclusion criteria	Type of test used	Supplier	Study Groups; Intervention (I) vs control (C)	Mean Age (years)	Nulliparous, number (%)	Outcome variables
									(defined as concentrations of creatinine >150 µmol/L or >200 µmol/L in chronic kidney disease a requirement for dialysis), or placental abruption. Secondary perinatal outcomes: gestation at delivery, preterm birth before 37 weeks of gestation, birthweight and birthweight centile, Apgar scores at 5 min after birth, admission to a neonatal unit, perinatal death (defined as deaths from 24 weeks of gestation, including those defined as stillbirths, until 7 completed days after birth), and late neonatal deaths (deaths between 8 and 27 complete days after birth). Post hoc analyses: ≥1 of necrotising enterocolitis stage 2 and 3, retinopathy of prematurity, intraventricular haemorrhage, respiratory distress syndrome, seizures, bronchopulmonary dysplasia, still birth, early neonatal death, and late neonatal death before or at 28 days. Maternal health care resource use: outpatient attendances and inpatient nights in hospital. Neonatal resource use: nights in the highest-level care (intensive and high-dependency care) and special care.

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Appendix 2. Included studies

Author Year Country	Study Design	Study Period	Inclusion criteria	Type of test used	Supplier	Study Groups; Intervention (I) vs control (C)	Mean Age (years)	Nulliparous, number (%)	Outcome variables
Sibiude 2025 France	RCT	April 26, 2018 to March 12, 2020	≥18 years Hospitalised for suspected PE[d] between gw 24+0 and 34+6 Singleton pregnancies	sFlt-1/PlGF ratio <38, 38-85, >85	Roche Cobas e analyzer (Roche Diagnostics Limited, Berlin	I: n=40 C: n= 40	I: 34 C: 33	I: 14 (35.0) C: 19 (47.5)	Primary outcome: proportion of patients hospitalized for more than 24 h. Secondary outcomes: composite (eclampsia, HELLP syndrome, abruptio placentae, DIC, delivery before 34 gw, IUGR <3d percentile, stillbirth); severe hypertension, confirmed diagnosis of PE, caesarean section rate, postpartum haemorrhage > 500 mL, eclampsia, HELLP syndrome, DIC, abruptio placentae, and time from randomization to delivery. Secondary neonatal outcomes: gestational age at delivery; birth weight; a composite of severe perinatal morbidity (including perinatal mortality, prematurity < 34 gw, birth weight < 3rd percentile).
Sharp 2018 UK Germany Austria and Australia	Cohort study	April 2014 to March 2016	Suspected PE[e] or FGR < gw 35	PlGF <12 pg/ml, 12-100 pg/ml, >100 pg/ml	Triage System (Alere, San Diego, CA, USA)	I (MAPPLE) revealed PlGF): n=396 C (PELICAN) concealed PlGF): n=287	I: 31 C: 32	I: 208 (52.7) C: 164 (57.1)	Primary outcome not defined. Final diagnosis of pre-eclampsia, maternal death, eclampsia, stroke, hypertensive encephalopathy, cortical blindness or retinal detachment, cardiovascular/respiratory, myocardial infarction, intubation (other than for caesarean section), pulmonary oedema, platelets < 50 × 10^9/L (withou transfusion), DIC, thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome, hepatic dysfunction (Alanine transaminase ≥ 70 IU/L), hepatic rupture; acute fatty liver of pregnancy, creatinine > 150 µmol/L, dialysis, placental abruption, infants with composite perinatal adverse outcome (perinatal death or neonatal adverse, perinatal death, stillbirth, early neonatal death, infants with neonatal adverse outcomes, neonatal adverse outcomes, respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular haemorrhage (Grade 3 or 4), necrotising

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Appendix 2. Included studies

Author Year Country	Study Design	Study Period	Inclusion criteria	Type of test used	Supplier	Study Groups; Intervention (I) vs control (C)	Mean Age (years)	Nulliparous, number (%)	Outcome variables
									enterocolitis, retinopathy of prematurity, infants admitted to neonatal unit.

NOTE: RCT, randomised controlled trial; gw, gestational week; UK, United Kingdom; CRT, cluster randomised trial; PE, preeclampsia; FGR, fetal growth restriction; HELLP, hemolysis, elevated liver enzymes, low platelet count; DIC, disseminated intravascular disease; IUGR, intrauterine growth restriction. [a]new onset elevated blood pressure or worsening of preexisting hypertension or new onset proteinuria (any protein in the urine >trace on dip-stick) or worsening of preexisting proteinuria or new onset headache, visual disturbance, edema or right upper quadrant pain, or any other clinical suspicion of preeclampsia. [b]Presenting with suspected pre-eclampsia (one or more of the following): Hypertension, dipstick proteinuria, headache, visual disturbances, epigastric or right upper quadrant pain, increasing oedema, suspected fetal growth restriction, if the healthcare provider deems that the woman requires further evaluation for possible pre-eclampsia. [c]Suspected pre-eclampsia was defines as new-onset or worsening of existing hypertension, dipstick proteinuria, epigastric or right upper-quadrant pain, a headache with visual disturbances, fetal growth restriction, or abnormal maternal blood tests that were suggestive of disease (such as thrombocytopenia or hepatic or renal dysfunction). [d]Hypertension (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg), proteinuria (> 0.3 g/24 h or 0.3 g/l or urine dipstick ≥ 3 + or proteinuria/creatinin ratio > 30 mg/mmol), epigastric pain, generalized edema, elevated liver enzymes (> 1.5 upper limit of normal (ULN)), or thrombocytopenia (< 150,000/mm3). [e]PELICAN: Symptoms or signs included headache, visual disturbances, epigastric or right upper quadrant pain, hypertension, dipstick proteinuria, or suspected fetal growth restriction. Participants were included if the healthcare provider deemed that the woman required evaluation for suspected preeclampsia. MAPPLE: Suspected pre-eclampsia or fetal growth restriction.

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Appendix 3. Excluded articles

Author, year	Reason for exclusion
ACOG, 2024	Wrong publication type, clinical practice update
Alhudhud, 2024	Wrong study design, non-comparative study
Alipova, 2025	Wrong study design, non-systematic review
Alvarez-Fernandez, 2014	cut off outside company's recommendation. Retrospective cohort study with few patients (378). no control group
Alvarez-Fernandez, 2016	Retrospective cohort study with too few patients (257), no control, cut off outside company's recommendation
Andersen, 2019	No intervention, no control
Andersen, 2021	Wrong study design, non-comparative study, no comparison test versus no test
Andersen, 2023	Wrong publication type, conference abstract
Anto, 2021	Wrong population, tested before gestational week 20
Anto, 2022	Wrong population, tested before gestational week 20
Anwer, 2025	Wrong study design, non-comparative study
Arechvo, 2024	Wrong population, routine visit
Audette, 2021	Wrong population, tested before gestational week 20
Azzi, 2025	Wrong population
Bacmeister, 2025	Wrong population, all women eligible not only suspected PE. Wrong intervention.
Basyir, 2021	Wrong study design, non-comparative study
Bednarek-Jedrzejek, 2025	Wrong study design, non-comparative study
Binder, 2020	Too small sample, no comparison
Bliyeva, 2025	Wrong population, women already diagnosed with PE.
Bongers-Karmaoui, 2021	Wrong study design, non-comparative study
Bongers-Karmaoui, 2022	Wrong study design, non-comparative study
Bucher, 2024	Wrong population (both HDP and PE), only prediction. No control.
Cerdeira, 2021a	Only accuracy of test PPV, no intervention.
Cerdeira, 2021b	Duplicate of Cerdeira 2021a, same reason for exclusion
Cerdeira, 2021c	Only accuracy of test PPV, no intervention.
Cerdeira, 2022	Only accuracy of test, no intervention or control.
Chaemsaithong, 2023	Wrong population (women without suspected PE).
Chaiworapongsa, 2023	Wrong population, already diagnosed with PE
Chantraine, 2021	Stand-alone for test, not as add on to standard care.
Chen, 2022	Wrong outcome, FGR not PE. Wrong population (gestational week 19).
Chen, 2024	Wrong study design, non-comparative study, all women tested
Danielli, 2022	Systematic review with a very broad scope, not only sFlt-1/PlGF, checked on references referring to sFlt-1/PlGF

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Appendix 3. Excluded articles

Author, year	Reason for exclusion
Dathan-Stumpf, 2022	Too small cohort (n=302). Prognosis, not correct outcome.
De Oliveira, 2023	Wrong population, 80-90% PE, not suspected PE
Diethelm, 2025	Wrong intervention, wrong study design, non-comparative study
Droge, 2021	Wrong study design, non-comparative study
Duhig, 2019c	Wrong publication type, meeting abstract
Duhig, 2019d	Wrong publication type, meeting abstract
Duhig, 2021a	Wrong population, already diagnosed with PE
Duhig, 2021b	Wrong population, already diagnosed with PE
Duhig, 2021c	Wrong outcome, comparison post hoc between different levels of PlGF.
Dymara-Konopka, 2023	Wrong study design, too few patients
Döbert, 2022	Wrong intervention, several screening markers, all women tested
Elawad, 2025	Wrong focus, looks at association between biomarkers and PE, but no testing
Elbarbary, 2025	Wrong intervention, several screening markers, included studies about PlGF are too old
Enengl, 2025	Wrong population, already diagnosed with PE
Espinoza, 2024	Wrong outcome
Farina, 2025a	Wrong population, routine visit, wrong study design, non-comparative study
Farina, 2025b	Wrong population, routine visit, wrong study design, non-comparative study
Gannoun, 2023	Wrong study design, too few patients, unclear when sFlt-1/PlGF was measured
Garay, 2023	Wrong PICO, health economic study
Garcia-Manau, 2021	Wrong study design, too few patients
Garcia-Manau, 2025	Wrong PICO
Garrido-Giménez, 2023	Wrong study design, non-comparative study, secondary analysis of RCT but only used population where every woman was tested
Garrido-Giménez, 2024	Wrong publication type, meeting abstract
Giardini, 2024	Wrong study design, too few patients, non-comparative study
Gibbone, 2021	Wrong intervention, markers with a focus on cardiovascular function
Gibson, 2025	Wrong population, all pregnant women and not with suspected PE
Gladstone, 2024	Wrong population, routine screening for gestational diabetes
Golob, 2024	Wrong population, wrong study design, every woman tested
Goutallier, 2025	Wrong PICO, health economic study
Guinazu, 2024	Wrong PICO, health economic study

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Appendix 3. Excluded articles

