Literature Review

Pre-eclampsia diagnosis and prognosis

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Guidelines and reviews on pre-eclampsia

Guidelines and reviews on pre-eclampsia

Guidelines

German guideline - Hypertensive Schwangerschaftserkrankungen: Diagnostik und Therapie

D. Schlembach and H. Stepan

AWMF online, 2019

Hypertensive Erkrankungen treten in 6 – 8 % aller Schwangerschaften auf, tragen zu 20 – 25 % der perinatalen Mortalität bei und stehen in Europa an führender Stelle der mütterlichen Todesursachen. Dabei ist die Präeklampsie von besonderer Bedeutung (10-15 % aller maternalen Todesfälle stehen in Zusammenhang mit einer Präeklampsie / Eklampsie), weltweit ist sie für mindestens 70.000 mütterliche Todesfälle pro Jahr verantwortlich (Übersicht bei: Lo et al.).[1] Auch heute noch sind in Europa mehr als 90% der maternalen Todesfälle durch Präeklampsie/Eklampsie potentiell vermeidbar.[2,3] In Europa beträgt die Inzidenz der Präeklampsie ca. 2 %.[1,4,5] Im klinischen Alltag gibt es dabei eine deutliche Schnittmenge mit anderen bzw. ähnlichen klinischen Manifestationsformen einer plazentaren Dysfunktion z.B. der IUGR. Beim derzeitigen Fehlen einer kausalen Therapie richtet sich der Schwerpunkt auf die Senkung der maternalen und kindlichen Morbidität und Mortalität durch möglichst frühe Erkennung, Risikostratifizierung und Erkennung von Zeichen einer klinischen Manifestation. Das Management dieser Schwangerschaftspathologie sollte so weit als möglich evidenzbasiert, interdisziplinär und in einer Klinik der richtigen Versorgungsstufe erfolgen. Aus diesem Grund adressiert diese Leitlinie auch alle medizinischen Professionen und Disziplinen, die in die Betreuung von Frauen mit hypertensiven Schwangerschaftserkrankungen einbezogen sind.

A literature review and best practice advice for second and third trimester risk stratification, monitoring, and management of pre-eclampsia

L. Poon, L. Magee, S. Verlohren, A. Shennan, P. von Dadelszen, E. Sheiner, et al.

Int J Gynaecol Obstet 2021 Vol. 154 Suppl 1 Issue Suppl 1 Pages 3-31

Pre-eclampsia is a multisystem disorder that typically affects 2%– 5% of pregnant women and is one of the leading causes of maternal and perinatal morbidity and mortality, especially when the condition is of early onset. Globally, 76 000 women and 500 000 babies die each year from this disorder. Furthermore, women in low- resource countries are at a higher risk of developing hypertensive disorders of pregnancy and pre-eclampsia compared with those in high- resource countries. This is because socioeconomic, educational, and environmental disadvantages have historically beset vulnerable communities, leading to nutritional disparities, poor- quality diet, obesity, and diabetes (before and during pregnancy), thus increasing the rates of pregnancy complications, in particular pre-eclampsia. Pre-eclampsia has been traditionally defined as the onset of hypertension accompanied by significant proteinuria after 20 weeks of gestation. Recently, the definition of pre- eclampsia has been broadened. Now the internationally agreed definition of preeclampsia is that proposed by the International Society for the Study of Hypertension in Pregnancy (ISSHP). According to ISSHP, pre-eclampsia is defined as systolic blood pressure at ≥140 mmHg and/or diastolic blood pressure at ≥90 mmHg on at least two occasions measured 4 hours apart in previously normotensive women and is accompanied by ≥1 of the following new- onset conditions at or after 20 weeks of gestation:

- Proteinuria: 24- hour urine protein ≥300 mg/day; spot urine protein/creatinine ratio ≥30 mg/mmoL or ≥0.3 mg/mg, or urine dipstick testing ≥2+
- Other maternal organ dysfunction:
  - Acute kidney injury (creatinine ≥90 µmol/L; >1.1 mg/dL); - Liver involvement (such as elevated liver transaminases >40 IU/L) with or without right upper quadrant or epigastric pain;
  - Neurological complications (including eclampsia, altered mental status, blindness, stroke, or more commonly hyperreflexia when accompanied by clonus, severe headaches, and persistent visual scotomata);
  - Hematological complications (thrombocytopenia– platelet count <150 000/µL, disseminated intravascular coagulation, hemolysis);
  - Uteroplacental dysfunction (such as fetal growth restriction, abnormal umbilical artery Doppler wave form or stillbirth).

Pre-eclampsia can be subclassified into:

1. Early-onset pre-eclampsia (with delivery at <34+0 weeks of gestation).
2. Preterm pre-eclampsia (with delivery at <37+0 weeks of gestation). 3. Late-onset pre-eclampsia (with delivery at ≥34+0 weeks of gestation).
3. Term pre-eclampsia (with delivery at ≥37+0 weeks of gestation).

National Institute for Health and Care Excellence - Guidelines

S. Findlay, J. Girling, S. Haslam, J. Meyers, A. Sharp, E. Sheehan, N. Simpson and M. Vatish

National Institute for Health and Care Excellence (NICE), 2022

This guidance represents the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, healthcare professionals are expected to take this guidance fully into account. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Commissioners and/or providers have a responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity, and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

The 2021 International Society for the Study of Hypertension in Pregnancy classification, diagnosis & management recommendations for international practice

L. Magee, M. Brown, D. Hall, S. Gupte, A. Hennessy, S. Karumanchi, et al.

Pregnancy Hypertens 2022 Vol. 27 Pages 148-169

All units managing hypertensive pregnant women should maintain and review uniform departmental management protocols and conduct regular audits of maternal & fetal outcomes. The cause(s) of pre-eclampsia and the optimal clinical management of the hypertensive disorders of pregnancy remain uncertain; therefore, we recommend that every hypertensive pregnant woman be offered an opportunity to participate in research, clinical trials and follow-up studies.

Guideline no. 426 - Hypertensive disorders of pregnancy: Diagnosis, prediction, prevention, and management

L. Magee, G. Smith, C. Bloch, A. Côté, V. Jain, K. Nerenberg, P. von Dadelszen, M. Helewa and E. Rey

J Obstet Gynaecol Can 2022 Vol. 44 Issue 5 Pages 547-571.e1

Objective
This guideline was developed by maternity care providers from obstetrics and internal medicine. It reviews the diagnosis, evaluation, and management of the hypertensive disorders of pregnancy (HDPs), the prediction and prevention of preeclampsia, and the postpartum care of women with a previous HDP.

Target Population
Pregnant women.

Benefits, Harms, and Costs
Implementation of the recommendations in these guidelines may reduce the incidence of the HDPs, particularly preeclampsia, and associated adverse outcomes.

Evidence
A comprehensive literature review was updated to December 2020, following the same methods as for previous Society of Obstetricians and Gynaecologists of Canada (SOGC) HDP guidelines, and references were restricted to English or French. To support recommendations for therapies, we prioritized randomized controlled trials and systematic reviews (if available), and evaluated substantive clinical outcomes for mothers and babies.

Validation Methods
The authors agreed on the content and recommendations through consensus and responded to peer review by the SOGC Maternal Fetal Medicine Committee. The authors rated the quality of evidence and strength of recommendations using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, along with the option of designating a recommendation as a “good practice point. The Board of the SOGC approved the final draft for publication.

Intended Users
All health care providers (obstetricians, family doctors, midwives, nurses, and anesthesiologists) who provide care to women before, during, or after pregnancy.

SOMANZ - Hypertension in pregnancy guidelines

A. Makris, R. Shanmugalingam. H. Barrett. A Beech, L. Bowyer et al.,

Aust N Z J Obstet Gynaecol, (TBC)

This guideline document is based upon literature searches last conducted in December 2020, and updated in December 2022. It is designed to assist with decision-making in matter related to the care of women with hypertension in pregnancy. It is not intended to define the standard of care but rather should be interpreted by clinicians based on the individual needs, preferences and values of their patient, the resources available to them and other constraints to practice that be unique to an institution. It is not compulsory to apply these guidelines and they do not override the responsibility of the clinician to make decisions appropriately. The Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) has made every effort to ensure there were no conflicts of interest between the members of the working group and their personal, professional or business interests. All members of the working group were required to complete, sign, and submit a disclosure and attestation form showing all such relationships that might be perceived as, or are actual conflicts of interest. Disclosures are published in the appendix of this document and are also held on file at SOMANZ. These are the recommendations of a multidisciplinary working party convened by SOMANZ. They reflect a thorough assessment of the current medical literature and the clinical experience of members of the working party.

Guidelines and reviews on pre-eclampsia

Reviews on pre-eclampsia

Pre-eclampsia: Pathophysiology and clinical implications

G. Burton, C. Redman, J. Roberts and A. Moffett

BMJ 2019 Vol. 366 Pages l2381

Pre-eclampsia is a common disorder that particularly affects first pregnancies. The clinical presentation is highly variable but hypertension and proteinuria are usually seen. These systemic signs arise from soluble factors released from the placenta as a result of a response to stress of syncytiotrophoblast. There are two sub-types: early and late onset pre-eclampsia, with others almost certainly yet to be identified. Early onset pre-eclampsia arises owing to defective placentation, whilst late onset pre-eclampsia may center around interactions between normal senescence of the placenta and a maternal genetic predisposition to cardiovascular and metabolic disease. The causes, placental and maternal, vary among individuals. Recent research has focused on placental-uterine interactions in early pregnancy. The aim now is to translate these findings into new ways to predict, prevent, and treat pre-eclampsia.

Preeclampsia: Recent advances in predicting, preventing, and managing the maternal and fetal life-threatening condition

K. Chang, K. Seow and K. Chen

Int J Environ Res Public Health 2023 Vol. 20 Issue 4

Preeclampsia accounts for one of the most common documented gestational complications, with a prevalence of approximately 2 to 15% of all pregnancies. Defined as gestational hypertension after 20 weeks of pregnancy and coexisting proteinuria or generalized edema, and certain forms of organ damage, it is life-threatening for both the mother and the fetus, in terms of increasing the rate of mortality and morbidity. Preeclamptic pregnancies are strongly associated with significantly higher medical costs. The maternal costs are related to the extra utility of the healthcare system, more resources used during hospitalization, and likely more surgical spending due to an elevated rate of cesarean deliveries. The infant costs also contribute to a large percentage of the expenses as the babies are prone to preterm deliveries and relevant or causative adverse events. Preeclampsia imposes a considerable financial burden on our societies. It is important for healthcare providers and policy-makers to recognize this phenomenon and allocate enough economic budgets and medical and social resources accordingly. The true cellular and molecular mechanisms underlying preeclampsia remain largely unexplained, which is assumed to be a two-stage process of impaired uteroplacental perfusion with or without prior defective trophoblast invasion (stage 1), followed by general endothelial dysfunction and vascular inflammation that lead to systemic organ damages (stage 2). Risk factors for preeclampsia including race, advanced maternal age, obesity, nulliparity, multi-fetal pregnancy, and co-existing medical disorders, can serve as warnings or markers that call for enhanced surveillance of maternal and fetal well-being. Doppler ultrasonography and biomarkers including the mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), and serum pregnancy-associated plasma protein A (PAPP-A) can be used for the prediction of preeclampsia. For women perceived as high-risk individuals for developing preeclampsia, the administration of low-dose aspirin on a daily basis since early pregnancy has proven to be the most effective way to prevent preeclampsia. For preeclamptic females, relevant information, counseling, and suggestions should be provided to facilitate timely intervention or specialty referral. In pregnancies complicated with preeclampsia, closer monitoring and antepartum surveillance including the Doppler ultrasound blood flow study, biophysical profile, non-stress test, and oxytocin challenge test can be arranged. If the results are unfavorable, early intervention and aggressive therapy should be considered. Affected females should have access to higher levels of obstetric units and neonatal institutes. Before, during, and after delivery, monitoring and preparation should be intensified for affected gravidas to avoid serious complications of preeclampsia. In severe cases, delivery of the fetus and the placenta is the ultimate solution to treat preeclampsia. The current review is a summary of recent advances regarding the knowledge of preeclampsia. However, the detailed etiology, pathophysiology, and effect of preeclampsia seem complicated, and further research to address the primary etiology and pathophysiology underlying the clinical manifestations and outcomes is warranted.

Pre-eclampsia

E. Dimitriadis, D. Rolnik, W. Zhou, G. Estrada-Gutierrez, K. Koga, R. Francisco, et al.

Nat Rev Dis Primers 2023 Vol. 9 Issue 1 Pages 8

Pre-eclampsia is a life-threatening disease of pregnancy unique to humans and a leading cause of maternal and neonatal morbidity and mortality. Women who survive pre-eclampsia have reduced life expectancy, with increased risks of stroke, cardiovascular disease and diabetes, while babies from a pre-eclamptic pregnancy have increased risks of preterm birth, perinatal death and neurodevelopmental disability and cardiovascular and metabolic disease later in life. Pre-eclampsia is a complex multisystem disease, diagnosed by sudden-onset hypertension (>20 weeks of gestation) and at least one other associated complication, including proteinuria, maternal organ dysfunction or uteroplacental dysfunction. Pre-eclampsia is found only when a placenta is or was recently present and is classified as preterm (delivery <37 weeks of gestation), term (delivery ≥37 weeks of gestation) and postpartum pre-eclampsia. The maternal syndrome of pre-eclampsia is driven by a dysfunctional placenta, which releases factors into maternal blood causing systemic inflammation and widespread maternal endothelial dysfunction. Available treatments target maternal hypertension and seizures, but the only 'cure' for pre-eclampsia is delivery of the dysfunctional placenta and baby, often prematurely. Despite decades of research, the aetiology of pre-eclampsia, particularly of term and postpartum pre-eclampsia, remains poorly defined. Significant advances have been made in the prediction and prevention of preterm pre-eclampsia, which is predicted in early pregnancy through combined screening and is prevented with daily low-dose aspirin, starting before 16 weeks of gestation. By contrast, the prediction of term and postpartum pre-eclampsia is limited and there are no preventive treatments. Future research must investigate the pathogenesis of pre-eclampsia, in particular of term and postpartum pre-eclampsia, and evaluate new prognostic tests and treatments in adequately powered clinical trials.

Guidelines and reviews on pre-eclampsia

Reviews on PlGF and sFlt-1 biochemistry

Circulating angiogenic factors and the risk of preeclampsia

R. Levine, S. Maynard, C. Qian, K. Lim, L. England, K. Yu, et al.

N Engl J Med 2004 Vol. 350 Issue 7 Pages 672-83

Background

The cause of preeclampsia remains unclear. Limited data suggest that excess circulating soluble fms-like tyrosine kinase 1 (sFlt-1), which binds placental growth factor (PlGF) and vascular endothelial growth factor (VEGF), may have a pathogenic role.

Methods

We performed a nested case-control study within the Calcium for Preeclampsia Prevention trial, which involved healthy nulliparous women. Each woman with preeclampsia was matched to one normotensive control. A total of 120 pairs of women were randomly chosen. Serum concentrations of angiogenic factors (total sFlt-1, free PlGF, and free VEGF) were measured throughout pregnancy; there were a total of 655 serum specimens. The data were analyzed cross-sectionally within intervals of gestational age and according to the time before the onset of preeclampsia.

