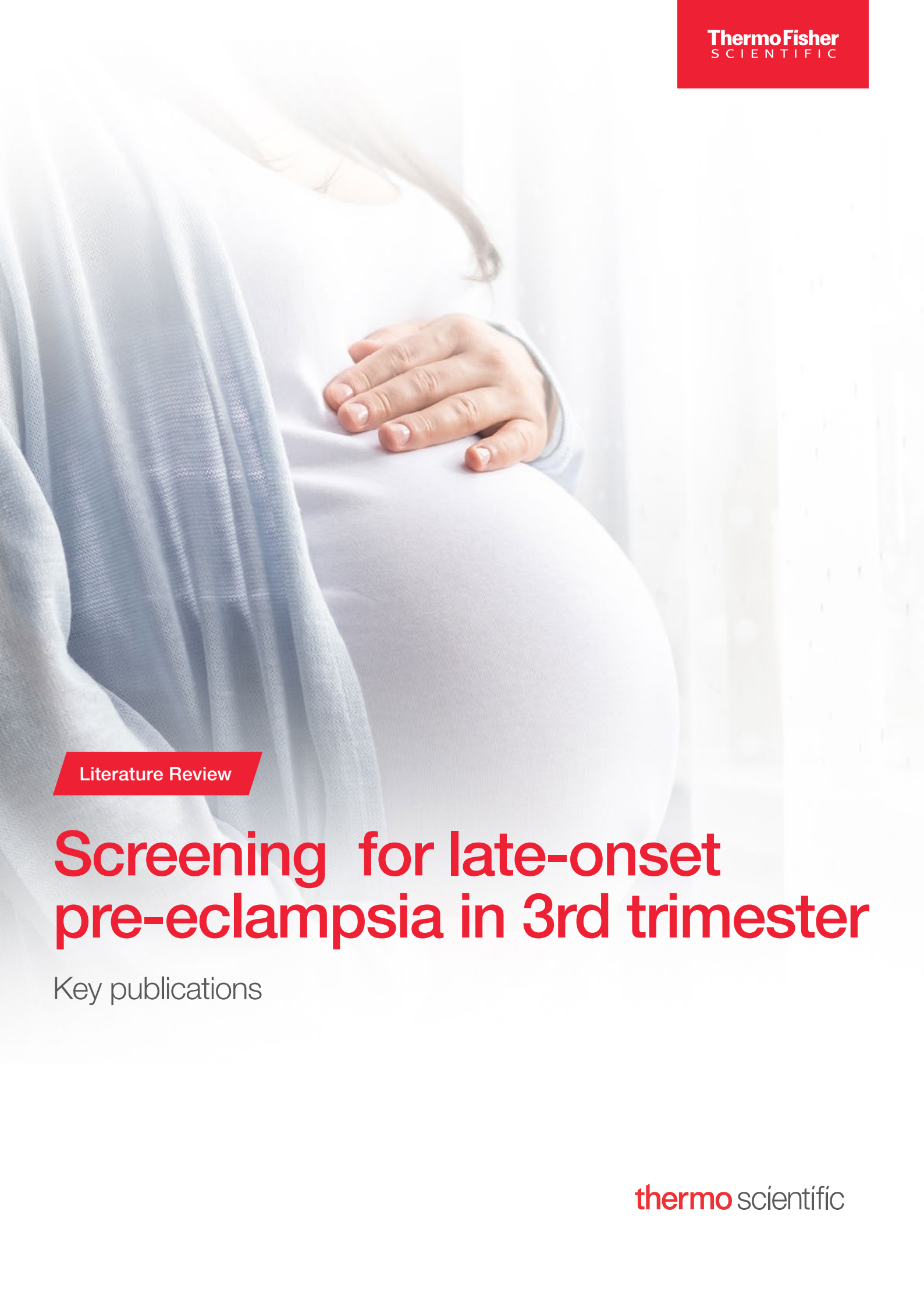

Literature Review

Screening for late-onset pre-eclampsia in 3rd trimester

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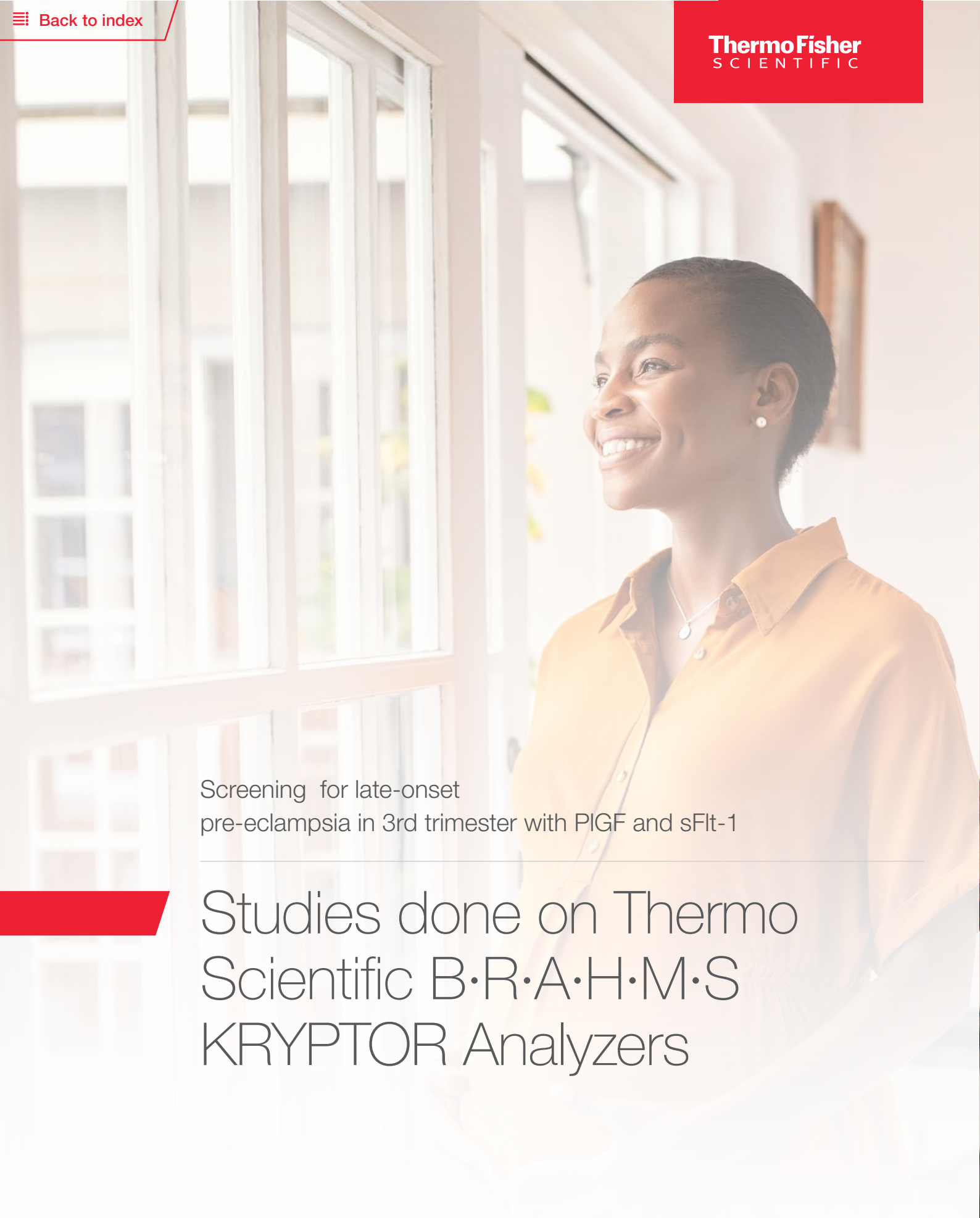
Screening for late-onset pre-eclampsia in 3rd trimester with PlGF and sFlt-1



