

REPORT

2020

HEALTH TECHNOLOGY ASSESSMENT:

Safety, clinical effectiveness, predictive accuracy and cost effectiveness of blood based tests for women with suspected preeclampsia

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Key messages

Two to eight percent of pregnant women are diagnosed with preeclampsia worldwide. Preeclampsia is a potentially life-threatening condition requiring hospital admission and close maternal and fetal monitoring in the second half of pregnancy. Tests based on biomarkers like placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1) may predict preeclampsia and lead to better pregnancy outcomes. Such tests are also proposed as a means of identifying women at low risk so that a) unnecessary admissions can be avoided, and b) they can return home reassured. In this health technology assessment, we address safety, effectiveness, predictive accuracy, and cost-effectiveness of these tests among pregnant women with suspected preeclampsia from gestational week 20.

Clinical effectiveness (three included studies)

- PlGF tests may reduce the time to a preeclampsia diagnosis and may reduce the risk of severe maternal adverse outcomes e.g. cerebral haemorrhage.
- We are unable to conclude whether sFlt-1/PlGF or PlGF testing improve neonatal outcomes or not.

Health services utilisation (two included studies)

- sFlt-1/PlGF ratio tests may increase admission rates the first 24 hours after the test, but this result is uncertain
- sFlt-1/PlGF ratio tests were associated with little or no differences in hospital admissions within the first week after the test, and for the remainder of the pregnancy.

Predictive accuracy (four included systematic reviews)

- the predictive accuracy of sFlt-1/PlGF ratio tests is fairly good, and may be useful to “rule out” suspected preeclampsia.

Budget impact of adding blood-based test to clinical practice

- We estimate that introducing sFlt-1/PlGF ratio or PlGF test for women with suspected preeclampsia will lead to a direct budget impact of approximately 12.4 million Norwegian

Title:

Safety, clinical effectiveness, predictive accuracy and cost effectiveness of blood-based tests for women with suspected preeclampsia: a health technology assessment

Type of publication:

Health technology assessment
Health technology assessment (HTA) is a multidisciplinary process that summarizes information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner. Its aim is to inform the development of safe, effective health policies that are patient focused and that seek to achieve best value.

Doesn't answer everything:

Use of biomarkers like sFlt-1/PlGF and PlGF for screening before gestational week 20

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Atle Fretheim, Research director
Norwegian Institute of Public Health

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Annetine Staff (Professor at University of Oslo), Kjell Åsmund Salvesen (Professor

kroner annually. Potential health care savings due to earlier diagnosis and reduction in maternal adverse outcomes remain to be explored. Therefore, the current evidence is insufficient to conclude about the comprehensive economic impact of introducing sFlt-1/PlGF or PlGF testing.

Benefit-, resource- and the severity criteria

The tests evaluated may aid to predict the risk of developing preeclampsia. We are, however, not sure how useful the tests are in clinical practice, and there are some serious limitations in the included studies. Using the tests might, or might not, reduce the use of health care resources. Preeclampsia is a very serious condition and early detection might prevent serious outcomes..

at Norwegian University of Science and Technology), Kristin Viste (Consultant physician/clinical chemist at Haukeland University Hospital), Tor A. Hervig (Professor at University of Bergen)

Executive summary (English)

Background

World-wide, two to eight percent of pregnant women are diagnosed with preeclampsia. Preeclampsia is defined as new onset hypertension arising after 20 weeks' gestation accompanied by proteinuria, or other signs of maternal organ dysfunction. Symptoms of preeclampsia are strong headache, visual disturbance, epigastric pain, swelling of hands, face or feet and low output of urine. Preeclampsia may develop rapidly to seizure (eclampsia), HELLP syndrome (haemolysis, elevated liver enzymes and low platelets), stroke, disseminated intravascular coagulation (DIC) and organ failure. Therefore, preeclampsia is regarded as a life-threatening condition that requires hospital admission and close maternal and fetal monitoring.

At antenatal consultation, all pregnant women have their blood pressure assessed and urine tested by a midwife or a general practitioner. Women with high risk of preeclampsia (e.g. women with diabetes mellitus, BMI above 35 and multiple pregnancies) are referred to hospitals for closer follow up. In addition to standard clinical management, tests based on the biomarkers placental growth factor (PlGF) and fms-like tyrosine kinase-1 (sFlt-1) have been developed to help predict preeclampsia from second trimester. PlGF and ultrasound of uterine blood flow are suggested for preeclampsia screening at 11-14 weeks, but that approach is not evaluated in this health technology assessment.

Such tests are proposed to identify pregnant women at increased risk of preeclampsia to reduce the risk of negative outcomes in the women and the neonates, and also as a means of identifying women at low risk so that a) unnecessary admissions can be avoided, and b) they can return home reassured. This should also result in cost-savings for the health services.

Objective

The objective of this health technology assessment is to address questions regarding:

- 1) safety, effectiveness and health services utilisation associated with the use of Elecsys immunoassay sFlt-1/PlGF ratio, Triage PlGF-test, DELFIA Xpress PlGF 1-2-3 test, BRAHMS sFlt-1 Kryptor/BRAHMS PlGF-pluss Kryptor PE ratio or other blood-based tests for predicting suspected preeclampsia in 2nd and 3rd trimester;
- 2) predictive accuracy of these tests;
- 3) cost-effectiveness and budgetary consequences of implementation;

and evaluate the intervention against the priority setting criteria applicable in Norway (benefit, resource use and severity).

Method

The study selection criteria for question of safety and effectiveness were:

Population: Pregnant women with suspected preeclampsia in 2nd or 3rd trimester (week 20 to 36 (+6 days))

Intervention: Elecsys immunoassay sFlt-1/PlGF ratio; Triage PlGF-test; DELFIA Xpress PlGF 1-2-3 test; BRAHMS sFlt-1 Kryptor/BRAHMS PlGF-pluss Kryptor PE ratio or other relevant blood-based tests used as add-on to standard clinical assessment for predicting preeclampsia in 2nd and 3rd trimester

Control: Standard clinical assessment, e.g. measuring blood pressure, testing urine for proteinuria, blood tests for haemoglobin (Hb), liver enzymes, bilirubin, headache, oedema, visual disturbance, fetal growth restriction or ultrasound

Outcomes: Mortality, morbidity (maternal and perinatal), health services utilisation (hospital admission, number of days admitted to hospital, number of days admitted at neonatal intensive care unit (NICU), consultations), induction of labour, caesarean, eclampsia, HELLP, gestational age, prematurity

Study design: Randomised controlled trials, non-randomized controlled trials, and controlled before-and-after studies. We included primary studies published after 2002.

The study selection criteria for question of predictive accuracy were:

Population: Pregnant women with suspected preeclampsia in 2nd or 3rd trimester (week 20 to 36 (+6 days))

Index tests: Elecsys immunoassay sFlt-1/PlGF ratio, Triage PlGF-test, DELFIA Xpress PlGF 1-2-3 test, BRAHMS sFlt-1 Kryptor/BRAHMS PlGF-pluss Kryptor PE ratio or other relevant blood-based tests for predicting preeclampsia in 2nd and 3rd trimester. Index tests used in conjunction with standard clinical assessment, or in conjunction with standard clinical assessment excluding quantitative determination of proteinuria.

Comparison: Direct comparison between tests listed as index tests, e.g. diagnostic accuracy of Elecsys immunoassay sFlt-1/PlGF ratio compared to Triage PlGF

Reference: A clinical diagnosis of preeclampsia based on standard clinical assessment: measuring blood pressure, testing urine for proteinuria, blood tests for haemoglobin (Hb), liver enzymes, bilirubin, headache, oedema, visual disturbance, foetal growth restriction and ultrasound with foetal growth assessment

Outcomes: Sensitivity, specificity, predictive values, and likelihood ratios

Study design: Systematic reviews of observational studies published after 2016.

Exclusion criteria: We excluded studies where tests were used for screening purposes.

To answer questions about safety and effectiveness, an information specialist searched for randomised controlled trials and controlled trials in three databases and searched for on-going studies in three registries (October 2019). To address the question of predictive accuracy, we searched for systematic reviews in five databases and for ongoing systematic reviews (June 2019).

Two reviewers independently assessed titles and abstracts of all records from the searches. Potentially relevant records were retrieved and evaluated in full text. Articles meeting our inclusion criteria were included. Disagreement in selection of studies, were solved by consulting one of the other review authors. We assessed risk of bias in controlled studies using the Cochrane risk of bias tool and methodological quality of included systematic reviews using the AMSTAR and QUIPS checklists.

The included studies evaluating the clinical effectiveness of these tests were too different to conduct meta-analyses. We therefore present the findings narratively. As one of the included systematic reviews included meta-analyses on sensitivity and specificity of one of the biomarkers, we report these findings. We assessed the certainty of evidence using the GRADE-approach.

Results of safety, effectiveness and health services utilisation

We included three controlled studies.

Clinical effectiveness

Two studies including 1706 women with suspected preeclampsia showed that PlGF tests may reduce the time to preeclampsia diagnosis (median time to pre-eclampsia diagnosis, days time ratio 0.36 (95% CI 0.15-0.87)), and may reduce the risk of severe adverse maternal outcomes (adjusted OR 0.32 (95% CI 0.11-0.96)). We are uncertain whether sFlt-1/PlGF or PlGF testing improve neonatal outcomes.

Health services utilisation

One randomised controlled trial evaluated the effects of adding sFlt-1/PlGF test to standard clinical management among 374 women with suspected preeclampsia. The study showed that the sFlt-1/PlGF ratio was associated with little or no differences in the rate of hospital admission, both during the first week after the test, and for the remainder of the pregnancy. The results may indicate an increased rate of admission to hospital within the first 24 hours after the test: 63 more admissions per 1000 women (from 29 fewer to 183 more). The relative risk for admission within 24 hours was 1.24 (95% CI 0.89- 1.70). This result is imprecise and needs to be interpreted cautiously. One study (1023 women) found that adding PlGF testing to standard clinical management led to a reduction in outpatient visits.

We did not identify studies evaluating the effects of PlGF test on hospital admissions.

Results of predictive accuracy

One systematic review with meta-analyses estimated that sFlt-1/PlGF ratio had a sensitivity around 0.85 (95% CI 0.66-0.94) and a specificity around 0.87 (95% CI 0.76-0.93). These meta-analyses included seven studies with 943 women at high risk (17%) of developing preeclampsia. If we apply sFlt-1/PlGF tests on a group of 1000 women, 25 of the 170 women who will develop preeclampsia will be wrongly classified as negative, and 145 will have a true positive test. Among the 830 women who don't have preeclampsia, 722 will be identified correctly whereas 108 will receive a false positive result. None of the included accuracy reviews included meta-analyses of PlGF tests. The evidence regarding PlGF tests is based on single studies with wide confidence intervals, so we are uncertain about the predictive accuracy of these tests.

Results of health economic evaluation

We estimated the direct cost of introducing preeclampsia tests as approximately 2 000 Norwegian kroner per tested woman, and the budget impact as approximately 12.4 million Norwegian kroner annually, given that 6000 pregnant women would be tested.

Discussion

The sFlt-1/PlGF and PlGF tests showed favourable results, but we assessed the certainty of evidence as moderate to low. The results of predictive accuracy correspond with earlier published systematic reviews.

The included controlled trials are from high income countries, but the results cannot be easily transferred to a Norwegian setting. The alternative diagnostic strategies we compare in our analysis are complex and context-specific, depending on multiple factors. Maternity and perinatal care is good in Norway, and therefore, the impact of introducing new preeclampsia test into a routine practice remains uncertain.

Benefit, resource use and severity.

Due to the methodological challenges as well as limitations in available evidence we were unable to perform a classic cost-utility analysis and thus quantify the benefit criterion as well as the severity criterion, i.e. calculate the expected QALY gain or the "absolute shortfall", also measured in QALYs. However, we trust that the description of the condition severity and above findings together with approximate net budget impact

will help inform decisions about implementing or not implementing the tests in routine practice.

The tests evaluated in this health technology assessment may aid to predict the risk of developing the condition. We are however not sure how useful the tests are in clinical practice, and there are limitations, as we have shown in the GRADE assessments, in the studies that have evaluated the test in clinical practice. Using the tests might, or might not, reduce the use of health care resources. Preeclampsia is a serious condition, and early diagnosis is important to reduce severe adverse outcomes.

Conclusion

PIGF tests may reduce the time to a preeclampsia diagnosis, and may reduce the risk of severe maternal adverse outcomes. The sFlt-1/PIGF ratio test may be useful to rule out suspected preeclampsia, but seems to be associated with little or no differences in the risk of short or long term admissions. We are uncertain whether the test can improve neonatal outcomes.

The direct cost of introducing preeclampsia tests is about 2 000 Norwegian kroner per tested woman, and the budget impact is approximately 12.4 million Norwegian kroner annually. It remains to be explored whether earlier and correct diagnosis translates into more favourable short- and long-term outcomes for mother and infant. Neither do we have evidence that identification of women at low risk of preeclampsia will lead to reduced use of specialist health care services and thus cost saving in Norwegian settings.

Hovedbudskap

To til åtte prosent av alle gravide kvinner i verden får preeklamsi (svangerskapsforgiftning). Preeklamsi kan være en livstruende tilstand som krever sykehusinnleggelse og tett overvåkning av mor og foster i siste del av svangerskapet. Tester basert på biomarkører som «placental growth factor» (PIGF) og «fms-like tyrosine kinase-1» (sFlt-1) kan predikere preeklamsi. Disse testene er foreslått å bruke for å identifisere kvinner som er i lav risiko for å utvikle preeklamsi for dermed a) unngå unødvendige innleggelser, og b) de kan reise hjem beroliget. I denne metodevurderingen svarer vi på spørsmål om sikkerhet, klinisk effekt, prediktiv nøyaktighet og kostnadseffektivitet av blodbaserte tester for gravide ved mistanke om preeklamsi fra 20. svangerskapsuke.

Klinisk effekt (tre inkluderte studier)

- PIGF reduserer muligens tiden det tar å stille en preeklamsidiagnose og kan muligens også redusere risikoen for at kvinner utsettes for alvorlige helseutfall (som hjerneblødning).
- Vi er usikre om sFlt-1/PIGF eller PIGF tester gir helsegevinst for nyfødte barn.

Bruk av helsetjenester (to inkluderte studier)

- sFlt-1/PIGF ratio tester kan muligens øke antall innleggelser de 24 første timer etter testing, men resultatet er usikkert.
- sFlt-1/PIGF ratio tester var assosiert med liten eller ingen forskjell i kortsiktig (få dager etter testen) eller langsiktig (fram til forløsning) innleggelse.

Prediktiv nøyaktighet (fire inkluderte oversikter)

- Den prediktive nøyaktigheten til sFlt-1/PIGF er ganske god, og denne testen kan være et nyttig bidrag til å utelukke en preeklamsi-diagnose

Budsjettpåvirkning

Sikkerhet, klinisk effekt, prediktiv nøyaktighet og kost-nytte for blodbaserte tester for gravide ved mistanke om preeklamsi: en fullstendig metodevurdering

Publikasjonstype

Metodevurdering

En metodevurdering er resultatet av å

- innhente
- kritisk vurdere og
- sammenfatte

relevante forskningsresultater ved hjelp av forhåndsdefinerte og eksplisitte metoder.

Minst ett av følgende tillegg er også med:

helseøkonomisk evaluering, vurdering av konsekvenser for etikk, jus, organisasjon eller sosiale forhold

Svarer ikke på alt:

Bruk av sFlt-1/PIGF eller PIGF tester i screeningøyemed før svangerskapsuke 20.

Hvem står bak denne publikasjonen?

Folkehelseinstituttet har gjennomført metodevurderingen på oppdrag fra fra Bestillerforum RHF

Når ble litteratursøket utført?

Søk etter studier ble avsluttet oktober 2019.

Vi estimerte den direkte budsjettpåvirkning av å ta i bruk Flt-1/PIGF eller PIGF tester, som tillegg til eksisterende klinisk praksis ved mistanke om preeklampsi, til 12.4 millioner norske kroner årlig. Mulige besparelser knyttet til tidligere diagnose og redusert risiko for alvorlige utfall hos mor er uklart. Basert på tilgjengelig dokumentasjon kan vi ikke estimere de totale økonomiske innvirkningene knyttet til s-Flt-1/ PIGF eller PIGF-testing.

Nytte- ressurs og alvorlighetskriterier

Testene som er evaluert i denne metodevurderingen kan muligens bidra til å predikere risikoen for å utvikle preeklampsi. Vi er usikre på hvor nyttig testene er i klinisk praksis ettersom det er noen alvorlige begrensninger i den inkluderte dokumentasjonen. Bruk av testene kan muligens eller muligens ikke redusere bruk av ressurser i helsetjenesten. Preeklampsi er alvorlig og tidlig diagnose kan muligens redusere alvorlige utfall.

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Sammendrag

To til åtte prosent av alle gravide kvinner verden over får diagnosen preeklampsi. Preeklampsi blir definert som nylig oppstått hypertensjon etter 20. svangerskapsuke ledsaget av proteinuri eller andre tegn på organsvikt hos mor. Typiske symptomer på preeklampsi er sterk hodepine, synsforstyrrelser, magesmerter, hevelse i hender, ansikt eller ben, samt lav urinproduksjon. Preeklampsi kan raskt utvikles til kramper (eklampsi), HELLP (hemolyse, elevated liver enzymes, low platelets), slag, disseminert intravaskulær koagulasjon (DIC) og organsvikt. Preeklampsi er alvorlig og kan anses som en livstruende tilstand som krever sykehusinnleggelse og tett oppfølging av mor og barn.

Som en del av standard oppfølging av gravide sjekkes blodtrykket og urinen ved hver konsultasjon av jordmor eller fastlege. Kvinner med høy risiko for preeklampsi (f.eks. kvinner med diabetes, KMI over 35, og flerlingesvangerskap) blir henvist til spesialisthelsetjenesten for tettere oppfølging. Som et tillegg til standard oppfølging av gravide med mistanke om preeklampsi er det utviklet tester basert på biomarkørene PIGF and sFlt-1/PIGF ratio for å predikere preeklampsi. PIGF og ultralyd for å måle arteriell blodstrøm er foreslått som preeklampsi screening ved 11-14 uker, men dette blir ikke evaluert i denne metodevurderingen.

Testene er foreslått for å kunne identifisere kvinner med økt risiko for å utvikle preeklampsi og dermed redusere negative helseutfall for kvinner og deres barn. Testene er også foreslått å kunne bidra til å identifisere kvinner med lav risiko slik at a) unødvendige innleggelser kan unngås b) kvinnene kan reise hjem betrygget. Dette kan potensielt føre til kostnadsbesparelser for helsevesenet.

Hensikt

Hensikten med denne fullstendige metodevurderingen er å svare på spørsmål om:

- 1) sikkerhet, klinisk effekt og bruk av ressurser i helsetjenesten av Elecsys immunoassay sFlt-1/PIGF ratio, Triage PIGF-test, DELFIA Xpress PIGF 1-2-3 test, BRAHMS sFlt-1 Kryptor/BRAHMS PIGF-pluss Kryptor PE ratio eller andre blodbaserte tester for å predikere preeklampsi fra og med 20. svangerskapsuke,
- 2) prediktiv nøyaktighet av disse testene;
- 3) kostnadseffektivitet og budsjettmessige konsekvenser av å implementere testene i klinisk praksis i Norge (klinisk nytte, ressursbruk og alvorlighetsgrad)

Metode

Inklusjonskriterier for spørsmål om sikkerhet og klinisk effekt:

Populasjon: Gravide kvinner med mistanke om preeklampsi i andre og tredje trimester (svangerskapsuke 20 til 36⁶)

Intervensjon: I tillegg til standard oppfølging, testing med Elecsys immunoassay sFlt-1/PIGF ratio; Triage PIGF-test; DELFIA Xpress PIGF 1-2-3 test; BRAHMS sFlt-1 Kryptor/BRAHMS PIGF-pluss Kryptor PE ratio eller andre relevante blodbaserte tester for å predikere preeklampsi i andre eller tredje trimester.