Results

During the last two months of pregnancy in the normotensive controls, the level of sFlt-1 increased and the level of PlGF decreased. These changes occurred earlier and were more pronounced in the women in whom preeclampsia later developed. The sFlt-1 level increased beginning approximately five weeks before the onset of preeclampsia. At the onset of clinical disease, the mean serum level in the women with preeclampsia was 4382 pg per milliliter, as compared with 1643 pg per milliliter in controls with fetuses of similar gestational age ($P<0.001$). The PlGF levels were significantly lower in the women who later had preeclampsia than in the controls beginning at 13 to 16 weeks of gestation (mean, 90 pg per milliliter vs. 142 pg per milliliter, $P=0.01$), with the greatest difference occurring during the weeks before the onset of preeclampsia, coincident with the increase in the sFlt-1 level. Alterations in the levels of sFlt-1 and free PlGF were greater in women with an earlier onset of preeclampsia and in women in whom preeclampsia was associated with a small-for-gestational-age infant.

Conclusions

Increased levels of sFlt-1 and reduced levels of PlGF predict the subsequent development of preeclampsia.

Total versus free placental growth factor levels in the pathogenesis of preeclampsia

E. Lecarpentier, Z. Zsengellér, S. Salahuddin, A. Covarrubias, A. Lo, B. Haddad, R. Thadhani and S. Karumanchi

Hypertension 2020 Vol. 76 Issue 3 Pages 875-883

Elevated circulating sFlt-1 (soluble fms-like tyrosine kinase) and low levels of its ligand, PlGF (placental growth factor), are key characteristics of preeclampsia. However, it is unclear if the low levels of plasma PlGF noted during preeclampsia are due to decreased placental production of PlGF or due to binding of PlGF by increased circulating sFlt-1. Here, we describe a biochemical procedure to dissociate PlGF-sFlt-1 complex ex vivo and when used in conjunction with an immunoassay platform, demonstrate a method to measure total and free PlGF in human blood samples. Using this method, we noted that plasma free PlGF levels were significantly lower in preeclampsia (N=22) than in nonhypertensive controls (N=24; mean, 314 versus 686 pg/mL, P<0.05), but total PlGF levels were not different (mean, 822 versus 800 pg/mL, P=0.49). In contrast, total sFlt-1 levels were significantly higher in preeclampsia than in nonhypertensive controls (mean, 16 957 versus 3029 pg/mL, P<0.01) and sFlt-1 levels correlated with bound PlGF levels (bound PlGF=total PlGF-free PlGF) in these samples (r(2)=0.68). We confirmed these findings in an independent cohort of subjects (N=49). Furthermore, we did not detect any difference in PlGF mRNA by quantitative polymerase chain reaction or in PlGF protein expression by immunohistochemistry in preeclamptic placentas when compared with nonhypertensive controls. In contrast, sFlt-1 mRNA and protein levels were upregulated in placentas from women with preeclampsia. Taken together with prior studies, our results provide evidence that decrease in circulating PlGF noted during preeclampsia is largely mediated by excess circulating sFlt-1.

From biomarkers to the molecular mechanism of preeclampsia. A comprehensive literature review

M. Rybak-Krzyszkowska, J. Staniczek, A. Kondracka, J. Bogusławska, S. Kwiatkowski, T. Góra, M. Strus and W. Górczewski

Int J Mol Sci 2023 Vol. 24 Issue 17

Preeclampsia (PE) is a prevalent obstetric illness affecting pregnant women worldwide. This comprehensive literature review aims to examine the role of biomarkers and understand the molecular mechanisms underlying PE. The review encompasses studies on biomarkers for predicting, diagnosing, and monitoring PE, focusing on their molecular mechanisms in maternal blood or urine samples. Past research has advanced our understanding of PE pathogenesis, but the etiology remains unclear. Biomarkers such as PlGF, sFlt-1, PP-13, and PAPP-A have shown promise in risk classification and preventive measures, although challenges exist, including low detection rates and discrepancies in predicting different PE subtypes. Future perspectives highlight the importance of larger prospective studies to explore predictive biomarkers and their molecular mechanisms, improving screening efficacy and distinguishing between early-onset and late-onset PE. Biomarker assessments offer reliable and cost-effective screening methods for early detection, prognosis, and monitoring of PE. Early identification of high-risk women enables timely intervention, preventing adverse outcomes. Further research is needed to validate and optimize biomarker models for accurate prediction and diagnosis, ultimately improving maternal and fetal health outcomes.

sFlt-1/PlGF ratio for prediction and diagnosis of pre-eclampsia

sFlt-1/PlGF ratio for prediction and diagnosis of pre-eclampsia

Key ratio publications

Implementation of the sFlt-1/PlGF ratio for prediction and diagnosis of pre-eclampsia in singleton pregnancy: Implications for clinical practice

H. Stepan, I. Herraiz, D. Schlembach, S. Verlohren, S. Brennecke, F. Chantraine, et al.

Ultrasound Obstet Gynecol 2015 Vol. 45 Issue 3 Pages 241-6

Pre-eclampsia (PE) is a leading cause of maternal and fetal/neonatal morbidity and mortality worldwide. Clinical diagnosis and definition of PE is commonly based on the measurement of non-specific signs and symptoms, principally hypertension and proteinuria. However, due to the recognition that measurement of proteinuria is prone to inaccuracies and the fact that PE complications often occur before proteinuria becomes significant, most recent guidelines also support the diagnosis of PE on the basis of hypertension and signs of maternal organ dysfunction other than proteinuria. Furthermore, the clinical presentation and course of PE is variable, ranging from severe and rapidly progressing early-onset PE, necessitating preterm delivery, to late-onset PE at term. There may be associated intrauterine growth restriction (IUGR), further increasing neonatal morbidity and mortality. These features suggest that the classical standards for the diagnosis of PE are not sufficient to encompass the complexity of the syndrome. Undoubtedly, proper management of pregnant women at high risk for PE necessitates early and reliable detection and intensified monitoring, with referral to specialized perinatal care centers, to reduce substantially maternal, fetal and neonatal morbidity

Predictive value of the sFlt-1:PlGF ratio in women with suspected preeclampsia

H. Zeisler, E. Llurba, F. Chantraine, M. Vatish, A. Staff, M. Sennström, et al.

N Engl J Med 2016 Vol. 374 Issue 1 Pages 13-22

Background

The ratio of soluble fms-like tyrosine kinase 1 (sFlt-1) to placental growth factor (PlGF) is elevated in pregnant women before the clinical onset of preeclampsia, but its predictive value in women with suspected preeclampsia is unclear.

Methods

We performed a prospective, multicenter, observational study to derive and validate a ratio of serum sFlt-1 to PlGF that would be predictive of the absence or presence of preeclampsia in the short term in women with singleton pregnancies in whom preeclampsia was suspected (24 weeks 0 days to 36 weeks 6 days of gestation). Primary objectives were to assess whether low sFlt-1:PlGF ratios (at or below a derived cutoff) predict the absence of preeclampsia within 1 week after the first visit and whether high ratios (above the cutoff) predict the presence of preeclampsia within 4 weeks.

Results

In the development cohort (500 women), we identified an sFlt-1:PlGF ratio cutoff of 38 as having important predictive value. In a subsequent validation study among an additional 550 women, an sFlt-1:PlGF ratio of 38 or lower had a negative predictive value (i.e., no preeclampsia in the subsequent week) of 99.3% (95% confidence interval [CI], 97.9 to 99.9), with 80.0% sensitivity (95% CI, 51.9 to 95.7) and 78.3% specificity (95% CI, 74.6 to 81.7). The positive predictive value of an sFlt-1:PlGF ratio above 38 for a diagnosis of preeclampsia within 4 weeks was 36.7% (95% CI, 28.4 to 45.7), with 66.2% sensitivity (95% CI, 54.0 to 77.0) and 83.1% specificity (95% CI, 79.4 to 86.3).

Conclusions

An sFlt-1:PlGF ratio of 38 or lower can be used to predict the short-term absence of preeclampsia in women in whom the syndrome is suspected clinically. (Funded by Roche Diagnostics).

Randomized Interventional Study on Prediction of Preeclampsia/Eclampsia in women with suspected preeclampsia: INSPIRE

A. Cerdeira, J. O'Sullivan, E. Ohuma, D. Harrington, P. Szafranski, R. Black, et al.

Hypertension 2019 Vol. 74 Issue 4 Pages 983-990

The ratio of maternal serum sFlt-1 (soluble fms-like tyrosine kinase 1) to PlGF (placental growth factor) has been used retrospectively to rule out the occurrence of preeclampsia, a pregnancy hypertensive disorder, within 7 days in women presenting with clinical suspicion of preeclampsia. A prospective, interventional, parallel-group, randomized clinical trial evaluated the use of sFlt-1/PlGF ratio in women presenting with suspected preeclampsia. Women were assigned to reveal (sFlt-1/PlGF result known to clinicians) or nonreveal (result unknown) arms. A ratio cutoff of 38 was used to define low (≤38) and elevated risk (>38) of developing the condition in the subsequent week. The primary end point was hospitalization within 24 hours of the test. Secondary end points were development of preeclampsia and other adverse maternal-fetal outcomes. We recruited 370 women (186 reveal versus 184 nonreveal). Preeclampsia occurred in 85 women (23%). The number of admissions was not significantly different between groups (n=48 nonreveal versus n=60 reveal; P=0.192). The reveal trial arm admitted 100% of the cases that developed preeclampsia within 7 days, whereas the nonreveal admitted 83% (P=0.038). Use of the test yielded a sensitivity of 100% (95% CI, 85.8-100) and a negative predictive value of 100% (95% CI, 97.1-100) compared with a sensitivity of 83.3 (95% CI, 58.6-96.4) and negative predictive value of 97.8 (95% CI, 93.7-99.5) with clinical practice alone. Use of the sFlt-1/PlGF ratio significantly improved clinical precision without changing the admission rate.

Placental growth factor testing to assess women with suspected pre-eclampsia: A multicentre, pragmatic, stepped-wedge cluster-randomised controlled trial

K. Duhig, J. Myers, P. Seed, J. Sparkes, J. Lowe, R. Hunter, A. Shennan, L. Chappell, on behalf of the PARROT trial group

Lancet 2019 Vol. 393 Issue 10183 Pages 1807-1818

Background

Previous prospective cohort studies have shown that angiogenic factors have a high diagnostic accuracy in women with suspected pre-eclampsia, but we remain uncertain of the effectiveness of these tests in a real-world setting. We therefore aimed to determine whether knowledge of the circulating concentration of placental growth factor (PlGF), an angiogenic factor, integrated with a clinical management algorithm, decreased the time for clinicians to make a diagnosis in women with suspected pre-eclampsia, and whether this approach reduced subsequent maternal or perinatal adverse outcomes.

Methods

We did a multicentre, pragmatic, stepped-wedge cluster-randomised controlled trial in 11 maternity units in the UK, which were each responsible for 3000-9000 deliveries per year. Women aged 18 years and older who presented with suspected pre-eclampsia between 20 weeks and 0 days of gestation and 36 weeks and 6 days of gestation, with a live, singleton fetus were invited to participate by the clinical research team. Suspected pre-eclampsia was defined as new-onset or worsening of existing hypertension, dipstick proteinuria, epigastric or right upper-quadrant pain, headache with visual disturbances, fetal growth restriction, or abnormal maternal blood tests that were suggestive of disease (such as thrombocytopenia or hepatic or renal dysfunction). Women were approached individually, they consented for study inclusion, and they were asked to give blood samples. We randomly allocated the maternity units, representing the clusters, to blocks. Blocks represented an intervention initiation time, which occurred at equally spaced 6-week intervals throughout the trial. At the start of the trial, all units had usual care (in which PlGF measurements were also taken but were concealed from clinicians and women). At the initiation time of each successive block, a site began to use the intervention (in which the circulating PlGF measurement was revealed and a clinical management algorithm was used). Enrolment of women continued for the duration of the blocks either to concealed PlGF testing, or after implementation, to revealed PlGF testing. The primary outcome was the time from presentation with suspected pre-eclampsia to documented pre-eclampsia in women enrolled in the trial who received a diagnosis of pre-eclampsia by their treating clinicians. This trial is registered with ISRCTN, number 16842031.

Findings

Between June 13, 2016, and Oct 27, 2017, we enrolled and assessed 1035 women with suspected pre-eclampsia. 12 (1%) women were found to be ineligible. Of the 1023 eligible women, 576 (56%) women were assigned to the intervention (revealed testing) group, and 447 (44%) women were assigned to receive usual care with additional concealed testing (concealed testing group). Three (1%) women in the revealed testing group were lost to follow-up, so 573 (99%) women in this group were included in the analyses. One (<1%) woman in the concealed testing group withdrew consent to follow-up data collection, so 446 (>99%) women in this group were included in the analyses. The median time to pre-eclampsia diagnosis was 4·1 days with concealed testing versus 1·9 days with revealed testing (time ratio 0·36, 95% CI 0·15-0·87; p=0·027). Maternal severe adverse outcomes were reported in 24 (5%) of 447 women in the concealed testing group versus 22 (4%) of 573 women in the revealed testing group (adjusted odds ratio 0·32, 95% CI 0·11-0·96; p=0·043), but there was no evidence of a difference in perinatal adverse outcomes (15% vs 14%, 1·45, 0·73-2·90) or gestation at delivery (36·6 weeks vs 36·8 weeks; mean difference -0·52, 95% CI -0·63 to 0·73).

Interpretation

We found that the availability of PlGF test results substantially reduced the time to clinical confirmation of pre-eclampsia. Where PlGF was implemented, we found a lower incidence of maternal adverse outcomes, consistent with adoption of targeted, enhanced surveillance, as recommended in the clinical management algorithm for clinicians. Adoption of PlGF testing in women with suspected pre-eclampsia is supported by the results of this study.

Funding

National Institute for Health Research.