Author, year	Reason for exclusion
Gupta, 2024	Wrong study design, too few patients, non-comparative study
Hayes-Ryan, 2021b	Wrong study design, too few patients, non-comparative study
Hendershot, 2022	Wrong intervention, validation of different assays and no focus on patient outcomes
Hughes, 2025	Wrong study design, too few patients, non-comparative study
Hurrell, 2024c	Wrong publication type, conference abstract
Hurrell, 2024a	Wrong control (secondary testing)
Hurrell, 2024b	Wrong control (secondary testing)
Kamphof, 2025	Wrong study design, too few patients, non-comparative study
Kanani, 2024	Wrong publication type, conference abstract
Khosla, 2021	Health economic study. Wrong population, too small cohort.
Kifle, 2022	Diagnostic accuracy
Kinugawa, 2025	Wrong study design, non-comparative study
Klein, 2016	Insufficient number of patients
Kluviers, 2025b	Duplicate of Kluviers, 2025a
Kluivers, 2025a	Wrong population, 36% with PE. Wrong intervention (combination of angiongenic markers and other factors)
Kosinska-Kaczynska, 2025	Systematic review with wrong focus/outcome, no studies on test versus no test
Kwiatkowski, 2021	Wrong study design, non-comparative study, every woman tested
Lafuente-Gabuza, 2020	No control group, cut off outside company's recommendation
Lau, 2022	Wrong population, no comparison.
Li, 2024	Wrong study design, non-comparative study, every woman tested
Litwinska, 2021a	Wrong population, wrong study design, every woman tested
Litwinska, 2021b	Wrong population, wrong study design, every woman tested
Luo, 2025	Wrong study design, too few patients, every woman tested
Magee, 2024	Wrong population, wrong study design, every woman tested
Manriquez Rocha, 2018	Wrong study design, non-randomised. Too small cohort.
McLaughlin, 2021	Wrong study design, every woman tested
Musilova, 2024	Wrong study design, case-control study, too few patients
Noonan, 2025	Wrong study design, non-comparative study, every woman tested

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Appendix 3. Excluded articles

Author, year	Reason for exclusion
Ohkuchi, 2021a	Insufficient number of patients.
Ohkuchi, 2021b	Based on the same study population as Ohkuchi, 2021a. See reason for exclusion for Ohkuchi, 2021a.
Ormesher, 2018	No comparison
Palma Dos Reis, 2025	Only accuracy of test, no intervention or control.
Pan, 2025	Wrong study design, non-comparative study, every woman tested
Papastefanou, 2024	Wrong population, all pregnant women not suspected PE
Parry, 2022	Wrong intervention, several screening markers, no focus on sFlt-1/PlGF
Patel, 2024	Wrong intervention, no comparison. Only prediction.
Peguero, 2021	Wrong population, already diagnosed with PE
Qi, 2025	Wrong study design, too few patients
Rahman, 2024	Wrong study design, no comparison of test versus no test
Rezk, 2023	Wrong study design, no comparison of test versus no test
Roubalova, 2025	Wrong population, only healthy women not suspected PE.
Sapantzoglou, 2023	Systematic review with wrong focus; investigated different levels of rations in twin versus singleton births
Sarno, 2021	Wrong population, only healthy women not suspected PE.
Satorres, 2023	Wrong population with healthy women as well and too few included.
Schiattarella, 2023	Wrong population, routine hospital visit
Shemies, 2022	Wrong study design, too few patients
Sovio, 2021	Wrong population, unselected patients, no suspected PE
Sovio, 2023	Wrong population, wrong study design, no comparison of test versus no test
Sroka, 2023	Wrong study design
Soundararajan, 2021	NICE post hoc, insufficient number of patients.
Suresh, 2023	Wrong population, already diagnosed with PE
Tanner, 2022	Wrong study design, too few patients, non-comparative study
Tarca, 2022	Wrong intervention, building a model using several markers including PLGF
Thadhani, 2022	Wrong population (confirmed PE)
Ukah, 2017	NICE post hoc, published before 2021.
Wah, 2024	Diagnostic accuracy, wrong outcome.

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Appendix 3. Excluded articles

Author, year	Reason for exclusion
Wang, 2025	Wrong study design, no comparison of test versus no test
Wind, 2022	Wrong intervention (sFlt-1/PlGF ratio in combination with the spot urine protein/creatinine ratio).
Yadav, 2022	Wrong study design, too few patients
Yang, 2022	Wrong study design, non-comparative study
Yang, 2024	Too small sample, no intervention
Zhang, 2025	Systematic review where all included studies were too old or with too few patients

PE, pre-eclampsia; PPV, positive predictive value; PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase-1; HDP, hypertensive disorders of pregnancy; RCT, randomised controlled trial; FGR, fetal growth restriction; PICO, population, intervention, comparison, outcome.

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* + No or minor problems
? Some problems
- Major problems

Appendix 4.1
Outcome variable: Maternal mortality

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Duhig et al., 2019a UK	Stepped-wedge CRT	1,023 I: 576 C: 447	I: 3 lost to follow up C: 1 withdrew consent	0/573	0/446	Follow-up time after birth not defined	+	?	-
Hayes-Ryan et al., 2021a Ireland	Stepped-wedge CRT	2,291 I: 1,057 C: 1,234	I: 9 lost to follow up, 1 withdrew consent, 30 recruited during transition phase C: 4 lost to follow up, 28 recruited during transition phase	1* /1,017 (0.1%)	0/1,202	Follow-up time after birth was 12 weeks. *10 weeks after birth due to acute complications of a known underlying cardiac condition (=indirect late maternal mortality).	+	?	-
Sharp et al., 2018 UK, Germany, Austria, Australia	Cohort study	683 I: 396 C: 287	Not reported	0/396	0/287	Follow-up time after birth not defined	-	-	-

C=control, CRT=cluster randomised trial, I=intervention, UK=United Kingdom

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* + No or minor problems
? Some problems
- Major problems

Appendix 4.3
Outcome variable: Maternal morbidity composite

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention n (%)	Control n (%)				
Duhig et al., 2019a UK	Stepped-wedge CRT	1,023 I: 576 C: 447	I: 3 lost to follow up C: 1 withdrew consent	22/573 (4) AOR* 0.32 (95% CI 0.11 to 0.96) P=0.043	24/446 (5)	*Adjusted for time and study site Women could have several adverse events No statistics	+	?/-	?
Hayes-Ryan et al., 2021a Ireland	Stepped-wedge CRT	2,291 I:1,057 C:1,234	I: 9 lost to follow up, 1 withdrew consent, 30 recruited during transition phase C: 4 lost to follow up, 28 recruited during transition phase	330/1017 (32.4a) Post hoc analysis (same composites as PARROT UK trial) 106 (10.42)	457/1202 (38.0) Risk ratio* 1.01 (0.76 to 1.36) P=0.92 Risk ratio** 1.02 (0.80 to 1.31) P=0.87 Post hoc analysis (same composites as PARROT UK trial) 131 (10.90) ARR 1.10 (95% CI 0.79 to 1.52) (Table S6)	*Adjusted Poisson: time and hospital ** Poisson regression models adjusted as pre-specified for age, body mass index, smoking, ethnic origin, gestational age at booking, public versus private obstetric care, and maternal comorbidities (chronic hypertension, chronic renal disease, systemic lupus erythematosus/antiphospholipid syndrome, and pre-existing diabetes).	+	?/-	?
Sibiude et al., 2025, France	RCT	81 I:40 C:40	1 excluded, unclear which group	GW<30: 47% P=0.57 GW 30-34: 40% P=0.47 Total 17/40 (42.5) P=0.37	GW<30: 57% GW 30-34: 50% Total 21/40 (52.5)	Divided into two subgroups: GW < 30 and GW between 30-34 Composite of adverse outcome included HELLP syndrome, delivery<34 WG, or prenatal suspicion of IUGR<3rd centile.	-	?	-

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* + No or minor problems
? Some problems
- Major problems

Appendix 4.3
Outcome variable: Maternal morbidity composite

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention n (%)	Control n (%)				
Sharp et al., 2018 UK, Germany, Austria, Australia	Cohort study	683 I:396 C:287	Not reported	47 (11.9) Risk ratio 1.17 (95% CI 0.76 to 1.82)	29 (10.1)		-	-	?

C=control, CI=confidence interval, I=intervention, UK=United Kingdom

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* + No or minor problems
? Some problems
- Major problems

Appendix 4.3
Outcome variable: Peri/neonatal mortality

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Duhig et al., 2019a UK	Stepped-wedge CRT	1,023 I: 576 C: 447	I: 3 lost to follow up C: 1 withdrew consent	Perinatal death 6/573 (1.04%) Early neonatal death 0/573 Late neonatal death 3/573 (0.52%) Neonatal mortality (early and late) 3/573 (0.52%) Intrauterine fetal deaths 7/573 (1.02%), includes 3 before viability (< 24 weeks (n=1) or >24 weeks but with birth weight <500g (n=2)) and 4 “viable” fetuses	Perinatal death 4/446 (0.70%) Early neonatal death 0/446 Late neonatal death 1/446 (0.22%) Neonatal mortality (early and late) 1/446 (0.22%) Intrauterine fetal death 6/446 (1.35%), includes 3 before viability (<24 week) and 3 “viable” fetuses	Perinatal death defined as deaths from 24 weeks of gestation, including those defined as stillbirths (also those with birthweight < 500g) and early neonatal death until 7 completed days after birth. Late neonatal death defined as deaths between 8–27 complete days of life. Intrauterine fetal death includes intrauterine fetal death before viability (<24 weeks but also >24 weeks with birthweight < 500g) No statistics in article.	+	?/-	+
Hayes-Ryan et al., 2021a Ireland	Stepped-wedge CRT	2,291 I:1,057 C:1,234	I: 9 lost to follow up, 1 withdrew consent, 30 recruited during transition phase	Perinatal death 8/1,017 (0.79%) RR 0.75 (95% CI 0.35 to 1.62) P= 0.47 Stillbirth 5/1,017 (0.49%) Neonatal death 3/1,017 (0.29%)	Perinatal death 17/1,202 (1.41%) Stillbirth 10/1,202(0.83%) Neonatal death 7/1,202 (0.58%)	Perinatal death or death before hospital discharge. Perinatal death not defined further. Component of primary neonatal morbidity composite.	+	?/-	-

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* + No or minor problems
? Some problems
- Major problems

Appendix 4.3
Outcome variable: Peri/neonatal mortality

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
			C: 4 lost to follow up, 28 recruited during transition phase			RR adjusted for time and hospital			
Sibiude et al., 2025, France	RCT	81 I:40 C:40	1 excluded, unclear which group	Perinatal death 0/40 Stillbirth 0/40 Neonatal death 0/40	Perinatal death 0/40 Stillbirth 0/40 Neonatal death 0/40	Stillbirth and neonatal death not defined	-	?	-
Sharp et al., 2018, UK, Germany, Austria, Australia	Cohort study	732 I:433 C:299	Not reported	Perinatal deaths 2/433 (0.46%) RR 0.16 (95% CI 0.03 to 0.74) Stillbirth 1/433 (0.23%) Early neonatal deaths 1/433 (0.23%) No statistics All perinatal deaths occurred in singletons: Perinatal deaths in singletons 2/356 (0.56%) Stillbirth 1/356 (0.28%) Early neonatal deaths 1/356 (0.28%) No statistics	Perinatal deaths 9/299 (3.01%) Stillbirth 7/299 (2.34%) Early neonatal deaths 2/299 (0.67%) All perinatal deaths occurred in singletons: Perinatal deaths in singletons 9/275 (3.27%) Stillbirth 7/275 (2.54%) Early neonatal deaths 2/275 (0.73%)	Multifetal pregnancies included, 9.1% in the intervention group and 4.2% in the control group.	-	-	-