Kontrollgruppe: Standard oppfølging (måling av blodtrykk, testing av urin for proteinuri, blodprøver av hemoglobin (Hb), leverenzymmer og bilirubin, vurdering av hodepine, ødem, synsforstyrrelser, hemmet fostervekst og/eller bruk av ultralyd).

Utfall: Mortalitet, morbiditet (hos mor og barn), bruk av helsetjenester (sykehusinnleggelser, antall dager innlagt på sykehus, antall dager innlagt på nyfødttintensiv (NICU), konsultasjoner), igangsetting av fødsel, keisersnitt, eklampsi, HELLP, gestasjonsalder ved forløsning og prematuritet.

Studiedesign: Randomiserte kontrollerte studier (RCTer), ikke-randomiserte kontrollerte studier og kontrollerte før og etter studier. Vi inkluderte enkeltstudier publisert etter 2002.

Inklusjonskriterier for spørsmål om prediktiv nøyaktighet:

Populasjon: Gravide kvinner med mistanke om preeklampsi i andre eller tredje trimester (svangerskapsuke 20-36⁶)

Indekstester: Elecsys immunoassay sFlt-1/PlGF ratio, Triage PlGF-test, DELFIA Xpress PlGF 1-2-3 test, BRAHMS sFlt-1 Kryptor/BRAHMS PlGF-pluss Kryptor PE ratio eller andre relevante blodbaserte tester for å predikere preeklampsi i andre eller tredje trimester. Indekstesten blir brukt sammen med standard oppfølging eller sammen med standard oppfølging uten måling av proteinuri.

Sammenlikning: Direkte sammenlikning mellom tester beskrevet som indekstester, for eksempel Elecsys immunoassay sFlt-1/PlGF ratio sammenliknet med Triage PlGF

Referanse: En klinisk diagnose av preeklampsi basert på standard oppfølging med måling av blodtrykk, testing av urin for proteinuri, blodprøver av hemoglobin (Hb), leverenzymmer og bilirubin, hodepine, ødem, synsforstyrrelser, hemmet fostervekst og/eller bruk av ultralyd.

Utfall: Sensitivitet, spesifisitet, prediktiv verdi, og sannsynlighetsratio

Studiedesign: Systematiske oversikter basert på observasjonsstudier med referansetest publisert etter 2016.

Eksklusjonskriterier: Vi ekskluderte studier der testene ble brukt til screening.

For å svare på spørsmål om sikkerhet og klinisk effekt, søkte en bibliotekar etter randomiserte kontrollerte studier og kontrollerte studier i tre databaser, samt etter pågående studier i tre registre (oktober 2019). For å svare på spørsmål om testenes prediktive nøyaktighet, søkte vi etter systematiske oversikter i fem databaser og etter pågående systematiske oversikter (juni 2019).

To forfattere vurderte treffene fra søket basert på tittel og abstrakt nivå uavhengig av hverandre. Vi vurderte relevante artikler i fulltekst. Uenighet om inklusjon og eksklusjon av artikler løste vi ved å konferere med en av de andre medforfatterne. Vi vurderte risiko for bias/systematiske feil i inkluderte kontrollerte studier med Cochrane's «risk of bias» verktøy og metodisk kvalitet på inkluderte systematiske oversikter med sjekklister til AMSTAR og QUIPS.

De inkluderte studiene om sikkerhet og klinisk effekt var for ulike til at vi kunne slå sammen resultatene i metaanalyser. Vi presenterer derfor disse resultatene beskrevet i tekst og tabeller. Vi presenterer sensitivitet og spesifisitet på en biomarkør fra en systematisk oversikt med metaanalyser. Vi vurderte tilliten til kunnskapsgrunnlaget med GRADE-tilnærmingen.

Resultat for sikkerhet, klinisk effekt og bruk av helsetjenester

Vi inkluderte tre kontrollerte studier.

Klinisk effekt

To studier som inkluderte 1706 kvinner med mistanke om preeklampsi viste at PlGF test muligens reduserer tiden det tar å stille en preeklampsi diagnose (median tid til diagnose, dager-time ratio 0.36 (95 % CI 0.15-0.87), og muligens kan redusere risiko for

alvorlige negative utfall hos mor (adjusted OR 0.32 (95 % KI 0.11-0.96)). Vi er usikre på om testing med sFlt-1/PIGF eller PIGF forbedrer utfall hos nyfødte.

Bruk av helsetjenester

Én randomisert kontrollert studie evaluerte effekten av standard oppfølging med sFlt-1/PIGF test hos 374 kvinner med mistanke om preeklampsi. Denne studien viste at sFlt-1/PIGF test var assosiert med liten eller ingen forskjell i raten for korttids (dager etter testen) eller langtids (inntil forløsning) innleggelser. Resultatene kan indikere økt rate for innleggelse innen 24 timer etter testing: Relativ Risiko 1.24 (95% KI 0.89-1.70), tilsvarende 63 flere kvinner per 1000 (fra 29 færre til 183 flere) testede. Resultatet var imidlertid upresist med bredt konfidensintervall, og må tolkes med forsiktighet. Én studie (1023 kvinner) fant at å legge til PIGF testing sammen med standard klinisk praksis førte til en reduksjon i antall polikliniske konsultasjoner.

Resultater for prediktiv nøyaktighet

Én systematisk oversikt med metaanalyser estimerte at sFlt-1/PIGF ratio hadde en sensitivitet rundt 0.85 (95% CI 0.66-0.94) og spesifisitet rundt 0.87 (95% CI 0.76-0.93). Disse metaanalysene inkluderte sju studier med 943 kvinner med høy risiko (17 %) for å utvikle preeklampsi. Hvis vi bruker sFlt-1/PIGF testing på en gruppe med 1000 kvinner, vil 25 av de 170 kvinnene som vil utvikle preeklampsi bli feilklassifisert som negative, og 145 vil ha en sann positiv test. Blant de 830 kvinnene som ikke har preeklampsi vil 722 bli klassifisert riktig, men 108 vil ha et falskt positivt resultat. Ingen av de inkluderte oversiktene hadde metaanalyser med PIGF testing. Kunnskapsgrunnlaget som gjelder PIGF testing er basert på enkeltstudier med brede konfidensintervaller så vi er usikre på den prediktive verdien av disse testene.

Resultater fra den helseøkonomiske evalueringen

Vi estimerte at den direkte kostnaden med å introdusere preeklampsi-tester til 2000 norske kroner per testet kvinne med en budsjettpåvirkning til omtrent 12.4 millioner norske kroner årlig, gitt at 6000 kvinner blir testet.

Diskusjon

Vår gjennomgang viser at både sFlt-1/PIGF og PIGF tester kan være et nyttig supplement til dagen praksis, men vi har moderat til lav tillit til disse resultatene. Våre resultater om prediktiv nøyaktighet er i tråd med andre tidligere publiserte systematiske oversikter.

De inkluderte studiene er fra høyinntektsland som er sammenliknbare med norske forhold, men i vår helseøkonomiske analyse er vi forsiktige med å anta direkte overførbarehet av disse resultatene til norsk kontekst. De diagnostiske forløpene vi sammenliknet i analysen, er komplekse og avhenger av mange faktorer. Svangerskaps- og fødselsomsorgen er allerede god i Norge, og derfor er merverdien av å ta i bruk disse testene i klinisk praksis usikker.

Nytte, ressursbruk og alvorlighetsgrad

Grunnet metodologiske utfordringer så vel som begrensninger i det tilgjengelige kunnskapsgrunnlaget var det ikke mulig å utføre en klassisk kost-nytte analyse og dermed kunne kvantifisere nytte så vel som alvorlighet, i.e. kalkulere QALYs "gained" eller "absolute shortfall", også målt som QALYs. Likevel, vi regner med at beskrivelsen av alvorlighetsgraden av preeklampsi og funnene som er rapportert i tillegg til den direkte kostnaden ved å innføre testing vil bidra til å informere beslutninger om å implementere eller ikke implementere testene i klinisk praksis.

Testene som er evaluert i denne metodevurderingen kan muligens bidra til å predikere risikoen for å utvikle preeklampsi. Men vi er usikre på hvor nyttige de er i klinisk praksis. Det er begrensninger som vist i GRADE-vurderingene, i studiene som har evaluert testene i klinisk praksis. Bruk av testene kan eller kan muligens ikke redusere bruk av ressurser i helsetjenesten. Preeklampsi er en alvorlig tilstand og tidlig diagnose er viktig for å redusere alvorlige utfall.

Konklusjon

PIGF tester kan muligens redusere tiden det tar å stille en preeklampsi-diagnose, og kan muligens også redusere risiko for alvorlige negative utfall hos mor.

Den prediktive nøyaktigheten til sFlt-1/PIGF tester er god, og kan egne seg til å utelukke en preeklampsi blant kvinner der man mistenker dette. Bruk av sFlt-1/PIGF-tester kan muligens være nyttig for å avkrefte «rule out» mistanke om preeklampsi, men er assosiert med liten eller ingen forskjell i innleggelses på kort eller lengre sikt. Vi er usikre på om testene forbedrer utfall hos nyfødte.

Den direkte kostnaden ved å introdusere disse testene er omkring 2000 norske kroner per testet kvinne, og den årlige budsjettpåvirkningen er omtrent 12.4 millioner norske kroner. Det trengs mer forskning for å avgjøre i hvilken grad tidligere og korrekt diagnose gir mer gunstige utfall hos mor og barn. Vi vet heller ikke om det å identifisere kvinner med lav risiko for å utvikle preeklampsi vil føre til redusert bruk av spesialisthelsetjenesten og om dette bidrar til sparte kostnader i en norsk kontekst.

Preface

The Commissioning Forum representing the four Regional Health Authorities (Bestillerforum RHF) requested a health technology assessment (HTA) from the Norwegian Institute of Public Health (NIPH, Folkehelseinstituttet) within the National System for Managed Introduction of New Health Technologies within the Specialist Health Service in Norway (Nye Metoder). The aim of this HTA was to evaluate safety, effectiveness, predictive accuracy and cost-effectiveness of blood-based tests for preeclampsia, and evaluate them against the priority setting criteria that apply in the Norwegian health care: the benefit, the resource use and the severity criterion. The project was initiated as a proposal for a single technology assessment from one of the manufacturers (Roche Diagnostics Norway) in May 2018. The background for this proposal was using the tests as means of identifying low risk woman, who can be reassured and avoid unnecessary admission to hospital. However, as multiple manufacturers were identified, it was converted into a full HTA October 2018.

The mandate did not include evaluation of these tests for screening or for routinely testing of high-risk groups in early pregnancy, according to the decision and clarification made by the Commissioning Forum on the 18th of March 2019.

The internal project group included the following members:

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Conflict of interest: All the authors of this HTA report no conflict of interest.

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Norwegian Institute of Public Health takes the full responsibility of views expressed in this health technology assessment.

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Introduction

Two to eight percent of pregnant women are diagnosed with preeclampsia worldwide (1). Preeclampsia has traditionally been characterised by new onset high blood pressure and proteinuria after gestational week 20. The definition of preeclampsia has changed over the last years, in recognition of its syndromic nature. Proteinuria is therefore no longer mandatory for diagnosing preeclampsia in guidelines like the ones published by the International Study of Hypertension in Pregnancy (ISSHP) (2) and the American College of Obstetrician and Gynecologists (ACOG) (3). These guidelines define preeclampsia as new onset hypertension arising after 20 weeks' gestation (Gestational hypertension) accompanied by one or more of the following new onset signs after 20 weeks' gestation:

- 1) Proteinuria
- 2) Other signs of maternal organ dysfunction, including one or more of the following:
 - Liver involvement (elevated transaminases, e.g. ALT or AST)
 - Neurological complications, e.g. eclampsia, stroke or persistent visual scotomata
 - Hematological complications, i.e. thrombocytopenia, disseminated intravascular coagulation or hemolysis)
 - Uteroplacental dysfunction, e.g. fetal growth restriction, stillbirth or abnormal fetal Doppler findings. This feature is not included as a criteria for diagnosing preeclampsia in most medical birth registries and many national clinical guidelines, such as the ACOG (3).

Symptoms and signs of preeclampsia include strong headache, visual disturbance, epigastric pain, swelling of the hands, face or feet and low output of urine. Preeclampsia is potentially a life-threatening condition that requires hospital admission and close maternal and fetal monitoring. It may develop rapidly to seizures (eclampsia), HELLP syndrome (haemolysis, elevated liver enzymes and low platelets), stroke (increased risk of cerebral haemorrhage due to maternal hypertension), disseminated intravascular coagulation (DIC) and organ failure.

Current national and international guidelines recommend inducing delivery when a woman with preeclampsia has reached 37 gestational weeks, in order to avoid the severe complications mentioned above. In preeclampsia with severe features, i.e. threatening maternal and/or fetal signs, delivery is effectuated when necessary at any gestational week. In Norway, 1/3 of all preeclamptic pregnancies are delivered preterm, often with a growth-restricted child, indicative of a more severe and premature placenta dysfunction in early-onset preeclampsia (4).

In Norway, women with expected normal pregnancies are offered eight consultations including an ultrasound screening at gestational week 17-20, according to national guidelines for antenatal care (5). Most women attend more consultations and ultrasound examinations during pregnancy (6). At each consultation, assessments of blood pressure

and testing of proteinuria by midwife or general practitioner are standard clinical assessments. Risk factors for preeclampsia such as previous severe preeclampsia, chronic hypertension, renal disease (including renal transplantation), assisted reproductive technology (ART), diabetes mellitus, BMI above 35, multiple pregnancies, or age higher than 40 years are evaluated at the first consultation. Pregnant women at high risk of developing preeclampsia are referred to specialist health care services for closer follow up (4), but doctors in Norway are advised to recommend preeclampsia prophylaxis with low-dose oral aspirin to women deemed at high risk of developing preeclampsia, e.g. 75 mg daily until delivery (any gestational week) (7).

Different blood-based tests like Elecsys sFlt-1 & PlGF, Triage PlGF-test, DELFIA Xpress PlGF 1-2-3 test, and BRAHMS sFlt-1 Kryptor/BRAHMS PlGF-pluss Kryptor PE ratio have been developed to predict preeclampsia from second trimester, whereas PlGF and ultrasound evaluation of uterine blood flow have been used in algorithms tested at 11-14 weeks screening for preeclampsia (the latter has not been evaluated in this health technology assessment). The blood tests aim to measure maternal circulating biomarkers that could identify placental dysfunction, as preeclampsia is a “placental dysfunction disease”. Such tests are also proposed as means of identifying women at low risk so that a) unnecessary admissions can be avoided, and b) they can return home reassured. The tests could guide clinical management and accurate diagnosis of preeclampsia or other conditions with placental dysfunction (eg. fetal growth restriction, placental abruption, spontaneous premature delivery). PlGF and sFlt-1 measures behave as positive and negative stress response proteins in preeclampsia. sFlt-1 (soluble Fms-like tyrosin kinase-1) is a circulating angiogenic protein produced by placenta. The production increases in preeclampsia. PlGF (placental growth factor) binds to Flt-1. During preeclampsia, the production of PlGF is reduced, leading to imbalance in the sFlt-1/PlGF ratio. Low PlGF in pregnancy reflects what cannot be seen clinically; placental syncytiotrophoblast stress, occurring in multiple clinical settings of placental dysfunction. Typically, a low PlGF and/or a high sFlt-1 can indicate placental dysfunction at > 20 weeks of pregnancy. The sFlt-1/PlGF- ratio cut-off of e.g. ≤ 38 is used in trials for “ruling out” short-term absence of preeclampsia in women for whom the syndrome is suspected (but not diagnosed clinically) (8). The clinical effectiveness and predictive properties of these tests are the topic of this review.

There are some systematic reviews on the predictive accuracy and cost-effectiveness of these blood-based tests for predicting preeclampsia among pregnant women in gestational week 20 to 36 (+6 days) (9-12). A diagnostics guidance from NICE (13), based on an HTA report published in 2016 (12), recommended combining the Triage PlGF test and Elecsys immunoassay sFlt-1/PlGF ratio with standard clinical assessment and clinical follow-up to help “ruling out preeclampsia” in women presenting with suspected preeclampsia in second and third trimester. This might have an impact on the utilisation of health services. Most importantly, at the time of writing the protocol we have data from one randomised trial, and information about two ongoing randomised trials. The results of these studies will probably provide better evidence to inform the decision on the use of tests in women with suspected preeclampsia. Therefore, we aimed to conduct an HTA with the following questions:

1. What is the safety and effectiveness and health services utilisation of Elecsys immunoassay sFlt-1/PlGF ratio, Triage PlGF-test, DELFIA Xpress PlGF 1-2-3 test, BRAHMS sFlt-1 Kryptor/BRAHMS PlGF-pluss Kryptor PE ratio or other relevant blood-based tests for predicting suspected preeclampsia in 2nd and 3rd trimester?
2. What is the predictive accuracy of the tests mentioned above?
3. What is the cost-effectiveness and the budgetary consequences of implementation of the tests mentioned (see question 1) for predicting suspected preeclampsia in 2nd and 3rd trimester?

4. What are the potential clinical benefits or harms for the woman and her offspring of implementing blood-based tests, as defined above, for predicting suspected preeclampsia in 2nd and 3rd trimester in Norway?

Method

We performed a health technology assessment (HTA) on the safety and effectiveness in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (14) and disseminated results from systematic reviews on the predictive accuracy in accordance with the PRISMA diagnostic test accuracy guideline (15).

We followed a population, intervention, comparator, outcome and study design (PICO) framework to set parameters for our literature search and study selection. Further steps in this process were literature searches, study selection, quality assessments, risk of bias assessments, data extraction, analysis and dissemination of available evidence. We used Grading of Recommendations Assessment, Development, and Evaluation (GRADE) to assess the certainty of evidence on diagnostic tests (16).

Study selection criteria

Due to different research questions, we selected articles according to the following inclusion criteria:

Table 1. Inclusion criteria for question 1 and 4 (safety and clinical effectiveness)

Population	Pregnant women with suspected preeclampsia in 2 nd or 3 rd trimester (week 20 to 36 (+6 days))
Interventions	In addition to standard clinical assessment: <ul style="list-style-type: none">• Elecsys immunoassay sFlt-1/PlGF ratio• Triage PlGF-test• DELFIA Xpress PlGF 1-2-3 test• BRAHMS sFlt-1 Kryptor/BRAHMS PlGF-pluss Kryptor PE ratio• Other relevant blood-based tests for predicting preeclampsia in 2nd and 3rd trimester
Control	Standard clinical assessment, e.g. measuring blood pressure, testing urine for proteinuria, blood tests for haemoglobin (Hb), liver enzymes, bilirubin, headache, oedema, visual disturbance, fetal growth restriction or ultrasound
Outcomes	Mortality, morbidity (maternal and perinatal), health services utilisation (hospital admission, days admitted to hospital, days admitted at neonatal intensive care unit (NICU), consultations), induction of labour, caesarean, eclampsia, HELLP, gestational age, prematurity
Study design	Randomised controlled trials (RCTs), non-randomized controlled trials, and controlled before-and-after studies. We included single studies published after 2002.