Clinical utility of sFlt-1 and PlGF in screening, prediction, diagnosis and monitoring of pre-eclampsia and fetal growth restriction

H. Stepan, A. Galindo, M. Hund, D. Schlembach, J. Sillman, D. Surbek and M. Vatish

Ultrasound Obstet Gynecol 2022

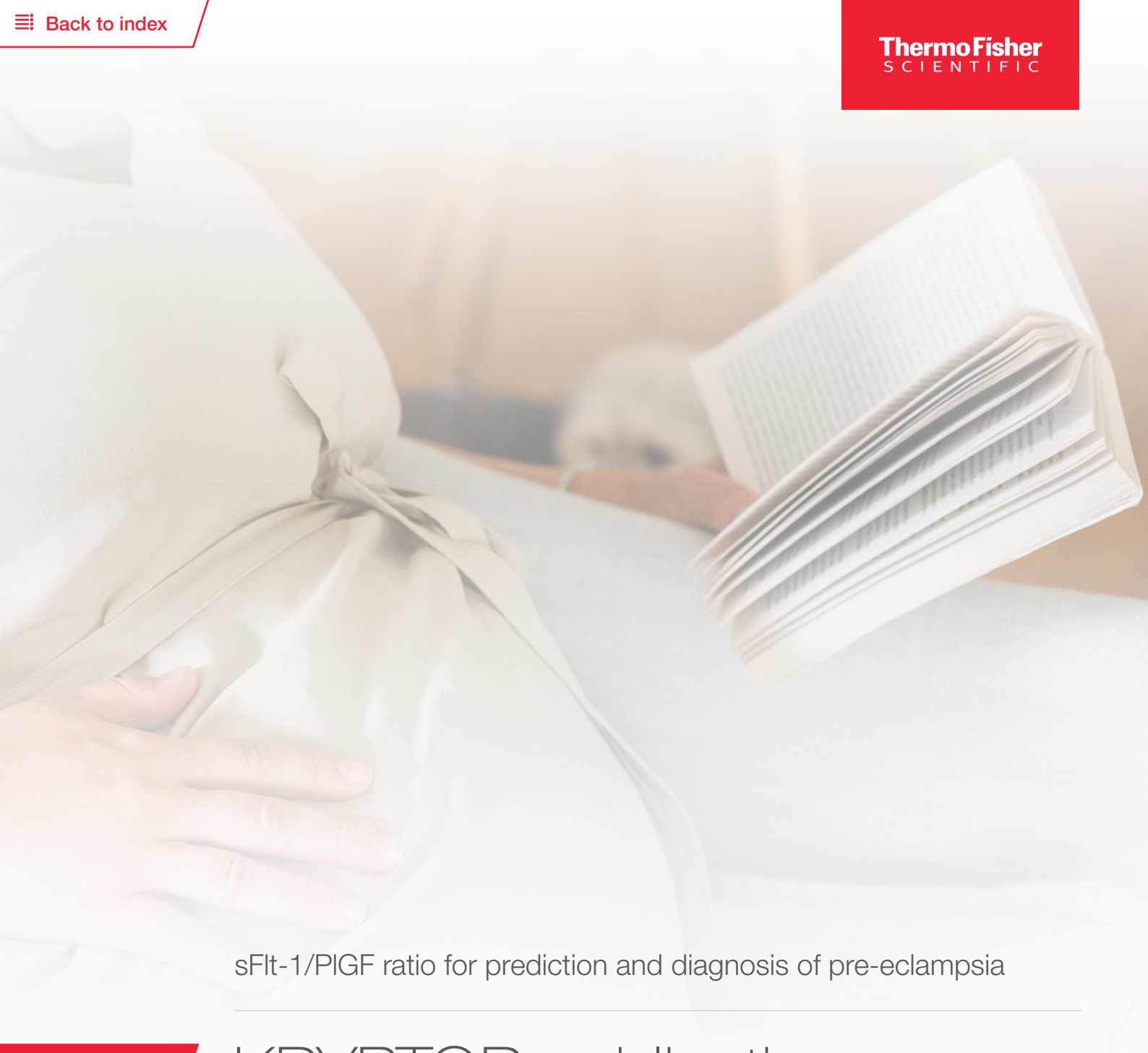
Preeclampsia (PE) is characterized by placental and maternal endothelial dysfunction, and associated with fetal growth restriction (FGR), placental abruption, preterm delivery and stillbirth. The angiogenic factors soluble fms-like tyrosine kinase 1 (sFlt-1) and placental growth factor (PlGF) are altered in pregnancies complicated by placental-related disorders. In this review, we summarize existing literature examining the performance of maternal PlGF, sFlt-1 and sFlt-1/PlGF ratio for a) screening and diagnosing PE, b) predicting PE development in the short term, c) monitoring established PE and d) predicting other placental-related disorders. We also discuss the performance of PlGF and the sFlt-1/PlGF ratio for predicting PE in twin pregnancies. For first trimester screening, a more accurate way of identifying high-risk women than current practices is to combine PlGF levels with clinical risk factors and ultrasound markers. To support diagnosis of PE later in pregnancy, the sFlt-1/PlGF ratio has advantages over PlGF because it has a higher pooled sensitivity and specificity for diagnosing and monitoring PE. The sFlt-1/PlGF ratio has clinical value because it can rule out the development of PE in the subsequent 1-4 weeks after the test. Once diagnosis of PE is established, repeated measurement of sFlt-1 and PlGF can help monitor progression of the condition and may inform clinical decision-making around optimal time for delivery. The sFlt-1/PlGF ratio is useful for predicting FGR and preterm delivery, but the association between stillbirth and the angiogenic factors remains unclear. The sFlt-1/PlGF ratio can also be used to predict PE in twin pregnancies, although different sFlt-1/PlGF ratio cut-offs to those of singleton pregnancies should be applied for optimal performance. In summary, PlGF, sFlt-1 and the sFlt-1/PlGF ratio are useful for screening, diagnosing, predicting, and monitoring placental-related disorders in singleton and twin pregnancies; we propose further integration of these angiogenic factor tests in clinical practice

Predictive value of the sFlt-1/PlGF ratio in women with suspected preeclampsia: An update (Review)

A. Velegrakis, E. Kouvidi, P. Fragkiadaki and S. Sifakis

Int J Mol Med 2023 Vol. 52 Issue 4

Preeclampsia (PE) is a major complication of pregnancy with an incidence rate of 2-8% and is a leading cause of maternal mortality and morbidity. The various consequences of severe preeclampsia for the fetus, neonate and child include intrauterine growth retardation (IUGR), fetal hypoxia, oligohydramnios, intrauterine fetal demise, increased perinatal mortality and morbidity, neurodevelopmental disorders and even irreversible brain damage (cerebral palsy). A number of studies have demonstrated that differences in maternal serum concentrations of angiogenic factors between preeclampsia and normotensive pregnancies can be used as biomarkers, either alone or in combination with other markers, to predict the development of PE. The presence in the maternal circulation of two proteins of placental origin, placental growth factor (PlGF) and soluble fms-like tyrosine kinase 1 (sFlt-1), has been shown to be of clinical value, as the sFlt-1/PlGF ratio appears to be the optimal predictive tool for the development of PE. The measurement of their concentration in maternal serum in screening models, serves as predictive marker for the development of PE or IUGR later in gestation. However, further research is required to improve its clinical applicability and provide guidelines for its use worldwide to achieve more consistent clinical management of women with PE.



sFlt-1/PlGF ratio for prediction and diagnosis of pre-eclampsia

KRYPTOR publications Analytical

Analytical validation of soluble fms-like tyrosine and placental growth factor assays on B·R·A·H·M·S KRYPTOR Compact Plus automated immunoassay platform

S. Chan, S. Rana, S. Chinthala, S. Salahuddin and K. Yeo

Pregnancy Hypertens 2018 Vol. 11 Pages 66-70

Background

Preeclampsia is one of the leading hypertensive disorders of pregnancy. Angiogenic biomarkers such as anti-angiogenic factor soluble fms-like tyrosine kinase 1 (sFlt-1) and pro-angiogenic factor placental growth factor (PlGF) are involved in the pathophysiology of preeclampsia.

Objective

The aim of this study is to validate the analytical performance of sFlt-1 and PlGF on the B·R·A·H·M·S KRYPTOR Compact Plus (ThermoFisher Scientific).

Study Design

We examined K(2)-EDTA plasma samples from 50 patients on B·R·A·H·M·S KRYPTOR Compact Plus, an automated immunoassay platform. QC materials were used to assess intra- and inter-precision of the assay. Lower limit of quantitation and interference studies were determined using pooled patient plasma.

Results

The sFlt-1 and PlGF assays demonstrated an analytical measuring range of 90-69,000 pg/mL and 11-7000 pg/mL, respectively ($r(2) > 0.99$). Lower limit of quantitation (20% CV) was interpolated to be 35 pg/mL for sFlt-1 and 10 pg/mL for PlGF. Total precision for both assay displayed CVs of <10%. Interference studies showed that both assays were not significantly affected by hemolysis up to an H-index of 1100 for sFlt-1 and 300 for PlGF; L- and I-index of 800 and 80 respectively for both assays. The Passing-Bablok regression analysis for sFlt-1/PlGF yielded an equation of $y = 1.05x + 0.02$, and the Bland Altman analysis showed an average bias of 0.84.

Conclusions

Plasma levels of sFlt-1 and PlGF measured on the B·R·A·H·M·S KRYPTOR Compact Plus platform demonstrate excellent analytical performance and are acceptable as clinical grade assays.

Inter-manufacturer comparison of automated immunoassays for the measurement of soluble FMS-like tyrosine kinase-1 and placental growth factor

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Pregnancy Hypertens 2019 Vol. 17 Pages 165-171

Objective

To assess inter-manufacturer automated immunoassays for soluble FMS-like tyrosine kinase 1 (sFlt-1) to placental growth factor (PlGF).

Methods

sFlt-1 and PlGF levels were measured using the AutoDelfia PlGF1-2-3 (PerkinElmer Inc. Turku, Finland), B·R·A·H·M·S KRYPTOR sFlt-1, PlGF plus and PlGF-2 (B·R·A·H·M·S ThermoFisher, Germany) and Cobas e411 Elecsys® sFlt-1 and PLGF (Roche Diagnostics GmbH, Mannheim, Germany) in 965 asymptomatic pregnancies between 20 and 39 weeks of gestation and in in-vitro samples with predefined levels of glycosylated PlGF isomers (1, 2 and 3), sFlt-1 in human male serum. Percentage PlGF isoform recovery and cross-reactivities were determined. Paired Bland-Altman and Passing-Bablok analyses were performed to determine bias, precision and accuracy. Inter-manufacturer sFlt-1:PlGF ratio were compared.

Results

PlGF-1 isomer recovery ranged from 36 to 39% for Elecsys® to 52-60% for PlGF plus and PlGF-1-2-3 assays. PlGF-2 and PlGF-3 isoform cross-reactivity was assay dependent, ranging from 10 to 21% and 16-36% respectively. B·R·A·H·M·S PlGF-2 assay had high cross-reactivity to PlGF-1 (37-41%) and PlGF-3 isomers (48-65%). Elecsys® recovery of sFlt-1 was 13% vs 6% for B·R·A·H·M·S. Passing-Bablok indicated significant proportional and systematic differences between all paired PlGF assay comparisons. PlGF Bland-Altman percentage biases ranged from 12 to 37% for PlGF and 18% for sFlt-1. A linear relationship existed between log transformed sFlt-1:PlGF ratios. The clinical equivalent of the B·R·A·H·M·S sFlt-1:PlGF plus to the Elecsys® sFlt-1:PlGF ratios of 38 and 110 are 55 and 188 respectively.

Conclusions

Inter-manufacture immunoassay differences are significantly different. sFlt-1:PlGF rule in/rule out criteria are manufacturer specific, not interchangeable and require separate clinical validation.

Stability of placental growth factor, soluble fms-like tyrosine kinase 1, and soluble fms-like tyrosine kinase 1 e15a in human serum and plasma

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Placenta 2019 Vol. 86 Pages 1-3

Placental growth factor (PlGF), total soluble fms-like tyrosine-kinase 1 (sFlt-1) and its placental-specific variant, sFlt-1 e15a, show promise as biomarkers for the prediction and diagnosis of preeclampsia. This study describes the degradation of PlGF, sFlt-1 and sFlt-1 e15a within maternal serum and plasma to assist clinical implementation. Whole blood was refrigerated at 4°C for up to 48 h prior to centrifugation for isolation of plasma and serum. PlGF and sFlt-1 were quantified using the B·R·A·H·M·S KRYPTOR Compact PLUS; sFlt-1 e15a via a custom ELISA. All three analytes are stable for at least 48 h at 4 °C. Serum and plasma performed comparably.

Elecsys® and KRYPTOR immunoassays for the measurement of sFlt-1 and PlGF to aid preeclampsia diagnosis: are they comparable?

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Clin Chem Lab Med 2019 Vol. 57 Issue 9 Pages 1339-1348

Background

For pregnant women with suspected preeclampsia, the soluble fms-like tyrosine-kinase 1 (sFlt-1)/placental growth factor (PlGF) ratio is a biomarker to aid diagnosis. We performed method comparisons between Elecsys® and KRYPTOR sFlt-1 and PlGF immunoassays and assessed the diagnostic performance for preeclampsia.

Methods

Serum samples from a case-control study involving 113 pregnant women with preeclampsia/elevated liver enzymes and low platelet count (HELLP) and 270 controls were analyzed. sFlt-1 and PlGF were measured using Roche Elecsys® and B·R·A·H·M·S KRYPTOR sFlt-1/PlGF immunoassays. The sFlt-1/PlGF ratios were calculated, and Passing-Bablok regression/Bland-Altman plots were performed. Gestation-specific cut-offs, ≤33 and ≥85/≥110, were assessed.

Results

Mean (±2 standard deviation [SD]) differences between the Elecsys® and KRYPTOR values were: sFlt-1, 173.13 pg/mL (6237.66, -5891.40); PlGF, -102.71 pg/mL (186.06, -391.48); and sFlt-1/PlGF, 151.74 (1085.11, -781.63). The Elecsys® and KRYPTOR immunoassays showed high correlation: Pearson's correlation coefficients were 0.913 (sFlt-1) and 0.945 (PlGF). Slopes were 1.06 (sFlt-1) and 0.79 (PlGF), resulting in ~20% lower values for KRYPTOR PlGF. Sensitivities and specificities using the sFlt-1/PlGF ≥85 cut-off for early-onset preeclampsia (20+0 to 33+6 weeks) were 88.1%/100.0% (Elecsys®) and 90.5%/96.2% (KRYPTOR), respectively, and using the ≥110 cut-off for late-onset preeclampsia (≥34+0 weeks) were 51.3%/96.5% (Elecsys®) and 78.9%/90.1% (KRYPTOR), respectively. Using Elecsys® and KRYPTOR sFlt-1/PlGF, 0% and 3.8% of women, respectively, were falsely ruled-in for early-onset, and 3.5% and 9.9%, respectively, for late-onset preeclampsia.

Conclusions

Despite high correlation between the Elecsys® and KRYPTOR immunoassays, we observed significant differences between sFlt-1/PlGF and PlGF results. Therefore, sFlt-1/PlGF cut-offs validated for Elecsys® immunoassays are not transferable to KRYPTOR immunoassays.

Decision-making based on sFlt-1/PlGF ratios: Are immunoassay results interchangeable for diagnosis or prognosis of preeclampsia?

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Clin Chem Lab Med 2021 Vol. 59 Issue 3 Pages e87-e89

To the Editor,

In a recent paper, Stepan et al. [1] compared, from a cohort of pregnant women with and without preeclampsia (PE), the blood levels of fms-like tyrosine kinase (sFlt-1) and placental growth factor (PlGF) using two different immunoassays: KRYPTOR (Thermo Fisher B·R·A·H·M·S, Germany) and Elecsys (Roche Diagnostics, France). The authors found a marked difference between the sFlt-1/PlGF ratio values, mainly due to PlGF differences between both assays. Indeed, the PlGF values obtained using KRYPTOR were lower by at least 50% compared with Elecsys [1]. Consequently, the KRYPTOR ratio values were higher than with Elecsys, with the increase reaching as much as 148% in the onset PE group . This nonconstant difference between ratios was particularly important for the category of high ratio values, where diagnosis and prognosis cutoff values for PE have been previously determined. The authors concluded that it was difficult to apply Roche's cutoff values to results obtained with Thermo Fisher. We herein report a clinical situation that clearly illustrates this difficulty of interchangeability between the two immunoassays.

Applying the concept of uncertainty to the sFlt-1/PlGF cut-offs for diagnosis and prognosis of preeclampsia

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Clin Chem Lab Med 2021 Vol. 59 Issue 7 Pages 1331

Objectives

Placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1) assays and the corresponding ratios (sFlt-1/PlGF) have been proposed to aid in the diagnosis by exclusion and/or prognosis of preeclampsia (PE). A method for evaluating ratio uncertainties (RUs), based on the theory of error propagation, was applied to the sFlt-1/PlGF ratio.