C=control, CI=confidence interval, CRT, cluster randomised trial, I=intervention, OR= odds ratio, RCT=randomised controlled trial, RR=relative risk, UK=United Kingdom

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Appendix 4.4
Outcome variable: Composite peri/neonatal outcome

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention n (%)	Control n (%)				
Duhig et al., 2019a UK	Stepped-wedge CRT	1,023 I: 576 C: 447	I: 3 lost to follow up C: 1 withdrew consent	86 (15.0%) AOR 1.45 (95% CI 0.73 to 2.90)	63 (14.1%)	Composite of intraventricular haemorrhage (any grade), seizures, retinopathy of prematurity (any grade), respiratory distress syndrome, bronchopulmonary dysplasia, necrotising enterocolitis (stage 2 or 3), perinatal death and late neonatal death. Adjusted for time and site.	+	?/-	+
Hayes-Ryan et al., 2021a Ireland	Stepped-wedge CRT	2,291 I:1,057 C:1,234	I: 9 lost to follow up, 1 withdrew consent, 30 recruited during transition phase C: 4 lost to follow up, 28 recruited during transition phase	Based on protocol amendment (excluding umbilical artery acidosis at birth) 482/1,017 (47.59%) RR 1.03 (0.89 to 1.12) P=0.67 Based on original protocol (including umbilical artery acidosis at birth) (N=366) 254/366 (69.4%) but in report written 69.67	Based on protocol amendment (excluding umbilical artery acidosis at birth) 527/1,202 (43.84%) Based on original protocol (including umbilical artery acidosis at birth) (N=594) 363/594 (61.11%)	• Perinatal death or death before hospital discharge • Neonatal intensive care unit admission for /+) hours • Birthweight ≤5th customised centile* • Apgar score <7 at 5 minutes • Umbilical artery acidosis at birth (cord pH <7.2)	+	?/-	+

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Appendix 4.4
Outcome variable: Composite peri/neonatal outcome

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention n (%)	Control n (%)				
				Post hoc analysis (same composites as PARROT UK trial) 87/1,017 (8.55%) ARR 1.66 (95% CI 0.81 to 3.42) p=0.17	Post hoc analysis (same composites as PARROT UK trial) 85/1,202 (7.07%)	• Admission to neonatal unit • Respiratory distress syndrome • Intraventricular haemorrhage • Retinopathy of prematurity • Confirmed infection (confirmed on blood or cerebrospinal fluid cultures) • Necrotising enterocolitis			
Sibiude et al., 2025, France	RCT	81 I:40 C:40	1 excluded, unclear which group	GW < 30: 33% P=0.78 GW 30-34: 36% P=0.31 Total 14/40 (35.0%) P=0.49	GW <30: 29% GW 30-34: 50% Total 17/40 (42.5%)	A composite of severe perinatal morbidity (including perinatal mortality, prematurity<34 GW, birth weight<3rd percentile. Divided into two subgroups: GW < 30 and GW between 30-34	-	?	-
Sharp et al., 2018 UK, Germany, Austria, Australia	Cohort study	732 I:433 C:299	Not reported	131/433 (30.3%)	60/299 (20.1%)	Infants with composite perinatal adverse outcome	-	-	+

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Appendix 4.4
Outcome variable: Composite peri/neonatal outcome

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention n (%)	Control n (%)				
				Specified in study as 30.4% RR 1.51 (95% CI 1.15 to 1.98)		(perinatal death or neonatal adverse outcome. • Respiratory distress syndrome (RDS) • Bronchopulmonary dysplasia (BPD) • Intraventricular haemorrhage (IVH), grad 3–4 • Necrotising enterocolitis (NEC) • Retinopathy of prematurity (ROP)			

BPD=bronchopulmonary dysplasia, C=control, GW=gestational week, I=intervention, NEC=necrotising enterocolitis, RCT=randomised controlled trial, RDS=respiratory distress syndrome, ROP=retinopathy pf prematurity, RR=Risk Ratio, UK=United Kingdom, aRR=adjusted Risk Ratio

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* + No or minor problems
? Some problems
- Major problems

Appendix 4.5
Outcome variable: Diagnosis of pre-eclampsia

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Cerdeira et al. 2019, UK	RCT	374 I: 188 C: 186	I: 2 lost to follow up C. 2 lost to follow up	Total pre-eclampsia 47/186 (25.2%)	Total pre-eclampsia 38/184 (20.6%)	The diagnosis of preeclampsia was made according to the following criteria: diastolic BP ≥90 mmHg or systolic blood pressure ≥140 mmHg together with proteinuria (urine protein/creatinine ≥30 mg/ mmol) or serum creatinine >97 µmol/L, elevated liver transaminases to twice the normal concentration or platelets <100,000/dL. Superimposed pre-eclampsia was defined as an elevation in diastolic BP of >15 mmHg or systolic blood pressure >30 mmHg, together with (urine protein/creatinine ≥30 mg/mmol), or serum creatinine >97 µmol/L, elevated liver transaminases to twice the normal concentration, platelets<100000/dL.	?	?	?
Duhig et al., 2019a UK	Stepped-wedge CRT	1023 I: 576 C: 447	I: 3 lost to follow up	Total pre-eclampsia 205/573 (36%) Primary diagnosis pre-eclampsia 175 (31%)	Total pre-eclampsia 155/446 (35%)	Diagnostic criteria ISSHP	+	?/-	+

Project: Clinical benefits and risks of angiogenic marker-guided management of women with suspected preterm pre-eclampsia

* + No or minor problems
? Some problems
- Major problems

Appendix 4.5
Outcome variable: Diagnosis of pre-eclampsia

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
			C: 1 withdrew consent	Superimposed pre-eclampsia 30 (5%)	Primary diagnosis pre-eclampsia 126 (28%) Superimposed pre-eclampsia 29 (7%)				
Hayes-Ryan et al., 2021a Ireland	Stepped-wedge CRT	2291 I:1057 C:1234	I: 9 lost to follow up, 1 withdrew consent, 30 recruited during transition phase C: 4 lost to follow up, 28 recruited during transition phase	Total pre-eclampsia 138/1,017 (13.57%) Superimposed pre-eclampsia (background CHT) 9 (0.88%) Superimposed pre-eclampsia (background renal disease) 0 (0.0%) Superimposed pre-eclampsia (background CHT and renal disease) 2 (0.20%)	Total pre-eclampsia 177/1,202 (14.73%) Superimposed pre-eclampsia (background CHT) 8 (0.67%) Superimposed pre-eclampsia (background renal disease) 7(0.58%) Superimposed preeclampsia (background CHT and renal disease) 4 (0.33%)	Presented in appendix at bmj.com trial was purposely based on the HSE and NICE guidelines for hypertension in pregnancy	+	?/-	+
Sibiude et al., 2025, France	RCT	81 I:40 C:40	1 excluded, unclear which group	10/40 (25.0%) P=0.62 RR 0.8 (95% 0.4-1.7)	12/40 (30.0%)	Pre-eclampsia diagnosis was made according to the following criteria: diastolic blood pressure ≥90 mmHg or systolic blood pressure ≥140 mmHg combined with proteinuria (≥0.3 g/24 hours)	-	?	-
Sharp et al., 2018 UK, Germany, Austria, Australia	Cohort study	683 I:396 C:287	Not reported	193/396 (52.9%) RR 0.86 (95% CI0.75–0.99)	176 /287 (61.3%)	Criteria for pre-eclampsia no reported	-	-	?

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* + No or minor problems
? Some problems
- Major problems

Appendix 4.5
Outcome variable: Diagnosis of pre-eclampsia

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				

BP=blood pressure, C=control, CHT= chronic hypertension; CI=confidence interval, CRT=cluster randomised trial, HSE=Health Service Executive, I=intervention, ISSHP=International Society for the Study of Hypertension in Pregnancy, NICE, National Institute for Health and Care Excellence, RCT=randomised controlled trial, RR=risk ratio, UK=United Kingdom

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* + No or minor problems
? Some problems
- Major problems

Appendix 4.6
Outcome variable: Eclampsia

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Duhig et al., 2019a UK	Stepped-wedge CRT	1,023 I: 576 C: 447	I: 3 lost to follow up C: 1 withdrew consent	0/573	2/446 (0.45%)		+	?/-	-
Hayes-Ryan et al., 2021a Ireland	Stepped-wedge CRT	2,291 I:1,057 C:1,234	I: 9 lost to follow up, 1 withdrew consent, 30 recruited during transition phase C: 4 lost to follow up, 28 recruited during transition phase	0/1,017	2/1,202 (0.17%)	Numbers presented in appendix at bmj.com	+	?/-	-
Sibiude et al., 2025, France	RCT	81 I:40 C:40	1 excluded, unclear which group	0/40	0/40		-	?	-
Sharp et al., 2018 UK, Germany, Austria, Australia	Cohort study	683 I:396 C:287	Not reported	0/396	1/287 (0.35%)		-	-	-

C=control, CRT=cluster randomised trial, I=intervention, RCT=randomised controlled trial, RR=risk ratio, UK=United Kingdom

Project: Clinical benefits and risks of angiogenic marker-guided management of women with suspected preterm pre-eclampsia

* + No or minor problems
? Some problems
- Major problems

Appendix 4.7
Outcome variable: Stroke

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Duhig et al., 2019a UK	Stepped-wedge CRT	1,023 I: 576 C: 447	I: 3 lost to follow up C: 1 withdrew consent	0/573	2/446 (0.45%)	One woman had a cardiac arrest as an additional event to a stroke.	+	?/-	+
Hayes-Ryan et al., 2021a Ireland	Stepped-wedge CRT	2,291 I: 1,057 C: 1,234	I: 9 lost to follow up, 1 withdrew consent, 30 recruited during transition phase C: 4 lost to follow up, 28 recruited during transition phase	0/1,017	0/1,202	Data are from supplementary Table S5	+	?/-	-
Sibiude et al., 2025, France	RCT	81 I: 40 C: 40	1 excluded, unclear which group	1/40 (2.5%)	0/40		-	?	-
Sharp et al., 2018 UK, Germany, Austria, Australia	Cohort study	683 I: 396 C: 287	Not reported	0/396	0/287	Stroke or hypertensive encephalopathy studied	-	-	-

C=control, CRT=cluster randomised trial, I=intervention, RCT=randomised controlled trial, RR=risk ratio, UK=United Kingdom

Project: Clinical benefits and risks of angiogenic marker-guided management of women with suspected preterm pre-eclampsia

* + No or minor problems
? Some problems
- Major problems

Appendix 4.8
Outcome variable: Cortical blindness

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Duhig et al., 2019a UK	Stepped-wedge CRT	1,023 I: 576 C: 447	I: 3 lost to follow up C: 1 withdrew consent	0/573	0/446		+	?/-	+
Hayes-Ryan et al., 2021a Ireland	Stepped-wedge CRT	2,291 I:1,057 C:1,234	I: 9 lost to follow up, 1 withdrew consent, 30 recruited during transition phase C: 4 lost to follow up, 28 recruited during transition phase	0/1,017	0/1,202	Numbers presented in appendix at bmj.com	+	?/-	-
Sharp et al., 2018 UK, Germany, Austria, Australia	Cohort study	683 I:396 C:287	Not reported	0/396	0/287		-	-	-