Table 2. Inclusion criteria for question 2 (predictive accuracy)

Population	Pregnant women with suspected preeclampsia in 2 nd or 3 rd trimester (week 20 to 36 (+6 days))
Index tests	<ul style="list-style-type: none"> • Elecsys immunoassay sFlt-1/PlGF ratio • Triage PlGF-test • DELFIA Xpress PlGF 1-2-3 test • BRAHMS sFlt-1 Kryptor/BRAHMS PlGF-pluss Kryptor PE ratio • Other relevant blood-based tests for predicting preeclampsia in 2nd and 3rd trimester <p>Index tests used in conjunction with standard clinical assessment, or in conjunction with standard clinical assessment excluding quantitative determination of proteinuria</p>
Comparison	Direct comparison between tests listed as index tests, e.g. diagnostic accuracy of Elecsys immunoassay sFlt-1/PlGF ratio compared to <i>Triage PlGF</i>
Reference	A clinical diagnosis of preeclampsia based on standard clinical assessment: measuring blood pressure, testing urine for proteinuria, blood tests for haemoglobin (Hb), liver enzymes, bilirubin, headache, oedema, visual disturbance, fetal growth restriction and ultrasound with fetal growth assessment
Outcome	Sensitivity, specificity, predictive values, and likelihood ratios
Study design	Systematic reviews of observational studies published after 2016

Exclusion criteria

We excluded studies based on:

- Use of these tests for screening purposes
- Use of tests for preeclampsia that were not blood based
- Animal studies

Search strategy

The information specialist planned and conducted all searches in collaboration with the research team. The search strategies combined index terms and text words relating to population/problem (preeclampsia), intervention and index tests. The search syntax was adapted to each database. Another information specialist peer reviewed this work.

The searches for question 1 (safety and clinical effectiveness) were conducted in October 2019. The information specialist (GH) searched for completed, ongoing or terminated (unpublished) randomised controlled trials and controlled trials in:

- Cochrane Central Register of Controlled Trials (Wiley)
- Medline (OVID)
- Embase (OVID)
- Clinical Trials (National Institutes of Health, US)
- International Clinical Trials Registry Platform (WHO)
- Australian New Zealand Clinical Trials Registry

In June 2019, the information specialist GH searched for systematic reviews and HTAs for question 2 (predictive accuracy). As we were aware of recent systematic reviews, we only searched for systematic reviews published after 2016. GH searched in:

- CRD database, HTA (Centre for Reviews and Dissemination, University of York)
- Cochrane Database of Systematic Reviews (Wiley):
- Epistemonikos
- Embase (OVID)
- Medline (NLM)
- POP database
- PROSPERO

The research team contacted experts and searched bibliographies for references not identified by the searches.

Article selection

Two reviewers (HTM, LMR) selected articles for question 1 and 2 by a two-step strategy. Both steps were carried out considering the selection detailed in Table 1 and Table 2. Disagreements at either stage were settled by discussion or consultation with a third person (SF). The article selection included the following steps:

1. Two reviewers (LMR, HTM) independently assessed title and abstracts of retrieved articles to determine relevant full-text articles to be examined. This first step was done in Rayyan (17).
2. Subsequently, two reviewers (LMR, HTM) independently assessed the full-text articles included in step 1 and decided which articles to include in the systematic review.

Assessment of methodological quality and risk of bias

We (LMR, HTM) assessed the methodological quality of the systematic reviews by AMSTAR (18) and the QUIPS tool (19). For the randomised controlled trials and controlled trials, we used the Cochrane risk of bias tool (20).. Two review authors (LMR, HTM) assessed the quality or risk of bias of the included studies independently. We resolved disagreements by discussions or by consulting one of the other review authors.

Data extraction

One review author (HTM) extracted data from the included studies and reviews and another review author (LMR) verified the data. We extracted the following data:

- Information about the study (authors, year of publication, setting, study design, clinical trial identification number and funding source)
- Participant characteristics (number of participants, age, procedure to be performed during intervention)
- Intervention and control characteristics
- Characteristics of index tests and reference tests
- Outcome data: for questions 1, 2, 4 we examined endpoints, methods used to analyse outcome data, length of follow up and loss to follow up.
 - For safety and effectiveness studies (question 1 and 4), we extracted outcomes on mortality, morbidity (maternal and perinatal), hospital admission, number of days admitted to hospital, number of days admitted at neonatal intensive care unit (NICU), consultations, induction of labour, caesarean, eclampsia, HELLP, gestational age, prematurity.
 - For predictive accuracy studies (question 2), we extracted information about diagnostic performance outcomes such as the number of true positives (TP), false positives (FP), false negatives (FN) and true negatives (TN), sensitivity, specificity, predictive values, likelihood ratios, prevalence and the area under the receiver operator characteristic (ROC) curve (AUC).

Statistical analyses

We planned to do meta-analyses of studies evaluating the clinical effectiveness of blood-based tests for preeclampsia, but concluded that the available studies were too different to justify pooling. Rather, we present results from available studies narratively. We also planned for meta-analyses of predictive accuracy, but as we identified other systematic reviews answering our review question, we decided to report findings from these reviews rather than performing our own analyses. The reported meta-analysis was based on hierarchical modelling of sensitivities and specificities from individual studies.

Subgroup and sensitivity analyses

We report the sub-group analysis of an included systematic review (21) referring to women with high risk of preeclampsia. No sensitivity analysis was done in the included systematic reviews.

Assessment of certainty of the evidence

Grading the certainty of evidence

Two review authors (LMR, HTM) independently assessed the certainty of the evidence for each outcome using the GRADE approach (Grading of Recommendations Assessment, Development, and Evaluation (16;22)). We resolved disagreements by consulting SF or KGB.

We assessed the certainty of the evidence by evaluating risk of bias, imprecision and inconsistency of the estimates, indirectness, and magnitude of effect, dose response gradient, publication bias and potential confounding factors. GRADE classifies the certainty of the evidence for each outcome as high, moderate, low, or very low (Table 3).

Table 3: Definition of each category for certainty of evidence in GRADE

Grade	Interpretation
High	We are very confident that the true effect lies close to that of the estimate of effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Ethics

We did not consider ethical consequences of the implementation of these tests.

Results – safety, effectiveness and health services utilisation

Results of the literature search

The literature search for randomised controlled trials and controlled trials yielded 1333 unique articles of which 1319 were excluded following screening of titles and abstracts. We considered fourteen articles as potentially relevant and read them in full text. Three of these articles met our inclusion criteria and were included (Figure 1).

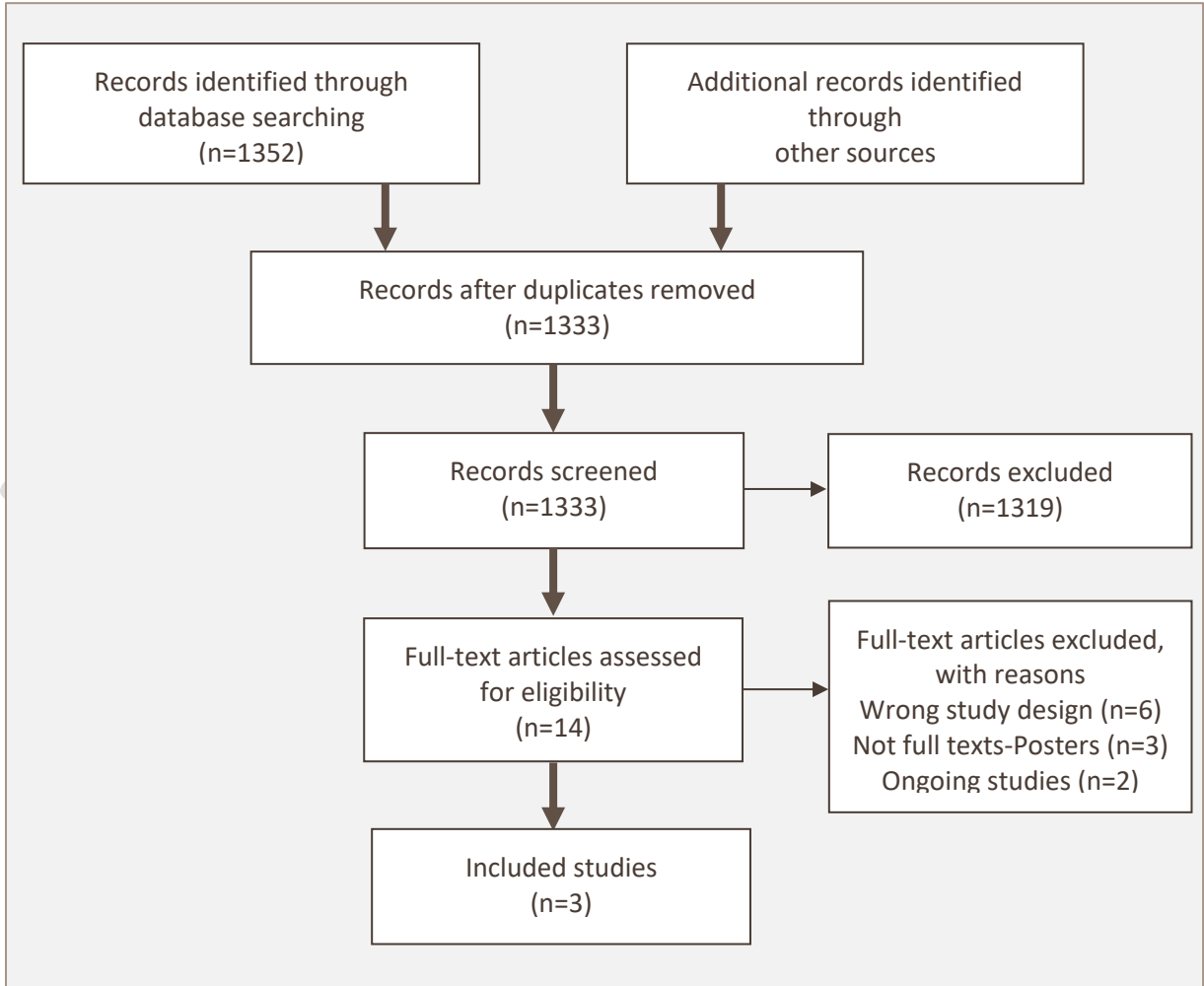


Figure 1. Selection of studies

Description of studies

Included studies

We included two randomised controlled trials by Cerdeira et al (23) and Duhig et al (24) from the United Kingdom (UK), and one controlled study by Sharp et al (25) from Australia, Austria, Germany and UK.

Cerdeira et al (23) evaluated the effectiveness of revealed sFlt-1/PlGF ratio results in addition to standard clinical management compared to standard clinical management with concealed sFlt-1/PlGF ratio results with the aim to rule out the occurrence of preeclampsia. Thereby they would identify women at low risk to avoid unnecessary admissions and those at high risk for a more targeted surveillance. The study included pregnant women, 18 years or older, with a clinical suspicion of preeclampsia at 24⁰-37⁰ gestational age (GA) weeks. The primary outcomes were hospital admission within 24 hours, until 7 days or until delivery. The study included 374 women and reported a ratio cut off of 38 implying that values higher than 38 were interpreted as elevated risk of developing preeclampsia the following week.

Duhig et al (24) evaluated the effectiveness of revealed circulating PlGF and the use of a clinical management algorithm compared to concealed PlGF results. Primary outcomes were time to diagnosis with preeclampsia, and adverse maternal and perinatal outcomes. They also reported, as secondary outcomes, maternal health resource use as mean outpatient visits and mean inpatient nights and outpatient visits. The study included women aged 18 years and older with suspected preeclampsia between 20-36⁶ GA weeks. Totally, 1023 women were included in this multicentre stepped wedge cluster randomised controlled trial.

The last included study was a controlled trial including two cohorts (MAPPLE and PELICAN) (25). In the MAPPLE cohort, the PlGF measurements were revealed, whereas in the PELICAN cohort the PlGF measurements were concealed. The study included pregnant women from United Kingdom, Austria, Germany and Australia. All participants were prior to 35 GA weeks with suspected preeclampsia or fetal growth restriction. As indication of PlGF testing (non-exclusive) new onset of hypertension was reported in 80% of the MAPPLE cohort (revealed group) and 54% of the PELICAN cohort (concealed group). In the MAPPLE cohort, 17% were tested based on suspected fetal growth restriction and 9% in the PELICAN cohort. Study outcomes were maternal and perinatal adverse outcomes. More information about the included studies are available in table 4.

We have not identified other relevant blood-based tests or biomarkers in safety- and effectiveness studies in 2nd and 3rd trimester, than those described above.

Excluded studies

We excluded eleven studies following full text screening. For more information, see Appendices, table 1.

Table 4. Characteristics of included studies on safety and clinical effectiveness

Author, year (country), Study design/Risk of bias, Funding	Population	Intervention (I) (context)	Comparison (C)	Outcome
<p>Cerdeira, 2019 (23) (The INSPIRE study, UK) RCT/Low risk of bias Funding: Roche Diagnostics GmbH and Roche Diagnostics Ltd. The University of Oxford sponsored the study.</p>	<p>Women 18 years or older with a clinical suspicion of preeclampsia GA 24⁰-37⁰ weeks Median GA week at recruitment: 34.4 (31.4-35.7) (C), 34.3 (31.3-36.0) (I) Mean age at recruitment, median: 31.1 (C), 30.9 (I) N=374</p>	<p>Standard clinical management and sFlt-1/PIGF ratio result (Revealed group) In the revealed arm, sFlt-1/PIGF ratio was incorporated into the clinical decision framework with a ratio of ≤ 38 (John Radcliffe a tertiary center)</p>	<p>Standard clinical management (Non-revealed group)</p>	<p>Primary outcome: Hospital admission (preeclampsia-related inpatient admission within 24 hours of the test, within 7 days, or by delivery) Secondary outcomes: Mean gestational age at delivery, admission to neonatal intensive care unit (NICU), small for gestational age</p>
<p>Duhig, 2019 (24) (The PARROT trial, UK) Stepped wedge cluster randomised controlled trial/ Low risk of bias Funding: National Institute for Health Research</p>	<p>Women aged 18 years and older who presented with suspected preeclampsia between 20⁰-36⁶ gestational weeks with a live, singleton fetus Median GA week at enrolment: 32.7 (C) and 32.3 (I) Mean age at recruitment, median: 31.5 (C), 31.9 (I) N=1023</p>	<p>Circulating PIGF measurement was revealed and a clinical management algorithm was used (11 UK maternity units)</p>	<p>At the start of the trial, all units had usual care (in which PIGF measurements were concealed)</p>	<p>Primary outcome: Time to diagnosis with preeclampsia The secondary maternal outcomes: severe adverse outcomes (e.g. mortality, eclampsia), caesarean section, mean outpatient visits, mean inpatient nights Perinatal outcomes: mean gestation at delivery, admission to a neonatal unit, mortality</p>
<p>Sharp, 2018 (25) (The MAPPLE and the PELICAN cohorts, UK, Austria, Germany and Australia) High risk of bias Funding: Alere-supported the MAPPLE database.</p>	<p>Women presenting prior to 35 weeks gestation with suspected preeclampsia or fetal growth restriction N=396 (MAPPLE cohort) N=287 (PELICAN cohort) Mean age at recruitment, median: 32 (C), 31 (I) Gestational age at sampling, (weeks; median, quartiles): 31.0 (27.9-33.4) (C), 30.7 (27.7-33.1) (I)</p>	<p>PIGF testing in line with local hospital policy. Clinicians were aware of the PIGF result and were expected to adjust care accordingly. (Four maternity units in UK, Austria, Germany and Australia).</p>	<p>Concealed PIGF testing (PELICAN) cohorts</p>	<p>Maternal adverse outcomes (e.g. mortality, eclampsia) Perinatal adverse outcomes: Gestational age at delivery, admission to NICU, mortality</p>

C (control group); G (gestational age); I (Intervention group); PE (preeclampsia); NICU (Neonatal intensive care unit); PlGF (placental growth factor); sFlt-1 (soluble fms-like tyrosine kinase-1).

Risk of bias in included studies

We assessed the risk of bias of the three included studies (23-25) using Cochrane Risk of bias tool (20). Both of the RCTs had low risk of bias on the majority of the domains. As the study of Cerdeira et al. (23) was funded by the test's manufacturer (Roche) and the study of Duhig et al. (24) may have had confounding effects because of secular trends in calendar time (stepped wedge design), the risk of 'other bias' is unclear. For Sharp et al. (25), we evaluated the risk of bias as high as the two included cohorts varied in several demographic features and the attrition rate was not reported. Our assessments are summarised in appendices, figure 1.

Effects of adding sFlt-1/PlGF ratio to clinical standard management

One study (23) investigated the effects of adding sFlt-1/PlGF ratio to clinical standard management compared to not having access to the sFlt-1/PlGF ratio. The results from this study and our assessment of the certainty of the evidence are presented in table 5.

Table 5. Effects of adding sFlt-1/PlGF ratio to clinical standard management.

Data below are from the RCT by Cerdeira 2019 (23) with 370 participants and low risk of bias

Outcome	Revealed group (I)	Concealed group (C)	Effect size (95% CI)	Certainty of evidence (GRADE)
Hospitalisation within 24 hours of the test	32% (60/186)	26% (48/184)	RR: 1.24 (0.89 - 1.70)	⊕⊕○○ Low ¹
Hospitalisation within 7 days of the test	38 % (70/186)	35% (65/184)	RR: 1.06 (0.81 - 1.39)	⊕⊕○○ Low ¹
Admission until delivery	67% (126/186)	73% (134/184)	RR: 0.93 (0.82 - 1.06)	⊕⊕⊕○ Moderate ²
Maternal platelets at delivery (IQR)	220 (192-263)	219.5 (174-274)	Not reported (NR)	
GA at delivery weeks, median (IQR)	38.4 (37.3 - 39.6)	38.1 (37.1 - 39.3)	NR	
Admission to NICU	18% (34/186)	15% (28/184)	NR	
Small for gestational age	17% (31/186)	17% (31/184)	NR	

¹ Downgraded two for imprecisions (wide confidence intervals); ² Downgraded one for imprecisions (wide confidence interval)

C (control group); CI (Confidence interval); I (intervention group); IQR (interquartile range); NICU (Neonatal intensive care unit);

Effects of adding PlGF to clinical standard management

Two studies (24;25) assessed the effects of adding measurement of PlGF to clinical standard management compared to not having access to PlGF results. We could not make any meta-analyses, due to the heterogeneity of the included studies. The results from the two studies and our assessment of the certainty of the evidence are summarised in table 6 and table 7.

Table 6. Effects of adding PlGF testing to clinical standard management.