Screening for late-onset
pre-eclampsia in 3rd trimester with PlGF and sFlt-1

Studies done on Thermo Scientific B·R·A·H·M·S KRYPTOR Analyzers

Screening for pre-eclampsia at 35-37 weeks' gestation

A. Panaitescu, A. Ciobanu, A. Syngelaki, A. Wright, D. Wright and K. H. Nicolaides

Ultrasound Obstet Gynecol 2018 Vol. 52 Issue 4 Pages 501-506

Objective

To examine the performance of screening for pre-eclampsia (PE) at 35-37 weeks' gestation by maternal factors and combinations of mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), serum placental growth factor (PlGF) and serum soluble fms-like tyrosine kinase-1 (sFlt-1).

Methods

This was a prospective observational study in women with singleton pregnancy attending for an ultrasound scan at 35+0 to 36+6 weeks as part of routine pregnancy care. Bayes' theorem was used to combine the prior distribution of gestational age at delivery with PE, obtained from maternal characteristics and medical history, with various combinations of biomarker multiples of the median (MoM) values to derive the patient-specific risks of delivery with PE. The performance of such screening was estimated.

Results

The study population of 13 350 pregnancies included 272 (2.0%) that subsequently developed PE. In pregnancies that developed PE, the MoM values of MAP, UtA-PI and sFlt-1 were increased and PlGF MoM was decreased. At a risk cut-off of 1 in 20, the proportion of the population stratified into high risk was about 10% of the total, and the proportion of cases of PE contained within this high-risk group was 28% with screening by maternal factors alone; the detection rate increased to 53% with the addition of MAP, 67% with the addition of MAP and PlGF and 70% with the addition of MAP, PlGF and sFlt-1. The performance of screening was not improved by the addition of UtA-PI. The performance of screening depended on the racial origin of the women; in screening by a combination of maternal factors, MAP, PlGF and sFlt-1 and use of the risk cut-off of 1 in 20, the detection rate and screen-positive rate were 66% and 9.5%, respectively, for Caucasian women and 88% and 18% for those of Afro-Caribbean racial origin.

Conclusion

Screening by maternal factors and biomarkers at 35-37 weeks' gestation can identify a high proportion of pregnancies that develop late PE. The performance of screening depends on the racial origin of the women.

Prediction of imminent preeclampsia at 35-37 weeks gestation

A. Ciobanu, A. Wright, A. Panaitescu, A. Syngelaki, D. Wright and K. H. Nicolaides

Am J Obstet Gynecol 2019 Vol. 220 Issue 6 Pages 584.e1-584.e11

Background

In the weeks preceding the clinical onset of preeclampsia, the maternal serum level of the angiogenic placental growth factor is decreased and that of the antiangiogenic factor soluble fms-like tyrosine kinase-1 is increased. Women presenting at specialist clinics with signs or symptoms of hypertensive disorders have been stratified according to concentrations of placental growth factor or the ratio of concentrations of soluble fms-like tyrosine kinase-1 and placental growth factor to determine clinical management for the subsequent 1-4 weeks. An alternative approach for the prediction of preeclampsia is use of the competing risks model, a Bayes' theorem based method, to derive patient-specific risk for preeclampsia by various combinations of maternal characteristics and medical history with multiples of the median values of biomarkers.

Objective

The purpose of this study was to compare the performance of screening for delivery with preeclampsia at ≤2 and ≤4 weeks after assessment at 35(+0)-36(+6) weeks gestation between the use of percentile cut-offs in placental growth factor alone or the soluble fms-like tyrosine kinase-1/placental growth factor ratio and the competing risks model.

Study Design

This was a prospective observational study in women who attended a routine hospital visit at 35(+0)-36(+6) weeks gestation in 2 maternity hospitals in England. The visits included the recording of maternal demographic characteristics and medical history and the measurement of serum placental growth factor and soluble fms-like tyrosine kinase-1 and mean arterial pressure. The areas under the receiver operating characteristics curves were used to compare the predictive performance for preeclampsia with delivery at ≤2 and ≤4 weeks from assessment of screening by placental growth factor alone and the soluble fms-like tyrosine kinase-1/placental growth factor ratio with that of a previously developed competing risks model with a combination of maternal factors, placental growth factor, soluble fms-like tyrosine kinase-1, and mean arterial pressure (triple test).