C=control, CRT=cluster randomised trial, I=intervention, UK=United Kingdom

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* + No or minor problems
? Some problems
- Major problems

Appendix 4.9
Outcome variable: Retinal detachment

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Sharp et al., 2018 UK, Germany, Austria, Australia	Cohort study	683 I: 396 C: 287	Not reported	0/396	0/287				

C=control, I=intervention, UK=United Kingdom

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* + No or minor problems
? Some problems
- Major problems

Appendix 4.10
Outcome variable: Pulmonary oedema

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Duhig et al., 2019a UK	Stepped-wedge CRT	1,023 I: 576 C: 447	I: 3 lost to follow up C: 1 withdrew consent	2/573 (0.35%)	0/446		+	?/-	+
Sharp et al., 2018 UK, Germany, Austria, Australia	Cohort study	683 I:396 C:287	Not reported	2/396 (0.51%)	2/287 (0.70%)		-	-	-

C=control, CRT=cluster randomised trial, I=intervention, UK=United Kingdom

Project: Clinical benefits and risks of angiogenic marker-guided management of women with suspected preterm pre-eclampsia

* + No or minor problems
? Some problems
- Major problems

Appendix 4.11
Outcome variable: Acute kidney injury

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Duhig et al., 2019a UK	Stepped-wedge CRT	1,023 I: 576 C: 447	I: 3 lost to follow up C: 1 withdrew consent	Severe acute kidney injury 7/573 (1.22%) Dialysis 0/573	Severe acute kidney injury 6/446 (1.35%) Dialysis 1/446 (0.22%)	Severe acute kidney injury defined as creatinine >150 µmol/L, creatinine >200 µmol/L in chronic kidney disease, dialysis. No statistics	+	?/-	+
Hayes-Ryan et al., 2021a Ireland	Stepped-wedge CRT	2,291 I: 1,057 C: 1,234	I: 9 lost to follow up, 1 withdrew consent, 30 recruited during transition phase C: 4 lost to follow up, 28 recruited during transition phase	Liver or kidney compromise 65/1,017 (6.39%) Control group vs intervention group: ARR 1.08 (95% CI 0.62 to 1.88) P=0.79	Liver or kidney compromise 82/1,202 (6.82%)	Outcome only shown for liver or kidney compromise combined. Kidney compromise defined as creatinine >150 µmol/L. Component of the primary maternal morbidity composite. Adjusted for time and hospital.	+	?/-	-
Sharp et al., 2018 UK, Germany, Austria, Australia	Cohort study	683 I: 396 C: 287	Not reported	Creatinine >150 µmol/L 7/396 (1.77%) Dialysis 2/396 (0.51%)	Creatinine >150 µmol/L 2/287 (0.70%) Dialysis 0/287	No statistics	-	-	-

ARR=adjusted risk ratio, C=control, CI=confidence interval, CRT=cluster randomised trial, I=intervention, UK=United Kingdom

Project: Clinical benefits and risks of angiogenic marker-guided management of women with suspected preterm pre-eclampsia

* + No or minor problems
? Some problems
- Major problems

Appendix 4.12
Outcome variable: Liver capsule haematoma or rupture

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Duhig et al., 2019a UK	Stepped-wedge CRT	1,023 I: 576 C: 447	I: 3 lost to follow up C: 1 withdrew consent	Haematoma or rupture 0/573 Hepatic dysfunction 1/573 (0.17%)	Haematoma or rupture 0/446 Hepatic dysfunction 0/446	Supplementary appendix, Table S2 Hepatic dysfunction was defined as an international normalisation ratio of more than 1.2 in the absence of disseminated intravascular coagulation.	+	?/-	+
Hayes-Ryan et al., 2021a Ireland	Stepped-wedge CRT	2,291 I: 1,057 C:1,234	I: 9 lost to follow up, 1 withdrew consent, 30 recruited during transition phase C: 4 lost to follow up, 28 recruited during transition phase	Hepatic or renal compromise 65/1,017 (6.39%) ARR 1.08 (95% CI 0.62 to 1.88) P=0.79	Hepatic or renal compromise 82/1,202 (6.82%)	Outcome only shown for liver or kidney compromise combined. Hepatic compromise (dysfunction) defined as ALT or AST >70 IU/L. Component of the primary maternal morbidity composite. Adjusted for time and hospital.	+	?/-	-
Sharp et al., 2018 UK, Germany, Austria, Australia	Cohort study	683 I:396 C:287	Not reported	Haematoma, rupture, acute fatty liver of pregnancy 1/396 (0.25%) 38/396 (9.60%) RR 5.45 (95% CI 3.45 to 8.60)	Haematoma, rupture, acute fatty liver of pregnancy 0/287 Hepatic dysfunction (ALAT ≥70 IU/L) 23/287 (8.01%)	RR adjusted for maternal age, BMI, nulliparity, proteinuria. Adjusted analysis only on singletons.	-	-	-

ALAT= alanine aminotransferase, AST=aspartate aminotransferase, BMI=body mass index, C=control, CI= confidence interval, CRT=cluster randomised trial, I=intervention, RR=risk ratio, UK=United Kingdom

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* + No or minor problems
? Some problems
- Major problems

Appendix 4.13
Outcome variable: Placental abruption

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Duhig et al., 2019a UK	Stepped-wedge CRT	1,023 I: 576 C: 447	I: 3 lost to follow up C: 1 withdrew consent	4 /573 (0.70%)	5/ 446 (1.12%)	No statistics	+	?/-	-
Hayes-Ryan et al., 2021a Ireland	Stepped-wedge CRT	2,291 I:1,057 C:1,234	I: 9 lost to follow up, 1 withdrew consent, 30 recruited during transition phase C: 4 lost to follow up, 28 recruited during transition phase	6/1,017 (0.59%) ARR= 1,87 (95% CI 0.21 to 16.28) P=0.57	12/1,202 (1.00%)	Adjusted for time, hospital, maternal age, ethnic origin, gestational age at booking	+	?/-	-
Sibiude et al., 2025, France	RCT	81 I:40 C:40	1 excluded, unclear which group	1/40 (2.5%)	0/40	Vaguely written; in the first paragraph it is written that no cases of abruptio placenta was reported, hence in the second paragraph it is written that severe morbidity was reported including one placental abruption.	-	?	-
Sharp et al., 2018 UK, Germany, Austria, Australia	Cohort study	683 I:396 C:287	Not reported	1 /396 (0.25%)	4 /287 (1.39%)	No statistics	-	-	-

ARR= adjusted risk ratio, C=control, CRT=cluster randomised trial, I=intervention, RCT= randomised controlled trial, UK= United Kingdom,

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* + No or minor problems
? Some problems
- Major problems

Appendix 4.14
Outcome variable: Postpartum haemorrhage

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Cedeira et al. 2019, UK	RCT	374 I: 188 C: 186	I: 2 lost to follow up C: 2 lost to follow up	Estimated blood loss at birth median (IQR) 400 (300-525) ml P=0.027	Estimated blood loss at birth median (IQR) 500 (300-600) ml		?	?	?
Duhig et al., 2019a UK	Stepped-wedge CRT	1,023 I: 576 C: 447	I: 3 lost to follow up C: 1 withdrew consent	Major postpartum haemorrhage 49/573 (8.55%) Transfusion of blood products 9/573 (1.57%)	Major postpartum haemorrhage 48/446 (10.76%) Transfusion of blood products 14/446 (3.14%)	Major postpartum haemorrhage not defined. No statistics	+	?/-	+
Hayes-Ryan et al., 2021a Ireland	Stepped-wedge CRT	2,291 I: 1,057 C: 1,234	I: 9 lost to follow up, 1 withdrew consent, 30 recruited during transition phase C: 4 lost to follow up, 28 recruited during transition phase	?/1.017	?/1,202	Not reported. But in Box 1 “haematological compromise" including transfusion is reported to be an outcome but data were not found in article or supplement i.e., only included in composite outcome.	+	?/-	-

C=control, CRT=cluster randomised trial, I=intervention, IQR=interquartile range, RCT= randomised controlled trial, UK= United Kingdom

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* + No or minor problems
? Some problems
- Major problems

Appendix 4.15
Outcome variable: Admission to intensive care unit

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Hayes-Ryan et al., 2021a Ireland	Stepped-wedge CRT	2,291 I: 1,057 C:1,234	I: 9 lost to follow up, 1 withdrew consent, 30 recruited during transition phase C: 4 lost to follow up, 28 recruited during transition phase	0/1,017	1/1,202 (0.08%)	Component of the primary maternal morbidity composite. No statistics.	+	?/-	-

C=control, CRT=cluster randomised trial, I=intervention

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* + No or minor problems
? Some problems
- Major problems

Appendix 4.16
Outcome variable: Intubation and mechanical ventilation

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Duhig et al., 2019a UK	Stepped-wedge CRT	1,023 I: 576 C: 447	I: 3 lost to follow up C: 1 withdrew consent	0/573	1/446 (0.22%)		+	?/-	+
Sharp et al., 2018 UK, Germany, Austria, Australia	Cohort study	683 I:396 C:287	Not reported	0/396	1/287 (0.35%)		-	-	-

C=control, I=intervention, CRT= cluster randomised trial, UK= United Kingdom

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* + No or minor problems
? Some problems
- Major problems

Appendix 4.17
Outcome variable: Time to pre-eclampsia diagnosis

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Cerdeira et al., 2019, UK	RCT	374 I: 188 C: 186	I: 2 lost to follow up C: 2 lost to follow up	Median (IQR) 7 days (0-29) P=0.6387	Median (IQR) 9.5 days (0-32)		?	?	?
Duhig et al., 2019a UK	Stepped-wedge CRT	1,023 I: 576 C: 447	I: 3 lost to follow up C: 1 withdrew consent	Median (IQR) time to diagnose pre-eclampsia in those diagnosed N=205 (36%) 1.9 days (0.5-9.2) *Adjusted time ratio for the time to diagnosis of pre-eclampsia 0.36 (95% CI 0.15–0.87). P=0.027	Median (IQR) time to diagnose pre-eclampsia in those diagnosed N=155 (35%) 4.1 days (0.8-14.7)	*Linear regression of logged time to diagnosis and adjusted for centre, time, gestational age at entry, previous preeclampsia, chronic hypertension, chronic kidney disease Includes only patients diagnosed within four weeks after testing.	+	?/-	+
Hayes-Ryan et al., 2021a UK	Stepped-wedge CRT	2,291 I: 1,057 C: 1,234	I: 9 lost to follow up, 1 withdrew consent, 30 recruited during transition phase C: 4 lost to follow up, 28 recruited during transition phase	Median (IQR) time to diagnose pre-eclampsia in those diagnosed N=138 (13.57%) 8 days (1-23)	Median (IQR) time to diagnose pre-eclampsia in those diagnosed N= 177 (14.73%) 7 days (1-25)	*Mixed-effects linear regression model, with log-transformed time to diagnosis and adjusted for time and hospital. Data from Table S6. Patient follow up 12 weeks according to S3.	+	?/-	?