Methods

RUs were calculated using data derived from sFlt-1 and PlGF Internal Quality Control (IQC) results collected from four centers using Elecsys (Roche) or KRYPTOR (Thermo Fisher) sFlt-1 and PlGF assays. The corresponding ratio uncertainties were defined for each ratio value.

Results

The RUs increased linearly with the sFlt-1/PlGF ratio values. The Elecsys RUs were lower than the KRYPTOR RUs. Although RUs cannot eliminate differences in ratio values observed among various immunoassays, it can affect interpretation of the sFlt-1/PlGF ratio, especially when results are within the range of predefined PE diagnosis or prognosis cut-offs.

Conclusions

Since RUs are only a function of PlGF and sFlt-1 precision, they can be calculated for each assay from each laboratory to adjust the interpretation of sFlt-1/PlGF ratio results in the context of PE.

Accurate prediction of total PlGF (Placental Growth Factor) from free PlGF and sFlt-1 (Soluble Fms-Like Tyrosine Kinase-1): Evidence for markedly elevated PlGF levels in women with acute fatty liver of pregnancy

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Hypertension 2021 Vol. 78 Issue 2 Pages 489-498

Acute fatty liver of pregnancy (AFLP) is characterized by elevated circulating sFlt-1 (soluble Fms-like tyrosine kinase-1), although the free circulating levels of its ligand, PlGF (placental growth factor) are not decreased. Here, we hypothesized that women with AFLP exhibit elevated PlGF production in comparison to women with preeclampsia or hemolysis elevated liver enzymes and low platelet count syndrome. Making use of the well-known mathematical formulas describing drug-receptor interactions, we established that serum total PlGF could be accurately predicted from sFlt-1 and free PlGF levels (n=42; mean calculated KD of 50 pmol/L), yielding similar values as the previously published method of thermal dissociation of the sFlt-1-PlGF complexes (r=0.94, P<0.0001). We found that median levels of free PlGF were significantly lower in women with preeclampsia (n=13; 117pg/mL) or hemolysis elevated liver enzymes and low platelet count syndrome (n=12; 59 pg/mL) compared with women without preeclampsia (n=11; 349pg/mL, P<0.0001). In contrast, median total PlGF did not differ between women with no preeclampsia, preeclampsia, and hemolysis elevated liver enzymes and low platelet count syndrome (354 versus 435 versus 344pg/mL), whereas it was markedly elevated in AFLP compared with all groups (2054 pg/mL, P<0.0001). Furthermore, in AFLP, both sFlt-1 and total PlGF declined rapidly postdelivery, with significantly higher predelivery total PlGF (n=12; median, 2054 pg/mL) than postpartum levels (n=14; median,163pg/ mL, P<0.0001), suggesting that in AFLP, PlGF is largely placenta-derived. Collectively, our findings indicate that like sFlt-1, PlGF production is significantly upregulated in AFLP, mainly originating from the placenta. Importantly, total PlGF can now be easily calculated from already available free PlGF and sFlt-1 levels, allowing subsequent evaluation of other groups in whom PlGF is altered.

Effect of race on the measurement of angiogenic factors for prediction and diagnosis of pre-eclampsia

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BJOG 2022

Objective
To examine the effect of self-declared race on serum PlGF and sFlt-1/PlGF ratio and the impact on pre-eclampsia (PE) prediction.

Design
Prospective observational study.

Setting
Two UK maternity hospitals.

Population
29,035 women with singleton pregnancies attending a routine 35(+0) to 36(+6) weeks' gestation hospital visit, including 654 (2.3%) who subsequently developed PE.

Methods
The predictive performance of PlGF and sFlt-1/PlGF for PE in minority racial groups (vs. White) was examined.

Main Outcome Measure
Delivery with PE.

Results
Compared with White women, mean PlGF was higher and sFlt-1/PlGF ratio lower in Black, South Asian, East Asian, and Mixed race women. In White women at a PlGF concentration cut-off corresponding to a screen-positive rate (SPR) of 10%, detection rates (DRs) were 49.1% for PE at any time, and 72.3% for PE within two weeks after screening. In Black women, at the same PlGF concentration cut-off for White women, the SPR was 5.5% and DRs 33.6% and 55.0%, respectively; the number of PE cases was too small to evaluate screening performance in other racial groups. Using a fixed cut-off in sFlt-1/PlGF ratio to identify women at risk of developing PE similarly diagnostically disadvantaged Black women. Bias was overcome by adjusting metabolite concentrations for maternal characteristics and use of the competing risks model to estimate patient-specific risks.

Conclusion
Screening for PE with fixed cut-offs in PlGF or sFlt-1/PlGF diagnostically disadvantages Black women. It is essential that measured levels of PlGF be adjusted for race as well as other maternal characteristics.

sFlt-1/PlGF ratio for prediction and diagnosis of pre-eclampsia

KRYPTOR publications Diagnosis

Diagnosis of preeclampsia with soluble Fms-like tyrosine kinase 1/placental growth factor ratio: An inter-assay comparison

L. Andersen, B. Frederiksen-Møller, K. Work Havelund, R. Dechend, J. Jørgensen, B. Jensen, et al.

J Am Soc Hypertens 2015 Vol. 9 Issue 2 Pages 86-96

The angiogenic factor ratio soluble Fms-kinase 1 (sFlt-1)/placental growth factor (PlGF) is a novel diagnostic tool for preeclampsia. We compared the efficacy of the KRYPTOR (B·R·A·H·M·S) automated assays for sFlt-1 and PlGF with the Elecsys (Roche) assays in a routine clinical setting. Preeclamptic women (n = 39) were included shortly after the time of diagnosis. Normotensive control pregnancies were matched by gestational age (n = 76). The KRYPTOR assays performed comparably or superior to Elecsys (sFlt-1/PlGF area under the curve 0.746 versus 0.735; P = .09; for non-obese 0.820 versus 0.805, P = .047). For early-onset preeclampsia, KRYPTOR area under the curve increased to 0.929 with a 100% specificity for preeclampsia at cut-off 85 and an 88.9% sensitivity for preeclampsia at cut-off 33. For women with preeclampsia and preterm delivery or Hemolysis, Elevated Liver enzymes, Low Platelet count (HELLP) syndrome, the KRYPTOR sFlt-1/PlGF ratio was manifold increased (P < .01). The sFlt-1/PlGF ratio proved especially useful in early-onset preeclampsia, preeclampsia with preterm delivery or HELLP, and among non-obese women.

Analytical evaluation of the novel soluble fms-like tyrosine kinase 1 and placental growth factor assays for the diagnosis of preeclampsia

J. van Helden and R. Weiskirchen

Clin Biochem 2015 Vol. 48 Issue 16-17 Pages 1113-9

Objective

Performance evaluation of the novel B·R·A·H·M·S KRYPTOR soluble fms-like tyrosine kinase 1 (sFlt-1) and placental growth factor (PlGF) assays.

Design and Methods

Intra- and inter-assay imprecision, functional sensitivity, linearity in dilution, method comparison, and diagnostic capacity were evaluated.

Results

Intra-assay coefficient of variations (CVs) were between 1.1% and 5.3% and inter-assay CVs between 3.9% and 11.1%. Functional sensitivity was 6.7ng/L for PlGF and 34ng/L for sFlt-1, respectively. The linearity in dilution was excellent (r>0.995) in the assay-specific relevant range of concentration. The KRYPTOR assay correlated well with the Elecsys sFlt-1 (r=0.996), Elecsys PlGF (r=0.990) and the Elecsys sFlt-1/PlGF ratio (r=0.947) with partially high mean bias values. The optimal cut points for diagnosis of preeclampsia were calculated for KRYPTOR assays at: 60.5ng/L (PlGF), 4725ng/L (sFlt-1), and 99.2 (sFlt-1/PlGF ratio) which were different with the corresponding Elecsys cut points. Nevertheless, the sensitivity, specificity, positive predictive values (PPVs), negative predictive values (NPVs), and areas under the curves (AUCs) were completely comparable in both assay platforms, even when applying the standard cut-off of 85 for sFlt-1/PlGF ratio or gestational age specific “rule in-rule-out” cut-offs for early and late onset preeclampsia.

Conclusion

The new B·R·A·H·M·S KRYPTOR sFlt-1 and PlGF immunoassay show excellent precision and reliability. The assay results and the diagnostic capacity were highly comparable to established fully automated immunoassays (Elecsys). Hence, sFlt-1/PlGF ratio generated on KRYPTOR immunoassay platform should be suitable for diagnosing preeclampsia in clinical routine laboratory.

Diagnosis of preeclampsia and fetal growth restriction with the sFlt-1/PlGF ratio: Diagnostic accuracy of the automated immunoassay KRYPTOR

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Pregnancy Hypertens 2017 Vol. 8 Pages 31-36

Objective

We aimed to characterize the diagnostic accuracy of the KRYPTOR assay for sFlt-1 and PlGF in maternal serum samples of uneventful singleton pregnancies and subjects with preeclampsia (PE) and PE-related outcomes such as fetal growth restriction (FGR). Longitudinal reference ranges of the sFlt-1 and PlGF level in the course of normal pregnancies were generated.

Methods

A cohort of subjects with PE and PE-related outcomes including FGR in the third trimester was compared to a cohort of women with uneventful outcome. Serum levels of sFlt-1, PlGF level as well as the sFlt-1/PlGF ratio was analysed with the KRYPTOR assay and compared between the case- and control groups. Cut-off values were generated and diagnostic accuracy examined.

Results

Longitudinal reference ranges of the sFlt-1 and PlGF level in healthy pregnancies were in line with those levels measured with other immunoassays. Comparison of the sFlt-1/PlGF ratio between PE-related outcomes including FGR or PE and healthy controls showed a high diagnostic accuracy with an area under the curve (AUC) of 0.917 for PE-related outcomes and 0.919 for PE.

Placental growth factor and soluble, Fms-like tyrosine kinase-1 in preeclampsia: A case-cohort (PEARL) study

A. Fillion, P. Guerby, C. Lachance, M. Comeau, M. Bussières, F. Doucet-Gingras, et al.

J Obstet Gynaecol Can 2020 Vol. 42 Issue 10 Pages 1235-1242

Objective

Preeclampsia is associated with a higher maternal blood levels of soluble fms-like tyrosine kinase-1 (sFlt-1) and lower levels of placental growth factor (PlGF) that appear before clinical onset. We aimed to estimate the normal progression of these biomarkers in normal pregnancies and in those affected by preeclampsia.

Methods

We conducted a case-cohort study including low-risk nulliparous women recruited at 11-13 weeks gestation (cohort) and women with preeclampsia (cases). Maternal blood was collected at different points during pregnancy including at the time of diagnosis of preeclampsia for cases. Maternal serum PlGF and sFlt-1 concentrations and the sFlt-1/PlGF ratio were measured using B·R·A·H·M·S plus KRYPTOR automated assays and were compared between patients in both groups matched for gestational age. Cases were stratified as early- (≤34 weeks), intermediate- (35-37 weeks) and late-onset (>37 weeks) preeclampsia.

Results

The cohort consisted of 45 women whose results were compared with those of 31 women who developed preeclampsia, diagnosed at a median gestational age of 32 weeks (range 25-38 weeks). We observed that sFlt-1, PlGF and their ratio fluctuated during pregnancy in both groups, with a significant correlation with gestational age after 28 weeks ($P < 0.05$). We observed a significant difference between cases and controls, with a median ratio 100 times higher in early preeclampsia ($P < 0.001$), 13 times higher in intermediate preeclampsia ($P < 0.001$), but no significant difference between groups in late-onset preeclampsia with matched controls.

Conclusion

PlGF, sFlt-1, and their ratio may be useful in the prediction and diagnosis of early- and intermediate-onset preeclampsia but are not useful for late-onset preeclampsia.

Correlation of KRYPTOR and Elecsys® immunoassay sFlt-1/PlGF ratio on early diagnosis of preeclampsia and fetal growth restriction: A case-control study

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Pregnancy Hypertens 2020 Vol. 20 Pages 44-49

Objectives

The measurement of the soluble fms-like tyrosine kinase-1 to placental growth factor (sFlt-1/PlGF) ratio on automated platforms has improved the detection of preeclampsia and fetal growth restriction (PE/FGR). The cut-off points of >38 and ≥85 has been defined for “rule in” and “aid in diagnosis”, respectively, using the Elecsys® platform. We aimed to compare the performance of these cut-offs between the Elecsys® and KRYPTOR platforms at 24-28 weeks.

Study Design

Observational case-control study of singleton pregnancies at high risk for PE/FGR and sFlt-1/PlGF measurement at 24-28 weeks’ gestation: 21 cases (9 early PE/FGR with delivery <32 weeks) were 1:1 matched for body mass index and parity with 21 controls. Correlations of the sFlt-1, PlGF and sFlt-1/PlGF values and diagnostic accuracy of the >38 and ≥85 cutoffs for early and late PE/FGR using Elecsys® and KRYPTOR assays were evaluated.

Main Outcome Measures

PE/FGR cases showed significantly higher median (IQR) sFlt-1/PlGF values at 24-28 weeks vs. controls, using both Elecsys® and KRYPTOR platforms: 55 (13-254) and 97 (13-530) vs. 4.1 (2.0-6.5) and 3.9 (1.8-7.7), respectively. The sFlt-1/PlGF correlation between both methods was excellent (r(2) = 0.95) although lower PlGF and higher sFlt-1/PlGF values were observed with KRYPTOR. The higher diagnostic accuracy was obtained for early PE/FGR with the ≥85 cutoff (95.2%; 95%CI: 83.8-99.4%) in both platforms.

Conclusions

sFlt-1/PlGF measurements correlates well between Elecsys® and KRYPTOR platforms, and the cutoffs of >38 and ≥85 exhibit high diagnostic accuracy for assessing early PE/FGR at 24-28 weeks with both methods.

sFlt-1/PlGF ratio for prediction and diagnosis of pre-eclampsia

KRYPTOR publications Prognosis

KRYPTOR-automated angiogenic factor assays and risk of preeclampsia-related adverse outcomes

S. Salahuddin, J. Wenger, D. Zhang, R. Thadhani, S. Karumanchi and S. Rana

Hypertens Pregnancy 2016 Vol. 35 Issue 3 Pages 330-45

Objective

To evaluate KRYPTOR assays for circulating soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF) in risk assessment of adverse outcomes in women with suspected preeclampsia.

Methods

We studied 412 women carrying a singleton pregnancy from a previous study cohort who were evaluated for suspected preeclampsia. Another 434 nonpreeclamptic patients with plasma samples drawn throughout pregnancy were used to derive normative data. Plasma sFlt-1 and PlGF levels were measured on the automated KRYPTOR platform and evaluated for prediction of adverse maternal and perinatal outcomes within 2 weeks. Normative values were used to create a ratio of markers and these values were reported as multiples of median (MoM) for women with and without adverse outcomes. The KRYPTOR assay results were also compared with previously reported measurements obtained using the automated Elecsys platform.