Results

First, the study population of 15,247 pregnancies included 326 pregnancies (2.1%) that subsequently experienced preeclampsia. Second, in the screening for delivery with preeclampsia at ≤2 and ≤4 weeks from assessment, the performance of the triple test was superior to that of placental growth factor alone or the soluble fms-like tyrosine kinase-1/placental growth factor ratio. The area under the receiver operating characteristics curves for preeclampsia at ≤2 weeks in screening by the triple test (0.975; 95% confidence interval, 0.964-0.985) was higher than that of placental growth factor alone (0.900; 95% confidence interval, 0.866-0.935; P<.0001) and the soluble fms-like tyrosine kinase-1/placental growth factor ratio (0.932; 95% confidence interval, 0.904-0.960; P=.0001). Similarly, the areas under the receiver operating characteristics curves for preeclampsia at ≤4 weeks in screening by the triple test (0.907; 95% confidence interval, 0.886-0.928) was higher than that of placental growth factor alone (0.827; 95% confidence interval, 0.800-0.854; P<.0001) or the soluble fms-like tyrosine kinase-1/placental growth factor ratio (0.857; 95% confidence interval, 0.830-0.883; P<.0001). Third, at most, screen-positive rates of 2-30% the detection rate of delivery with preeclampsia at ≤2 and ≤4 weeks that was achieved by the triple test was approximately 10% higher than that of the soluble fms-like tyrosine kinase-1/placental growth factor ratio and 20% higher than that of placental growth factor alone; the negative predictive value was similar for the 3 tests.

Conclusion

The purpose of this study was to compare the performance of screening for delivery with preeclampsia at ≤2 and ≤4 weeks after assessment at 35(+0)-36(+6) weeks gestation between the use of percentile cut-offs in placental growth factor alone or the soluble fms-like tyrosine kinase-1/placental growth factor ratio and the competing risks model.

Ophthalmic artery Doppler in combination with other biomarkers in prediction of pre-eclampsia at 35-37 weeks' gestation

M. Sarno, A. Wright, N. Vieira, I. Sapantzoglou, M. Charakida and K. H. Nicolaides

Ultrasound Obstet Gynecol 2021 Vol. 57 Issue 4 Pages 600-606

Objective

To examine the potential value of maternal ophthalmic artery Doppler at 35-37 weeks' gestation in combination with the established biomarkers of pre-eclampsia (PE), including mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), serum placental growth factor (PlGF) and serum soluble fms-like tyrosine kinase-1 (sFlt-1), in the prediction of subsequent development of PE.

Methods

This was a prospective observational study in women attending for a routine hospital visit at 35 + 0 to 36 + 6 weeks' gestation. This visit included recording of maternal demographic characteristics and medical history, ultrasound examination for fetal anatomy and growth, assessment of flow velocity waveforms from the maternal ophthalmic arteries, and measurement of MAP, UtA-PI, serum PlGF and serum sFlt-1. The competing-risks model was used to estimate the individual patient-specific risks of delivery with PE at any time and at < 3 weeks after assessment by a combination of maternal demographic characteristics and medical history with biomarkers. The area under the receiver-operating-characteristics curve and detection rate (DR) of delivery with PE, at a 10% false-positive rate (FPR), in screening by combinations of maternal factors with ophthalmic artery second to first peak of systolic velocity ratio (PSV ratio), MAP, UtA-PI, serum PlGF and serum sFlt-1 were determined. The modeled performance of screening for PE was also estimated.

Results

The study population of 2287 pregnancies contained 60 (2.6%) that developed PE, including 19 (0.8%) that delivered with PE at < 3 weeks after assessment. The PSV ratio improved the prediction of PE with delivery at any stage after assessment provided by maternal factors alone (from 25.4% to 50.6%), maternal factors and MAP (54.3% to 62.7%), maternal factors, MAP and PlGF (68.3% to 70.8%) and maternal factors, MAP, PlGF and sFlt-1 (75.7% to 76.7%), at a FPR of 10%. The PSV ratio also improved the prediction of PE with delivery at < 3 weeks after assessment provided by maternal factors alone (from 31.0% to 69.4%), maternal factors and MAP (74.1% to 83.4%), maternal factors, MAP and UtA-PI (77.1% to 85.0%) and maternal factors, MAP and PlGF (84.8% to 88.6%). The empirical results for DR at a 10% FPR were consistent with the modeled results. Screening by a combination of maternal factors with MAP and PSV ratio also detected 59.4% (95% CI, 58.6-82.5%) of cases of gestational hypertension with delivery at any stage after assessment, and 86.7% (95% CI, 82.4-100%) of those with delivery at < 3 weeks after assessment.

Conclusion

Ophthalmic artery Doppler could potentially improve the performance of screening for PE at 35-37 weeks, especially imminent PE with delivery within 3 weeks after assessment, but further studies are needed to validate this finding.

Pravastatin Versus Placebo in Pregnancies at High Risk of Term Preeclampsia

M. Döbert, A. N. Varouxaki, A. C. Mu, A. Syngelaki, A. Ciobanu, R. Akolekar, et al.

Circulation 2021 Vol. 144 Issue 9 Pages 670-679

Background

Effective screening for term preeclampsia is provided by a combination of maternal factors with measurements of mean arterial pressure, serum placental growth factor, and serum soluble fms-like tyrosine kinase-1 at 35 to 37 weeks of gestation, with a detection rate of ≈75% at a screen-positive rate of 10%. However, there is no known intervention to reduce the incidence of the disease.