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* + No or minor problems
? Some problems
- Major problems

Appendix 4.17
Outcome variable: Time to pre-eclampsia diagnosis

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
				Geometric mean difference* 0.92 (95% CI 0.56-1.49) P=0.73					

C=control, CI=confidence interval, CRT=cluster randomised trial, I=intervention, IQR=interquartile range, RCT= randomised controlled trial. UK= United Kingdom

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* + No or minor problems
? Some problems
- Major problems

Appendix 4.18
Outcome variable: Admission to hospital care

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Cerdeira et al., 2019, UK	RCT	374 I: 188 C: 186	I: 2 lost to follow up C: 2 lost to follow up	Within 24 h of the test 60/186 (32.26%) Within 7 days of the test 70/186 (37.6%) Until delivery 126/186 (67.7%)	Within 24 h of the test 48/184 (26.1%) Within 7 days of the test 65/184 (35.3%) Until delivery 134/184 (72.8%)	RR 1.24 (95% CI 0.89 to 1.70) RD 0.06 (95% CI -0.03 to 0.15) RR 1.06 (95% CI 0.1 to 1.39) RD 0.02 (95% CI -0.07 to 0.12) RR 0.93 (95% CI 0.82 to 1.06) RD -0.05 (95% CI -0.14 to 0.04)	?	?	?

C=control, CI=confidence interval, I=intervention, RCT=randomised controlled trial, RD=risk difference, RR=risk ratio, UK= United Kingdom

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* + No or minor problems
? Some problems
- Major problems

Appendix 4.19
Outcome variable: Inpatient nights

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Duhig et al., 2019a UK	Stepped-wedge CRT	1,023 I: 576 C: 447	I: 3 lost to follow up C: 1 withdrew consent	7.43 (0.36) Mean difference –0.06 (95% CI 0.22 to 0.09)	7.26 (0.38)	Mean (SE)			
Hayes-Ryan et al., 2021a Ireland	Stepped-wedge CRT	2,291 I:1,057 C:1,234	I: 9 lost to follow up, 1 withdrew consent, 30 recruited during transition phase C: 4 lost to follow up, 28 recruited during transition phase	PlGF <12, n=108 9.5 (6,15) PlGF 12-100, n=320 6 (4, 10) PlGF >100, n=589 5 (3, 7)	5 (3, 9)	"Total inpatient nights" Median (IQR)			
Sebuide et al., 2025, France	RCT	81 I:40 C:40	1 excluded, unclear which group	2 (1-4) P=1.0 Hospitalization ≥48 h N=20 (50.0%) RR 0.8 (95% CI 0.6-1.2) P=0.37	2 (1-3) Hospitalization ≥48 h N=24 (60.0%)	Duration of hospitalization (among women not delivered during 1st hospitalization), days, median (IQR)			
Sharp et al., 2018 UK, Germany, Austria, Australia	Cohort study	683 I:396 C:287	Not reported	PlGF < 12, n=116 2.3 (4.8) PlGF 12-100, n=137		"Antenatal inpatient nights" Mean (SD)			

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*	+ No or minor problems
	? Some problems
	- Major problems

Appendix 4.19
Outcome variable: Inpatient nights

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
				3.7 (5.8) PlGF >100, n=143 3.8 (5.7) Total n= 396 2.88 (5.52)					

C=control, CRT, cluster randomised trial, I=intervention, PlGF=placental growth factor, RCT=randomised controlled trial, RR=relative risk, SD=standard difference, SE=standard error, UK=United Kingdom,

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* + No or minor problems
? Some problems
- Major problems

Appendix 4.20
Outcome variable: Outpatient visits

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention n (%)	Control n (%)				
Duhig et al., 2019a UK	Stepped-wedge CRT	1,023 I: 576 C: 447	I: 3 lost to follow up C: 1 withdrew consent	6.14 (0.53)	9.44 (0.81)	Mean (SE), no statistics			
Hayes-Ryan et al., 2021a Ireland	Stepped-wedge CRT	2,291 I:1,057 C:1,234	I: 9 lost to follow up, 1 withdrew consent, 30 recruited during transition phase C: 4 lost to follow up, 28 recruited during transition phase	GP Visits 0/588 <u>ANC:</u> PlGF<12, n=108 0 (0,1) PlGF 12-100, 320 2 (0.5-3) PlGF >100, n=589 3 (2,5) <u>Day Ward Visits:</u> PlGF<12, n=108 0 (0,2) PlGF 12-100, 320 1 (0-3) PlGF >100, n=589 1 (0,2) <u>Emergency out of hours visits:</u> PlGF<12, n=108 0 (0,0) PlGF 12-100, 320 0 (0-1) PlGF >100, n=589 0 (0,1)	GP Visits 0/955 <u>ANC:</u> 2 (1,4) <u>Day Ward Visits:</u> 1 (0,2) <u>Emergency out of hours visits:</u> 0 (0,1)	Median (IQR)			

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*	+	No or minor problems
	?	Some problems
	-	Major problems

Appendix 4.20
Outcome variable: Outpatient visits

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention n (%)	Control n (%)				
Sharp et al., 2018 UK, Germany, Austria, Australia	Cohort study	683 I:396 C:287	Not reported	PlGF<12, n=116 2.3 (4.8) PlGF 12-100, 137 3.7 (5.3) PlGF >100, n=143 5.2 (5.5) Total N=396 3.90 (5.48)	n/a	"Antenatal clinic or assessment unit visits" Mean (SD)			

ANC=antenatal care, C=control, CRT=cluster randomised trial, GP= general practitioner, I=intervention UK=United Kingdom, SD=standard deviation, SE=standard error. n/a=not available

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* + No or minor problems
? Some problems
- Major problems

Appendix 4.21
Outcome variable: Intraventricular haemorrhage

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Duhig et al., 2019a UK	Stepped-wedge CRT	1,023 I: 576 C: 447	I: 3 lost to follow up C: 1 withdrew consent	7/573 (1.22%)	11/446 (2.47%)	Any grade of intraventricular haemorrhage. No statistics.	+	?/-	+
Hayes-Ryan et al., 2021a Ireland	Stepped-wedge CRT	2,291 I: 1,057 C: 1,234	I: 9 lost to follow up, 1 withdrew consent, 30 recruited during transition phase C: 4 lost to follow up, 28 recruited during transition phase	3/1,017 (0.29%) 0.25% in table	6/1,202 (0.50%) 0.59% in table	Any grade of intraventricular haemorrhage. Component of primary neonatal morbidity composite. Discrepancy between number and percentages in Intervention and Control, as compared to publication. No statistics, RR not estimable.	+	?/-	-
Sharp et al., 2018, UK, Germany, Austria, Australia	Cohort study	732 I:433 C:299	Not reported	4/433 (0.92%)	0/299 (0.0%)	Intraventricular haemorrhage grade 3-4. Multifetal pregnancies included, 9.1% in the intervention group and 4.2% in the control group. No statistics.	-	-	-

C=control, CRT=cluster randomised trial, I=intervention, RR=risk ratio, UK=United Kingdom

Project: Clinical benefits and risks of angiogenic marker-guided management of women with suspected preterm pre-eclampsia

* + No or minor problems
? Some problems
- Major problems

Appendix 4.22
Outcome variable: Necrotising enterocolitis

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Duhig et al., 2019a UK	Stepped-wedge CRT	1,023 I: 576 C: 447	I: 3 lost to follow up C: 1 withdrew consent	7/573 (1.22%)	7/446 (1.57%)	NEC stage 2 and 3	+	?/-	+
Hayes-Ryan et al., 2021a Ireland	Stepped-wedge CRT	2,291 I:1,057 C:1,234	I: 9 lost to follow up, 1 withdrew consent, 30 recruited during transition phase C: 4 lost to follow up, 28 recruited during transition phase	4/1,017 (0.39%)	2/1,202 (0.17%)		+	?/-	-
Sharp et al., 2018 UK, Germany, Austria, Australia	Cohort study	732 I:433 C:299	Not reported	7/433 (1.62%)	4/299 (1.34%)		-	-	-

C=control, CRT=cluster randomised trial, NEC=necrotising enterocolitis, I=intervention, UK=United Kingdom

Project: Clinical benefits and risks of angiogenic marker-guided management of women with suspected preterm pre-eclampsia

*	+	No or minor problems
	?	Some problems
	-	Major problems

Appendix 4.23
Outcome variable: Neonatal seizures

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Duhig et al., 2019a UK	Stepped-wedge CRT	1,023 I: 576 C: 447	I: 3 lost to follow up C: 1 withdrew consent	0/573	2/446 (0.45%)		+	?/-	+

C=control, CRT=cluster randomised trial, I=intervention, UK=United Kingdom

Project: Clinical benefits and risks of angiogenic marker-guided management of women with suspected preterm pre-eclampsia

* + No or minor problems
? Some problems
- Major problems

Appendix 4.24
Outcome variable: Respiratory diseases (respiratory distress syndrome and bronchopulmonary dysplasia)

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Duhig et al., 2019a UK	Stepped-wedge CRT	1023 I: 576 C: 447	I: 3 lost to follow up C: 1 withdrew consent	Respiratory distress syndrome 78/573 (13.61%) Bronchopulmonary dysplasia 5/573 (0.87%)	Respiratory distress syndrome 54/446 (12.10%) Bronchopulmonary dysplasia 3/446 (0.67%)	Component of primary neonatal morbidity composite. No statistics	+	?/-	+
Hayes-Ryan et al., 2021b Ireland	Stepped-wedge CRT	2291 I:1057 C:1234	I: 9 lost to follow up, 1 withdrew consent, 30 recruited during transition phase C: 4 lost to follow up, 28 recruited during transition phase	Respiratory distress syndrome 76/1,017 (7.47%) RR 1.49 (95% CI 0.65 to 3.42) P=0.35	Respiratory distress syndrome 80/1,202 (6.66%)	Component of primary neonatal morbidity composite. RR adjusted for time and hospital.	+	?/-	?
Sharp et al., 2018, UK, Germany, Austria, Australia	Cohort study	732 I:433 C:299	Not reported	Respiratory distress syndrome 128/433 (29.56%) * Bronchopulmonary dysplasia 28/433 (6.47%)	Respiratory distress syndrome 46/299 (15.38%) Bronchopulmonary dysplasia 6/299 (2.01%)	Multifetal pregnancies included, 9.1% in the intervention group and 4.2% in the control group. *Numbers and percentage in Intervention inconsistent in publication (reported). No statistics.	-	-	+

C=control, CRT=cluster randomised trial, CI=confidence interval, I=intervention, RCT=randomised controlled trial, RR=risk ratio, UK=United Kingdom.