Results

Among participants presenting at <34 weeks (N = 110), patients with subsequent adverse outcome had higher sFlt-1, lower PlGF, and higher sFlt-1/PlGF ratio compared with women without adverse outcomes: the median (25th, 75th centile) sFlt-1 (pg/ml), 9030 (3197, 12,140) versus 1976 (1248, 2937); PlGF (pg/ml), 36 (16, 111) versus 318 (108, 629); and ratio, 285.6 (32.2, 758.5) versus 6.1 (2.3, 20.3) (all $p < 0.0001$). Higher sFlt-1/PlGF ratio correlated negatively with timing of delivery ($r = -0.60$, $p < 0.001$) and the risk of adverse outcomes was markedly elevated among women in highest tertile compared with lower tertile (odds ratio, 14.77; 95% confidence interval (CI), 4.28-51.00). The addition of sFlt-1/PlGF ratio (≥85) to hypertension and proteinuria significantly improved the prediction for subsequent adverse outcomes (AUC 0.89 (95% CI): 0.82, 0.95) for hypertension, proteinuria, and sFlt-1/PlGF (AUC = 0.75 (0.65, 0.85)) for hypertension alone ($p = 0.002$). Compared with normative controls, women who were evaluated for preeclampsia without adverse outcomes had higher MoM for sFlt-1/PlGF ratio; these values were further elevated in women with adverse outcomes. sFlt-1/PlGF ratios measured on the KRYPTOR platform were highly correlated with measurements obtained using Elecys platform ($r = 0.97$, $p < 0.001$).

Conclusions

In women with suspected preeclampsia presenting prior to 34 weeks of gestation, KRYPTOR assays for circulating sFlt-1 and PlGF when used in conjunction with standard clinical evaluation performs well in the prediction of adverse maternal and perinatal outcomes occurring within 2 weeks of presentation.

Angiogenic factor estimation as a warning sign of preeclampsia-related peripartum morbidity among hospitalized patients

J. Lopes Perdigao, S. Chinthala, A. Mueller, R. Minhas, H. Ramadan, R. Nasim, et al.

Hypertension 2019 Vol. 73 Issue 4 Pages 868-877

Preeclampsia-related morbidity and mortality is rising predominantly because of delayed identification of patients at risk for preeclampsia with severe features and associated complications. This study explored the association between angiogenic markers (sFlt-1 [soluble fms-like tyrosine kinase-1]) and PlGF [placental growth factor]) and preeclampsia-related peripartum complications. Normotensive women or those with hypertensive disorders of pregnancy were enrolled. Blood samples were collected within 96 hours before delivery, and angiogenic markers were measured on an automated platform. Our study included 681 women, 375 of which had hypertensive disorders. Of these, 127 (33.9%) had severe preeclampsia, and 71.4% were black. Compared with normotensive women, women with severe preeclampsia had higher levels of sFlt-1 (9372.5 versus 2857.0 pg/mL; P<0.0001), lower PlGF (51.0 versus 212.0 pg/mL; P<0.0001), and a high sFlt-1/PlGF (212.0 versus 14.0; all P<0.0001). A similar trend in sFlt-1, PlGF, and sFlt-1/PlGF was found in those women with complications secondary to preeclampsia (all P<0.001). The highest tertile of sFlt-1/PlGF was strongly associated with severe preeclampsia in a multivariable analysis. Among patients with a hypertensive disorder of pregnancy, 340 (90.7%) developed postpartum hypertension, of which 50.4% had mild, and 40.3% had severe postpartum hypertension. The sFlt-1/PlGF ratio was significantly higher for severe and mild postpartum hypertension compared with women with normal postpartum blood pressures (73.5, 46.0, and 13.0, respectively; P values<0.0001). Furthermore, the highest tertile of antepartum sFlt-1/PlGF was associated with postpartum hypertension (P=0.004). This study demonstrates a significant association between an abnormal angiogenic profile before delivery and severe preeclampsia and peripartum complications.

Angiogenic marker prognostic models in pregnant women with hypertension

H. Perry, J. Binder, E. Kalafat, S. Jones, B. Thilaganathan and A. Khalil

Hypertension 2020 Vol. 75 Issue 3 Pages 755-761

Angiogenic markers such as PlGF (placental growth factor) and sFlt-1 (soluble Fms-like tyrosine kinase-1) have been shown to be useful for predicting adverse outcome in women suspected of having preeclampsia. The aim of the current study was to evaluate the prognostic value of angiogenic markers and maternal risk factors in pregnant women with hypertension. This was a prospective study of pregnancies complicated by preeclampsia, gestational hypertension, or chronic hypertension presenting to 1 of 2 tertiary referral hospitals between May 2013 and May 2018. Maternal characteristics along with blood samples for angiogenic marker analysis were obtained from participants. The primary outcome was delivery related to preeclampsia within 1 and 2 weeks. In total, 302 women with hypertension were included in the study cohort. The baseline model included maternal body mass index, mean arterial pressure, and clinical diagnosis at the time of assessment. The use of sFlt-1/PlGF ratio combined with the baseline model significantly improved the area under the curve values for predicting delivery within a week (0.83 versus 0.88; P=0.025) or in 2 weeks (0.86 versus 0.93; P=0.001) due to preeclampsia-related events in gestational ages <35 weeks. The magnitude of increase in accuracy was 7.9% (-0.5% to 16.4%, posterior probability of increase: 96.7%) for sFlt-1/PlGF ratio. Our results emphasize the additive value of angiogenic biomarkers and the superior performance of a continuous scale of sFlt-1/PlGF ratio in the model. The added utility of angiogenic markers diminishes after 35 weeks' gestation.

Evaluation of the prognostic value of the sFlt-1/PlGF ratio in early-onset preeclampsia

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Am J Perinatol 2021 Vol. 38 Issue S 01 Pages e292-e298

Objective

Increased expression of soluble fms-like tyrosine kinase 1 (sFlt-1), associated with a decrease in placental growth factor (PlGF), plays a key role in the pathogenesis of preeclampsia (PE). We evaluated the prognostic value of the sFlt-1/PlGF ratio for the onset of adverse maternofetal outcomes (AMFO) in case of early-onset PE with attempted expectant management.

Study Design

From October 2016 through November 2018, all singleton pregnancies complicated by early-onset PE (before 34 weeks of gestation) were included in a cohort study. The plasma levels of sFlt-1 and PlGF were blindly measured on admission. For the statistical analysis, we performed a bivariate analysis, a comparison of the receiving operating characteristic curves and a survival analysis estimated by the Kaplan-Meier method.

Results

Among 109 early PE, AMFO occurred in 87 pregnancies (79.8%), mainly hemolysis, elevated liver enzymes, and low platelet count syndrome and severe fetal heart rate abnormalities requiring urgent delivery. The area under the curve (AUC) of sFlt-1/PlGF ratio was 0.82 (95% confidence interval [CI]: 0.73-0.88) for the risk of AMFO and the difference between the AUCs was significant for each separate standard parameter ($p = 0.018$ for initial diastolic blood pressure, $p = 0.013$ for alanine aminotransferase, $p < 0.001$ for uric acid). Pregnancies were best classified by a cutoff ratio of 293, with a sensitivity of 95% and a specificity of 50%. With a ratio value less than 293, no pregnancy was complicated or had been stopped during the first 5 days. A ratio more than 293 was associated with an increased risk of AMFO onset (hazard ratio [HR]: 3.61; 95% CI: 2.13-6.10; $p < 0.001$) and had a significant association with the length of time between the diagnosis of PE and delivery (HR: 2.49; 95% CI: 1.56-3.96; $p < 0.001$).

Conclusions

The sFlt-1/PlGF ratio is an additional tool in the prediction of AMFO in proven early-onset PE, which is likely to improve care by anticipating severe complications.

KEY POINTS:

- The sFlt-1/PlGF ratio is associated with AMFO.
- It is an additional tool for physician.
- We proposed a 293 cutoff value for the ratio

The effect of comorbidities on the sFlt-1:PlGF ratio in preeclampsia

M. Tanner, D. de Guingand, M. Reddy, S. Rowson, D. Rolnik, M. Davey, et al.

Pregnancy Hypertens 2022 Vol. 29 Pages 98-100

Research indicates that soluble fms-like tyrosine kinase 1 (sFlt-1) and placental growth factor (PLGF) have diagnostic and prognostic significance for women with preeclampsia. However, sparse research has studied these biomarkers in women with preexisting comorbidities such as chronic hypertension, diabetes mellitus, systemic lupus erythematosus and chronic kidney disease. We undertook a prospective longitudinal cohort study to compare the sFlt-1: PlGF ratio between women with and without comorbidities who did and did not go on to develop preeclampsia. We found that women with comorbidities may develop preeclampsia with a milder elevation in sFlt-1: PlGF than do women without comorbidities. This has clinical and research implications.

Circulating angiogenic factor levels in hypertensive disorders of pregnancy

R. Thadhani, E. Lemoine, S. Rana, M. Costantine, V. Calsavara, K. Boggess, et al.

NEJM Evidence 2022 Vol. 1 Issue 12 Pages EVIDoa2200161

This study measured serum soluble fms-like tyrosine kinase 1 to placental growth factor values in pregnant women hospitalized with hypertension. In women with a hypertensive disorder of pregnancy presenting between 23 and 35 weeks' gestation, a soluble fms-like tyrosine kinase 1: placental growth factor ratio ≥40 provided stratification of the risk of progressing to severe preeclampsia within 2 weeks.

sFlt-1/PlGF ratio for prediction and diagnosis of pre-eclampsia

KRYPTOR publications Prediction

Prediction of preeclampsia with angiogenic biomarkers. Results from the prospective Odense child cohort

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Hypertens Pregnancy 2016 Vol. 35 Issue 3 Pages 405-19

Objective

We aimed to investigate how maternal serum soluble Fms-like kinase 1 (sFlt-1), placental growth factor (PlGF), and sFlt-1/PlGF ratio prospectively associate to preeclampsia (PE) and clinical subtypes.

Methods

In an unselected cohort of 1909 pregnant women, sFlt-1 and PlGF were measured with KRYPTOR assays in gestational weeks (GW) 8-14 and 20-34. Associations to PE were assessed by receiver operating characteristics and logistic regression.

Results

Concentrations of sFlt-1, PlGF, and sFlt-1/PlGF in GW20-34 were predictive of PE development, but not in GW8-14. PlGF outperformed sFlt-1/PlGF ratio with an area under curve (AUC) of 0.755 vs. 0.704, p = 0.002. The highest AUC values for PlGF and sFlt-1/PlGF ratio were seen for severe early-onset PE (0.901 and 0.883). Negative predictive values were high for all PE types, but positive predictive values were low.

Conclusions

PlGF and sFlt-1/PlGF had good predictive value for PE at GW20-34 in a population-based unselected cohort, however with low positive predictive value.

Midpregnancy testing for soluble fms-like tyrosine kinase 1 (sFlt-1) and placental growth factor (PlGF): An inter-assay comparison of three automated immunoassay platforms

C. Black, A. Al-Amin, D. Rolnik, S. Kane, C. Stolarek, A. White F. da Silva Costa and S. Brenneckea

Placenta 2019 Vol. 86 Pages 11-14

We performed an inter-assay comparison among three immunoassay platforms for midpregnancy testing of sFlt-1, PlGF and the sFlt-1/PlGF ratio, which are established markers for pre-eclampsia. Maternal blood was collected 19-22 weeks' gestation. Raw data values were converted to multiples of the median (MoM). PlGF and sFlt-1 values among platforms were highly correlated (< 0.001). There was significant variation in raw data values for PlGF and sFlt-1 among platforms, eliminated following conversion to MoM. When directly comparing raw data values among platforms, platform-specific reference ranges values should be used. MoM values were equivalent among platforms, allowing direct inter-assay result comparison.

Midpregnancy prediction of pre-eclampsia using serum biomarkers sFlt-1 and PlGF

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Pregnancy Hypertens 2019 Vol. 16 Pages 112-119

Objectives
Pre-eclampsia remains a significant cause of morbidity and mortality. Placental biomarkers soluble Fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF) have been investigated previously for their ability to predict pre-eclampsia. We compared the performance of these biomarkers for midpregnancy pre-eclampsia prediction using three different immunoassay platforms.

Study Design
Prospective study including singleton pregnancies 19-22 weeks' gestation. Maternal bloods were collected at recruitment. Screening performances using receiver operating characteristic (ROC) curves for PlGF and sFlt-1/PlGF ratio raw data and MoM values in isolation were evaluated for three immunoassay platforms using selected cut-off values.

Main Outcome Measures
Pre-eclampsia was defined as early-onset (<34 weeks' at delivery) and preterm (<37 weeks' at delivery).

Results
For prediction of preterm pre-eclampsia, PlGF MoM and sFlt-1/PlGF ratio MoM performed similarly, with areas under the curve (AUC), detection rates (DR) and false positive rates (FPR) for PlGF MoM and sFlt-1/PlGF ratio MoM being 0.77-0.79 and 0.71-0.74, 62.5% for both and 9.7-14.9 and 10.7-17.7, respectively. For the prediction of early-onset pre-eclampsia, sFlt-1/PlGF ratio raw data and MoM values performed similarly, with AUC, DR and FPR being 0.92-0.97 and 0.93-0.96, 100% for both, and 4.13-16.9 and 9.4-12.2, respectively.

Conclusions
For midpregnancy prediction of preterm pre-eclampsia, PlGF MoM for all three platforms and sFlt-1/PlGF ratio MoM for the two platforms that tested sFlt-1 performed similarly. For midpregnancy prediction of early-onset pre-eclampsia at midpregnancy, sFlt-1/PlGF ratio raw data and MoM values using the early-onset cut-off for the two platforms that tested sFlt-1 gave similar performance from a clinical perspective.

Longitudinal changes in placental biomarkers in women with early versus late placental dysfunction

M. Hendrix, K. Palm, S. Van Kuijk, O. Bekers, M. Spaanderman, J. Bons and S. Al-Nasiry

Hypertens Pregnancy 2019 Vol. 38 Issue 4 Pages 268-277

Objective

To evaluate longitudinal changes of angiogenic biomarkers in early- (EO-PD) versus late-onset (LO-PD) placental dysfunction.

Methods

Serum PlGF and sFlt-1 measured at different intervals in EO-PD (n= 43), LO-PD (n= 31) and controls (n = 133).

Results

sFlt-1/PlGF ratio was higher at 16 weeks (30.6 vs 17.5), 20 weeks (29.3 vs 8.9) and 30 weeks (16.6 vs 6.7) in EO-PD vs controls (all $p< 0.05$), but not in LO-PD. Longitudinal changes for all intervals had higher AUC than single measurements.

Conclusions

Longitudinal biomarker change between 12 and 30 weeks could improve prediction of EO-PD compared to single measurements.

The sFlt-1/PlGF ratio as a triage tool to identify superimposed preeclampsia in women with chronic hypertension in emergency rooms

J. Hernández-Pacheco, C. Rosales-Zamudio, H. Borboa-Olivares, A. Espejel-Núñez, S. Parra-Hernández, G. Estrada-Gutiérrez, et al.

Pregnancy Hypertens 2020 Vol. 21 Pages 38-42

Objectives
Assess the usefulness of the sFlt-1/PlGF ratio for the differential diagnosis of uncontrolled chronic hypertension vs. superimposed preeclampsia.

Study Design
We performed a cross-sectional study from 2015 to 2017 and 42 women with initial diagnosis of superimposed preeclampsia were enrolled in the emergency room. After a 12 week follow up patients were grouped as superimposed preeclampsia (Group A) and uncontrolled chronic hypertension (Group B) according to the American College of Obstetricians and Gynecologist criteria. A group of 33 healthy women paired by gestational age were included as controls (Group C). Maternal serum levels of sFlt-1 and PlGF were measured at enrollment, and the ratios of the groups were compared.