Tabled data are from the RCT by Duhig, 2019 (24) with 1019 participants and low risk of bias

Outcome	Revealed group (I)	Concealed group (C)	Effect size (95% CI)	Certainty of evidence (GRADE)
Days to diagnosis of preeclampsia in those diagnosed	1.9 (0.5-9.2)	4.1 (0.8-14.7)	Time ratio: 0.36 (0.15 - 0.87) p=0.027	⊕⊕○○ Low ¹
Number of women with severe adverse outcomes	22 (4%)	24 (5%)	aOR 0.32 (0.11 - 0.96) p= 0.043	⊕⊕○○ Low ¹
Eclampsia	0	2 (<1%)	-	
Stroke	0	2 (<1%)	-	
Placenta abruption	4 (1%)	5 (1%)	NR	
Pre-labour caesarean section	170 (30%)	130 (29%)	NR	
In-labour caesarean section	150 (26%)	94 (21%)	NR	
Mean outpatient visits (SE)	6.14 (0.53)	9.44 (0.81)	NR	
Mean inpatients nights (SE)	7.43 (0.36)	7.26 (0.38)	NR	
Adverse perinatal outcomes	86 (15%)	63 (14%)	NR	
Intrauterine fetal death	7 (1%)	6 (1%)	NR	
Perinatal death	6 (1%)	4 (1%)	NR	
Admission NICU	195 (34%)	146 (33%)	NR	
Gestational age at delivery, mean (SD)	36.6 (3.03)	36.8 (3.03)	Mean difference -0.52 (-0.63 - 0.73)	⊕⊕⊕○ Moderate ¹

¹ Downgraded two due to imprecision (wide CI), result based on a single trial, and inconsistencies between the analytical approach described in study protocol and in the main report

aOR (adjusted odds ratio); C (control group); CI (Confidence interval); I (intervention group); NICU (Neonatal intensive care unit); SD (standard deviation); SE (standard error)

Table 7. Effects of on revealed PIGF in addition to clinical standard management.
The tabled data are from non-randomised controlled trial by Sharp et al. (25) with 683 participants and high risk of bias

Outcome	Revealed group (I)	Concealed group (C)	Effect size (95% CI)	Certainty of evidence (GRADE)
Women with adverse maternal outcomes	47 (11.9%)	29 (10.1%)	RR 1.17 (0.76-1.82)	⊕○○○ Very low ^{1,2}
Maternal death	0	0	-	
Eclampsia	0	1	-	
Stroke	0	0	-	
Myocardial infarction	0	0	-	
Placenta abruption	1	4	-	
Gestational age at delivery, (weeks, median, quartiles)	34.9 (32.0-37.1)	36.7 (33.6-38.6)	Median: -1.4 (-0.9 – -2.0)	⊕○○○ Very low ^{1,2}
Infants with neonatal adverse outcomes, (n, %)	131 (30.4)	51 (17.1)	RR: 1.78 (1.32-2.41)	⊕○○○ Very low ^{1,2}
Admission to NICU, n (%)	190 (45.5)	117 (39.8)	RR: 1.14 (0.95-1.37)	⊕○○○ Very low ^{1,2}
Perinatal death, n (%)	2 (0.5)	9 (3.0)	RR: 0.16 (0.03-0.74)	⊕○○○ Very low ^{1,2}

¹Observational study- starting at low, ² Downgraded for imprecision (wide CI)
C (control group); CI (Confidence interval); I (intervention group); NICU (Neonatal intensive care unit); RR (relative risk)

Summary of effects of testing sFlt-1/PIGF ratio or PIGF

The results reported here suggest that the use of sFlt-1/PIGF testing might be associated with little or no difference in hospital admission rates within seven days or admission until delivery. However, the results may indicate an increased risk of admission within 24 hours of the test among 63 more per 1000 women (from 29 fewer to 183 more). This result was imprecise and needs to be interpreted cautiously. One study suggests that adding PIGF testing to standard clinical management may reduce the time to a preeclampsia diagnosis and may reduce the number of women with severe adverse outcomes. This study also found reduction in outpatient visits. The use of PIGF testing probably makes little or no difference in mean gestation age at delivery. This result is based on the two included RCTs and not the non-randomised controlled trial.

We are uncertain whether sFlt-1/PIGF or PIGF testing improve neonatal outcomes.

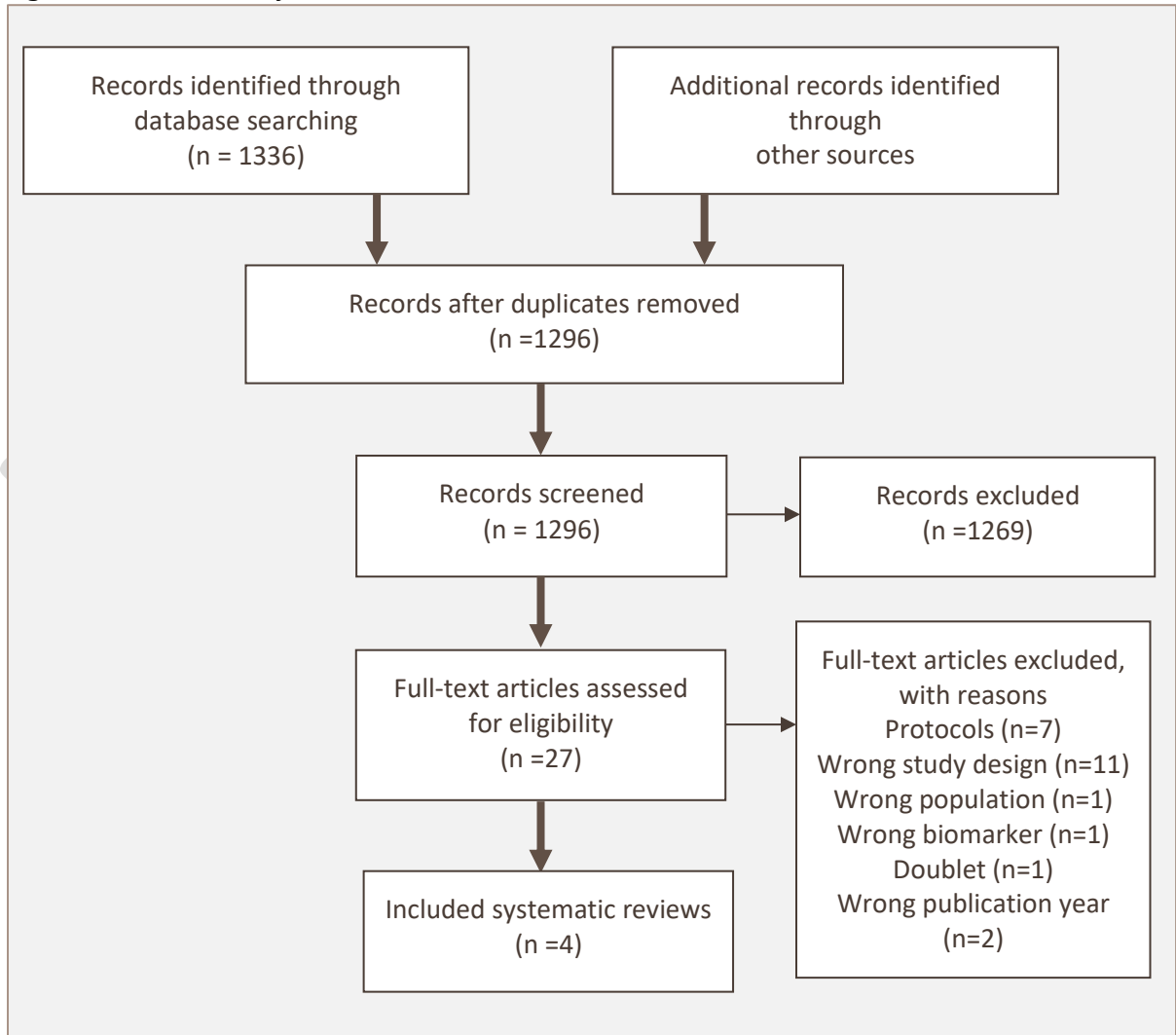
Results-predictive accuracy

Our literature search for systematic reviews yielded 1336 hits, where 1296 were unique references. We retrieved 27 articles in full text and identified four reviews fulfilling our inclusion criteria (Figure 3).

Description of studies

Results of literature search

Figure 3. Selection of systematic reviews



Included systematic reviews

Four systematic reviews met our inclusion criteria (10;21;26;27). Maesa et al. (26) summarised studies on sensitivity and specificity of the sFlt-1/PlGF ratio. Ukah et al. (10) summarised studies on the abilities of PlGF or sFlt-1/PlGF ratio to predict adverse maternal and fetal outcomes, whereas Agrawal et al. (21) summarised studies on the sensitivity and specificity of the sFlt-1/PlGF ratio in blood for predicting preeclampsia. Townsend et al. (27) summarised systematic reviews on different biomarkers for predicting preeclampsia. The literature searches in Ukah et al. (10) and Agrawal et al. (21) were conducted in January 2017, in March 2017 for Townsend et al. (27) and for Maesa et al. (26) the final search date was not reported. See characteristics of included systematic reviews in table 8.

We have not identified other blood-based tests or biomarkers for predicting preeclampsia in 2nd and 3rd trimester, than those described above.

Excluded articles

We excluded 23 articles following full text screening. They are listed in the Appendices, table 2.

Table 8. Characteristics of included systematic reviews on predictive accuracy of blood- based tests for women with suspected preeclampsia

Authors (methodological quality)	N of included studies/reviews	Population	Biomarker	Outcome
Maesa et al, 2019 (26) (Low)	Updated NICE 2016 (12) with Bahlmann 2016 (28), Stepan 2016 (case-control)(29), Zeisler 2016 (8), Tarasviciene 2016 (case-control) (30), Sovio 2017 (cohort) (31), Dragan 2017 (cohort) (32), Liu 2015 (meta-analysis) (33)	Women with clinical signs of preeclampsia (suspected PE) from 20-40 GA weeks N= 26447	sFlt-1/PIGF ratio	Diagnostic accuracy (Sensitivity, specificity, PPV, NPV and area under the ROC curve)
Agrawal et al, 2018 (21) (Moderate)	Included 15 studies, where 7 studies included pregnant women with suspected PE (8;34-39).	Pregnant women with suspected PE Median age: Not reported GA: 24-36 weeks N=943	sFlt-1/PIGF ratio	Sensitivity, specificity, PPV, NPV, PLR, NLR, risk odds ratio
Townsend et al, 2018 (27) (High)	The following reviews were included on sFlt-1 and/or PIGF to predict preeclampsia: Widmer 2007 (40), Kleirouweler 2012 (41), Allen 2014 (42), Wu 2015 (9), Zhong 2015 (43)	Pregnant women in first, second and third trimester N=8124 (tested by sFlt-1/PIGF) N= 23658 (tested by PIGF).	sFlt-1/PIGF ratio	Early -onset of preeclampsia All preeclampsia Sensitivity, specificity OR, LR
Ukah et al, 2017 (10) (High)	Included 17 studies, 11 studies included pregnant women with suspected PE and included in our review: (Palomaki 2015 (44), Alvarez-Fernandez 2016 (45), Chaiworapongsa 2011 (37) , Chaiworapongsa 2014 (46), Chappell 2013 (47), Ukah 2017 (48), Woelkers 2016 (49), Moore 2012 (50), Rana 2012 (51), Salahuddin 2016 (52), Rana et al 2012 (twins)) (53)	Pregnant women with suspected PE Age range (median): 24-34 years GA: 23-37 weeks Nulliparity: 40-76% N=2980	PIGF sFlt-1/ PIGF ratio	Maternal outcome (eclampsia, preterm delivery, postpartum haemorrhage, severe preeclampsia, mortality, hepatic dysfunction, acute renal insufficiency, retinal detachment, dialysis, low platelets) Fetal outcome (small for gestational age, stillbirth, neonatal death). Sensitivity, specificity, LR, AUROC

AUROC (Area Under the Receiver Operating Characteristics); GA (gestational age); LR (likelihood ratio); NICU (Neonatal intensive care unit); NPV (negative predictive value); OR (odds ratio); PE (preeclampsia); PIGF (placental growth factor); PLR (positive likelihood ration); PPV (positive predictive value); NLR (negative likelihood ration); sFlt-1 (soluble fms-like tyrosine kinase-1)

Methodological quality of included systematic reviews

The four included systematic reviews (10;21;26;27) were assessed for methodological quality by AMSTAR (18). We evaluated the overall methodological quality of Maesa as low, Agrawal as moderate, and Townsend and Ukah as high (Appendices, table 3). The included systematic reviews were also assessed by QUIPS (19) (Appendices, table 3 and 4).

Predictive value of sFlt-1/PlGF ratio

Of the four included systematic reviews, only Agrawal et al. (21) presented meta-analyses. One meta-analysis was restricted to patients with high risk of developing preeclampsia. The analysis included seven studies with a total of 943 participants of which 158 were diagnosed with preeclampsia. The summary operating point across the seven studies was a sensitivity of 85% (95% CI 0.66-0.94) and a specificity of 87% (95% CI 0.76-0.93) of sFlt-1/PlGF.

However, considerable heterogeneity was observed across individual studies, an observation that can be related to variations in test properties. Individual studies used ratio cut-offs ranging from 5.5 (35) to 55 (34) implying that limited emphasis should be placed on the summary operating point. Rather, one has to expect some variation in sensitivity and specificity around the summary operating point between different laboratories.

The sensitivity and specificity reported by Agrawal et al. (21) can be used to outline how the use of a sFlt-1/PlGF test may impact the patient flow. The following anticipated numbers of women are provided for illustrative purposes, and for this reason we do not consider uncertainty (e.g., due to sampling error). If we apply a sFlt-1/PlGF test on a group consisting of 1000 women with high risk of preeclampsia, we can anticipate that 170 have the diagnosis. A sFlt-1/PlGF test can be expected to predict the risk preeclampsia correctly for 867 of 1000 patients, of whom 722 patients will not experience preeclampsia, and 145 will. Among the 170 patients who, on average, experience preeclampsia the sFlt-1/PlGF test will correctly detect 145 as having preeclampsia, whereas 25 will erroneously be classified as not having preeclampsia (false negatives). If applied on a group consisting of 1000 women, one can also expect 108 false positives (women who will not experience preeclampsia but provide a positive test). We assessed the confidence of these estimates as moderate, based on the GRADE approach (see table 9).

Table 9. Results estimates and the certainty of the evidence

Outcome	Biomarker	Number of participants (included studies)	Risk of bias	Pooled results	Certainty of the evidence (GRADE)
Sensitivity	sFlt-1/PlGF	943 (7)	Unclear	0.85 (95% CI 0.66-0.94)	⊕⊕⊕○ ¹ Moderate
Specificity	sFlt-1/PlGF	943 (7)	Unclear	0.87 (95% CI 0.76-0.93)	⊕⊕⊕○ ¹ Moderate ¹

¹Downgraded -1 for inconsistency;

In the systematic review of Ukah et al. (10), five more studies (46;50-53) assessed the predictive accuracy of sFlt-1/PlGF in women with suspected preeclampsia GA weeks 23-37. Different cut offs were used, like Chaiworapongsa et al. (46) used a cut off of ≤ 0.005 MOM, Rana et al. (51) and Rana et al. (53) used ≥ 85 and Moore et al. (50) reported use of (R&D systems) for the biomarker, due to different manufacturers (Roche Diagnostics, R & D systems and Kryptor). The sensitivity and specificity in these studies were 92% and 62% (46); not reported (50); 73% and 94% (51) and not reported in Rana et al. (53) respectively. The study of Chaiworapongsa et al. (37) was included in both Ukah et al. (10) and in the meta-analyses of Agrawal et al. (21).

Predictive value of PlGF

Only Ukah et al. (10) reported the predictive values of PlGF alone. As Ukah et al. (10) did not conduct any relevant meta-analyses, we report estimates from relevant single studies included in Ukah et al. (10) (see table 10).

Table 10. Results from single-studies on predictive accuracy of PIGF-test

Author (year), Risk of bias	Included single studies	Biomarker	Used cut off	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)	AUROC (95% CI)
Ukah, 2017 (10) Low risk of bias	Chaiworapongsa et al. 2011 (37)	PIGF	≤0.4 MOM	Preterm delivery due to severe PE	94.3 (84.6–98.1)	70.6 (53.8–83.2)	3.2 (1.9–5.4)	0.08 (0.03–0.25)	0.87 (0.79–0.95)
			≤0.15 MOM	Delivered within 2 wk for GA<34 wk	81.5 (63.3–91.8)	84.4 (68.3–93.1)	5.21 (2.29–12)	0.22 (0.10–0.49)	0.85 (0.75–0.95)
	Chappell et al. 2013 (47)	PIGF	< 5th centile	Preeclampsia requiring delivery within 14 days for women with GA <35	96.0 (89.0–99.0)	55.0 (48.0–61.0)	2.1 (1.8–2.5)	0.07 (0.02–0.22)
				Preeclampsia requiring delivery within 14 days for women with GA at enrolment 35-36 ⁶	0.70 (0.58–0.81)	0.64 (0.52–0.75)	2.0 (1.4–2.8)	0.46 (0.31–0.71)	
				Preeclampsia requiring delivery within 14 days for women with GA at enrolment ≥37 ⁰	0.57 (0.46–0.68)	0.77 (0.68–0.84)	2.4 (1.7–3.5)	0.56 (0.43–0.73)	
				Small for gestational age singleton infants <1 st centile among women enrolled before GA weeks 35	0.93 (0.84–0.98)	0.53 (0.46–0.60)	2.0 (1.7–2.3)	0.14 (0.06–0.30)	

AUROC (area under the receiver operating characteristic curve); CI (95% confidence interval); GA (gestational age); LR (likelihood ratio); MOM (multiples of median); PE (preeclampsia); PIGF (placental growth factor); wk (week)

We evaluated the certainty of evidence in these single studies as very low, due to wide confidence intervals and because the evidence was based on single studies.

Summary of predictive accuracy of sFlt-1/PlGF ratio or PlGF

Based on the results from the included systematic reviews the predictive accuracy of the sFlt-1/PlGF seems reasonably good. The test is associated with a reasonably low number of false negatives, implying that the test may be useful to “rule out” preeclampsia among women with suspected preeclampsia. We have moderate confidence in the predictive value of sFlt-1/PlGF. The predictive value of PlGF alone is more uncertain, as the latter test is only investigated in few small studies.

Health economic evaluation

METHOD

General

The basic aim of any economic evaluation is to identify, measure and compare costs and consequences of the alternatives under consideration in an incremental analysis—one in which the differences in costs are compared with differences in consequences. Results of economic evaluations can be expressed as an incremental cost-effectiveness ratio (ICER), which is defined by the following equation:

$$ICER = \frac{Cost_{intervention} - Cost_{comparator}}{Effect_{intervention} - Effect_{comparator}} = \frac{\Delta C}{\Delta E}$$

In order to assess the economic effectiveness of implementation of the Elecsys immunoassay sFlt-1/PlGF ratio, Triage PlGF-test, DELFIA Xpress PlGF 1-2-3 test, BRAHMS sFlt-1 Kryptor/BRAHMS PlGF-pluss Kryptor PE ratio or other relevant blood-based tests for predicting preeclampsia in 2nd and 3rd trimester compared to the current standard assessment we performed a cost-effectiveness analysis. We used cost per tested patient and cost per additional early-diagnosed case of preeclampsia as outcome in the analysis. We expressed relevant costs in 2020 Norwegian kroner (NOK).

In the initial phase of the project, we contacted suppliers of relevant tests to procure information about technical details, unit costs as well as investment requirements for establishing routine testing in the Norwegian laboratories. We received feedback from three suppliers of the following tests: Elecsys immunoassay sFlt-1/PlGF ratio, Triage PlGF-test, BRAHMS sFlt-1 Kryptor/BRAHMS PlGF-pluss Kryptor. Therefore, we limited our analysis to these tests.