Methods

In this multicenter, double-blind, placebo-controlled trial, we randomly assigned 1120 women with singleton pregnancies at high risk of term preeclampsia to receive pravastatin at a dose of 20 mg/d or placebo from 35 to 37 weeks of gestation until delivery or 41 weeks. The primary outcome was delivery with preeclampsia at any time after randomization. The analysis was performed according to intention to treat. RESULTS: A total of 29 women withdrew consent during the trial. Preeclampsia occurred in 14.6% (80 of 548) of participants in the pravastatin group and in 13.6% (74 of 543) in the placebo group. Allowing for the effect of risk at the time of screening and participating center, the mixed-effects Cox regression showed no evidence of an effect of pravastatin (hazard ratio for statin/placebo, 1.08 [95% CI, 0.78-1.49]; P=0.65). There was no evidence of interaction between the effect of pravastatin, estimated risk of preeclampsia, pregnancy history, adherence, and aspirin treatment. There was no significant between-group difference in the incidence of any secondary outcomes, including gestational hypertension, stillbirth, abruption, delivery of small for gestational age neonates, neonatal death, or neonatal morbidity. There was no significant between-group difference in the treatment effects on serum placental growth factor and soluble fms-like tyrosine kinase-1 concentrations 1 and 3 weeks after randomization. Adherence was good, with reported intake of ≥80% of the required number of tablets in 89% of participants. There were no significant between-group differences in neonatal adverse outcomes or other adverse events.

Conclusion

Pravastatin in women at high risk of term preeclampsia did not reduce the incidence of delivery with preeclampsia

Competing-risks model for pre-eclampsia and adverse pregnancy outcomes

A. Syngelaki, L. A. Magee, P. V. Dadelszen, R. Akolekar, A. Wright, D. Wright, et al.

Ultrasound Obstet Gynecol 2022 Vol. 60 Issue 3 Pages 367-372

Objective

The competing risks model for assessment of risk for pre-eclampsia (PE) at 35-36 weeks' gestation identifies the majority of women whose pregnancies are at high-risk for subsequent delivery with PE. To objective of this study was to examine, according to the estimated risk of delivery with PE, the incidence of adverse pregnancy outcomes and relative risks for such outcomes, by stratum of risk.

Methods

Prospective non-intervention observational study in women with singleton pregnancies attending a routine hospital visit at 35 0/7 to 36 6/7 weeks' gestation. The risk of delivery with PE for each patient in the study population was estimated by the competing risks model, combining the prior distribution of gestational age at delivery with PE, together with likelihoods from multiple of the median values of mean arterial pressure, placental growth factor and soluble fms-like tyrosine kinase (sFlt-1). The patients were assigned to one of the following five risk categories: A: ≥1 in 2; B: 1 in 5 to 1 in 3; C: 1 in 20 to 1 in 6; D: 1 in 50 to 1 in 21; and E: <1:50. The outcome measures were delivery with PE, gestational hypertension (GH), birth of small for gestational age (SGA) neonates, delivery by cesarean section, stillbirth, neonatal death, perinatal death and admission to the neonatal unit (NNU) for a minimum of 48 hours. In each risk category proportions of women for each adverse outcome were determined and the risk ratios (RR) calculated, relative to the lowest-risk group E.

Results

In the study population of 29,035 women, 1.6%, 2.7%, 8.2%, 9.8%, and 77.7% were in the risk strata A, B, C, D and E, respectively. Compared with women in the <1:50 stratum, women in higher-risk strata were more likely to have an adverse outcome. For example, the RR (95% confidence interval) of delivery with PE in group A relative to group E was 65.5 (54.1, 79.1) and the respective values were 11.9 (9.1, 15.5) for GH, 1.8 (1.5, 2.1) for delivery by emergency cesarean section, 1.5 (1.2, 1.8) for delivery by elective cesarean section, 8.9 (7.4, 10.8) for SGA with birthweight <3(rd) percentile, 4.8 (4.3, 5.4) for SGA with birthweight <10(th) percentile, 5.3 (1.4, 20.5) for stillbirth, and 3.4 (2.8, 4.2) for NNU admission for ≥48 hours. The higher RR for these pregnancy complications in higher risk categories (vs. category E) was more marked for deliveries within two weeks of assessment. In the case of SGA, both for birth weight <10(th) and <3(rd) percentile, the observed trend in all cases was stronger than that observed when the analysis was confined to normotensive pregnancies. The rates of neonatal death were too small for meaningful comparisons between risk categories.

Conclusion

Women with pregnancies identified by the competing risks model to be at high-risk of PE are also at increased risk of GH, cesarean section, stillbirth, SGA, and NNU admission for ≥48 hours.

STATIN trial: predictive performance of competing-risks model in screening for pre-eclampsia at 35-37 weeks' gestation

M. Döbert, A. Wright, A. N. Varouxaki, A. C. Mu, A. Syngelaki, A. Rehal, et al.

Ultrasound Obstet Gynecol 2022 Vol. 59 Issue 1 Pages 69-75

Objective

To examine the predictive performance of a previously reported competing-risks model of screening for pre-eclampsia (PE) at 35-37 weeks' gestation by combinations of maternal risk factors, mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), serum placental growth factor (PlGF) and serum soluble fms-like tyrosine kinase-1 (sFlt-1) in a validation dataset derived from the screened population of the STATIN study.

Methods

This was a prospective third-trimester multicenter study of screening for PE in singleton pregnancies by means of a previously reported algorithm that combines maternal risk factors and biomarkers. Women in the high-risk group were invited to participate in a trial of pravastatin vs placebo, but the trial showed no evidence of an effect of pravastatin in the prevention of PE. Patient-specific risks of delivery with PE were calculated using the competing-risks model, and the performance of screening for PE by maternal risk factors alone and by various combinations of risk factors with MAP, UtA-PI, PlGF and sFlt-1 was assessed. The predictive performance of the model was examined by, first, the ability of the model to discriminate between the PE and no-PE groups using the area under the receiver-operating-characteristics curve (AUC) and the detection rate at a fixed false-positive rate of 10%, and, second, calibration by measurements of calibration slope and calibration-in-the-large.