Main Outcome Measures
Superimposed preeclampsia vs. uncontrolled chronic hypertension.

Results
After follow-up, group distribution was 30 women in Group A, 12 women in Group B, and 25 women in Group C. The sFlt-1/PlGF ratio was higher in women with superimposed preeclampsia than in women with uncontrolled chronic hypertension (215.5 vs. 9.65, $p < 0.001$). The control group displayed lower ratio values (3.66, $p < 0.001$). The sFlt-1 concentration was higher in Group A than in Group B (7564 vs. 1281 pg/mL, $p < 0.001$) and the PlGF level was lower in Group A (34.39 vs. 169 pg/mL, $p < 0.001$).

Conclusions
The sFlt-1/PlGF ratio exhibits good performance for the differential diagnosis of superimposed preeclampsia vs. uncontrolled chronic hypertension.

Decision threshold for KRYPTOR sFlt-1/PlGF ratio in women with suspected preeclampsia: Retrospective study in a routine clinical setting

L. Andersen, A. Helt, L. Sperling and M. Overgaard

J Am Heart Assoc 2021 Vol. 10 Issue 17 Pages e021376

Background

The objective was to evaluate predictive performance and optimal decision threshold of the KRYPTOR soluble fms-like tyrosine kinase-1 (sFlt-1)/placental growth factor (PlGF) ratio when implemented for routine management of women presenting with symptoms of preeclampsia.

Methods and Results

Observational retrospective study of a cohort of 501 women with suspected preeclampsia after 20 weeks of gestation. Women referred to maternity ward for observation of preeclampsia had an sFlt-1/PlGF ratio test included in routine diagnostic workup. Maternal and offspring characteristic data included maternal risk factors, outcomes, delivery mode, and indication for suspected preeclampsia. Biochemical measurements to determine sFlt-1/PlGF ratio were performed using the B·R·A·H·M·S KRYPTOR sFlt-1/PlGF ratio immunoassays. Results were analyzed by area under receiver-operating characteristic curve. Preeclampsia occurred in 150 of 501 (30%) of symptomatic women with an sFlt-1/PlGF ratio determined before the time of diagnosis. Area under receiver-operating characteristic curve for diagnosis of early-onset preeclampsia within 1 and 4 weeks was 0.98 (95% CI, 0.96-1.00) and 0.95 (95% CI, 0.92-0.98), respectively. For late-onset preeclampsia, predictive performance within 1 and 4 weeks was lower: 0.90 (95% CI, 0.85-0.94) and 0.85 (95% CI, 0.80-0.90), respectively. The optimal single sFlt-1/PlGF ratio threshold for all preeclampsia and late-onset preeclampsia within 1 and 4 weeks was 66. The negative and positive predictive values for ruling out and ruling in developing preeclampsia within 1 week were 96% and 70%, respectively.

Conclusions

The KRYPTOR sFlt-1/PlGF ratio is a useful clinical tool ruling out and in preeclampsia within 1 week. Prediction within 4 weeks is superior for early-onset preeclampsia. A single decision threshold of 66 is indicated for use in clinical routine.

Value of soluble fms-like tyrosine kinase-1/placental growth factor test in third trimester of pregnancy for predicting preeclampsia in asymptomatic women

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J Perinat Med 2022

Objectives

To estimate the value of screening maternal serum soluble fms-like tyrosine kinase/placental growth factor (sFlt-1/PlGF) ratio in asymptomatic women during 3rd trimester to predict preeclampsia (PE) development.

Methods

The investigated group comprised of 178 pregnant women. During this gestation, 24 cases had developed PE and 12 isolated gestational hypertension (GH); whereas 142 remained normotensive. Blood samples were collected between 180 and 259 gestational days (g.d.) when the participants were asymptomatic. Serums were analyzed using the B·R·A·H·M·S sFlt-1 KRYPTOR PlGF plus KRYPTOR PE ratio test (Thermo Fisher Scientific, Henningdorf, Germany). High-risk pregnancies for the PE development were defined as sFlt-1/PlGF>38.

Results

The detection rate (DR) for manifestation of PE≤30 days after sampling was 83.3% and overall DR during pregnancy 58.3%. Ten of 15 women having false positive prediction of PE suffered from GH, preterm birth and/or delivery of a small-for-gestational-age-newborn. False positive rate was significantly higher at 239-253 g.d. compared to sampling at 210-224 g.d. and 225-238 g.d. (21.9% vs. 7.8% and 5.3%; $p < 0.05$).

Conclusions

The sFlt-1/PlGF test during 180-259 g.d. detected approximately half of subsequent PE cases. An optimal time to use the test for screening purposes was estimated 225-238 g.d. (DR 66.7%). False positive test results were more common to cases with other adverse pregnancy outcomes and samples drawn at higher gestational age.

Comparison of circulating total sFlt-1 to placental-specific sFlt-1 e15a in women with suspected preeclampsia

S. Rowson, M. Reddy, D. De Guingand, A. Langston-Cox, S. Marshall, F. da Silva Costa and K. Palmer

Placenta 2022 Vol. 120 Pages 73-78

Introduction

Soluble fms-like tyrosine kinase 1 (sFlt-1), a circulating anti-angiogenic factor that binds and antagonizes placental growth factor (PlGF), appears key to preeclamptic pathophysiology. Two main sFlt-1 splice variants exist: sFlt-1 e15a and sFlt-1 i13. Total sFlt-1/PlGF ratios are increasingly used clinically; we explore whether using placental-specific sFlt-1 e15a improves test performance compared with total sFlt-1 in preeclampsia diagnosis.

Methods

Consent was obtained for serum sampling from 96 women with suspected preeclampsia. Total sFlt-1 and PlGF were quantified using the B·R·A·H·M·S KRYPTOR Compact Plus automated immunoassay platform, and sFlt-1 e15a by custom enzyme-linked immunosorbent assay. Test performance was then assessed by subsequent diagnosis.

Results

Of 96 participants, 32 did not develop preeclampsia, 32 had early-onset (<34 weeks') disease and 32 had late-onset (≥34 weeks') disease. In those with preeclampsia, median sFlt-1 and sFlt-1 e15a were significantly increased (7361.0 vs 2463.0 pg/mL, and 946.6 vs 305.4 ng/mL respectively; $p < 0.001$ for both), and PlGF significantly reduced (43.5 vs 154.4 pg/mL; $p < 0.001$) compared to those without preeclampsia. Those with early-onset, compared to late-onset, preeclampsia chiefly had lower median PlGF levels (16.0 vs 57.3; $p < 0.001$), which contributed to higher sFlt-1/PlGF and sFlt-1 e15a/PlGF ratios (830.1 vs 86.7, and 109258.9 vs 12608.7 respectively; $p < 0.001$ for both).

Discussion

sFlt-1 e15a performs comparably to total sFlt-1 in women with suspected preeclampsia, however with higher translational burden. Our results support the expanding clinical use of the sFlt-1/PlGF ratio in suspected preeclampsia, particularly early-onset, to assist with disease diagnosis.

sFlt-1/PlGF ratio for prediction and diagnosis of pre-eclampsia

KRYPTOR publications
Other indications

Predictive value of sFlt-1, PlGF, sFlt-1/PlGF ratio and PAPP-A for late-onset preeclampsia and IUGR between 32 and 37 weeks of pregnancy

C. Birdir, L. Droste, L. Fox, M. Frank, J. Fryze, A. Enekwe, A. Köninger, R. Kimmig, B. Schmidt and A. Gellhaus

Pregnancy Hypertens 2018 Vol. 12 Pages 124-128

Objectives

The aim of this study was to investigate, whether maternal serum levels of sFlt-1, PlGF and PAPP-A at third trimester of pregnancy are associated with late-onset PE and intrauterine growth retardation (IUGR) after 34 weeks of pregnancy.

Methods

This was a prospective study measuring the maternal serum levels of soluble tyrosine kinase-1 (sFlt-1), placental growth factor (PlGF) and pregnancy-associated plasma protein-A (PAPP-A) at 32-37 weeks of pregnancy: 730 patients were enrolled and 676 had neither intrauterine growth restriction (IUGR) nor preeclampsia (PE) or pregnancy induced hypertension (PIH) throughout the pregnancy. 22 patients developed IUGR, 32 PE and 24 PIH.

Results

Linear regression analyses after adjusting for maternal age, gestational age at the blood sampling and maternal BMI showed associations between PE and serum sFlt-1 levels (Exp(ß) = 3.29; 95% CI: 2.69-4.04), serum PlGF levels (Exp(ß) = 0.18; 95% CI: 0.13-0.24), sFlt-1/PlGF ratio (Exp(ß) = 15.59; 95% CI: 10.64-22.84) and serum PAPP-A (Exp(ß) = 1.48; 95% CI 1.15-1.89). sFlt-1, PlGF and sFlt-1/PlGF-Ratio showed comparable area under the curve (AUC) estimates with a predictive ability to discriminate pregnancies developing PE and IUGR from controls. The predictive ability of PAPP-A for PE was only slightly better than chance.

Conclusions

This study supported the ability of a single measurement of sFlt-1/PlGF ratio at third trimester to predict PE and IUGR occurring after 34 weeks of pregnancy. However, larger multicentre studies are needed to replicate our results.

Intrauterine growth restriction, soluble fms-like tyrosine kinase-1 to placental growth factor ratio increase and preeclampsia

H. Boulanger, D. Drouin, C. Largilliere and G. Lefèvre.

J Gynecol Obstet Hum Reprod 2019 Vol. 48 Issue 8 Pages 695-697

Background

Intrauterine growth restriction (IUGR) and preeclampsia (PE) share common features such as ischemic placental disease but also differ in their clinical expression regarding maternal diseases. The reason why IUGRremains isolated in some cases yet is followed by clinical manifestations of PE in other cases remains unexplained.

Case Report

A 40-year old woman, gravida two, para one, experienced early-onset IUGR with a significant increase in the ratio of soluble fms-like tyrosine kinase 1 (sFlt-1) to placental growth factor (PlGF) but, surprisingly, without any maternal clinical manifestations of PE.

Conclusions

IUGR and a significant increase in sFlt-1/PlGF ratio without PE raise the issue of a missing factor enabling IUGR, a significant increase in sFlt-1/PlGF ratio, and PE to be linked.

Teaching Points

(1) Early-onset IUGR and a significant increase in sFlt-1/PlGF ratio do not necessarily mean the onset of PE. (2) Combining early-onset IUGR and a significant increase in sFlt-1/PlGF ratio without PE raises the question of an additional factor responsible for the onset of PE.

Course of the sFlt-1/PlGF ratio in fetal growth restriction and correlation with biometric measurements, feto-maternal doppler parameters and time to delivery

A. Andrikos, D. Andrikos, B. Schmidt, C. Birdir, R. Kimmig, A. Gellhaus and A. Köninger

Arch Gynecol Obstet 2022 Vol. 305 Issue 3 Pages 597-605

Purpose

The study aimed to assess the course of the soluble Fms-like tyrosine kinase 1 (sFlt-1)/placental growth factor (PlGF) ratio in pregnant women with fetal growth restriction (FGR) and to evaluate potential associations between the sFlt-1/PlGF ratio and feto-maternal Doppler parameters, fetal biometric measurements and the time between study inclusion and birth ("time to delivery").

Methods

This was a retrospective longitudinal single center study including 52 FGR cases. The serum levels of sFlt-1 and PlGF were measured by using the B·R·A·H·M·S KRYPTOR Compact PLUS. Fetal biometric and Doppler parameters, as well as the sFlt-1/PlGF ratio, were obtained both upon study inclusion and upon birth.

Results

Various associations between the levels of the biomarkers in maternal blood upon study inclusion and upon birth and sonographic parameters were observed in FGR cases: umbilical artery ($p < 0.01$), uterine arteries ($p < 0.01$), ductus venosus ($p < 0.05$), cerebroplacental ratio (CPR) ($p < 0.01$), femur length ($p < 0.01$) and birth weight ($p < 0.01$). The higher the sFlt-1/PlGF ratio upon study inclusion, the shorter the "time to delivery" ($p < 0.01$). The multivariate regression analysis showed that the greater the daily percentage increase of the angiogenic markers, the shorter the "time to delivery" ($p < 0.01$).

Conclusions

The fetal well-being, as measured by feto-maternal Doppler parameters such as CPR and the severity of the placental dysfunction, as measured by the urgency of birth and birth weight, is reflected by the level of the sFlt-1/PlGF ratio in the maternal serum. A rapid daily increase of the sFlt-1/PlGF ratio is significantly associated with the clinical progression of the disease.

Placental biomarkers and fetoplacental dopplers in combination reliably predict preterm birth in pregnancies complicated by fetal growth restriction

J. Hong, K. Crawford, E. Cavanagh, F. da Silva Costa and S. Kumar

Ultrasound Obstet Gynecol 2023

Objective

To assess the association between placental biomarkers (placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1)/PlGF ratio) and fetoplacental Dopplers - Umbilical Artery Pulsatility Index (UA PI) and Uterine Artery Pulsatility Index (UtA PI) in various combinations for the likelihood of preterm birth (PTB) in women with fetal growth restriction (FGR).

Methods

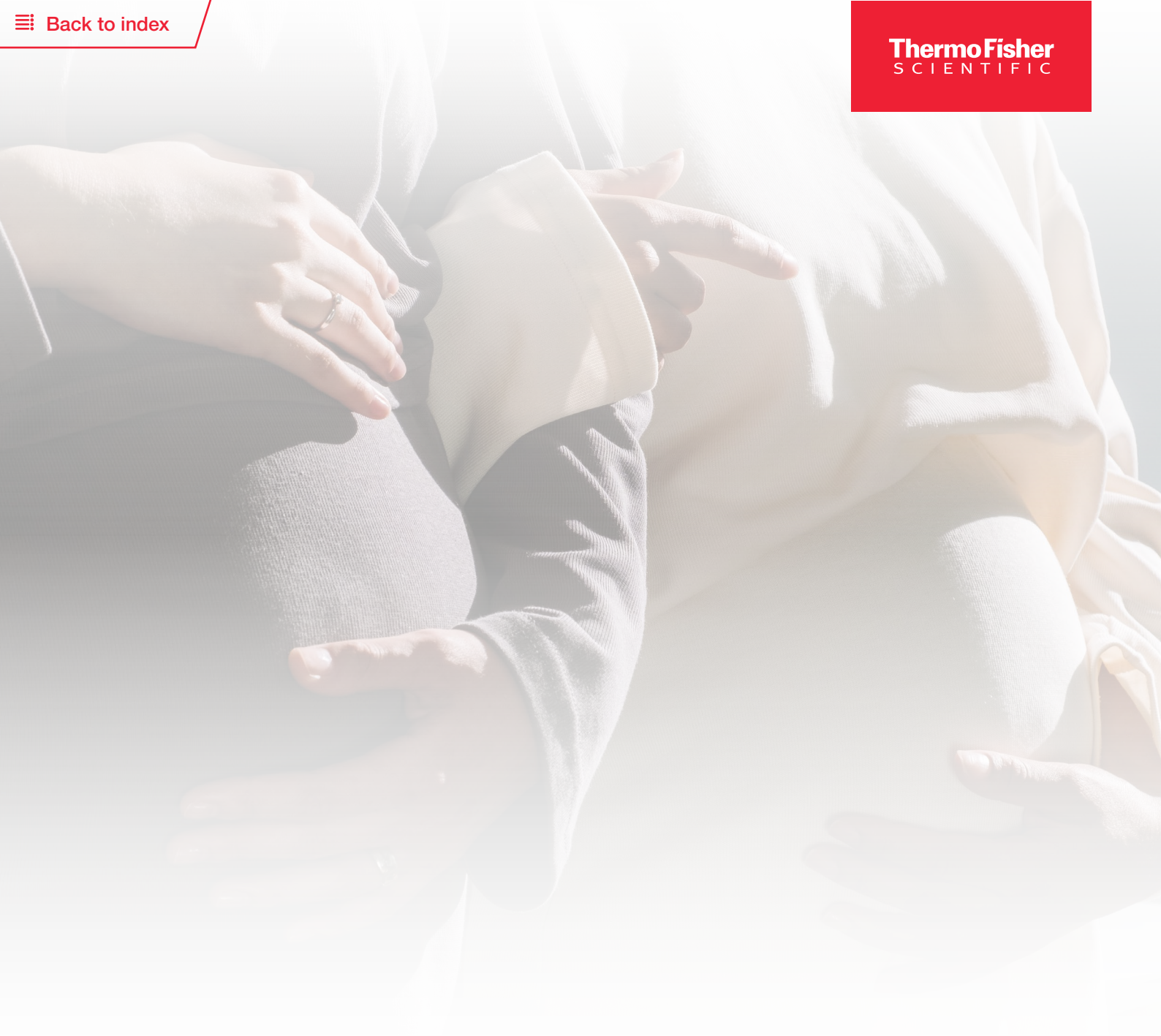
A prospective cohort study of pregnancies complicated by FGR. Maternal serum PlGF levels, sFlt-1/PlGF ratio, UA PI and UtA PI were measured at 4-weekly intervals from recruitment to delivery. Harrell's concordance statistic was used to evaluate various combinations of placental biomarkers and fetoplacental Dopplers to ascertain the ideal combination to predict PTB (<37 weeks). Multivariable Cox regression was used as time-varying covariates.