We have explored impact of uncertainty around the main parameter – cost of testing, by performing a one-way sensitivity analysis using the lower and upper bound for the test cost estimate. We also estimated the budgetary consequences of adding preeclampsia prediction tests to the current routine practice for women with suspected preeclampsia in 2nd and 3rd trimester of pregnancy.

Population, interventions and model structure

In Norway, pregnant women with normal pregnancies attend regular consultations at the primary health care level, performed by either a general practitioner or a midwife. At each consultation, measurements of blood pressure and tests for proteinuria are per-

formed. Primary care giver refers women at high risk for developing preeclampsia (specified in the introduction chapter) to the specialist health care where they receive further evaluation.

For the purpose of this analysis we estimated that 6 000 women annually would present with a suspicion of preeclampsia and would be assessed in the specialist health care, which constitutes around 10% of all pregnancies in Norway. We compared two diagnostic paths: standard assessment and standard assessment together with test.

The current diagnostic standard assessment included measurements of hypertension and proteinuria together with other clinical measures, such as maternal blood abnormalities, small for gestational date foetus and maternal symptoms. The suggested role of the tests of PlGF and sFlt-1/PlGF ratio would be adjunction (add-on) to the standard clinical assessment.

Two management options were available to the pregnant women with suspicion of preeclampsia: intensive management requiring admission to the hospital and less intensive follow-up on an outpatient basis. We have built a decision tree to model these management options (as shown in figure 4)

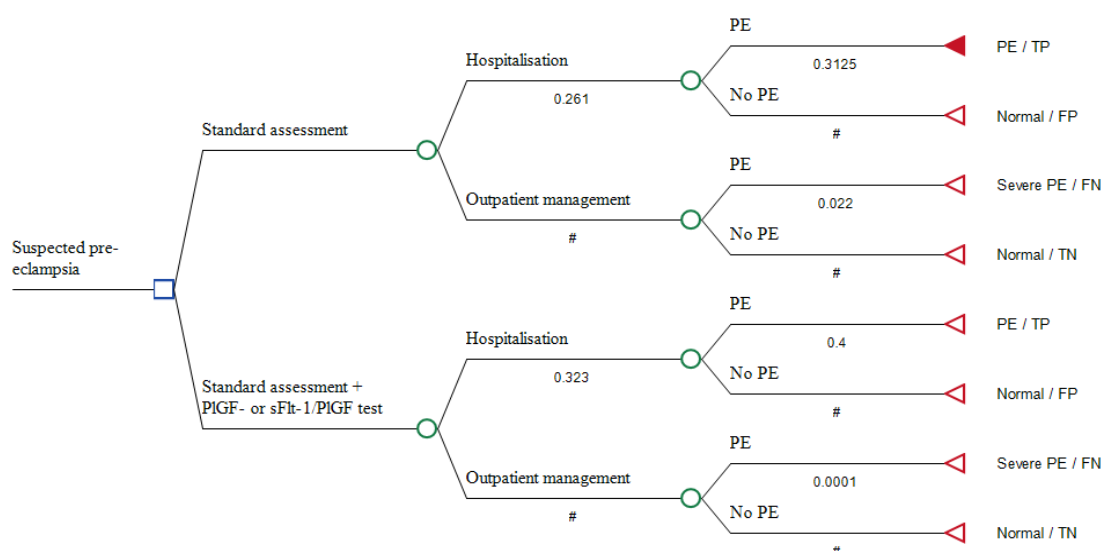


Figure 4 Decision tree comparing two alternative assessment strategies in evaluating women with suspected preeclampsia. Squares represent decision nodes and circles represent chance nodes. PE = preeclampsia, TP = true positive, TN = true negative, FP = false positive, FN = false negative

Model parameters

Transition probabilities, that is admission and preeclampsia rates were derived from the INSPIRE study by Cerdeira et al. (23). We used the RR of 1.24 (95% CI 0.89 to 1.72) for hospitalization within 24 hours, as well as PE rates under the assumption that these results are transferable to the Norwegian settings.

Costs of testing for suspected preeclampsia

Based on feedback about prices received from the suppliers of three tests: Elecsys immunoassay sFlt-1/PlGF ratio, Triage PlGF-test, BRAHMS sFlt-1 Kryptor/BRAHMS PlGF-

pluss Kryptor PE ratio, we have calculated unit costs of performing these tests in laboratories of the Norwegian health care. All costs include laboratory personnel time, testing kits as well and calibrators and controls.

The calculated estimate is based on the assumption that each laboratory analyses at least 500 tests annually, performing testing 5 times per week, with varying number of individual tests performed. Capital costs of investment in testing instruments are not included, (average cost approximately 250 000 NOK), as many such instruments are already in use in the laboratories. Costs of taking blood samples were not separately accounted for, as these costs are included in the cost estimate for the initial appointment in an outpatient specialist clinic. Based on the above, we estimated a cost of a single test to 1 252 Norwegian kroner (994 – 1 510 NOK).

Other costs

We included all direct cost associated with the diagnosis and management of pregnant women with suspected preeclampsia in both management strategies. We follow the patients from the initial appointment to delivery. Costs related to delivery or to admission to neonatal unit as well as cost related to treatment of maternal adverse outcomes were not included. Moreover, we assumed that initial assessment costs were equal in both strategies, whereas additional cost of testing (PIGF or sFlt-1/PIGF) were added on in the strategy including testing. The hospitalised patients were assigned inpatient management costs depending on whether the diagnosis of preeclampsia was confirmed or not. We further assumed that patients assigned to outpatient management were coming twice a week for a re-assessment for the period of three weeks. Patients who were initially not admitted to a hospital but eventually developed preeclampsia were assigned both costs of outpatient follow-up and hospital-based preeclampsia management.

We derived most cost estimates from the Norwegian DRG database (ISF 2020 (54)). The cost did not include the value added tax and overheads. All costs were measured in 2020 Norwegian kroner (NOK). Table 11 provides an overview of unit costs used as input in the analysis.

Table 11. Unit costs used in the analysis

Cost	Estimate in NOK	Source	Comments
Initial appointment (outpatient consultation)	1 191	ISF 2020 (DRG 914P) (54)	
Test PIGF or ratio sFlt-1/PIGF	1 247 (994 – 1 510)		Average calculated costs (55)
Intermediate intensity management (outpatient)	7 146	Assumption	3 weeks *twice per week follow-up on outpatient basis (54)
Hospital-based management of PE	31 378	ISF 2020 (DRG 383)	Costs of management for all patients with confirmed preeclampsia
Hospital-based management for suspected PE	18 827	ISF 2020 (DRG 384)	Inpatient costs for hospitalized patients without PE diagnosis

Sensitivity analysis

In order to explore how variation in cost of testing (between 994 and 1 510 NOK) impact the results, we ran the analysis for the two boundaries and reported the respective results.

Budget impact

Budget impact analysis can be defined as an assessment of the financial consequences of adopting a new intervention at an aggregate population level. In other words, budget impact is the total incremental cost of introduction of an intervention versus non-introduction. We estimated the total incremental cost of preeclampsia test for women with suspicion of preeclampsia in 2nd and 3rd trimester of pregnancy as an adjunct to the standard clinical assessment. We estimate that the number of eligible women is stable over time and will follow a rough calculation of about 10% of all pregnant women.

RESULTS

In a cohort of 6 000 pregnant women assessed for suspected preeclampsia there will be 376 more women admitted within 24 hours of assessment in the test arm than in the standard assessment arm (RR 1.24). This change, together with incremental costs related to the introduction of adjutant testing, generated total incremental cost of 12.4 million Norwegian kroner (approximately 2 000 NOK per tested woman).

At the same time, among all the hospitalized, 287 more women were early diagnosed in the test arm, with a cost of 43 000 NOK per additional earlier diagnosis of preeclampsia. In table 12 we present summary of these results.

Table 12. Results of the analysis for unit testing costs equal to 1 252 NOK

	STANDARD ASSESSMENT	STANDARD ASSESSMENT+ TEST	INCREMENTAL CHANGE
Cohort for initial assessment	6 000	6 000	
Admitted within 24hrs	1 566	1 942	376 (-172; 1 096)*
Total cost per cohort	77 518 090	89 966 165	12 448 075
Cost per tested woman	12 920	14 994	2 075 (1 696; 4080)*
Correctly early identified cases of PE	489	777	287 (68; -12)*
Cost per additional correctly identified PE			43 319

*Results for lower and upper bound of admission rate from the INSPIRE study (23)

Sensitivity analysis

Below, we present the results of one-way sensitivity analysis around the cost of test parameter. Results with minimal test cost equal to 994 Norwegian kroner is presented in the table 13, while results for the test cost equal to 1 510 NOK is presented in table 14.

Table 13. Results of the analysis for unit testing costs equal to 994 NOK

	STANDARD ASSESSMENT	STANDARD ASSESSMENT+ TEST	INCREMENTAL CHANGE
Cohort for initial assessment	6 000	6 000	
Admitted within 24hrs	1 566	1 942	376 (-172; 1 096)*
Total cost per cohort	77 518 090	88 418 165	10 900 075
Cost per patient	12 920	14 736	1 817 (1 438; 3 822)*
Correctly early identified cases of PE	489	777	287 (68; -12)*
Cost per additional correctly identified PE			37 932

Table 14. Results of the analysis for unit testing costs equal to 1 510 NOK

	STANDARD ASSESSMENT	STANDARD ASSESSMENT+ TEST	INCREMENTAL CHANGE
Cohort for initial assessment	6 000	6 000	
Admitted within 24hrs	1 566	1 942	376 (-172; 1 096)*
Total cost per cohort	77 518 090	91 514 165	13 996 075
Cost per patient	12 920	15 252	2 333 (1 954; 4 338)*
Correctly early identified cases of PE	489	777	287 (68; -12)*
Cost per additional correctly identified PE			48 706

Budget impact

We estimated the direct budget impact of introducing tests measuring sFlt-1/PlGF ratio or PlGF as adjunct to standard clinical assessment of women with suspected preeclampsia to approximately 12.4 million Norwegian kroner annually.

Discussion

Key findings summary

Clinical effectiveness

One randomised trial showed that PlGF tests may reduce the time to a preeclampsia diagnosis, and may also reduce the risk of severe maternal adverse outcomes (eg. cerebral hemorrhage). Testing probably makes no difference in mean gestation age at delivery. We are uncertain whether sFlt-1/PlGF ratio or PlGF tests improve neonatal outcomes.

Health services utilisation

One randomised controlled trial found that sFlt-1/PlGF ratio test was associated with little or no differences in the risk of short (days after the test) or long term (until delivery) admissions. Another study found a reduction in outpatient visits.

Predictive accuracy

Of the four included systematic reviews, one (21) reported the predictive accuracy of sFlt-1/PlGF test in addition to standard clinical assessments in meta-analyses. The meta-analyses showed high sensitivity and specificity of the sFlt-1/PlGF test in predicting preeclampsia among women at high risk of preeclampsia. Importantly, the analyses showed that the predictive accuracy of sFlt-1/PlGF ratio tests are good, and can probably be useful to “rule out” a suspected diagnosis of preeclampsia.

One systematic review (10) reported the predictive accuracy of the PlGF test, but included no meta-analysis. However, the systematic review reported that the PlGF test could be a useful test in predicting preterm delivery, but less predictive of adverse maternal outcomes. As these estimates are based on single studies only, we have limited confidence in this body of evidence.

Health economy

We estimated the direct cost of introducing preeclampsia tests as approximately 2 000 Norwegian kroner per tested woman and budget impact as approximately 12.4 million Norwegian kroner annually. With an assumption of about 6 000 women tested annually, our analysis showed that 287 more women were diagnosed earlier in the test arm, cost of 43 000 NOK per additional earlier diagnosis of preeclampsia. The extent to which earlier correct diagnosis translates into more favourable short- and long-term outcomes for mother and infant, and thus saved costs in the Norwegian settings remains to be explored.

Interpretation of findings

The sensitivity and specificity of sFlt-1/PlGF ratio was 0.85 and 0.87, respectively. The prevalence of pre-eclampsia among the tested women is below 20 percent implying that the negative predictive value is good, and the negative consequences associated with false negative tests are limited in a Norwegian context. We therefore conclude that

sFlt-1/PlGF ratio is good at ruling out a suspected diagnosis of pre-eclampsia. These results may indicate that the test can be used to detect women who are not in need of close follow-up at the hospital, hereby avoiding unnecessary hospitalisation. This interpretation is challenged by randomised controlled trials indicating that the use of blood based test has limited impact on health service utilisation. One small randomised controlled trial suggests the use of blood based test can probably reduce the time to a preeclampsia diagnosis, and may also reduce the risk of severe maternal adverse outcomes (eg. cerebral hemorrhage), but these findings are not what one should expect if the test was used to “rule out” pre-eclampsia. Hence, the purpose of introducing the test needs to be defined more clearly, and more studies are needed before we can conclude that the use of test serves its purpose.

Generalisability of findings

The included controlled trials are from high income countries. However, in our health economic analysis we did not assume direct transferability of these efficacy results to the Norwegian settings. The alternative diagnostic paths we seek to compare are complex and context-specific, depending on multiple factors. Maternity and perinatal care is relatively good in Norway, with an index of 2.8 perinatal deaths per 1 000 births, compared with an average of 6.0/1 000 for EU countries and 7.1/1 000 for the whole European region (all data for 2015)(56). Between 1996 and 2011 the Norwegian Society for Gynecology and Obstetrics (57) reported 15 maternal deaths caused by preeclampsia (annual average: about 1 case per 58 805 births), i.e. about one maternal death per year due to preeclampsia related complications. We lack data on how many mothers get other serious complications for pre-eclampsia than death, eclampsia and HELLP syndrome, e.g. cerebral haemorrhage. Such complication are not necessarily deadly, but can have major consequences for the mother and her family and trigger large treatment and rehabilitation costs. There is certainly a potential for further improvement in the quality of maternal care in Norway. Based on available data, however, it is challenging to outline to which extent the introduction of angiogenic biomarker testing in suspected preeclampsia will improve the quality of maternal care in Norway.

The included trials demonstrated neither beneficial nor harmful neonatal effects of biomarker testing. One might speculate whether earlier diagnosis of preeclampsia might lead to earlier interventions. Earlier deliveries probably lead to fewer serious events for the mother, but may lead to more serious perinatal outcomes as more children are born prematurely. Some results also suggest that taking the test increases the chance of interventions and hospital admissions. Test-induced hospital admissions don't necessarily lead to improved outcomes for mother or child, at least if we take into consideration that the quality of antenatal care in Norway is generally good and Norway already can show to low rates of maternal and perinatal deaths. There are good routines to identify and follow up women with suspected preeclampsia in the general antenatal care, but they do at the present not include assessment of placenta function, neither by abdominal ultrasound (assessing fetal size, amniotic fluid and fetoplacental blood flow patterns), nor by circulating placenta-associated angiogenic biomarker levels (as the latter is not available from any routine laboratories).

The impact of introducing the preeclampsia tests into a routine practice on resource use in the health care system is uncertain. Assuming that improved precision in predicting preeclampsia will indeed lead to reduction of severe maternal adverse outcomes, it is likely that the expense of 12.4 mil NOK would be compensated for or result in savings for the Norwegian health care system. However, this is very uncertain.

In our economic analysis we compared two management options for pregnant women with suspected preeclampsia: intensive management requiring admission to the hospital and less intensive follow-up on an outpatient basis. In practice, along with clinical assessment, some pragmatic considerations may have an impact on how these women are managed. Due to Norwegian topography and demographics, factors like distance to hospital and transport options may impact decisions regarding in- or outpatient follow-up of women at high-risk for preeclampsia. Moreover, if the tests are established as rule-out tools in hospitals, re-referral of some women to the primary care givers will also affect the costs. However, none of the included systematic reviews have discussed the possibility of re-referral to primary care. This might reflect that sensitivity near 85% is not regarded sufficiently trustworthy to defend re-referrals to primary care. Even more important, a test specificity below 90% suggest that the specificity of blood-based test are currently too poor for screening purposes in a low or moderate risk population – the number of false positive test results would be too high.

Certainty of evidence

The certainty of evidence for safety and effectiveness and health services utilisation

We assessed the certainty of evidence as moderate to low for the outcomes admission (hospitalization) within 24 hours, until 7 days after the test, until delivery, the time to diagnosis and number of women with severe adverse outcomes. Low certainty of evidence indicates that the true effect may be substantially different from the current estimate.

As the included non-randomised controlled study of Sharp et al. (25) was associated with high risk of bias and wide confidence intervals, we have very limited confidence in the evidence.

The certainty of evidence for predictive accuracy

We evaluated the certainty of the evidence of the sFlt-1/PlGF test's sensitivity and specificity as moderate. The evidence was based on seven studies including 943 participants. The certainty of the evidence of the PlGF test was evaluated to very low, since the evidence was based on single studies with wide confidence intervals.

Strengths and weaknesses

This HTA shows that there are high quality systematic reviews available that investigate the predictive accuracy of sFlt-1/PlGF and PlGF, but these systematic reviews include single studies with high risk of biases. The literature searches from these systematic reviews were conducted early 2017, implying that newer predictive accuracy studies are not included in this HTA

We identified few randomised controlled trials that assessed the safety and effectiveness of using sFlt-1/PlGF or PlGF as add-ons to standard clinical assessment. None of the available trials reported the number of days admitted to hospital, number of consultations, HELLP events or induction of labour. However, we have identified two on-going randomised controlled trials (See Appendices). Both of these studies assess the effectiveness of sFlt-1/PlGF and are expected to be completed by the end of 2020. Still, there is a need of rigorous trials assessing maternal and perinatal adverse outcomes of biomarkers with similar cut off.

In our health economic analysis we did not make distinctions between PlGF and sFlt-1/PlGF ratio tests. We did not find studies that compared the tests, and we therefore assumed that they were equally effective, which might not be the case. The costs of testing one woman is estimated to 1 252 Norwegian kroner (994 – 1 510 Norwegian kroner), depending on type of test and volume of tests performed. The estimate is based on calculations from a single Norwegian laboratory (55). There might be variations in the routines and costs, and a big university hospital may not be representative for the whole country. There is a wide variation in cost of the test kits among manufacturers. The given costs are derived from price lists and can be different when they are subject to public tendering processes.

The costs of equipment (analysers) are not included in the calculation. Many Norwegian hospitals possess the required instruments (Cobas 411, e601/e602/e801 from Roche, Triage MeterPro from Quidel, Nordic distributor- Reagent Oy Ltd., Brahms Kryptor from ThermoFisher). New instruments, for laboratories needing an investment cost about 250 000 NOK (exclusive VAT but inclusive installation and training). The costs of taking blood samples are not separately included in the calculations. The DRG post used as an approximate for outpatient assessment in out-patient setting is a compound estimate comprising costs of acquiring samples for analyses (54). Costs of sending samples to remote laboratory facilities are not included in the costs of testing. Such consignments should be done in temperature-controlled conditions.

In our analysis we based the hospital admission rates on the rates reported in the INSPIRE study. The randomised controlled trial by Cerdeira et al. (23) observed increased hospitalisation rates in acute phase after testing and until delivery. However, these differences were not statistically significant. The rates that we have used can be both under- and overestimated, but in the results chapter we have presented results for a range of hypothetical admission rates. We have also calculated the number of women who get an early diagnosis and the unit cost per early diagnosis.