Project: Clinical benefits and risks of angiogenic marker-guided management of women with suspected preterm pre-eclampsia

* + No or minor problems
? Some problems
- Major problems

Appendix 4.25
Outcome variable: Confirmed neonatal infection

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Hayes-Ryan et al., 2021a Ireland	Stepped-wedge CRT	2,291 I:1,057 C:1,234	I: 9 lost to follow up, 1 withdrew consent, 30 recruited during transition phase C: 4 lost to follow up, 28 recruited during transition phase	Confirmed infection 11/1,017 (1.08%)	Confirmed infection 11/1,202 (0.92%)	Component of primary neonatal morbidity composite. No data on late onset infection. No statistics.	+	?/-	-

C=control, CRT=cluster randomised trial, I=intervention

Project: Clinical benefits and risks of angiogenic marker-guided management of women with suspected preterm pre-eclampsia

* + No or minor problems
? Some problems
- Major problems

Appendix 4.26
Outcome variable: Admission to neonatal care unit

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Cerdeira et al. 2019, UK	RCT	374 I: 188 C: 186	I: 2 lost to follow up C. 2 lost to follow up	34 (18.3%)	28 (15.2%)		?	?	?
Duhig et al., 2019a UK	Stepped-wedge CRT	1,023 I: 576 C: 447	I: 3 lost to follow up C: 1 withdrew consent	Neonatal unit admissions 195 (34%)* Neonatal intensive and high-dependency nights: 15.2 (SE 1.7) Mean difference –10.6 (95% CI –20.81 to –0.47) NS for nights spent in special care baby unit (no exact data for number of nights in article)	Neonatal unit admissions 146 (33%)* Neonatal intensive and high-dependency nights: 24.2 (SE 3.8)	*Paper stated no differences observed in NICU admissions. All outcomes were adjusted for time and centre	+	?/-	+
Hayes-Ryan et al., 2021a Ireland	Stepped-wedge CRT	2,291 I:1,057 C:1,234	I: 9 lost to follow up, 1 withdrew consent, 30 recruited during transition phase C: 4 lost to follow up, 28 recruited during transition phase	Any NICU 314/1,017 (30.88%) RR 0.95 (95% CI 0.75 to 1.20 P=0.65 NICU ≥48 h 217/1,017 (21.34%) RR 0.81 (95% CI 0.60 to 1.10)	Any NICU 378/1,202 (31.45%) NICU ≥48 h 291/1,202 (24.21%)	RR adjusted for time and hospital Component of primary neonatal morbidity composite.	+	?/-	+

Project: Clinical benefits and risks of angiogenic marker-guided management of women with suspected preterm pre-eclampsia

* + No or minor problems
? Some problems
- Major problems

Appendix 4.26
Outcome variable: Admission to neonatal care unit

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
				P=0.19					
Sibiude et al., 2025, France	RCT	81 I:40 C:40	1 excluded, unclear which group	16/40 (41.0%) P=0.31	12/40 (30.0%)		-	?	?
Sharp et al., 2018 UK, Germany, Austria, Australia	Cohort study	732 I:433 C:299	Not reported	190/433 (43.9%)	117/299 (39.1%)		-	-	?

C=control, CRT=cluster randomised trial, CI=confidence interval, I=intervention, NICU= neonatal intensive care unit, NS=not significant, RCT=randomised controlled trial, RR= risk ratio, SE=standard error, UK=United Kingdom

Project: Clinical benefits and risks of angiogenic marker-guided management of women with suspected preterm pre-eclampsia

* + No or minor problems
? Some problems
- Major problems

Appendix 4.27
Outcome variable: Gestational age at delivery

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Cerdeira et al., 2019, UK	RCT	374 I:188 C:186	2 lost to follow up in I and C respectively	38.4 (37.3-39.6) (n=186) P=0.479	38.1 (37.1-39.3) (n=184)	Weeks, median (IQR) Mean variance estimation (SD): I: 38.4 (SD: 1.7) C: 38.2 (SD: 1.6)	?	?	?
Duhig et al., 2019a UK	Stepped-wedge CRT	1,023 I: 576 C: 447	I: 3 lost to follow up C: 1 withdrew consent	36.6 (3.0) (n=573)	36.8 (3.0) (n=446) Mean difference (adjusted for time and hospital) –0.52 (95% CI –0.63 to 0.73)	Weeks, mean (SD)	+	?/-	+
Hayes-Ryan et al., 2021a Ireland	Stepped-wedge CRT	2,291 I:1057 C:1234	I: 9 lost to follow up, 1 withdrew consent, 30 recruited during transition phase C: 4 lost to follow up, 28 recruited during transition phase	264.90 (17.30) (n=1,017)	265.14 (18.03) (n=1,202) Mean difference (adjusted for time and hospital) –0.83 (95% CI –3.93 to 2.27) P=0.60	Days, mean (SD)	+	?/-	+
Sibiude et al., 2025, France	RCT	81 I:40 C:40	1 excluded (from I or C?)	35.2	35.0	Weeks	-	?	-
Sharp et al., 2018 UK, Germany, Austria, Australia	Cohort study	732 I:433 C:299	Not reported	Weeks, median (IQR) 34.9 (32.0-37.1)	Weeks, median (IQR) 36.7 (33.6-38.6) Median difference –1.4 (95% CI –0.9 to –2.0)	Different number of mothers and neonates in the respective cohorts. Weeks, median (IQR)	-	-	?

C=control, CRT=cluster randomised trial, I=intervention, CI=confidence interval, IQR=interquartile range, RCT=randomised controlled trial, SD=standard deviation, UK=United Kingdom

Project: Clinical benefits and risks of angiogenic marker-guided management of women with suspected preterm pre-eclampsia

* + No or minor problems
? Some problems
- Major problems

Appendix 4.28
Outcome variable: Birth weight deviation (small for gestational age)

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention n (%)	Control n (%)				
Cerdeira et al. 2019, UK	RCT	374 I: 188 C: 186	I: 2 lost to follow up C. 2 lost to follow up	31/184 (16.85%)	31/186 (16.67%) No statistics	SGA was defined as birth weight <10th centile adjusted for newborn sex	?	?	?
Duhig et al., 2019a UK	Stepped-wedge CRT	1,023 I: 576 C: 447	I: 3 lost to follow up C: 1 withdrew consent	32/573 (5.58%) Birthweight <10th centile 124 (21.8%) Birthweight <3rd centile 58 (10.2%)	28/446 (6,28%) Birthweight <10th centile 98 (22.1%) Odds ratio 0.82 (0.46 to 1.44) Birthweight <3rd centile 43 (9.7%) Odds ratio 0.89 (0.40 to 2.00)	SGA reported under secondary maternal outcome Birthweight <10th centile and <3rd centile from Supplementary appendix	+	?/-	+
Hayes-Ryan et al., 2021a Ireland	Stepped-wedge CRT	2,291 I:1,057 C:1,234	I: 9 lost to follow up, 1 withdrew consent, 30 recruited during transition phase C: 4 lost to follow up, 28 recruited during transition phase	307/1,017 (30.19%)	338/1,202 (28.12%) Risk ratio 1.06 (95% CI 0.96-1.16) P=0.26	Defined as birth weight ≤5th customised centile	+	?/-	+
Sibiude et al., 2025, France	RCT	81 I:40 C:40	1 excluded, unclear which group	Birthweight <3rd centile 5/40 (12.5%)	5/40 (12.5%) (according to the study, 12.8%)	Incorrect calculation	-	?	-

Project: Clinical benefits and risks of angiogenic marker-guided management of women with suspected preterm pre-eclampsia

* + No or minor problems
? Some problems
- Major problems

Appendix 4.28
Outcome variable: Birth weight deviation (small for gestational age)

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention n (%)	Control n (%)				
Sharp et al., 2018 UK, Germany, Austria, Australia	Cohort study	683 I:396 C:287	Not reported	Small for gestational age infant <10th centile: 181 (42.2%) Small for gestational age infant < 3rd centile: 124 (28.9%)	Small for gestational age infant <10th centile: 145 (48.5%) Risk ratio 0.87 (0.74-1.02) Small for gestational age infant < 3rd centile: 108 (36.1%) Risk ratio 0.80 (0.65-0.99)		-	-	?

C=control, CRT=cluster randomised trial, I=intervention, RCT=randomised controlled trial, UK=United Kingdom

Project: Use of angiogenic markers in clinical management of suspected pre-eclampsia
Appendix 5 Critical appraisal of included studies
Aspects regarding directness and study limitations identified during the assessment process contributing to the study being categorised as having no/minor (+), some (?) or major (-) problems.

Author Year Country Study design	**Problems contributing to downgrading the study in the assessment**					
	Directness[1]		**Risk of bias[1]**		**Precision[1]**	
Cerdeira, 2019 RCT	?	One centre in UK only, tertiary care, population from 24 instead of 20 weeks (implies that potentially severe early cases are not included) and comparatively late recruitment, as this is , unclear whether acute care unit	?	Not blinded, study registered after study start, industry reviewed protocol, not all outcomes reported	?	Lack of clarity regarding assumptions of sample size calculation (which timepoint and base rate of admission rate the sample size calculation is based on)
Duhig, 2019a, UK Stepped wedge CRT	+	Yet noted: directness regarding ethnicity unclear, higher prescription of aspirin than in Sweden, no information on screening (individual consent although stepped wedge and information on refuse to participate not provided).	?/-	Risk of confounding factors due to stepped wedge design with few centres, no possibility to conceal allocation, lack of clarity on randomisation process, not blinded	+ to -	Concerns dependent on different outcomes
Hayes Ryan, 2021a Ireland, Stepped wedge CRT	+	Yet noted: high proportion with suspected faetal growth restriction at baseline (although this is not an inclusion criteria in the study and actual birth weight is not in line with the baseline data), unclear	?/-	Risk of confounding factors due to stepped wedge design with few centres, no possibility to conceal allocation, lack of clarity on randomisation process, not blinded	+ to -	Concerns dependent on different outcomes Does not achieve the planned sample size, broad CI

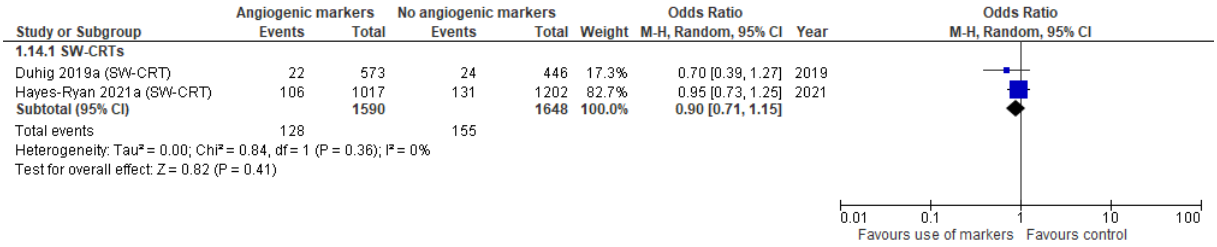
Project: Use of angiogenic markers in clinical management of suspected pre-eclampsia
Appendix 5 Critical appraisal of included studies
Aspects regarding directness and study limitations identified during the assessment process contributing to the study being categorised as having no/minor (+), some (?) or major (-) problems.