Results

There were 320 pregnancies in the study cohort - 179 (55.9%) were FGR and 141 (44.1%) were AGA. In the FGR cohort, both low PlGF levels and elevated sFlt-1/PlGF ratio significantly affected time to PTB. Low PlGF was a better predictor of PTB than either sFlt-1/PlGF ratio or combination of PlGF and sFlt-1/PlGF ratio (Harrell's C 0.81, 0.79, 0.75 respectively). Similarly, although both UA PI and UtA PI >95(th) centile for gestation significantly affected the time to PTB, in combination, they were better predictors than either measure alone (Harrell's C 0.82, 0.75, 0.76 respectively). The predictive utility was highest when PlGF <100ng/L, UA PI and UtA PI >95(th) centile was combined (Harrell's C 0.88) (HR 32.99 95% CI 10.74, 101.32).

Conclusions

Low maternal PlGF levels (<100ng/L) and abnormal fetoplacental Dopplers (UA PI and UtA PI >95(th) centile) in combination have greatest predictive utility for PTB in pregnancies complicated with FGR and may help guide clinical management of these complex pregnancies.



Health economics

Health economics

Asia

Economic evaluation of the sFlt-1/PlGF ratio for the short-term prediction of preeclampsia in a Japanese cohort of the PROGNOSIS Asia study

A. Ohkuchi, H. Masuyama, T. Yamamoto, T. Kikuchi, N. Taguchi, C. Wolf and S. Saito

Hypertens Res 2021 Vol. 44 Issue 7 Pages 822-829

The PRediction of short-term Outcomes in preGNant wOmen with Suspected preeclampsIa Study (PROGNOSIS) Asia validated the use of the soluble fms-like tyrosine 1/placental growth factor (sFlt-1/PlGF) ratio cutoff value of ≤38 to rule out the occurrence of preeclampsia in the short term in Asian women. We assessed the economic impact of the introduction of the sFlt-1/PlGF ratio test for predicting preeclampsia in Japan using data from the Japanese cohort of PROGNOSIS Asia. The cost analysis was developed with estimates in either a no-test scenario, with clinical decisions based on standard diagnostic procedures alone, or a test scenario, in which the sFlt-1/PlGF ratio test was used in addition to standard diagnostic procedures. For both scenarios, rates of hospitalization and other test characteristics were obtained from the results for the Japanese cohort in PROGNOSIS Asia. The total cost per patient was the main outcome of this cost analysis model. Introduction of the sFlt-1/PlGF ratio test using a cutoff value of 38 resulted in a reduced hospitalization rate compared with the rate in the no-test scenario (14.4% versus 8.7%). The reduction in the rate of hospitalizations led to an estimated 16 373 JPY reduction in healthcare costs per patient. The sFlt-1/PlGF ratio test is likely to reduce the unnecessary hospitalization of women at low risk of developing preeclampsia in the short term while also identifying high-risk individuals requiring appropriate management. Reducing unnecessary hospitalizations would result in significant cost savings in the Japanese healthcare system.

Health economics

Canada

Placental Growth Factor (PlGF) – Based biomarker testing to help diagnose pre-eclampsia in people with suspected pre-eclampsia: A health technology assessment

K. McMartin, M. Wang, J. Antony, C. Holubowich, H. Higgins et al.

ONTARIO HEALTH TECHNOLOGY ASSESSMENT SERIES, 2023

What Is This Health Technology Assessment About?

Pre-eclampsia is a potentially serious condition that affects up to 1 in 20 pregnant people, most often after 20 weeks of pregnancy. Diagnosing pre-eclampsia can be difficult because symptoms and signs differ from person to person. Assessment begins during routine pregnancy appointments, when blood pressure is measured and risk factors for pre-eclampsia are checked. Blood tests have been developed to measure placental growth factor (PlGF), a protein that indicates the function of the placenta. The tests are used along with standard clinical assessment.

This health technology assessment looked at how effective and cost-effective PlGF-based biomarker testing is to help diagnose pre-eclampsia. It also looked at the budget impact of publicly funding PlGF-based biomarker testing and at the experiences, preferences, and values of people with confirmed or suspected pre-eclampsia.

What Did This Health Technology Assessment Find?

Compared with standard clinical assessment alone, PlGF-based biomarker testing likely improves prediction of pre-eclampsia in people who are between 20 weeks and 36 weeks plus 6 days' gestation. It also may reduce time to diagnosis, severe adverse maternal outcomes, and length of stay in the neonatal intensive care unit, although the evidence is uncertain. PlGF-based biomarker testing may result in little to no difference in other clinical outcomes such as maternal admission to hospital and perinatal adverse outcomes.

We could not determine the cost-effectiveness of PlGF-based biomarker testing given uncertain evidence around important clinical outcomes. We estimate that publicly funding PlGF-based biomarker testing for people with suspected pre-eclampsia in Ontario over the next 5 years would cost an additional $1.83 million.

The people we spoke with valued PlGF-based biomarker testing to help diagnose pre-eclampsia. They felt that patient education and equitable access should be requirements for implementation, particularly in rural and underserved areas.

Health economics

Europe

sFlt-1/PlGF ratio test for pre-eclampsia: an economic assessment for the UK

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Ultrasound Obstet Gynecol 2016 Vol. 48 Issue 6 Pages 765-771

Objectives

To assess the economic impact of introducing into clinical practice in the UK the soluble fms-like tyrosine kinase (sFlt-1) to placental growth factor (PlGF) ratio test for guiding the management of pre-eclampsia.

Methods

We used an economic model estimating the incremental value of information, from a UK National Health Service payer's perspective, generated by the sFlt-1/PlGF ratio test, compared with current diagnostic procedures, in guiding the management of women with suspected pre-eclampsia. The economic model estimated costs associated with the diagnosis and management of pre-eclampsia in pregnant women between 24 + 0 and 36 + 6 weeks' gestation, managed in either a 'test' scenario in which the sFlt-1/PlGF test is used in addition to current diagnostic procedures, or a 'no-test' scenario in which clinical decisions are based on current diagnostic procedures alone. Test characteristics and resource use were derived from PROGNOSIS, a non-interventional study in women presenting with clinical suspicion of pre-eclampsia. The main outcome measure from the economic model was the cost per patient per episode of care, from first suspicion of pre-eclampsia to birth.

Results

Introduction of the sFlt-1/PlGF ratio test into clinical practice is expected to result in cost savings of £344 per patient compared with a no-test scenario. Savings are generated primarily through an improvement in diagnostic accuracy and subsequent reduction in unnecessary hospitalization.

Conclusions

Introducing the sFlt-1/PlGF ratio test into clinical practice in the UK was shown to be cost-saving by reducing unnecessary hospitalization of women at low risk of developing pre-eclampsia. In addition, the test ensures that those women at higher risk are identified and managed appropriately.

Budget impact analysis of sFlt-1/PlGF ratio as prediction test in Italian women with suspected preeclampsia

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J Matern Fetal Neonatal Med 2017 Vol. 30 Issue 18 Pages 2166-2173

Introduction

Preeclampsia (PE) is a pregnancy disease which represents a leading cause of maternal and perinatal mortality and morbidity. Accurate prediction of PE risk could provide an increase in health benefits and better patient management.

Objectives

To estimate the economic impact of introducing Elecsys sFlt-1/PlGF ratio test, in addition to standard practice, for the prediction of PE in women with suspected PE in the Italian National Health Service (INHS).

Methods

A decision tree model has been developed to simulate the progression of a cohort of pregnant women from the first presentation of clinical suspicion of PE in the second and third trimesters until delivery. The model provides an estimation of the financial impact of introducing sFlt-1/PlGF versus standard practice. Clinical inputs have been derived from PROGNOSIS study and from literature review, and validated by National Clinical Experts. Resources and unit costs have been obtained from Italian-specific sources.

Results

Healthcare costs associated with the management of a pregnant woman with clinical suspicion of PE equal €2384 when following standard practice versus €1714 using sFlt-1/PlGF ratio test.

Conclusions

Introduction of sFlt-1/PlGF into hospital practice is cost-saving. Savings are generated primarily through improvement in diagnostic accuracy and reduction in unnecessary hospitalization for women before PE's onset.

Economic assessment of the use of the sFlt-1/PlGF ratio test to predict preeclampsia in Germany

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BMC Health Serv Res 2018 Vol. 18 Issue 1 Pages 603

Background

The PRediction of short-term Outcome in preGNant wOmen with Suspected preeclampsIa Study (PROGNOSIS) demonstrated that a soluble fms-like tyrosine kinase 1/placental growth factor (sFlt-1/PlGF) ratio ≤ 38 ruled out the occurrence of preeclampsia in the next week with a negative predictive value of 99.3%; a ratio > 38 indicates an increased risk of developing preeclampsia in the next 4 weeks. We performed an assessment of the economic impact of the sFlt-1/PlGF ratio test for short-term prediction of preeclampsia in Germany.

Methods

We adapted a cost-effectiveness model, which had been developed to estimate the incremental value of adding the sFlt-1/PlGF ratio test with a cut-off ratio of 38 to standard diagnostic procedures for guiding the management of women with suspected preeclampsia in the UK. We used the adapted model to estimate the incremental value of the sFlt-1/PlGF ratio test (cut-off 38) for guiding the management of women with suspected preeclampsia from a German Diagnosis-Related Group (DRG) payer perspective. The economic model estimated costs associated with diagnosis and management of preeclampsia in women managed in either a 'no-test' scenario in which clinical decisions are based on standard diagnostic procedures alone, or a 'test' scenario in which the sFlt-1/PlGF test is used in addition to standard diagnostic procedures. Test characteristics and rates of hospitalization were derived from patient-level data from PROGNOSIS. The main outcome measure from the economic model was the total cost per patient.

Results

In the model adapted to the German DRG payer system, introduction of the sFlt-1/PlGF ratio test with a cut-off value of 38 could reduce the proportion of women hospitalized in Germany from 44.6 to 24.0%, resulting in an expected cost saving of €361 per patient.

Conclusions

The sFlt-1/PlGF ratio test is likely to reduce unnecessary hospitalization of women with a low risk of developing preeclampsia, and identify those at high risk to ensure appropriate management. Even within the restrictions of the DRG system in Germany, this results in substantial cost savings for women with suspected preeclampsia.

Placental growth factor testing for suspected pre-eclampsia: A cost-effectiveness analysis

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BJOG 2019 Vol. 126 Issue 11 Pages 1390-1398

Objective
To calculate the cost-effectiveness of implementing PlGF testing alongside a clinical management algorithm in maternity services in the UK, compared with current standard care.

Design
Cost-effectiveness analysis.

Setting
Eleven maternity units participating in the PARROT stepped-wedge cluster-randomised controlled trial.

Population
Women presenting with suspected pre-eclampsia between 20(+0) and 36(+6) weeks' gestation.

Methods
Monte Carlo simulation utilising resource use data and maternal adverse outcomes.

Main Outcome Measures
Cost per maternal adverse outcome prevented.

Results
Clinical care with PlGF testing costs less than current standard practice and resulted in fewer maternal adverse outcomes. There is a total cost-saving of UK£149 per patient tested, when including the cost of the test. This represents a potential cost-saving of UK£2,891,196 each year across the NHS in England.

Conclusions
Clinical care with PlGF testing is associated with the potential for cost-savings per participant tested when compared with current practice via a reduction in outpatient attendances, and improves maternal outcomes. This economic analysis supports a role for implementation of PlGF testing in antenatal services for the assessment of women with suspected pre-eclampsia.

Tweetable Abstract
Placental growth factor testing for suspected pre-eclampsia is cost-saving and improves maternal outcomes.

sFlt-1/PlGF ratio as a predictive marker in women with suspected preeclampsia: An economic evaluation from a Swiss perspective

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Dis Markers 2019 Vol. 2019 Pages 4096847

In Switzerland, 2.3% of pregnant women develop preeclampsia. Quantification of the soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF) ratio has shown a diagnostic value in the second and third trimesters of pregnancy, in particular in ruling out preeclampsia within one week. We estimated the economic impact of implementing sFlt-1/PlGF ratio evaluation, in addition to the standard of care (SOC), for women with suspected preeclampsia from a Swiss healthcare system's perspective. A decision tree model was developed to estimate direct medical costs of diagnosis and management of a simulated cohort of Swiss pregnant women with suspected preeclampsia (median week of gestation: 32) until delivery. The model compared SOC vs. SOC plus sFlt-1/PlGF ratio, using clinical inputs from a large multicenter study (PROGNOSIS). Resource use data and unit costs were obtained from hospital records and public sources. The assumed cost for sFlt-1/PlGF evaluation was €141. Input parameters were validated by clinical experts in Switzerland. The model utilized a simulated cohort of 6084 pregnant women with suspected preeclampsia (representing 7% of all births in Switzerland in 2015, n = 86,919). In a SOC scenario, 36% of women were hospitalized, of whom 27% developed preeclampsia and remained hospitalized until birth. In a sFlt-1/PlGF test scenario, 76% of women had a sFlt-1/PlGF ratio of ≤38 (2% hospitalized), 11% had a sFlt-1/PlGF ratio of >38-<85 (55% hospitalized), and 13% had a sFlt-1/PlGF ratio of ≥85 (65% hospitalized). Total average costs/pregnant woman (including birth) were €10,925 vs. €10,579 (sFlt-1/PlGF), and total costs were €66,469,362 vs. €64,363,060 (sFlt-1/PlGF). Implementation of sFlt-1/PlGF evaluation would potentially achieve annual savings of €2,105,064 (€346/patient), mainly due to reduction in unnecessary hospitalization. sFlt-1/PlGF evaluation appears economically promising in predicting short-term absence of preeclampsia in Swiss practice. Improved diagnostic accuracy and reduction in unnecessary hospitalization could lead to significant cost savings in the Swiss healthcare system.