Consistency with other reviews

Our results correspond with the results reported in Townsend et al. (27). Townsend et al. concluded that there is need of randomized controlled trials and that no single marker had a test performance suitable for routine clinical use.

Frampton et al. (12) published an HTA in 2016, and reported a good predictive sensitivity of sFlt-1/PlGF for ruling out preeclampsia within a week and a good sensitivity of PlGF test for predicting preeclampsia requiring delivery within 14 days of testing. This HTA included three observational studies (8;45;47) assessed to have low risk of bias. Due to heterogeneity of outcomes, no meta-analysis was conducted. The Chapell study (47) was included in Ukah et al. (10) and the Zeisler study (8) was included in Agrawal et al. (21). The predictive accuracy results presented in the current HTA correspond well with the results of Frampton (12).

Consistency of the economic evaluation with other studies

We identified a number of studies that sought to investigate the impact on resource use in the health sector following the introduction of a test for preeclampsia. A majority of these studies (appendices, table 6) estimated net savings to the health sector per woman tested, ranging from low to moderate. These savings were generated as the cost of the tests were offset mainly by fewer admissions to hospital among the tested women. There was some degree of variation in the results, even when the studies were based in the

same efficacy data and from the same country. This might be attributed to the valuation and type of resources measured in the studies. Hodel et al. (58), Schlembach et al. (59), Paolini et al. (60), Frusca et al (61) and Vatish et al. (62) were all based on a non-interventional study PROGNOSIS, which stipulated that introduction of the sFlt-1/PlGF ratio test improves diagnostic accuracy and consequently generates savings through reducing unnecessary admissions. This last claim however, finds no support in available evidence from randomised controlled trials (23;24).

We identified one within-trial cost-effectiveness analysis based on the PARROT UK trial (63) Apart from including direct costs related to testing and management for preeclampsia, the authors calculated the incremental cost per maternal adverse event prevented associated with implementing PlGF testing in maternity services in the National Health Service (NHS) in England, compared with current standard care. In the trial arm including PlGF testing there were on average 15 fewer maternal adverse events per 1000 women tested compared with standard care. Although maternal inpatient admission costs were greater with PlGF testing, the average weighted cost-saving per woman with PlGF testing was £147 in 66.6% of iterations. It was a 72% probability that the intervention was cost-effective at a willingness to pay 20,000 British pounds for each prevented adverse event. Introducing PlGF or sFlt-1/PlGF testing in Norway can lead to similar effects on resource use in health care, but the number of complications with current practice and the expected reduction in maternal adverse events following implementation of blood-based tests are uncertain. It is therefore challenging to quantify how changes in short- and long-term outcomes for mother and child due to testing would impact resource use in a Norwegian setting.

Implication of results for practice

There is substantially uncertainty in the results we present in the health technology assessment. The tests are reasonably good to predict the risk of developing of preeclampsia (and rule out preeclampsia) as an addition to current clinical practice for women with suspect preeclampsia. We are however not sure how effective the test is for clinical outcomes or the use of health care resources. The available evidence does not justify implementation of sFlt-1/PlGF- and PlGF routine testing in several Norwegian laboratories, which is necessary if an additional national test programme for early detection of preeclampsia should be implemented.

Current evidence from similar populations from UK might hinder funding of such large-scale studies in Norway. Collaborations across other countries have proven extremely expensive – the Roche sponsored PROGNOSIS study has been reported to cost more than 100 million NOK. As studies are available, it may also be challenging to recruit patients and hospitals to participate in RCTs. A second option might be to introduce step-wedged randomized controlled trials to investigate health and economical effects in a Norwegian setting. A third approach is to implement a regimen similar to the UK angiogenic biomarker program in one health region to gain practical experience with clinical use of these tests.

Introduction of sFlt-1/PlGF or PlGF testing into Norwegian clinical practice would require a careful analysis of organisational aspects. Questions about centralisation of laboratory facilities and logistical challenges should be considered.

Assessment of findings against priority setting criteria

There are three primary criteria for setting priorities in the Norwegian health care sector: the benefit criterion, the resource criterion, and the severity criterion. The benefit criterion primarily refers to a technology's expected health gains: increased longevity and/or improved health-related quality of life. According to the resource criterion, priority increases, as fewer resources are needed for the intervention.

According to the severity criterion, priority increases with expected future health loss resulting from the disease. Severity is measured as "absolute shortfall", defined as the expected loss of future health (in quality-adjusted life-years, QALYs) associated with a specified diagnosis. For treatment of a diagnosed disease, severity is the average expected absolute shortfall for the relevant patient group given the current standard treatment.

Preeclampsia is a serious condition. The tests evaluated in this health technology assessment may aid to predict the risk of developing the condition. We are however not sure how useful the tests are in clinical practice, and there are limitations, as we have shown in the GRADE assessments, in the studies that have evaluated the test in clinical practice. Using the tests might, or might not, reduce the use of health care resources.

Due to the methodological challenges as well as limitations in available evidence we were unable to perform a classic cost-utility analysis and thus quantify the benefit criterion as well as the severity criterion, i.e. calculate the expected QALY gain or the "absolute shortfall", also measured in QALYs. However, we trust that the description of the condition severity and above findings together with approximate net budget impact will help inform decisions about implementing or not implementing the tests in routine practice.

Need for further research

We need more knowledge about:

The effectiveness and safety of adding sFlt-1/PlGF or PlGF to standard clinical assessment for women with suspected preeclampsia. Outcomes of interest are maternal and perinatal adverse outcomes, number of days admitted at hospital (mother) and number of days admitted to NICU.

We are aware of an ongoing randomised controlled trial, PARROT Ireland (64) This study will investigate the effect of PlGF-test on maternal and neonatal morbidity. We contacted the authors in June 2020 and they have replied that they hope to have submitted their results for publication before September.

Conclusion

Clinical studies suggest that adding PIGF tests to clinical standard management may reduce the time to a preeclampsia diagnosis and reduce the number of women with severe adverse outcomes. Adding sFlt-1/PIGF ratio tests to current clinical practice was associated with unimportant changes in the risk of short and long term admissions. However, we are uncertain whether the tests can help to improve neonatal outcomes. There is a need for more rigorous controlled trials that investigate the safety and effectiveness of these biomarkers among pregnant women with suspected preeclampsia.

The sFlt-1/PIGF ratio test may be useful in “ruling out” suspected preeclampsia, but with a sensitivity near 85% false negative results are inevitable. However, the predictive accuracy of the PIGF test remains uncertain due to limited confidence in the body of evidence.

The direct cost of introducing preeclampsia tests is about 2 000 Norwegian kroner per tested woman, and the budget impact is approximately 12.4 million Norwegian kroner annually. It remains to be explored whether earlier and correct diagnosis translates into more favourable short- and long-term outcomes for mother and infant, and thus save costs in Norwegian settings.

Benefit-, resource- and the severity criteria

The tests evaluated probably aid to predict the risk of developing preeclampsia and may aid to reduce severe adverse outcomes. We are, however, not sure how useful the tests are in clinical practice as there are some serious limitations in the included evidence. Using the tests might, or might not, reduce the use of health care resources.

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64. Hayes-Ryan D, Hemming K, Breathnach F, Cotter A, Devane D, Hunter A, et al. PARROT Ireland: Placental growth factor in Assessment of women with suspected pre-eclampsia to reduce maternal morbidity: a Stepped Wedge Cluster Randomised Control Trial Research Study Protocol. *BMJ open* 2019;9(2):e023562.

Appendices

Abbreviations

AUROC	Area under the receiver operating characteristic curve
Budget impact analysis	Financial and organizational consequences of adopting a new health care technology without directly taking health consequences into account
CEA	Cost-effectiveness analysis, a form of economic analysis that compares the relative costs and outcomes (effects) of different courses of action (treatment/diagnostic strategies). The outcomes are measured and presented in natural units.
CI	Confidence interval
CMA	Cost minimization analysis, a form of economic evaluation comparing the costs of alternative interventions that have equal effects
Commissioning Forum	An Ordering Forum, Bestillerforum RHF, consisting of the four medical directors (one for each regional health authority) and two delegates from the Norwegian Directorate of Health, has the mandate to prioritize the STAs and HTAs to be conducted on the basis of submitted proposals and horizon scanning reports
GA	Gestational age
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HTA	Health technology assessment includes a systematic review of safety, effectiveness and cost effectiveness analysis. It might include organisational and ethical considerations.
PIGF	Placental growth factor

Preeclampsia (PE)	New onset hypertension arising after 20 weeks' gestation (Gestational hypertension) accompanied by ONE or MORE of the following new onset signs after 20 weeks' gestation : 1. Proteinuria 2. Other signs of maternal organ dysfunction, including one or more of the following: <ul style="list-style-type: none"> ○ Liver involvement (elevated transaminases, e.g. ALT or AST) ○ Neurological complications (e.g. eclampsia, stroke, persistent visual scotomata) ○ Hematological complications (thrombocytopenia, Disseminated Intravascular Coagulation; hemolysis) Uteroplacental dysfunction (e.g. fetal growth restriction, still-birth, abnormal fetal Doppler findings).
PROSPERO	International prospective register of systematic reviews- https://www.crd.york.ac.uk/prospero/
PPV	Positive predictive value
Proteinuria	<ul style="list-style-type: none"> ○ ≥ 0.3 g per 24 hours (time-consuming and rarely performed nowadays) ○ Spot urine protein / creatinine ratio > 0.3 mg/mmol (equals > 0.26 mg/mg) ○ $\geq 1+$ proteinuria on urine dip stick test (acceptable if above tests are unavailable), preferably on at least two occasions
LR	Likelihood ratio
MOM	Multiples of median
NICU	Neonatal intensive care unit
NPV	Negative predictive value
OR	Odds ratio
QALY	Quality-adjusted life-year. Kvalitetsjusterte leveår
RCTs	Randomised controlled trials
Second to third trimester-	Week 13 to the end of the pregnancy
SD	Standard deviation
SE	Standard error
sFlt-1	Soluble fms-like tyrosine kinase-1
SR	Systematic review
Wk	Week

Search strategy for question related to safety and effectiveness

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to October 21, 2019>
Search date: 2019-10-22

- 1 Preeclampsia/ (29767)
- 2 (preeclamp* or pre eclamp*).tw. (30299)
- 3 (tox?emi* adj5 pregnan*).tw. (3470)
- 4 gestosis.tw. (1221)
- 5 (pregnan* adj3 hypertensi*).tw. (11344)
- 6 (gestation* adj3 hypertensi*).tw. (3552)
- 7 ((maternal or maternity) adj3 hypertens*).tw. (1506)
- 8 Hypertension, Pregnancy-Induced/ (3030)
- 9 or/1-8 (50175)
- 10 Placenta Growth Factor/ (1587)
- 11 (PlGF and (triage or test* or assay* or diagnos* or detect* or measur* or assessment* or predict*).tw. (1319)
- 12 ((Placenta* adj growth adj factor) and (triage or test* or assay* or diagnos* or detect* or measur* or assessment* or predict*).tw. (1566)
- 13 Diagnostic Tests, Routine/ (11311)
- 14 Maternal Serum Screening Tests/ (447)
- 15 (fms-like adj tyrosine adj kinase*).tw. (2427)
- 16 (("FLT 1" or "sFLT 1" or "FLT1" or "sFLT1") and (triage or test* or assay* or diagnos* or detect* or measur* or assessment* or predict*).tw. (2042)
- 17 ((soluble adj fms-like adj tyrosine adj kinase) and (triage or test* or assay* or diagnos* or detect* or measur* or assessment* or predict*).tw. (762)
- 18 elecsys.af. (832)
- 19 roche.af. (33433)
- 20 alere.af. (534)
- 21 delfia.af. (392)
- 22 brahms.af. (507)
- 23 kryptor.af. (148)
- 24 thermo.af. (13573)
- 25 or/10-24 (65473)
- 26 9 and 25 (1631)
- 27 animals/ (6496666)
- 28 humans/ (18064252)
- 29 27 not (27 and 28) (4602086)
- 30 26 not 29 (1525)
- 31 "Systematic Review"/ (115406)
- 32 systematic review.kw. (14518)
- 33 meta-analysis.pt. (106835)
- 34 ((systematic* or literature) adj3 (overview or review* or search*).ti,ab. (452850)
- 35 (meta-anal* or metaanal* or meta-regression* or umbrella review* or overview of reviews or review of reviews or (evidence* adj2 synth*) or synthesis review*).ti,ab. (165605)
- 36 or/31-35 (554447)
- 37 30 and 36 (55)
- 38 limit 37 to yr="2014 - 2017" (23)
- 39 (quasi experimental design or quasi experimental study or quasi experimental study design or repeated measurement or repeated measurements or repeated measures or time series).kw. or non-randomized controlled trials as topic/ or interrupted time series analysis/ or controlled before-after studies/ or randomized controlled trial.pt. or controlled clinical trial.pt. or multicenter study.pt. or pragmatic clinical trial.pt. or (randomis* or randomiz* or randomly).ti,ab. or groups.ab. or (trial or multicenter or multi center or multicentre or multi centre).ti,ab. or (intervention? or effect? or impact? or controlled or control group? or (before adj5 after) or quasiexperiment* or quasi experiment* or pseudo experiment* or pseudoexperiment* or evaluat* or time series or time point? or repeated measur*).ti,ab. (10329389)
- 40 30 and 39 (882)

41 limit 40 to yr="2002 -Current" (872)

42 38 or 41 (880)

Database: Embase <1974 to 2019 October 21>

Search date: 2019-10-22

- 1 *preeclampsia/ or *"eclampsia and preeclampsia"/ (25630)
- 2 (preeclamp* or (pre adj eclamp*)).tw. (46048)
- 3 (tox?emi* adj5 pregnan*).tw. (1747)
- 4 gestosis.tw. (1251)
- 5 (pregnan* adj3 hypertensi*).tw. (16362)
- 6 (gestation* adj3 hypertensi*).tw. (5902)
- 7 ((maternal or maternity) adj3 hypertens*).tw. (2370)
- 8 *maternal hypertension/ (6792)
- 9 *pregnancy toxemia/ (1810)
- 10 or/1-9 (63257)
- 11 (PlGF and (triage or test* or assay* or diagnos* or detect* or measur* or assessment* or predict*)).tw. (2628)
- 12 ((Placenta* adj growth adj factor) and (triage or test* or assay* or diagnos* or detect* or measur* or assessment* or predict*)).tw. (2568)
- 13 (("FLT 1" or "sFLT 1" or "FLT1" or "sFLT1") and (triage or test* or assay* or diagnos* or detect* or measur* or assessment* or predict*)).tw. (3375)
- 14 (fms-like adj tyrosine adj kinase*).tw. (3534)
- 15 elecsys.af. (2662)
- 16 roche.af. (126273)
- 17 alere.af. (1549)
- 18 delfia.af. (734)
- 19 brahms.af. (1411)
- 20 kryptor.af. (462)
- 21 thermo.af. (24337)
- 22 or/11-21 (161353)
- 23 10 and 22 (2716)
- 24 exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/ (26641761)
- 25 human/ or normal human/ or human cell/ (20364287)
- 26 24 not (24 and 25) (6337766)
- 27 23 not 26 (2399)
- 28 "systematic review"/ (223663)
- 29 meta analysis/ (174167)
- 30 ((systematic* or literature) adj3 (overview or review* or search*)).ti,ab,kw. (556531)
- 31 (((systematic* or literature) adj3 (overview or review* or search*)) or (meta-anal* or metaanal* or meta-regression* or umbrella review* or overview of reviews or review of reviews or (evidence* adj2 synth*) or synthesis review*)).ti,ab,kw. (669287)
- 32 or/28-31 (730587)
- 33 27 and 32 (81)
- 34 limit 33 to yr="2014 - 2017" (38)
- 35 random:.tw. (1471651)
- 36 clinical trial:.mp. (1664251)
- 37 Randomized controlled trial/ (577628)
- 38 Quasi Experimental Study/ (6102)
- 39 Time Series Analysis/ (24315)
- 40 Experimental Design/ (17679)
- 41 Multicenter Study/ (233895)
- 42 (effect or impact or trial or intervention).ti. (1589889)

- 43 ("quasi-experiment*" or quasiexperiment* or "quasi random*" or quasirandom* or "quasi control*" or quasicontrol* or ((quasi* or experimental) adj3 (method* or study or trial or design* or controlled))).ti,ab,hw. (196463)
- 44 repeated measure*.ti,ab. (62112)
- 45 ((before adj5 after) or control group*).ti,ab. (1090744)
- 46 (quasi experimental design or quasi experimental study or quasi experimental study design or repeated measurement or repeated measurements or repeated measures or time series).kw. (4743)
- 47 or/35-46 (4770330)
- 48 27 and 47 (529)
- 49 limit 48 to yr="2002 -Current"] (524)
- 50 34 or 49 (550)

Database: Epistemonikos

Search date: 2019-10-23

(title:((title:(preeclampsia OR preeclampsia OR ((maternal OR maternity OR pregnan* OR gestation*) AND (hypertens*))) OR abstract:(preeclampsia OR preeclampsia OR ((maternal OR maternity OR pregnan* OR gestation*) AND (hypertens*)))))) OR abstract:((title:(preeclampsia OR preeclampsia OR ((maternal OR maternity OR pregnan* OR gestation*) AND (hypertens*))) OR abstract:(preeclampsia OR preeclampsia OR ((maternal OR maternity OR pregnan* OR gestation*) AND (hypertens*)))))) AND (title:(plgf OR "placental growth factor" OR "sFlt-1" OR "sFlt1" OR PIGF OR "sFlt-1/PIGF" OR "SFlt1/PLGF" OR "soluble FMS-like tyrosine kinase-1" OR diagnos* OR elecsys OR roche OR alere OR delfia OR brahms OR kryptor OR thermo) OR abstract:(plgf OR "placental growth factor" OR "sFlt-1" OR "sFlt1" OR PIGF OR "sFlt-1/PIGF" OR "SFlt1/PLGF" OR "soluble FMS-like tyrosine kinase-1" OR diagnos* OR elecsys OR roche OR alere OR delfia OR brahms OR kryptor OR thermo)) 2014-2017: 4 broad synthesis, 1 structured summary, 75 systematic reviews

Database: PROSPERO

Search date: 2019-10-23

Plgf: 12

Placental growth factor: 12

(preeclampsia OR preeclampsia) AND (tyrosine kinase): 3

Elecsys: 6

(preeclampsia OR preeclampsia) AND roche:2

Alere: 19

Delfia: 2

Brahms: 3

Kryptor: 4

Thermo: 14

Database: Cochrane Library

Search date: 2019-10-22

- | | | |
|----|--|------|
| #1 | MeSH descriptor: [Preeclampsia] explode all trees | 870 |
| #2 | (preeclamp* or (pre NEXT eclamp*)):ti,ab,kw | 3205 |
| #3 | ((toxemi* or toxaemi*) NEAR/4 pregnan*):ti,ab,kw | 50 |
| #4 | gestosis:ti,ab,kw | 24 |
| #5 | (pregnan* NEAR/2 hypertensi*):ti,ab,kw | 1209 |
| #6 | (gestation* NEAR/2 hypertensi*):ti,ab,kw | 420 |
| #7 | ((maternal or maternity) NEAR/2 hypertens*):ti,ab,kw | 579 |

#8 MeSH descriptor: [Hypertension, Pregnancy-Induced] explode all trees
1013

#9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 with Cochrane Library publi-
cation date Between Jan 2014 and Dec 2017, in Cochrane Reviews 46