Results

The study population of 29 677 pregnancies contained 653 that developed PE. In screening for PE by a combination of maternal risk factors, MAP, PlGF and sFlt-1 (triple test), the detection rate at a 10% false-positive rate was 79% (95% CI, 76-82%) and the results were consistent with the data used for developing the algorithm. Addition of UtA-PI did not improve the prediction provided by the triple test. The AUC for the triple test was 0.923 (95% CI, 0.913-0.932), demonstrating very high discrimination between affected and unaffected pregnancies. Similarly, the calibration slope was 0.875 (95% CI, 0.831-0.919), demonstrating good agreement between the predicted risk and observed incidence of PE.

Conclusion

The competing-risks model provides an effective and reproducible method for third-trimester prediction of term PE. © 2021 International Society of Ultrasound in Obstetrics and Gynecology.

The implications of the Fetal Medicine Foundation 35- to 36-week preeclampsia prediction competing-risk model on timing of birth

P. von Dadelszen, A. Syngelaki, A. Wright, R. Akolekar, L. A. Magee, D. Wright, et al.

Am J Obstet Gynecol 2022

Background

Preeclampsia is associated with increased risks of life-threatening, -altering, and -ending complications. Assessment of risk for preeclampsia at 35 to 36 weeks' gestation by the Fetal Medicine Foundation 36-week competing-risk model identifies approximately 75% of women who will develop term preeclampsia, at a 10% screen-positive rate. OBJECTIVE: This study aimed to assess whether the Fetal Medicine Foundation 36-week model can provide personalized guidance to women about the probable timing of their delivery, whether or not they develop pregnancy hypertension.

Study Design

In this prospective nonintervention screening study at 2 maternity hospitals in England, women who did not have preeclampsia (American College of Obstetricians and Gynecologists definition) and were attending a routine hospital visit at 35 0/7 to 36 6/7 weeks' gestation underwent assessment of risk for preeclampsia, including maternal demographic characteristics, medical history, mean arterial pressure, and serum placental growth factor and soluble fms-like tyrosine kinase-1. Fetal Medicine Foundation 36-week model risk categories for subsequent preeclampsia were defined as: A, ≥0.500; B, 0.20 to 0.499; C, 0.05 to 0.199; D, 0.020 to 0.049; and E, <0.020. Obstetrical records were examined for all women to identify their gestational age at delivery, and whether they experienced a spontaneous onset of labor (irrespective of mode of delivery) or had a medically indicated birth (either induction of labor or unlabored cesarean delivery). The cumulative incidence of delivery and risk ratios, for all deliveries and for spontaneous deliveries, was assessed.

Results

Among 29,035 women with singleton pregnancies, 1.0%, 2.9%, 3.3%, 5.0%, 9.9%, and 77.9% were in A, B, C, D, and E risk strata, respectively. In the A (vs E) stratum, 71.95% (vs 33.52%) of births were medically indicated. Compared with women in stratum E, women in higher risk strata were more likely to deliver, and to deliver following spontaneous labor, before their due date. For example, of the women in stratum A (vs E), 14.2% (vs 1.1%; risk ratio, 12.5 [95% confidence interval, 9.45-15.35]), 48.5% (vs 5.1%; risk ratio, 8.47 [7.48-9.35]), 69.6% (vs 15.5%; risk ratio, 3.86 [3.59-4.08]), and 90.1% (vs 44.8%; risk ratio, 6.72 [4.53-9.95]) gave birth before 37 0/7, 38 0/7, 39 0/7, and 40 0/7 weeks, respectively. For women in stratum A (vs E), when censored for medically indicated births, spontaneous labor occurred more commonly before 37 0/7 (risk ratio, 4.31 [1.99-6.57]), 38 0/7 (risk ratio, 3.71 [2.48-4.88]), 39 0/7 (risk ratio, 2.87 [2.22-3.46]), and 40 0/7 (risk ratio, 1.42 [1.14-1.77]) weeks.

Conclusion

Women in higher-risk strata gave birth earlier, and more frequently following medically indicated delivery, compared with those in lower-risk strata. Importantly, the proportion of women who gave birth following spontaneous onset of labor before their due date was also greater in higher-risk than in lower-risk women. The Fetal Medicine Foundation 36-week competing-risk model incorporates biomarkers of placental aging, including angiogenic imbalance; these results imply that a fetoplacental response to placental aging may be an important trigger for the onset of labor at term.

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

A. Wright, P. von Dadelszen, L. A. Magee, A. Syngelaki, R. Akolekar, D. Wright, et al.

BJOG 2023 Vol. 130 Issue 1 Pages 78-87

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

Design
Prospective observational study.

Settings
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 (versus 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 2 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.

Screening for late-onset pre-eclampsia in 3rd trimester with PlGF and sFlt-1

Studies done on other instruments

Competing-risks model in screening for pre-eclampsia by maternal factors and biomarkers at 35-37 weeks' gestation

S. Andrietti, M. Silva, A. Wright, D. Wright and K. H. Nicolaides

Ultrasound Obstet Gynecol 2016 Vol. 48 Issue 1 Pages 72-9

Objective

To develop a model for prediction of term pre-eclampsia (PE) based on a combination of maternal factors and late third-trimester biomarkers.

Methods

Data were derived from prospective screening for adverse obstetric outcomes in women attending their routine hospital visit at 35-37 weeks' gestation in two maternity hospitals in the UK. Uterine artery pulsatility index (UtA-PI) was measured in 5362 pregnancies, mean arterial pressure (MAP) in 5386 and serum placental growth factor (PlGF) and serum soluble fms-like tyrosine kinase-1 (sFlt-1) in 3920. Bayes' theorem was used to combine the a-priori risk of PE from maternal factors with various combinations of biomarkers, expressed as multiples of the median (MoM). Five-fold cross-validation was used to estimate the performance of screening for PE, requiring delivery at some stage after assessment. The empirical performance of screening was compared to model predictions.