Diagnostic utility of angiogenic biomarkers in pregnant women with suspected preeclampsia: A health economics review

D. Schlembach, M. Hund, C. Wolf and M. Vatish

Pregnancy Hypertens 2019 Vol. 17 Pages 28-35

Preeclampsia is a major cause of morbidity and mortality, can be difficult to diagnose, and is associated with significant healthcare costs. The prediction, diagnosis and prognosis of preeclampsia have depended on repeated assessment of women with known risk factors, including intensive monitoring and hospitalization. Many of these women may never go on to develop preeclampsia. Recent developments in the pathogenesis of preeclampsia have shown that maternal serum biomarkers can be used to predict preeclampsia. When the ratio of the anti-angiogenic soluble fms-like tyrosine kinase-1 (sFlt-1) and the pro-angiogenic placental growth factor from the placenta is altered, preeclampsia becomes more likely, providing a diagnostic measurement for risk. The use of angiogenic biomarkers in addition to standard clinical tests can more accurately predict which women are at risk of developing preeclampsia and which are at low or moderate risk, which is likely to streamline the management of pregnant women and target resources in a more efficient way. The studies reviewed here all demonstrate cost savings from use of angiogenic biomarker tests as an addition to standard care.

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

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Norwegian Institute of Public Health, 2023

Two to eight percent of pregnant women are diagnosed with preeclampsia worldwide. Preeclampsia is a potentially lifethreatening 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.

Enhancing the value of the sFlt-1/PlGF ratio for the prediction of preeclampsia: Cost analysis from the Belgian healthcare payers' perspective

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Pregnancy Hypertens 2021 Vol. 26 Pages 31-37

Objective

To evaluate the economic impact of introducing the soluble fms-like tyrosine kinase (sFlt-1) to placental growth factor (PlGF) ratio test into clinical practice in Belgium for the prediction of preeclampsia (PE).

Study Design

We developed a one-year time-horizon decision tree model to evaluate the short-term costs associated with the introduction of the sFlt-1/PlGF test for guiding the management of women with suspected PE from the Belgian public healthcare payers' perspective. The model estimated the costs associated with the diagnosis and management of PE in pregnant women managed in either a test scenario, in which the sFlt-1/PlGF test is used in addition to current clinical practice, or a no test scenario, in which clinical decisions are based on current practice alone. Test characteristics were derived from PROGNOSIS, a non-interventional study in women presenting with clinical suspicion of PE. Unit costs were obtained from Belgian-specific sources. The main model outcome was the total cost per patient.

Results

Introduction of the sFlt-1/PlGF ratio test is expected to result in a cost saving of €712 per patient compared with the no test scenario. These savings are generated mainly due to a reduction in unnecessary hospitalizations.

Conclusions

The sFlt-1/PlGF test is projected to result in substantial cost savings for the Belgian public healthcare payers through reduction of unnecessary hospitalization of women with clinical suspicion of PE that ultimately do not develop the condition. The test also has the potential to ensure that women at high risk of developing PE are identified and appropriately managed.

sFlt-1/PlGF ratio for prediction of preeclampsia in clinical routine: A pragmatic real-world analysis of healthcare resource utilisation

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PLoS One 2022 Vol. 17 Issue 2 Pages e0263443

Background

We investigated the impact of the soluble fms-like tyrosine kinase 1 (sFlt-1)/placental growth factor (PlGF) ratio to predict short-term risk of preeclampsia on clinical utility and healthcare resource utilisation using real-world data (RWD), and compared findings with health economic modelling from previous studies.

Methods and Findings

This retrospective analysis compared data from the German population of a multicentre clinical study (PROGNOSIS, n = 203; sFlt-1/PlGF ratio blinded and unavailable for decision-making) with RWD from University Hospital Leipzig, Germany (n = 281; sFlt-1/PlGF ratio used to guide clinical decision-making). A subgroup of the RWD cohort with the same inclusion criteria as the PROGNOSIS trial (RWD prediction only, n = 99) was also included. sFlt-1/PlGF ratio was measured using fully automated Elecsys® sFlt-1 and PlGF immunoassays (cobas e analyser; Roche Diagnostics). A similar proportion of women in the RWD and PROGNOSIS cohorts experienced preeclampsia (14.95% vs. 13.79%; p = 0.7938); a smaller proportion of women in the RWD prediction only cohort experienced preeclampsia versus PROGNOSIS (6.06%; p = 0.0526). In women with preeclampsia, median gestational age at delivery (weeks) was comparable in the RWD and PROGNOSIS cohorts (34.0 vs. 34.3, p = 0.5895), but significantly reduced in the RWD prediction only cohort versus PROGNOSIS (27.1, p = 0.0038). sFlt-1/PlGF ratio at baseline visit was not statistically significantly different for the RWD and PROGNOSIS cohorts, irrespective of preeclampsia outcome. Hospitalisations for confirmed preeclampsia were significantly shorter in the RWD cohort versus PROGNOSIS (median 1 vs. 4 days, p = 0.0093); there was no significant difference between RWD prediction only and PROGNOSIS (3 days, p = 0.9638). All-cause hospitalisations were significantly shorter in the RWD (median 1 day; p<0.0001) and RWD prediction only (1 day; p<0.0001) cohorts versus PROGNOSIS (3 days).

Conclusions

This study supports the findings of previous studies, showing that routine clinical use of the sFlt-1/PlGF ratio may result in shorter duration of hospitalisations, with potential economic benefits.

Clinical value and cost analysis of the sFlt-1/PlGF ratio in addition to the spot urine protein/creatinine ratio in women with suspected pre-eclampsia: PREPARE cohort study

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BMC Pregnancy Childbirth 2022 Vol. 22 Issue 1 Pages 910

Background

This study investigated the clinical value of adding the sFlt-1/PlGF ratio to the spot urine protein/creatinine ratio (PCr) in women with suspected pre-eclampsia.

Methods

This was a prospective cohort study performed in a tertiary referral centre. Based on the combination of PCr (<30) and sFlt-1/PlGF (≤38) results, four groups were described: a double negative result, group A-/-; a negative PCr and positive sFlt-1/PlGF, group B-/+; a positive PCr and negative sFlt-1/PlGF, group C+/-; and a double positive result, group D+/+. The primary outcome was the proportion of false negatives of the combined tests in comparison with PCr alone in the first week after baseline. Secondary, a cost analysis comparing the costs and savings of adding the sFlt-1/PlGF ratio was performed for different follow-up scenarios.

Results

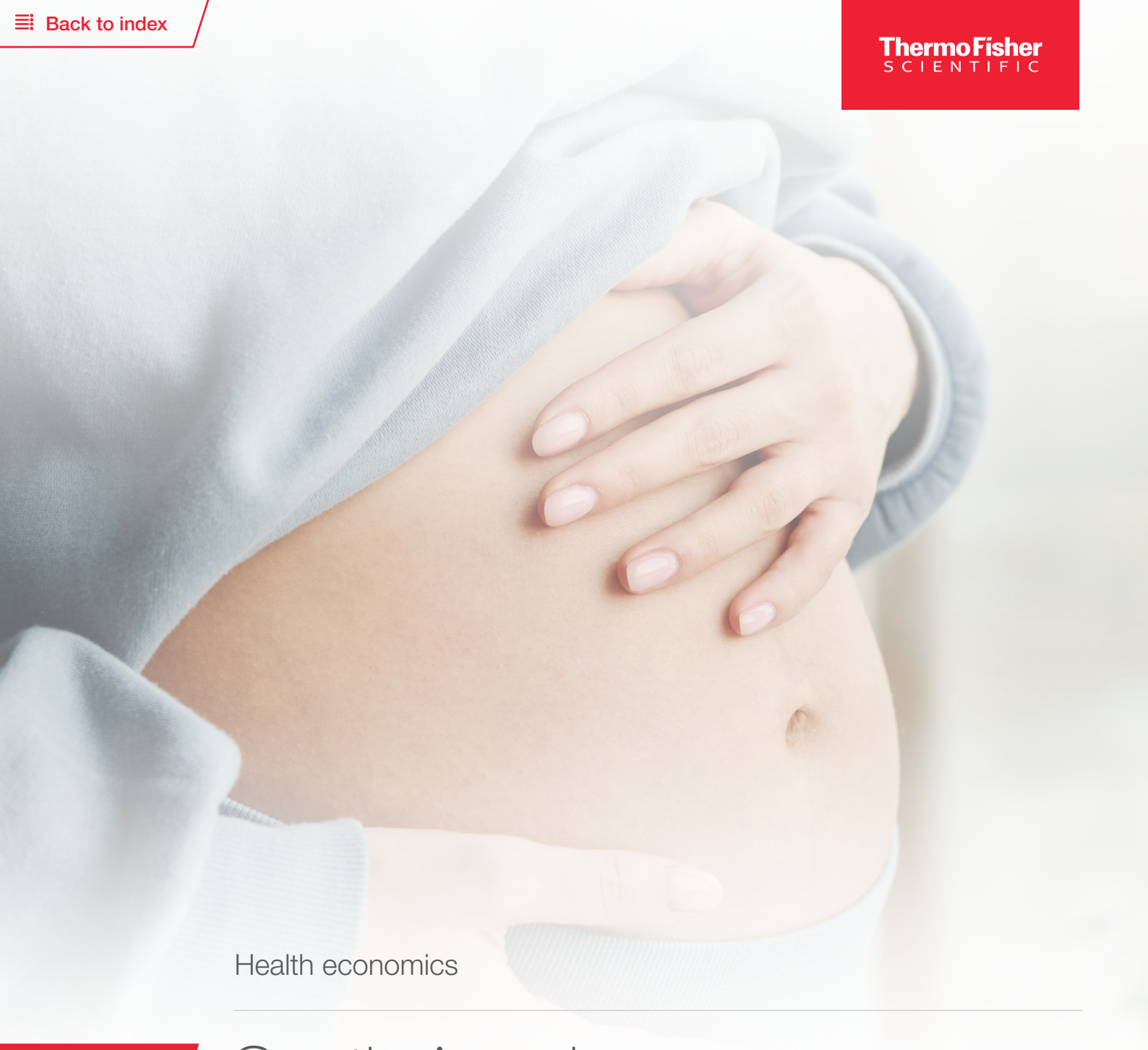
A total of 199 women were included. Pre-eclampsia in the first week was observed in 2 women (2%) in group A-/-, 12 (26%) in group B-/+, 4 (27%) in group C+/-, and 12 (92%) in group D+/+. The proportion of false negatives of 8.2% [95% CI 4.9-13.3] with the PCr alone was significantly reduced to 1.6% [0.4-5.7] by adding a negative sFlt-1/PlGF ratio. Furthermore, the addition of the sFlt-1/PlGF ratio to the spot urine PCr, with telemonitoring of women at risk, could result in a reduction of 41% admissions and 36% outpatient visits, leading to a cost reduction of €46,- per patient.

Conclusions

Implementation of the sFlt-1/PlGF ratio in addition to the spot urine PCr, may lead to improved selection of women at low risk and a reduction of hospital care for women with suspected pre-eclampsia.

Trial Registration

Netherlands Trial Register (NL8308).



Health economics

South America

Economic evaluation of sFlt-1/PlGF ratio test in pre-eclampsia prediction and diagnosis in two Brazilian hospitals

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Pregnancy Hypertens 2018 Vol. 13 Pages 30-36

Objectives

To assess the economic impact of introducing the soluble FMS-like tyrosine kinase (sFlt-1) to placental growth factor (PlGF) ratio test into clinical practice in two Brazilian hospitals.

Methods

An economic model estimating the incremental value of the information from a Brazilian public and private healthcare payer perspective generated by the sFlt-1/PlGF ratio test, compared with current diagnostic procedures, in guiding the management of women with suspected pre-eclampsia. A cohort of 1000 pregnant women between 24 weeks and 36 + 6 weeks of gestation were managed in either a 'test' scenario in which the sFlt-1/PlGF test is used in addition to current diagnostic procedures, or a 'no-test' scenario. Information on the costs associated with diagnosis, prediction and management were derived from the cost database of Hospital M'Boi Mirim (public) and Hospital Einstein (private). The probabilities used in the decision tree were derived from PROGNOSIS. The main outcome measure from the model was the cost per patient per episode of care (from first suspicion of pre-eclampsia to birth).

Results

Introduction of the sFlt-1/PlGF ratio test resulted in cost savings in both settings (M'Boi Mirim: R$185.06 and Einstein: R$635.84 per patient) compared with a 'no-test' scenario. Savings are generated primarily through an improvement in diagnostic accuracy and a reduction in unnecessary hospitalization.

Conclusions

The sFlt-1/PlGF ratio test has the potential to improve clinical decision-making and allocation of scarce resources by reducing unnecessary hospitalization of women at low risk of developing pre-eclampsia, and ensuring that women at higher risk are identified and managed appropriately.

Economic impact analysis of incorporation of Elecsys sFlt-1/PlGF ratio into routine practice for the diagnosis and follow-up of pregnant women with suspected preeclampsia in Argentina

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Value Health Reg Issues 2023 Vol. 34 Pages 1-8

Objectives

Preeclampsia (PE) is a hypertensive disorder of pregnancy that can cause severe complications and adverse fetal/maternal outcomes. We aimed to estimate the annual economic impact of incorporating Elecsys® sFlt-1/PlGF PE ratio, which measures soluble fms-like tyrosine kinase-1 and placental growth factor, into routine clinical practice in Argentina to aid diagnosis of PE and hemolysis, elevated liver enzymes, and low platelets syndrome from second trimester onward in pregnancies with clinical suspicion of PE.

Methods

A decision tree was used to estimate annual economic impact on the Argentine health system as a whole, including relevant costs associated with diagnosis, follow-up, and treatment from initial presentation of clinically suspected PE to delivery. Annual costs of a standard-of-care scenario and a scenario including PE ratio (reference year 2021) were analyzed.

Results

The economic model estimated that using the sFlt-1/PlGF ratio would enable the overall health system to save ~$6987 million Argentine pesos annually (95% confidence interval $12 045-$2952 million), a 39.1% reduction in costs versus standard of care, mainly due to reduced hospitalizations of women with suspected PE. The economic impact calculation estimated net annual savings of approximately $80 504 Argentine pesos per patient with suspected PE. Based on the assumed uncertainty of the parameters, the likelihood the intervention would be cost saving was 100% for the considered scenarios.

Conclusions

Our analysis suggests that the implementation of the sFlt-1/PlGF ratio in women with suspected PE in Argentina will enable the health system to achieve significant savings, contributing to more efficient clinical management through the likely reduction of unnecessary hospitalizations, depending on assumptions. Results rest on the payers' ability to recover savings generated by the intervention.

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Automated immunofluorescent assay for the quantitative determination of the concentration of sFlt-1 (soluble FMS-like Tyrosine Kinase 1, also known as VEGF receptor-1) in human serum and plasma (EDTA).

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- Excellent precision

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References

1. IFU B·R·A·H·M·S sFlt-1 KRYPTOR
2. IFU B·R·A·H·M·S PlGF plus KRYPTOR

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