#10 (preeclamp* or (pre NEXT eclamp*)) 3491

#11 ((toxemi* or toxaemi*) NEAR/4 pregnan*) 59

#12 gestosis 25

#13 (pregnan* NEAR/2 hypertensi*) 1537

#14 (gestation* NEAR/2 hypertensi*) 525

#15 (((maternal or maternity) NEAR/2 hypertensi*)) 631

#16 #1 or #10 or #11 or #12 or #13 or #14 or #15 or #8 with Cochrane Library
publication date Between Jan 2002 and Jan 2019, in Trials 2084

#17 #1 or #10 or #11 or #12 or #13 or #14 or #15 or #8 with Cochrane Library
publication date Between Jan 2014 and Dec 2017, in Cochrane Protocols 29

#18 MeSH descriptor: [Placenta Growth Factor] explode all trees 29

#19 (PIGF and (triage or test* or assay* or diagnos* or detect* or measur* or assess-
ment* or predict*)) 166

#20 ((Placenta* NEXT growth NEXT factor) and (triage or test* or assay* or diag-
nos* or detect* or measur* or assessment* or predict*)) 182

#21 MeSH descriptor: [Diagnostic Tests, Routine] explode all trees 214

#22 MeSH descriptor: [Maternal Serum Screening Tests] explode all trees 4

#23 (fms-like NEXT tyrosine NEXT kinase*) 165

#24 (("FLT-1" or "sFLT 1" or "FLT1" or "sFLT1") and (triage or test* or assay* or di-
agnos* or detect* or measur* or assessment* or predict*)) 140

#25 ((soluble NEXT fms-like NEXT tyrosine NEXT kinase) and (triage or test* or as-
say* or diagnos* or detect* or measur* or assessment* or predict*)) 61

#26 (elecsys or roche or alere or delfia or brahms or kryptor or thermo) 3712

#27 #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 4327

#28 #9 and #27 10

#29 #16 and #27 86

#30 #17 and #27 1

#31 #28 or #29 or #30 97

Database: CRD database, HTA (Centre for Reviews and Dissemination, University of York)

Search date: 2019-10-22

1 MeSH DESCRIPTOR Hypertension,Pregnancy-Induced EXPLODE ALL TREES

128 2 (((preeclamp* or (pre NEXT eclamp*))) 225

3 (((((toxemi* or toxaemi*) NEAR4 pregnan*))) 1

4 ((gestosis)) 0

5 (((pregnan* NEAR2 hypertensi*))) 32

6 (((gestation* NEAR2 hypertensi*))) 30

7 (((((maternal or maternity) NEAR2 hypertensi*))) 6

8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 264

9 * FROM 2014 TO 2017 14357

10 #8 AND #9 31

Database: Clinical Trials (National Institutes of Health, US)

Search date: 2019-10-22

Plgf: 45

Placental growth factor: 21

(preeclampsia OR preeclampsia) AND (tyrosine kinase): 12

Elecsys: 1

(preeclampsia OR preeclampsia) AND roche: 6
(preeclampsia OR preeclampsia) AND Alere: 0
(preeclampsia OR preeclampsia) AND Delfia: 0
(preeclampsia OR preeclampsia) AND Brahms: 1
(preeclampsia OR preeclampsia) AND Kryptor: 0
(preeclampsia OR preeclampsia) AND Thermo: 2

Database: International Clinical Trials Registry Platform (WHO)

Search date: 2019-10-22

Plgf: 43

Placental growth factor: 21

(preeclampsia OR preeclampsia) AND (tyrosine kinase): 12

Elecsys: 1

(preeclampsia OR preeclampsia) AND roche: 6

(preeclampsia OR preeclampsia) Alere: 0

(preeclampsia OR preeclampsia) Delfia: 0

(preeclampsia OR preeclampsia) Brahms: 1

(preeclampsia OR preeclampsia) Kryptor: 0

(preeclampsia OR preeclampsia) Thermo: 2

Search strategy for question related to predictive accuracy

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to June 12, 2019

Search date: 2019-06-14

- 1 Preeclampsia/ (29313)
- 2 (preeclamp* or pre eclamp*).tw. (29518)
- 3 (tox?emi* adj5 pregnan*).tw. (3468)
- 4 gestosis.tw. (1221)
- 5 (pregnan* adj3 hypertensi*).tw. (11063)
- 6 (gestation* adj3 hypertensi*).tw. (3412)
- 7 ((maternal or maternity) adj3 hypertens*).tw. (1465)
- 8 Hypertension, Pregnancy-Induced/ (2915)
- 9 or/1-8 (49148)
- 10 Placenta Growth Factor/ (1537)
- 11 (PlGF and (triage or test* or assay* or immunoassay* or diagnos* or detect* or surveillance or screen* or measur* or analys* or analyz* or determin* or sensitivity or specificity or accuracy or accurate or assessment* or predict* or positive or negative or electrochemiluminescen*).tw. (1543)
- 12 ((Placenta* adj growth adj factor) and (triage or test* or assay* or immunoassay* or diagnos* or detect* or surveillance or screen* or measur* or analys* or analyz* or determin* or sensitivity or specificity or accuracy or accurate or assessment* or predict* or positive or negative or electrochemiluminescen*).tw. (1856)
- 13 Vascular Endothelial Growth Factor Receptor-1/bl (891)
- 14 ("VEGFR1" or "VEGFR 1").tw. (2621)
- 15 Early Diagnosis/ or Diagnosis/ (41515)
- 16 Diagnostic Tests, Routine/ or Diagnostic Equipment/ or "Diagnostic Techniques, Obstetrical and Gynecological"/ or Diagnostic Services/ (13666)
- 17 Maternal Serum Screening Tests/ (426)
- 18 Serologic Tests/ (19582)
- 19 Pregnancy Proteins/ (5834)
- 20 Membrane Proteins/ (148641)

- 21 Biological Markers/ (250878)
- 22 (fms-like adj tyrosine adj kinase*).tw. (2336)
- 23 (("FLT 1" or "sFLT 1" or "FLT1" or "sFLT1") and (triage or test* or assay* or immunoassay* or diagnos* or detect* or screen* or measur* or analys* or analyz* or determin* or sensitivity or specificity or accuracy or accurate or (prognostic adj assessment*) or predict* or positive or negative or electrochemiluminescen*).tw. (2754)
- 24 ((soluble adj fms-like adj tyrosine adj kinase) and (triage or test* or assay* or immunoassay* or diagnos* or detect* or measur* or analys* or analyz* or determin* or sensitivity or specificity or accuracy or accurate or assessment* or predict* or positive or negative or electrochemiluminescen*).tw. (830)
- 25 elecsys.af. (803)
- 26 roche.af. (32166)
- 27 alere.af. (511)
- 28 delfia.af. (388)
- 29 brahms.af. (495)
- 30 kryptor.af. (142)
- 31 thermo.af. (13069)
- 32 or/10-31 (524033)
- 33 9 and 32 (3953)
- 34 animals/ (6416472)
- 35 humans/ (17781684)
- 36 34 not (34 and 35) (4554780)
- 37 33 not 36 (3798)
- 38 limit 37 to (yr="2017 -Current" and "reviews (maximizes sensitivity)") (543)

Database: Embase 1974 to 2019 June 13

Search date: 2019-06-14

- 1 *preeclampsia/ or *"eclampsia and preeclampsia"/ (24932)
- 2 (preeclamp* or (pre adj eclamp*).tw. (44611)
- 3 (tox?emi* adj5 pregnan*).tw. (1740)
- 4 gestosis.tw. (1246)
- 5 (pregnan* adj3 hypertensi*).tw. (15917)
- 6 (gestation* adj3 hypertensi*).tw. (5672)
- 7 ((maternal or maternity) adj3 hypertens*).tw. (2292)
- 8 *maternal hypertension/ (6570)
- 9 *pregnancy toxemia/ (1810)
- 10 or/1-9 (61465)
- 11 (PlGF and (triage or test* or assay* or immunoassay* or diagnos* or detect* or surveillance or screen* or measur* or analys* or analyz* or determin* or sensitivity or specificity or accuracy or accurate or assessment* or predict* or positive or negative or electrochemiluminescen*).tw. (2957)
- 12 ((Placenta* adj growth adj factor) and (triage or test* or assay* or immunoassay* or diagnos* or detect* or surveillance or screen* or measur* or analys* or analyz* or determin* or sensitivity or specificity or accuracy or accurate or assessment* or predict* or positive or negative or electrochemiluminescen*).tw. (2930)
- 13 ("VEGFR1" or "VEGFR 1").tw. (4277)
- 14 (fms-like adj tyrosine adj kinase*).tw. (3377)
- 15 (("FLT 1" or "sFLT 1" or "FLT1" or "sFLT1") and (triage or test* or assay* or immunoassay* or diagnos* or detect* or screen* or measur* or analys* or analyz* or determin* or sensitivity or specificity or accuracy or accurate or (prognostic adj assessment*) or predict* or positive or negative or electrochemiluminescen*).tw. (4295)
- 16 ((soluble adj fms-like adj tyrosine adj kinase) and (triage or test* or assay* or immunoassay* or diagnos* or detect* or measur* or analys* or analyz* or determin*

or sensitivity or specificity or accuracy or accurate or assessment* or predict* or positive or negative or electrochemiluminescen*).tw. (1230)
 17 elecsys.af. (2546)
 18 roche.af. (122686)
 19 alere.af. (1452)
 20 delfia.af. (726)
 21 brahms.af. (1358)
 22 kryptor.af. (440)
 23 thermo.af. (22480)
 24 exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/ (25980828)
 25 human/ or normal human/ or human cell/ (19821923)
 26 24 not (24 and 25) (6215492)
 27 or/11-23 (160399)
 28 10 and 27 (2832)
 29 28 not 26 (2490)
 30 limit 29 to ("reviews (maximizes sensitivity)" and yr="2017 -Current") (288)

Database: Cochrane Library (CDSR reviews and protocols)

Search date: 2019-06-14

#1 MeSH descriptor: [Preeclampsia] explode all trees 843
 #2 (preeclamp* or (pre NEXT eclamp*)):ti,ab,kw 3130
 #3 ((toxemi* or toxaemi*) NEAR/4 pregnan*):ti,ab,kw 50
 #4 gestosis:ti,ab,kw 24
 #5 (pregnan* NEAR/2 hypertensi*):ti,ab,kw 1188
 #6 (gestation* NEAR/2 hypertensi*):ti,ab,kw 408
 #7 ((maternal or maternity) NEAR/2 hypertens*):ti,ab,kw 562
 #8 MeSH descriptor: [Hypertension, Pregnancy-Induced] explode all trees 983
 #9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 with Cochrane Library publication date Between Jan 2017 and Dec 2019, in Cochrane Reviews 33
 #10 (preeclamp* or (pre NEXT eclamp*)) 3410
 #11 ((toxemi* or toxaemi*) NEAR/4 pregnan*) 59
 #12 gestosis 25
 #13 (pregnan* NEAR/2 hypertensi*) 1511
 #14 (gestation* NEAR/2 hypertensi*) 511
 #15 ((maternal or maternity) NEAR/2 hypertens*) 612
 #16 #1 or #10 or #11 or #12 or #13 or #14 or #15 or #8 with Cochrane Library publication date Between Jan 2017 and Dec 2019, in Cochrane Protocols 24

Database: CRD database, HTA (Centre for Reviews and Dissemination, University of York), Search date: 2019-06-14

1 MeSH DESCRIPTOR Hypertension, Pregnancy-Induced EXPLODE ALL TREES 128
 2 ((preeclamp* or (pre NEXT eclamp*))) 225
 3 (((toxemi* or toxaemi*) NEAR4 pregnan*)) 1
 4 (gestosis) 0
 5 ((pregnan* NEAR2 hypertensi*)) 32
 6 ((gestation* NEAR2 hypertensi*)) 30
 7 (((maternal or maternity) NEAR2 hypertens*)) 6
 8 #1 OR #2 OR #3 OR #4 OR #5 OR #7 264
 9 * FROM 2017 TO 2019 506
 10 #8 AND #9 2

Database: Epistemonikos**Search date: 2019-06-15**

(title:((title:(preeclampsia OR preeclampsia OR ((maternal OR maternity OR pregnan* OR gestation*) AND (hypertens*))) OR abstract:(preeclampsia OR preeclampsia OR ((maternal OR maternity OR pregnan* OR gestation*) AND (hypertens*)))))) OR abstract:((title:(preeclampsia OR preeclampsia OR ((maternal OR maternity OR pregnan* OR gestation*) AND (hypertens*))) OR abstract:(preeclampsia OR preeclampsia OR ((maternal OR maternity OR pregnan* OR gestation*) AND (hypertens*)))))): 8 broad synthesis, 0 structured summaries (2017-2019)

(title:((title:(preeclampsia OR preeclampsia OR ((maternal OR maternity OR pregnan* OR gestation*) AND (hypertens*))) OR abstract:(preeclampsia OR preeclampsia OR ((maternal OR maternity OR pregnan* OR gestation*) AND (hypertens*)))))) OR abstract:((title:(preeclampsia OR preeclampsia OR ((maternal OR maternity OR pregnan* OR gestation*) AND (hypertens*))) OR abstract:(preeclampsia OR preeclampsia OR ((maternal OR maternity OR pregnan* OR gestation*) AND (hypertens*)))))) AND (title:(plgf OR "placental growth factor" OR "sFlt-1" OR "sFlt1" OR VEGFR1 OR "VEGFR-1" OR PIGF OR "sFlt-1/PIGF" OR "SFlt1/PLGF" OR "soluble FMS-like tyrosine kinase-1" OR diagnos* OR elecsys OR roche OR alere OR delfia OR brahms OR kryptor OR thermo) OR abstract:(plgf OR "placental growth factor" OR "sFlt-1" OR "sFlt1" OR VEGFR1 OR "VEGFR-1" OR PIGF OR "sFlt-1/PIGF" OR "SFlt1/PLGF" OR "soluble FMS-like tyrosine kinase-1" OR diagnos* OR elecsys OR roche OR alere OR delfia OR brahms OR kryptor OR thermo)): 1 broad synthesis, 0 structured summaries, 86 systematic reviews (2017-2019)

Database: PROSPERO**Search date: 2019-06-14**

370 records found for (preeclampsia OR preeclampsia OR ((maternal OR maternity OR pregnan* OR gestation*) AND (hypertens*))) AND (plgf OR "placental growth factor" OR "sFlt-1" OR "sFlt1" OR VEGFR1 OR "VEGFR-1" OR PIGF OR "sFlt-1/PIGF" OR "SFlt1/PLGF" OR "soluble FMS-like tyrosine kinase-1" OR diagnos* OR elecsys OR roche OR alere OR delfia OR brahms OR kryptor OR thermo)

Database: POP-database**Search date: 2019-06-14**

MeSH term C13.703.395 Hypertension, Pregnancy-Induced : 1
 preeclampsia : 1
 preeclampsia : 1

Table 1. Excluded studies for safety and effectiveness

	Full references	Reason for exclusion
1	Cheng YKY, Law LW, Leung TY, Chan OK, Sahota DS. Soluble fms-like tyrosine kinase-1, placental growth factor and their ratio as a predictor for preeclampsia in East Asians. <i>Pregnancy Hypertens.</i> 2018;11:61-5.	Wrong study design
2	Duhig K, Myers J, Seed P, Shennan A, Chappell L. Placental growth factor measurements in the assessment of women with suspected preeclampsia; a stratified analysis of the PARROT trial data. <i>BJOG: An International Journal of Obstetrics and Gynaecology.</i> 2019;126:e138	Not full text-Poster
3	Duhig K, Myers J, Sharp A, Seed P, Shennan A, Chappell L, et al. Repeated placental growth factor measurements in the assessment of women with suspected preeclampsia. <i>BJOG: An International Journal of Obstetrics and Gynaecology.</i> 2019;126:e137-e8	Not full text-Poster

4	Dunn L, Flatley C, Kumar S. Maternal placental growth factor levels between 37 and 42 weeks gestation. Australian and New Zealand Journal of Obstetrics and Gynaecology. 2017;57:40-1	Not full text-Poster
5	Nct. MorbiMortality Amelioration in Preeclamptic Primiparas Study. MoMA Pre Prim Study. https://clinicaltrials.gov/show/NCT00763672 . 2008	Protocol-Not available
6	Nct. Preeclampsia Ratio (sFlt-1/PlGF). https://clinicaltrials.gov/show/NCT03289611 . 2017.	Protocol-Not available
7	Sharp A, Jackson R, Cornforth C, Harrold J, Turner MA, Kenny L, et al. A prediction model for short-term neonatal outcomes in severe early-onset fetal growth restriction. Eur J Obstet Gynecol Reprod Biol. 2019;241:109-18.	Wrong study design
8	Ukah UV, Mbofana F, Rocha BM, Loquiha O, Mudenyanga C, Usta M, et al. Diagnostic Performance of Placental Growth Factor in Women With Suspected Preeclampsia Attending Antenatal Facilities in Maputo, Mozambique. Hypertension. 2017;69(3):469-74.	Wrong study design
9	Veisani Y, Jenabi E, Delpisheh A, Khazaei S. Angiogenic factors and the risk of preeclampsia: A systematic review and meta-analysis. Int. 2019;17(1).	Wrong study design
10	Nct. MorbiMortality Amelioration in Preeclamptic Primiparas Study. MoMA Pre Prim Study. https://clinicaltrials.gov/show/NCT00763672 . 2008.	Wrong study design- On- going study
11	Nct. Preeclampsia Ratio (sFlt-1/PlGF). https://clinicaltrials.gov/show/NCT03289611 . 2017.	Wrong study design- On- going study