Results

In pregnancies that developed PE, the values of MAP, UtA-PI and sFlt-1 were increased and PlGF was decreased compared to unaffected pregnancies. For all biomarkers evaluated, the deviation from normal was inversely related to the gestational age at which delivery became necessary for maternal or fetal indications. Screening by maternal factors and by a combination of maternal factors with all biomarkers predicted 35% and 84% of PE, respectively, at a 10% false-positive rate.

Conclusion

A combination of maternal factors and biomarkers at 35-37 weeks' gestation can provide effective screening for term PE.

Proposed clinical management of pregnancies after combined screening for pre-eclampsia at 35-37 weeks' gestation

A. M. Panaitescu, D. Wright, A. Militello, R. Akolekar and K. H. Nicolaides

Ultrasound Obstet Gynecol 2017 Vol. 50 Issue 3 Pages 383-387

Objective

To estimate the patient-specific risk of pre-eclampsia (PE) at 35-37 weeks' gestation by a combination of maternal characteristics and medical history with multiples of the median (MoM) values of mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), serum placental growth factor (PlGF) and serum soluble fms-like tyrosine kinase-1 (sFlt-1), and stratify women into high-, intermediate- and low-risk management groups.

Methods

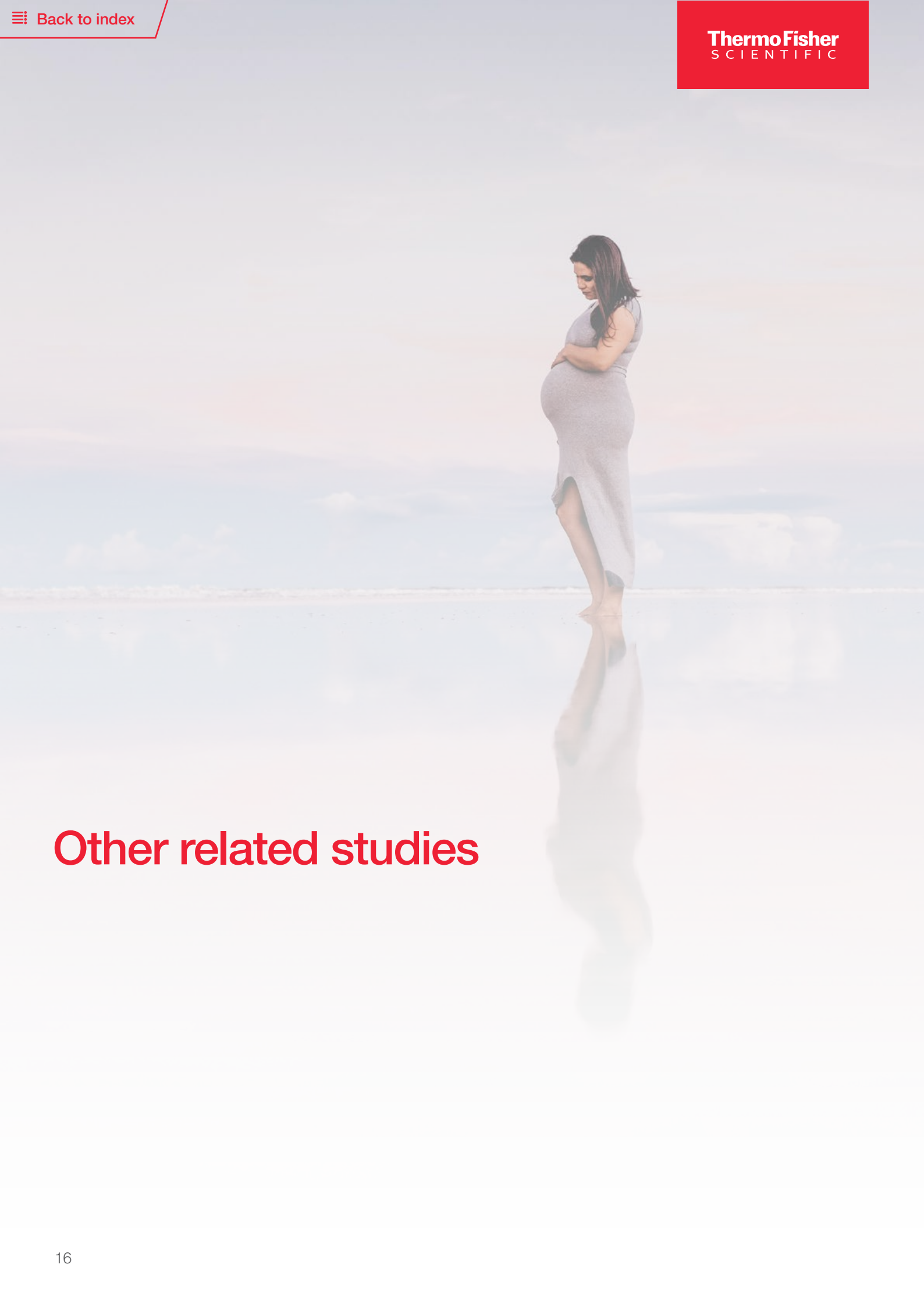
This was a prospective observational study in women attending a third-trimester ultrasound scan at 35-37 weeks as part of routine pregnancy care. Patient-specific risks of delivery with PE at < 4 weeks from assessment and PE at < 42 weeks' gestation were calculated using the competing-risks model to combine the prior risk from maternal characteristics and medical history with MoM values of MAP, UtA-PI, PlGF and sFlt-1. On the basis of these risks, the population was stratified into high-, intermediate- and low-risk groups. Different risk cut-offs were used to vary the proportion of the population stratified into each risk category and the performance of screening for delivery with PE at < 40 and ≥ 40 weeks' gestation was estimated.