Author Year Country Study design	**Problems contributing to downgrading the study in the assessment**					
	Directness[1]		**Risk of bias[1]**		**Precision[1]**	
		why the recruitment aim was not reached (availability of personnel, what does this imply?)				
Sibiude J, 2025 France RCT		Only hospitalized patients. Number of screened patients is not given.	′?	Evaluators were not blinded, study sponsor revised study protocol, long delay to publication, errors in tables.	? to -	Concerns dependent on different outcomes Did not reach prespecified inclusion goal.
Sharp A, 2018, UK, Germany, Austria and Australia Cohort study	-	Inclusion of cases with faetal growth restriction which in itself is not part of the PICO in our HTA, no information on screening for eligibility	-	No published protocol, two different cohorts with data collected in different centres and at different times, no information on drop out, limited adjustment for confounders, no blinding, industry funded,	+ to -	Concerns dependent on different outcomes No power calculation

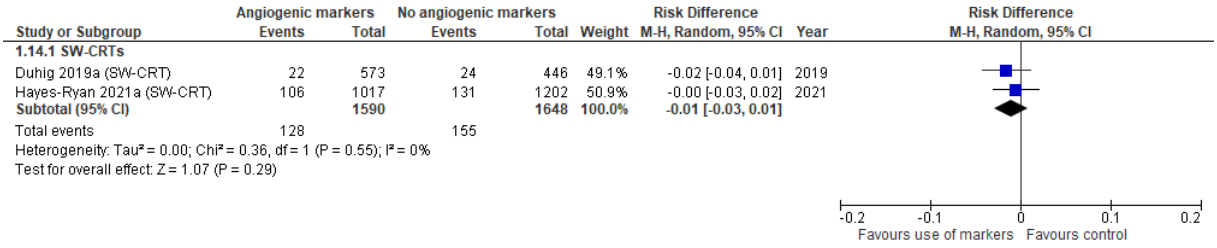
[1] Assessed using the checklist developed by HTA-centrum: no/minor (+), some (?), or major (-) problems

Appendix 6. Supplementary Figures: Crude OR and Risk Difference

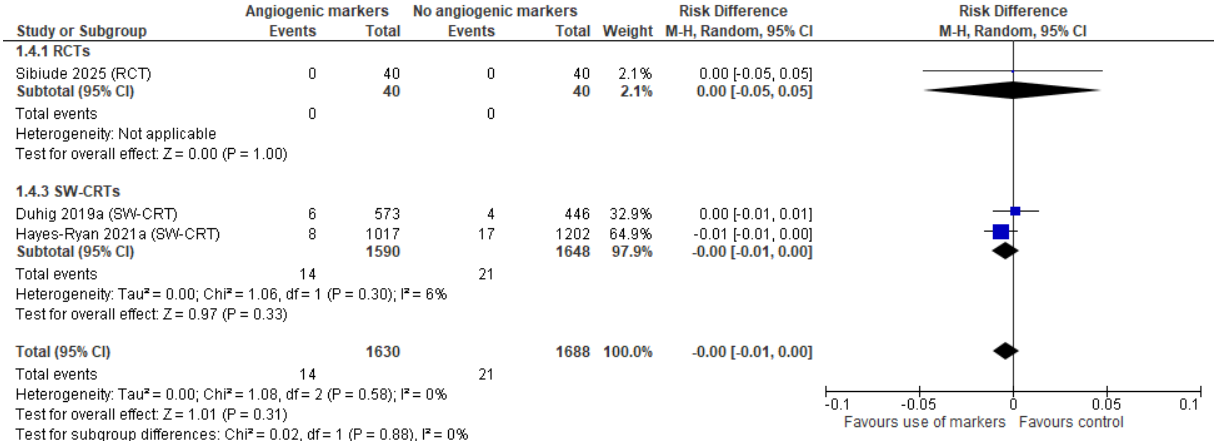
Supplementary Figure 1. Composite maternal outcome, odds ratio based on crude numbers



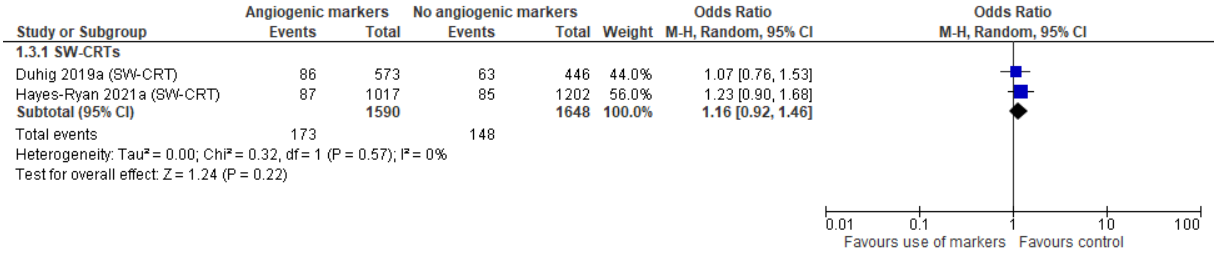
Supplementary Figure 2. Composite maternal outcome, risk difference based on crude numbers



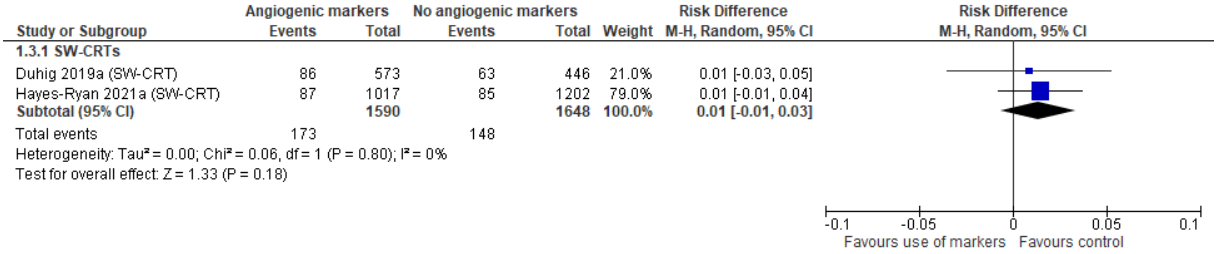
Supplementary Figure 3. Peri/neonatal mortality, risk difference based on crude numbers



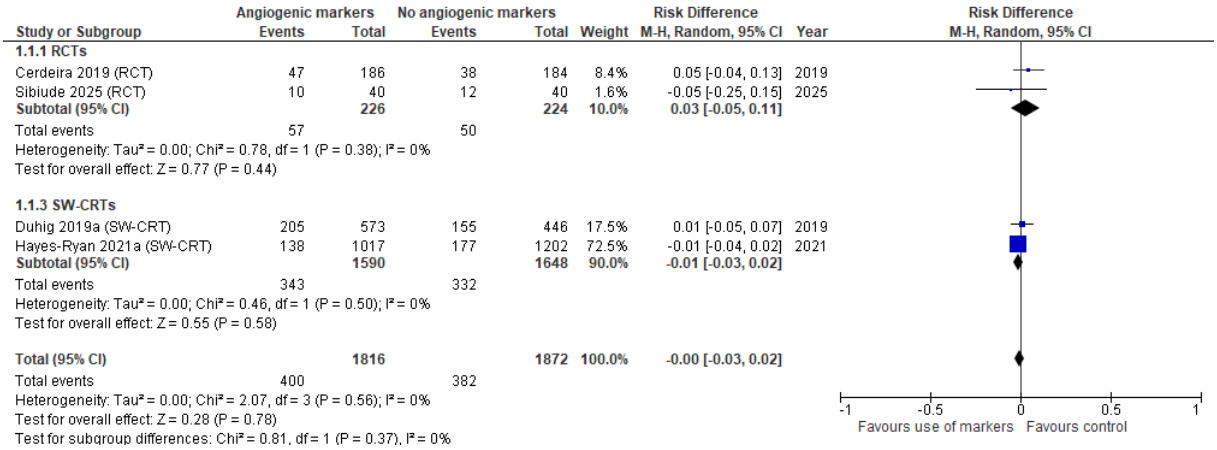
Supplementary Figure 4. Composite neonatal outcome, odds ratio based on crude numbers



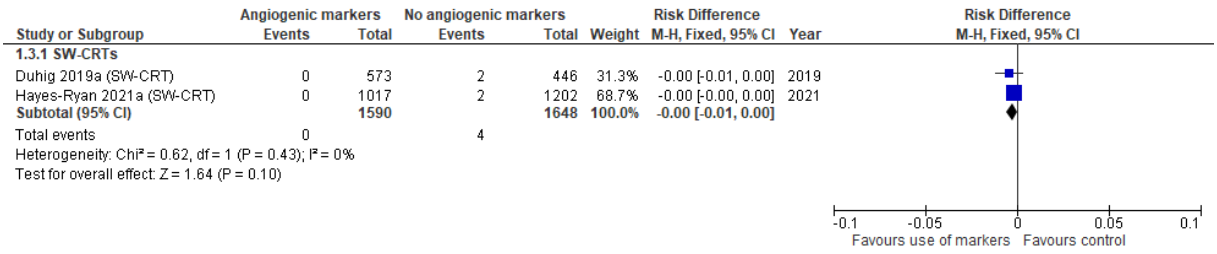
Supplementary Figure 5. Composite neonatal outcome, risk difference, based on crude numbers



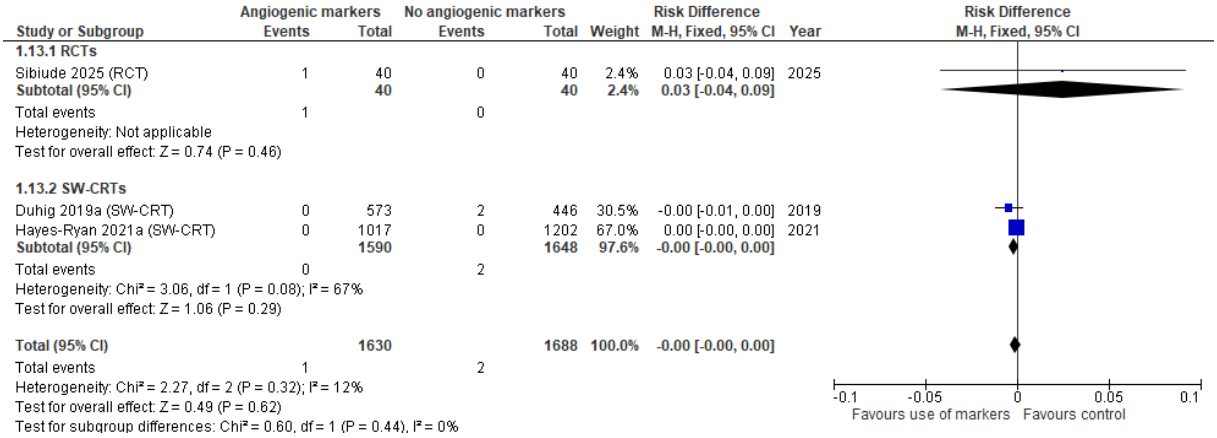
Supplementary Figure 6. Outcome diagnosis of pre-eclampsia, risk difference based on crude numbers