Table 2. Excluded systematic reviews for question about predictive accuracy

Number	Full references	Reason for exclusion
1	Seshadri Reddy V, Manne M, Duggina P, Varma N. A diagnostic test accuracy meta-analysis of maternal serum ischemia-modified albumin for detection of preeclampsia. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians. 2019;32(13):1-151.	Wrong biomarker
2	Geoff Frampton JLLPMR. The Triage PlGF test, Elecsys immunoassay sFlt-1 / PlGF ratio, DELFIA Xpress PlGF 1-2-3 test and BRAHMS sFlt-1 Kryptor / PlGF plus Kryptor PE ratio to aid the assessment of suspected preeclampsia: systematic review and economic evaluation.	Wrong publication year
3	Heazell AEP, Whitworth M, Duley L, Thornton JG. Use of biochemical tests of placental function for improving pregnancy outcome. Cochrane Database of Systematic Reviews 2015, Issue 11. Art. No.: CD011202. DOI: 10.1002/14651858.CD011202.pub2.	Wrong publication year
4	Chau K, Hennessy A, Makris A. Placental growth factor and preeclampsia. Journal of Human Hypertension. 2017;31(12):782-6.	Wrong study design
5	Duhig K, Myers J, Seed P, Shennan A, Chappell L. Evaluation of the impact of revealed placental growth factor testing in women with suspected preeclampsia: A stratified analysis of	Wrong study design

	the PARROT trial. BJOG: An International Journal of Obstetrics and Gynaecology. 2019;126:38.	
6	Duhig K, Myers J, Seed P, Shennan A, Chappell L. Placental growth factor measurements in the assessment of women with suspected preeclampsia; a stratified analysis of the PARROT trial data. BJOG: An International Journal of Obstetrics and Gynaecology. 2019;126:e138.	Wrong study design
7	Govender N, Moodley J, Naicker T. The Use of Soluble FMS-like Tyrosine Kinase 1/Placental Growth Factor Ratio in the Clinical Management of Preeclampsia. African Journal of Reproductive Health. 2018;22(4):135-43.	Wrong study design
8	Hayes Ryan D, McCarthy FP, O'Donoghue K, Kenny LC. Placental growth factor: A review of literature and future applications. Pregnancy Hypertension. 2018;14:260-4.	Wrong study design
9	Herraiz I, Llurba E, Verlohren S, Galindo A, Bartha JL, De La Calle M, et al. Update on the Diagnosis and Prognosis of Preeclampsia with the Aid of the sFlt-1/PlGF Ratio in Singleton Pregnancies. Fetal Diagnosis and Therapy. 2018;43(2):81-9.	Wrong study design
10	Hirashima C, Ohmaru-Nakanishi T, Nagayama S, Takahashi K, Suzuki H, Takahashi H, et al. Serum soluble LIGHT in the early third trimester as a novel biomarker for predicting late-onset preeclampsia. Pregnancy Hypertension. 2018;14:174-6.	Wrong study design
11	Kosinska-Kaczynska K, Wielgos M. How to identify pregnant women at risk of preeclampsia? - a review of the current literature. Ginekologia Polska. 2018;89(6):335-8.	Wrong study design
12	Nobakht MGBF. Application of metabolomics to preeclampsia diagnosis. Systems Biology in Reproductive Medicine. 2018;64(5):324-39.	Wrong study design
13	Pillay P, Moodley K, Moodley J, Mackraj I. Placenta-derived exosomes: potential biomarkers of preeclampsia. International Journal of Nanomedicine. 2017;12:8009-23	Wrong study design
14	Zhao M, Zhu Z, Liu C, Zhang Z. Dual-cutoff of sFlt-1/PlGF ratio in the stratification of preeclampsia: a systematic review and meta-analysis. Archives of Gynecology & Obstetrics. 2017;295(5):1079-87.	Wrong study design
15	Swati A. The ratio of soluble fms-like tyrosine kinase-1 and placental growth factor as a predictive tool in women with preeclampsia: a systematic review and meta-analysis.	Doublet
16	Amanda Pastorello Rodrigues LWPJD. Evaluation of the sflt-1/plgf rate as a maternal-fetal outcomes marker: a systematic review.	Protocol only

17	Andric Christopher Perez-Ortiz EM-OBE-MAD-NEL-RMFO-TJAI-LVS-MES-CD. Identification of potential genomic biomarkers predictors for preeclampsia risk: a systematic review and meta-analysis.	Protocol only
18	Deirdre H-R. Placental growth factor (PlGF) as a predictor of adverse maternal and fetal outcomes in women with multiple pregnancy and suspected/confirmed hypertensive disorders of pregnancy (HDPs): a systematic review.	Protocol only
19	Melanie Griffin DLAHLC. Systematic review and meta-analysis of prognostic accuracy studies to evaluate the ability of late pregnancy maternal tests to predict adverse pregnancy outcomes associated with placental dysfunction (specifically fetal growth restriction and preeclampsia).	Protocol only
20	Regionali ANpiSS. Elecsys® sFlt-1/PlGF (Preeclampsia): test in preeclampsia diagnosis (prosjekt registrert i pop-databasen)2019 2019.	Protocol only
21	Swati Agrawal SSMV. The role of PlGF in the prediction of preeclampsia: a systematic review and meta-analysis.	Protocol only
22	zhiqing zhu mzczz. Diagnostic value of sFlt1/PlGF in preeclampsia: a systemic review and meta analysis.	Protocol only
23	Sherrell H, Dunn L, Clifton V, Kumar S. Systematic review of placental growth factor in late pregnancy as a predictor of adverse intrapartum and perinatal outcomes. BJOG: An International Journal of Obstetrics and Gynaecology. 2018;125:76-7.	Wrong population

Figure 1. Risk of bias of included studies

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Cerdeira et al 2019	+	+	+	+	+	+	?
Duhig et al 2019	+	+	+	+	+	+	?
Sharp et al 2018	-	-	+	+	-	?	?

Table 3. Assessment of included systematic reviews by AMSTAR

Items	Maesa 2019	Agrawal 2018	Townsend 2018	Ukah 2017
Was an 'a priori' design provided?	Yes	Yes	Yes	Yes
Was there duplicate study selection and data extraction?	No	Yes	Yes	Yes
Was a comprehensive literature search performed?	Unclear	Yes	Yes	Yes
Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Unclear	Yes	Yes	Yes
Was a list of studies (included and excluded) provided?	No	Yes	Yes	Yes
Were the characteristics of the included studies provided?	Yes	Yes	Yes	Yes
Was the scientific quality of the included studies assessed and documented?	Unclear, report use of AMSTAR and CASP, but do not show the results of the evaluations.	Unclear, report use of QUADAS-2, but do not show the results of the evaluations.*	Yes	Yes
Was the scientific quality of the included studies used appropriately in formulating conclusions?	Unclear	Unclear, not used GRADE and not showed the Risk of bias assessments- only the overall risk of bias of the studies.	Yes	Yes
Were the methods used to combine the findings of studies appropriate?	Unclear	Yes	Yes (Not applicable-OoO)	No meta-analysis done
Was the likelihood of publication bias assessed?	No	Yes	Yes	No

*We contacted the authors for information about this issue at the end of February 2020, but received no reply.

Table 4. Assessment of included systematic reviews by QUIPS

Assessment of included systematic reviews by QUIPS (19) (assessed as low, unclear/moderate and high risk of bias)

Assessment criteria	Maesa 2019	Agrawal 2018	Townsend 2018	Ukah 2017
<p>Population: The study authors have considered how well the primary study samples represent the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.</p>	High	Moderate	Moderate	Low
<p>Study attrition: The study authors have assessed whether loss to follow-up is associated with key characteristics sufficient to limit potential bias to the reported relationship between candidate predictor and outcome.</p>	Unclear, Not reported	Unclear, Not reported	Low	High
<p>Prognostic factor measurements: The study authors have considered if the measurement of the candidate predictor was measured in a reliable and valid way for participants in studies pooled for analysis.</p>	High	High	Low	Low
<p>Outcome measurements: The study authors have considered whether the reference test (outcome) was measured reliably and in a similar fashion across all studies pooled for analysis.</p>	High	High	Low	Unclear (Not reported)
<p>Study confounding: The study authors have considered whether the primary studies have accounted for important potential confounders and reported the effect of these covariables on their findings.</p>	High	Unclear, Not reported	Unclear (OoO)	Unclear (Not reported)

Table 5. Results from single studies addressing predictive accuracy

Author (year), Risk of bias	Included single studies	Test/ manufacturer	Used cut off	Outcome	Total (n) Outcome (%)	Sensitivity (95% CI)/	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)	AUROC (95% CI)
Ukah, 2017 Low risk of bias (søkt Jan+august 2017)	Chaiworapongsa 2011	Plasma PIGF/ ELISA (R&D Systems)	≤0.4 MOM	Preterm delivery due to severe PE	87 (60.9)	94.3 (84.6–98.1)	70.6 (53.8–83.2)	3.2 (1.9–5.4)	0.08 (0.03–0.25)	0.87 (0.79–0.95)
	Chaiworapongsa 2014			Preterm delivery due to severe PE	85 (56.5)	91.7 (79.1–97.3)	62.2 (44.8–77.1)	2.4 (1.6–3.7)	0.13 (0.05–0.4)
	Chaiworapongsa 2011	Plasma PIGF/ ELISA (R&D Systems)	≤0.15 MOM	Delivered within 2 wk for GA<34 wk	59 (45.8)	81.5 (63.3–91.8)	84.4 (68.3–93.1)	5.21 (2.29–12)	0.22 (0.10–0.49)	0.85 (0.75–0.95)
	Chaiworapongsa 2014			Delivered within 2 wk for GA<34 wk	43 (41.9)	72.2 (46.4–89.3)	92.0 (72.5–98.6)	9.0 (2.3–35)	0.30 (0.1–0.6)
	Chapell 2013	Plasma PIGF/ (Alere Triage Assay)	<5th centile for gestation	Confirmed preeclampsia within 14 days for GA <35	287 (55.1)	96.0 (89.0–99.0)	55.0 (48.0–61.0)	2.1 (1.8–2.5)	0.07 (0.02–0.22)
	Moore 2012	Serum sFlt-1/PIGF ratio (R&D Systems)		Severe PE (Composite maternal outcomes: elevated transaminases (AST or ALT >70 U/l), thrombocytopenia (platelet count <100,000 plts/ml ³), hemolysis (schistocytes on peripheral smear), oliguria (<500 ml/d), acute renal failure	276 (28.3)	0.76 (0.66–0.85)

				(creatinine >1.2 mg/dl), seizure, pulmonary edema (clinical diagnosis by physical examination and/or chest radiograph), cerebral hemorrhage (head CT), or maternal death).						
	Rana 2012	Plasma sFlt-1/PIGF (Roche Diagnostics)	ratio ≥85	Severe PE: Composite maternal outcomes: hypertension (BP ≥140/90 mm Hg on 2 occasions 2 hours to 2 weeks apart) plus one of the following: elevated aspartate amino-transferase or alanine aminotransferase (ALT; 80 U/L), platelet count 100*10 ⁹ /L, disseminated intravascular coagulation, abruption (clinical and/or pathological), pulmonary edema, cerebral hemorrhage, seizure (in a woman without underlying seizure disorder), acute renal failure (creatinine 114.4 Umol/L), or maternal death.	176 (33.5)	72.9 (59.5–83.3)	94.0 (87.6–97.4)	12.2 (5.8–25.4)	0.29 (0.19–0.44)	0.93 (0.89–0.97)
				Severe PE: Composite at	79 (65.8)					0.75

Ukah, 2017 Low risk of bias (søkt Jan+august 2017)	Rana 2012 (twins)	Plasma sFlt-1/PIGF (Roche Diagnostics)	ratio ≥85	2 weeks; twins: Composite maternal and fetal outcome: hemolysis, elevated liver enzymes, and low platelets syndrome; disseminated intravascular coagulation; abruption; pulmonary edema; cerebral hemorrhage; maternal, fetal, and neonatal death; eclampsia; acute renal failure; small for gestational age; and indicated delivery.						(0.64–0.86)
				Composite at 2 weeks; twins; presenting <34 wk	38 (57.9)					0.81 (0.66–0.96)
	Salahuddin 2016	Plasma sFlt-1/PIGF (KRYPTOR)+ SBP+proteinuria	ratio ≥85	Composite; GA<34 wk at Presentation: Severe PE: Composite maternal outcomes: hypertension (BP ≥140/ 90 mmHg on two occasions 2 h to 2 weeks apart) plus one of the following: elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) (≥80 U/l), platelet	110 (30.9)					0.89 (0.82–0.95)

				count ≤100,000 per µl, disseminated intravascular coagulation (DIC), abruption (clinical and/or pathological), pulmonary edema, cerebral hemorrhage, seizure (in a woman without underlying seizure disorder), acute renal failure (creatinine >1.5 mg/dl), or maternal death.						
					Results based on meta-analysis (see below)					
Agrawal, 2018 (Unclear) (søkt (31.01. 2017)	Diab, Zeisler, Moore Simas, Doherty, Hanita, Villa, Chaiwora- pongsa.	sFlt-1/PIGF Elecsys (Rosche), Kryptor		Prediction of preeclampsia		0.85 (0.66-0.94) 75.39 (56.95-93.84)	0.87 (0.76-0.93) 78.80 (53.49- 94.12)			
Maesa, 2019 (High risk of bias)	Liu (meta-analysis) Bahlmann 2016 Stepan 2016	sFlt-1/PIGF	---	---		78 (77-86)	84 (77-89)			0.88 (0.85-0.91)
			≥69.69	Confirm PE		78.5	80			
			≤33	Reject PE < 34 SG		94.0 (86.5-98.0)				0.98
			≥85	Confirm PE < 34 SG			99.4 (96.8-99.9)			(0.97-0.99)

			≤33	Reject PE ≥ 34 SG		89.5 (81.5-94.8)				0.88 (0.85-0.93)
			≥ 110	Confirm PE ≥ 34 SG			95.4 (91.7-97.8)		99.3 (97.9-99.9)	
	Zeisler 2016		Included in Agrawal meta-analysis (see above)							
	Taraseviciene 2016		≥ 35	Risk of PE ≥ 34 SG		95.8	96.2			0.98
			≥ 54	Risk of PE <34 SG		97.5	97.5			0.99
	Sovio, 2017		>38	Risk of PE 28 SG		23.1 (6.9-39.3)	99.7 (99.5-99.8)	31.6 (10.7-52.5)	99.5 (99.3-99.7)	0.80 (0.70-0.89)
			≥85	Confirm PE 28 SG		15.4 (1.5-29.3)	99.9 (99.8-100)	57.1 (20.5-93.8)	99.4 (99.2-99.7)	
			>38	Risk of PE 36 SG		54.7 (45.2-64.2)	86.2 (85-87.3)	80.6 (77.5- 83.6)	87.4 (86.2-88.5)	0.81 (0.77-0.86)
			≥110	Confirm PE 36 SG		19.8 (12.2-27.4)	98.7 (98.3-99)	30.0 (19.3-40.7)	97.7 (97.2-98.2)	
	Dragan, 2017		>38	PE in <1 week		-	-	1.9 (0.8-3)	99.9 (99.9-100)	-
				PE in < 4 weeks		-	-	10.4 (7.9-12.9)	99.8 (99.7-99.9)	
	Included systematic reviews					Results based on meta-analysis (see below)				
	Widmer 2007	sFlt-1	NR	Early onset PE	1173	Narrative				
	Kleinrouweler 2012			Early onset PE	5337	OR 6.6 (3.1 to 13.7)				
	Allen 2014			Early onset PE	569	OR 1.2 (0.33 to 4.41)				

Townsend, 2018 (OoO) Low risk of bias (søkt mars 2017)				All PE	1045	OR 1.3 (1.02 to 1.65)						
	Wu 2015	PIGF	NR	Early onset PE	NR	37% (27-48%)	79% (78-81%)					
				All PE	NR	65% (63-67%)	89% (89-89%)					
	Zhong 2015			Early onset PE	8424			6.05 (5.55 to 6.55)	0.48 (0.43 to 0.52)			
				All PE	8424			4.01 (3.74 to 4.289)	0.67 (0.64 to 0.69)			
	Widmer 2007			Early onset PE	2045	Narrative						
	Allen 2014			Early onset PE	1590	OR 3.41 (1.61 to 7.24)						
				All PE	987	OR 1.94 (0.81 to 4.67)						
				Kleinrouweler 2012	All PE	10612	OR 9.0 (5.6 to 14.5)					

List of relevant ongoing trials for question of safety and effectiveness

The following on-going studies are expected to be completed within the end of 2020:

Figueira IF et al, CoLab, PREPARE, Prematurity Reduction by Preeclampsia Care: <https://ClinicalTrials.gov/show/NCT03073317>; 2016 2016

Pau FI et al., Institute CIH, CAIBER SCRN-. Randomized Open-label Control Trial to Evaluate if the Incorporation of sFlt1/PlGF Ratio in the Diagnosis and Classification of PE Improves Maternal and Perinatal Outcomes in Women With the Suspicion of the Disease: <https://ClinicalTrials.gov/show/NCT03231657>; 2018 2018.

List of ongoing systematic reviews for question of accuracy

The following ongoing systematic reviews are identified in PROSPERO:

Amanda Pastorello Rodrigues LWPJD. Evaluation of the sflt-1/plgf rate as a maternal-fetal outcomes marker: a systematic review.

Deirdre H-R. Placental growth factor (PlGF) as a predictor of adverse maternal and fetal outcomes in women with multiple pregnancy and suspected/confirmed hypertensive disorders of pregnancy (HDPs): a systematic review.

Melanie Griffin et al. Systematic review and meta-analysis of prognostic accuracy studies to evaluate the ability of late pregnancy maternal tests to predict adverse pregnancy outcomes associated with placental dysfunction (specifically fetal growth restriction and preeclampsia).

Swati Agrawal et al. The role of PlGF in the prediction of preeclampsia: a systematic review and meta-analysis.

Table 6. Description of cost data

Study	Country	Gestational week	Intervention	Source efficacy	Cost per woman tested
Duckworth 2016	UK	<35	PlGF+CM	prospective cohort	GBP -582
Duhig 2019	UK	20+0-36	PlGF+CM	PARROT UK	GBP -149
Duva 2017	Colombia	unclear	sFlt-1/PlGF	unclear	COL -182
Figueira 2018	Brazil	24-36+6	sFlt-1/PlGF+CM	PROGNOSIS	BRL 185/686
Frusca 2016	Italy	24-36+6	sFlt-1/PlGF+CM	PROGNOSIS	
Hadker 2013	Germany	12-40	sFlt-1/PlGF+CM	literature	euro -637
Ho 2019	Brazil	24-36+6	sFlt-1/PlGF+CM	PROGNOSIS	BRL -3 014

Hodel 2019	Switzerland	mean week 32	sFlt-1/PIGF+CM	PROGNOSIS	euro -346
Hunter 2013	UK	<35	PIGF+CM	prospective cohort	GBP -582
Paoloini 2016	Italy	24-36+6	,	PROGNOGIS + literature	euro -671
Schlembach 2018	Germany	24-36+6	sFlt-1/PIGF+CM	PROGNOSIS	euro -361
Schnettler 2018	USA	<34	sFlt-1/PIGF+CM	Prospective cohort	USD -1215

Table 7. Log (in Norwegian)

Aktiviteter	Dato
MedNytt: Egnethetsvurdering av forslag Nye Metoder ID2018_049	23.08.2018
Oppdrag om full metodevurdering gitt av Bestillerforum RHF	22.10.2018
Fagekspertter oppnevnt fra de regionale helseforetak	07.02.2019
Oppstartsmøte med intern prosjektgruppe FHI	14.02.2019
Første møte med fagekspertgruppe og intern prosjektgruppe	01.03.2019
Avgrensning av oppdrag fra Bestillerforum RHF	18.03.2019
Utkast til prosjektplan sendt til interne fagfeller	12.04.2019
Utkast til prosjektplan sendt til fagekspertter/eksterne fagfeller for kommentarer	12.04.2019
Prosjektplan godkjent av ledergruppe FHI	14.05.2019
Søkt etter systematiske oversikter om prediktiv nøyaktighet	17.06.2019
Informasjon til fagekspertter/eksterne fagfeller om status per mail	06.06.2019
Prosjektplan publisert	24.06.2019
Møte med fagekspert Annetine Staff vedr. metode og foreløpige resultater	17.10.2019
Søkt etter kontrollerte studier om sikkerhet og effekt	23.10.2019
Andre møte med fagekspertter/eksterne fagfeller vedr. metode og foreløpige resultater	26.11.2019
Utkast rapport sendt til interne fagfeller	12.02.2020
Utkast rapport sendt til fagekspertter/eksterne fagfeller	26.02.2020
Rapport ikke godkjent i klyngeledermøtet	før påske.2020
Rapport til fagfelleevaluering (intern), ventetid.	Mars og april 2020
Ny fagfelle	05.05.2020
Rapport revidert etter fagfelle	29.05.2020
Utkast rapport sendt til sekretariatet i Bestillerforum RHF	24.06.2020

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