Results

The study population of 3703 singleton pregnancies included 38 (1.0%) with PE < 40 weeks' gestation and 22 (0.6%) with PE ≥ 40 weeks. Using a risk cut-off of 1 in 50 for PE delivering at < 4 weeks after assessment to define the high-risk group and a risk cut-off of < 1 in 100 for PE delivering at < 42 weeks' gestation to define the low-risk group, the proportion of the population stratified into high, intermediate and low risk was 12.7%, 28.8% and 58.5%, respectively. The high-risk group contained 92% of pregnancies with PE at < 40 weeks' gestation and 73% of those with PE at ≥ 40 weeks. The intermediate-risk group contained a further 27% of women with PE at ≥ 40 weeks. In the low-risk group, none of the women developed PE at < 40 or ≥ 40 weeks' gestation.

Conclusion

The study population of 3703 singleton pregnancies included 38 (1.0%) with PE < 40 weeks' gestation and 22 (0.6%) with PE ≥ 40 weeks. Using a risk cut-off of 1 in 50 for PE delivering at < 4 weeks after assessment to define the high-risk group and a risk cut-off of < 1 in 100 for PE delivering at < 42 weeks' gestation to define the low-risk group, the proportion of the population stratified into high, intermediate and low risk was 12.7%, 28.8% and 58.5%, respectively. The high-risk group contained 92% of pregnancies with PE at < 40 weeks' gestation and 73% of those with PE at ≥ 40 weeks. The intermediate-risk group contained a further 27% of women with PE at ≥ 40 weeks. In the low-risk group, none of the women developed PE at < 40 or ≥ 40 weeks' gestation.



Other related studies

Planned early delivery or expectant management for late preterm pre-eclampsia (PHOENIX): a randomised controlled trial

L. C. Chappell, P. Brocklehurst, M. E. Green, R. Hunter, P. Hardy, E. Juszczak, et al.

Lancet 2019 Vol. 394 Issue 10204 Pages 1181-1190

Background

In women with late preterm pre-eclampsia, the optimal time to initiate delivery is unclear because limitation of maternal disease progression needs to be balanced against infant complications. The aim of this trial was to determine whether planned earlier initiation of delivery reduces maternal adverse outcomes without substantial worsening of neonatal or infant outcomes, compared with expectant management (usual care) in women with late preterm pre-eclampsia.

Methods

In this parallel-group, non-masked, multicentre, randomised controlled trial done in 46 maternity units across England and Wales, we compared planned delivery versus expectant management (usual care) with individual randomisation in women with late preterm pre-eclampsia from 34 to less than 37 weeks' gestation and a singleton or dichorionic diamniotic twin pregnancy. The co-primary maternal outcome was a composite of maternal morbidity or recorded systolic blood pressure of at least 160 mm Hg with a superiority hypothesis. The co-primary perinatal outcome was a composite of perinatal deaths or neonatal unit admission up to infant hospital discharge with a non-inferiority hypothesis (non-inferiority margin of 10% difference in incidence). Analyses were by intention to treat, together with a per-protocol analysis for the perinatal outcome. The trial was prospectively registered with the ISRCTN registry, ISRCTN01879376. The trial is closed to recruitment but follow-up is ongoing. FINDINGS: Between Sept 29, 2014, and Dec 10, 2018, 901 women were recruited. 450 women (448 women and 471 infants analysed) were allocated to planned delivery and 451 women (451 women and 475 infants analysed) to expectant management. The incidence of the co-primary maternal outcome was significantly lower in the planned delivery group (289 [65%] women) compared with the expectant management group (338 [75%] women; adjusted relative risk 0·86, 95% CI 0·79-0·94; p=0·0005). The incidence of the co-primary perinatal outcome by intention to treat was significantly higher in the planned delivery group (196 [42%] infants) compared with the expectant management group (159 [34%] infants; 1·26, 1·08-1·47; p=0·0034). The results from the per-protocol analysis were similar. There were nine serious adverse events in the planned delivery group and 12 in the expectant management group.

Interpretation

There is strong evidence to suggest that planned delivery reduces maternal morbidity and severe hypertension compared with expectant management, with more neonatal unit admissions related to prematurity but no indicators of greater neonatal morbidity. This trade-off should be discussed with women with late preterm pre-eclampsia to allow shared decision making on timing of delivery.

Fetal cardiac function at 35-37 weeks' gestation in pregnancies that subsequently develop pre-eclampsia

J. Semmler, C. Garcia-Gonzalez, A. Sanchez Sierra, M. Gallardo Arozena, K. H. Nicolaides and M. Charakida

Ultrasound Obstet Gynecol 2021 Vol. 57 Issue 3 Pages 417-422

Objective

To compare fetal cardiac morphology and function between pregnancies that subsequently developed pre-eclampsia (PE) and those that remained normotensive.

Methods

This was a prospective observational study in 1574 pregnancies at 35-37 weeks' gestation, including 76 that subsequently developed PE. We carried out comprehensive assessment of fetal cardiac morphology and function including novel imaging modalities, such as speckle-tracking echocardiography, and measured uterine artery pulsatility index, mean arterial pressure (MAP), serum placental growth factor (PlGF), soluble fms-like tyrosine kinase-1 (sFlt-1) and cerebroplacental ratio (CPR). The findings in the group that subsequently developed PE were compared to those in pregnancies that remained normotensive.

Results

In fetuses of mothers who subsequently developed PE, compared to those from normotensive pregnancies, there was a more globular right ventricle, as shown by reduced right ventricular sphericity index, reduced right ventricular systolic contractility, as shown by reduced global longitudinal strain, and reduced left ventricular diastolic function, as shown by increased E/A ratio. On multivariable regression analysis, these indices demonstrated an association with PE, independent of maternal characteristics and fetal size. In pregnancies that subsequently developed PE, compared to those that remained normotensive, MAP, sFlt-1 and the incidence of low birth weight were higher, whereas serum PlGF, CPR and the interval between assessment and delivery were lower. These findings demonstrate that, in pregnancies that develop PE, there is evidence of impaired placentation, reflected in low PlGF and reduced birth weight, placental ischemia, evidenced by increased sFlt-1 which becomes apparent in the interval of 2-4 weeks preceding the clinical onset of PE, and consequent fetal hypoxia-induced redistribution in the fetal circulation, reflected in the low CPR.