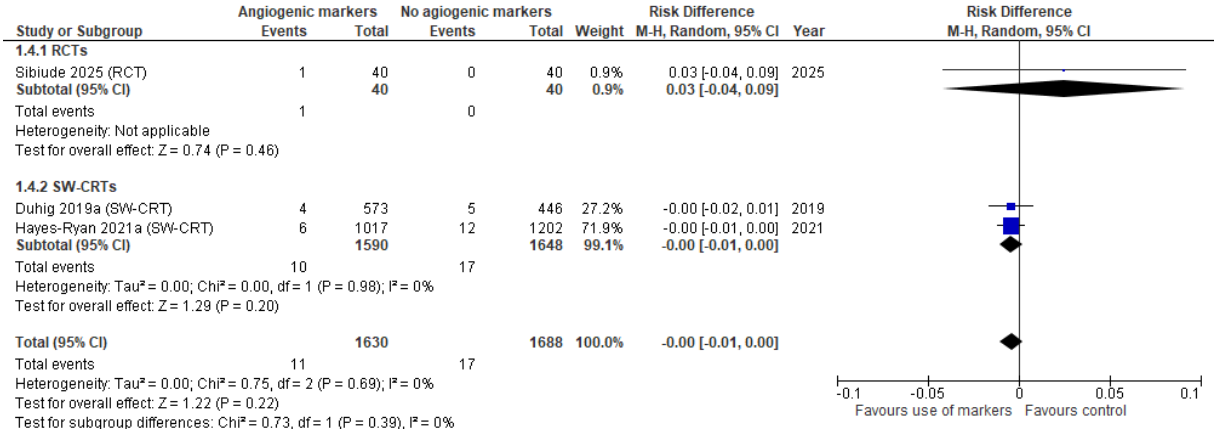
Supplementary Figure 7. Outcome eclampsia, risk difference based on crude numbers



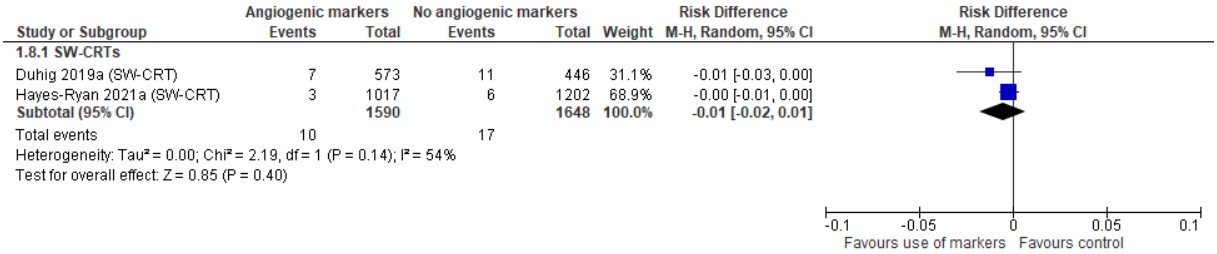
Supplementary Figure 8. Outcome stroke, risk difference based on crude numbers



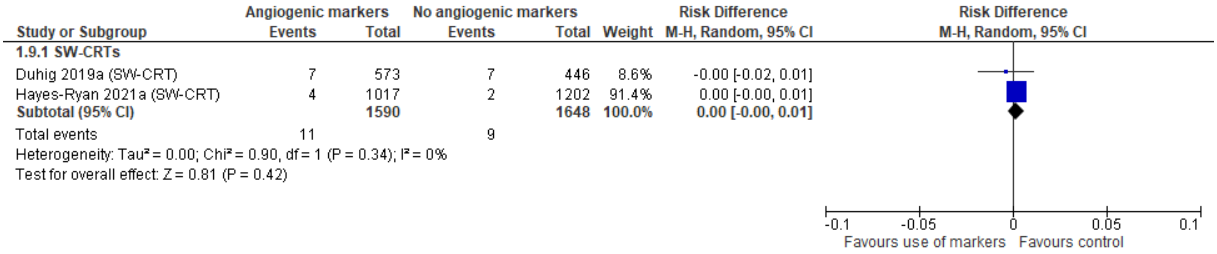
Supplementary Figure 9. Outcome placental abruption, risk difference based on crude numbers



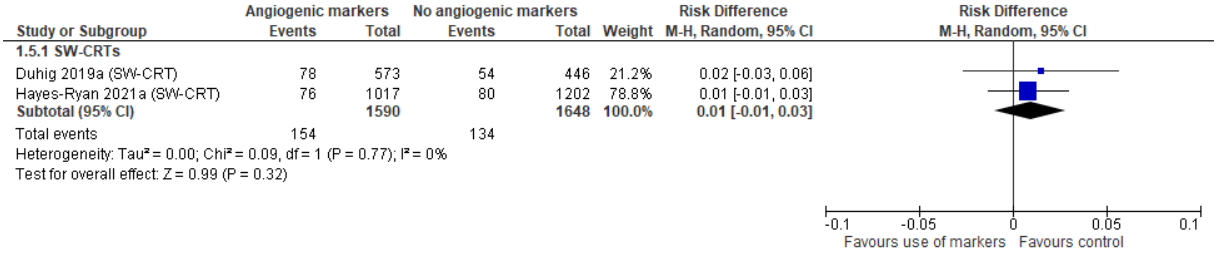
Supplementary Figure 10. Outcome intraventricular haemorrhage, risk difference based on crude numbers



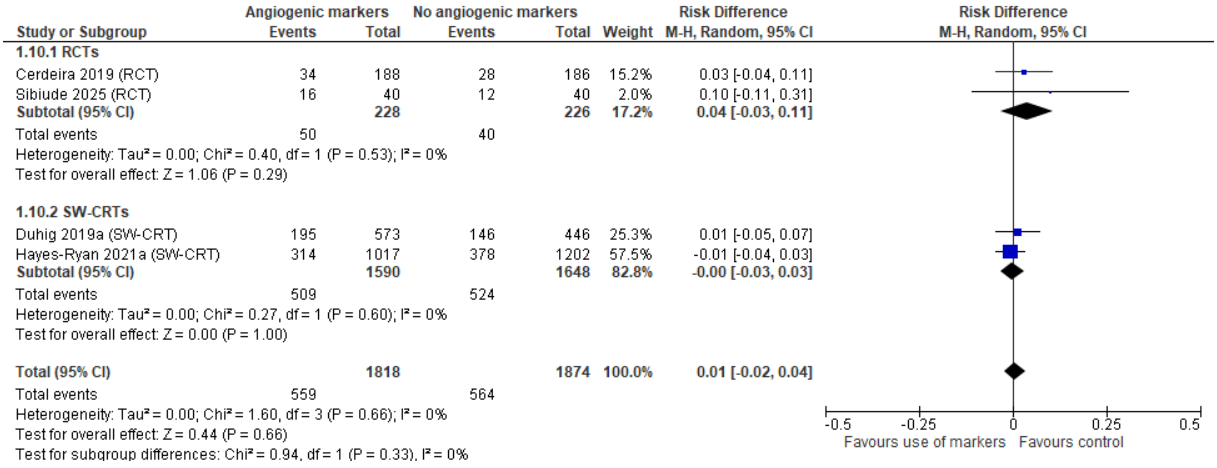
Supplementary Figure 11. Outcome necrotising enterocolitis, risk difference based on crude numbers



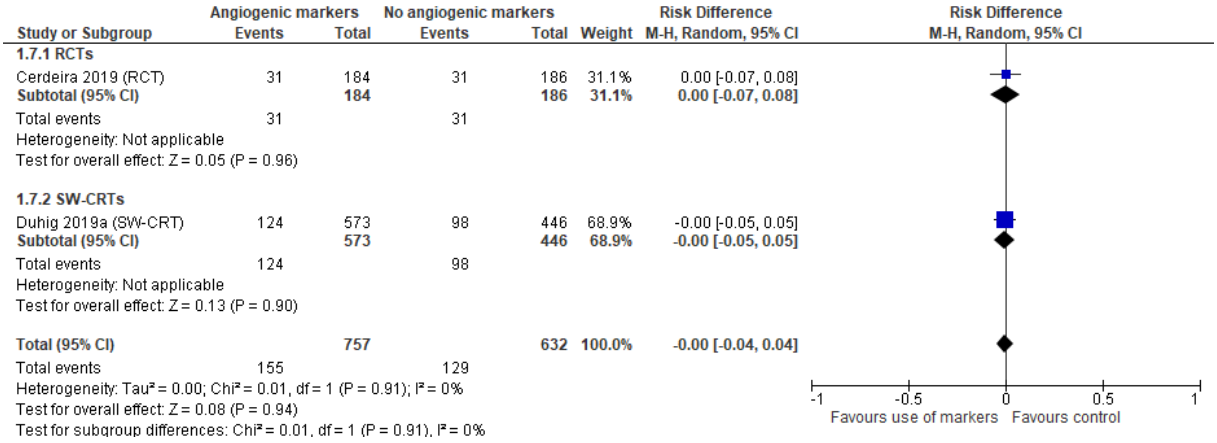
Supplementary Figure 12. Outcome respiratory distress syndrome, risk difference based on crude numbers



Supplementary Figure 13. Outcome admission to neonatal unit, risk difference based on crude numbers



Supplementary Figure 14. Outcome birth weight deviation (SGA<10th centile), risk difference based on crude numbers


Angiogenic markers
No angiogenic markers
Risk Difference
Risk Difference
Study or Subgroup
Events
Total
Events
Total
Weight
M-H, Random, 95% CI
M-H, Random, 95% CI
1.7.1 RCTs
Cerdeira 2019 (RCT) 31 184 31 186 31.1% 0.00 [-0.07, 0.08]
Subtotal (95% CI) 184 186 31.1% 0.00 [-0.07, 0.08]
Total events 31 31
Heterogeneity: Not applicable
Test for overall effect: Z = 0.05 (P = 0.96)
1.7.2 SW-CRTs
Duhig 2019a (SW-CRT) 124 573 98 446 68.9% -0.00 [-0.05, 0.05]
Subtotal (95% CI) 573 446 68.9% -0.00 [-0.05, 0.05]
Total events 124 98
Heterogeneity: Not applicable
Test for overall effect: Z = 0.13 (P = 0.90)
Total (95% CI) 757 632 100.0% -0.00 [-0.04, 0.04]
Total events 155 129
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.91); I² = 0%
Test for overall effect: Z = 0.08 (P = 0.94)
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.91), I² = 0%
-1
-0.5
0
0.5
1
Favours use of markers
Favours control

Supplementary Table 1. Diagnostic criteria for pre-eclampsia

Pre-eclampsia criteria	
Pre-eclampsia: Multiorgan syndrome with onset after 20 weeks of gestation	
Blood pressure	Systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg measured at least twice
Combined with the new onset of one or more of the following:	
Kidney engagement	Proteinuria with albumin/creatinine ≥8 mg/mmol, protein/creatinie≥30 mg/mmol or u-protein/creatinine ≥0,3 g/24 h. Kidney insufficiency (creatinine >90 µmol/L, oliguria (<500 mL/24 hours)
Liver engagement	Elevated transaminases two times over reference value Epigastric pain
Neurological engagement	Severe headache, persistent sight deficiency, eclampsia, clonus, stroke
Haematological engagement	Platelet counts $<100x10^9$ /L Hemolysis (haptoglobine<0,25 g/L or LD U/L or 10.0 ukat/L
Circulation engagement	Pulmonary edema Chest pain
Uteroplacental dysfunction	Intrauterine growth restriction