Conclusion

Although the etiology of the observed fetal cardiac changes in pregnancies that subsequently develop PE remains unclear, it is possible that the reduction in right-heart systolic function is the consequence of high afterload due to increased placental resistance, whilst the early left ventricular diastolic changes could be due to fetal hypoxia-induced redistribution in the fetal circulation.

Competing-risks model for prediction of small-for-gestational-age neonate at 36 weeks' gestation

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Ultrasound Obstet Gynecol 2022 Vol. 60 Issue 5 Pages 612-619

Objective

To develop further a competing-risks model for the prediction of a small-for-gestational-age (SGA) neonate by including sonographically estimated fetal weight (EFW) and biomarkers of impaired placentation at 36 weeks' gestation, and to compare the performance of the new model with that of the traditional EFW < 10(th) percentile cut-off.

Methods

This was a prospective observational study in 29 035 women with a singleton pregnancy undergoing routine ultrasound examination at 35 + 0 to 36 + 6 weeks' gestation. A competing-risks model for the prediction of a SGA neonate was used. The parameters included in the prior-history model were provided in previous studies. An interaction continuous model was used for the EFW likelihood. A folded plane regression model was fitted to describe likelihoods of biomarkers of impaired placentation. Stratification plans were also developed. The new model was evaluated and compared with EFW percentile cut-offs.

Results

The performance of the model was better for predicting SGA neonates delivered closer to the point of assessment. The prediction provided by maternal factors alone was improved significantly by the addition of EFW, uterine artery pulsatility index (UtA-PI) and placental growth factor (PlGF) but not by mean arterial pressure or soluble fms-like tyrosine kinase-1. At a 10% false-positive rate, maternal factors and EFW predicted 77.6% and 65.8% of SGA neonates < 10(th) percentile delivered before 38 and 42 weeks, respectively. The respective figures for SGA < 3(rd) percentile were 85.5% and 74.2%. Addition of UtA-PI and PlGF resulted in marginal improvement in prediction of SGA < 3(rd) percentile requiring imminent delivery. A competing-risks approach that combines maternal factors and EFW performed better when compared with fixed EFW percentile cut-offs at predicting a SGA neonate, especially with increasing time interval between assessment and delivery. The new model was well-calibrated.

Conclusion

A competing-risks model provides effective risk stratification for a SGA neonate at 35 + 0 to 36 + 6 weeks' gestation and is superior to EFW percentile cut-offs. The use of biomarkers of impaired placentation in addition to maternal factors and fetal biometry results in small improvement of the predictive performance for a neonate with severe SGA.

Planned delivery or expectant management in preeclampsia: an individual participant data meta-analysis

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Am J Obstet Gynecol 2022 Vol. 227 Issue 2 Pages 218-230.e8

Objective

Pregnancy hypertension is a leading cause of maternal and perinatal mortality and morbidity. Between 34(+0) and 36(+6) weeks gestation, it is uncertain whether planned delivery could reduce maternal complications without serious neonatal consequences. In this individual participant data meta-analysis, we aimed to compare planned delivery to expectant management, focusing specifically on women with preeclampsia. DATA SOURCES: We performed an electronic database search using a prespecified search strategy, including trials published between January 1, 2000 and December 18, 2021. We sought individual participant-level data from all eligible trials. STUDY ELIGIBILITY CRITERIA: We included women with singleton or multifetal pregnancies with preeclampsia from 34 weeks gestation onward.

Methods

The primary maternal outcome was a composite of maternal mortality or morbidity. The primary perinatal outcome was a composite of perinatal mortality or morbidity. We analyzed all the available data for each prespecified outcome on an intention-to-treat basis. For primary individual patient data analyses, we used a 1-stage fixed effects model. RESULTS: We included 1790 participants from 6 trials in our analysis. Planned delivery from 34 weeks gestation onward significantly reduced the risk of maternal morbidity (2.6% vs 4.4%; adjusted risk ratio, 0.59; 95% confidence interval, 0.36-0.98) compared with expectant management. The primary composite perinatal outcome was increased by planned delivery (20.9% vs 17.1%; adjusted risk ratio, 1.22; 95% confidence interval, 1.01-1.47), driven by short-term neonatal respiratory morbidity. However, infants in the expectant management group were more likely to be born small for gestational age (7.8% vs 10.6%; risk ratio, 0.74; 95% confidence interval, 0.55-0.99).

Conclusion

Planned early delivery in women with late preterm preeclampsia provides clear maternal benefits and may reduce the risk of the infant being born small for gestational age, with a possible increase in short-term neonatal respiratory morbidity. The potential benefits and risks of prolonging a pregnancy complicated by preeclampsia should be discussed with women as part of a shared decision-making process.

Cost-Utility Analysis of Planned Early Delivery or Expectant Management for Late Preterm Pre-eclampsia (PHOENIX)

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Pharmacoecon Open 2022 Vol. 6 Issue 5 Pages 723-733

Aim

There is currently limited evidence on the costs associated with late preterm pre-eclampsia beyond antenatal care and post-natal discharge from hospital. The aim of this analysis is to evaluate the 24-month cost-utility of planned delivery for women with late preterm pre-eclampsia at 34(+0)-36(+6) weeks' gestation compared to expectant management from an English National Health Service perspective using participant-level data from the PHOENIX trial.

Methods

Women between 34(+0) and 36(+6) weeks' gestation in 46 maternity units in England and Wales were individually randomised to planned delivery or expectant management. Resource use was collected from hospital records between randomisation and primary hospital discharge following birth. Women were followed up at 6 months and 24 months following birth and self-reported resource use for themselves and their infant(s) covering the previous 6 months. Women completed the EQ-5D 5L at randomisation and follow-up.

Results

A total of 450 women were randomised to planned delivery, 451 to expectant management: 187 and 170 women, respectively, had complete data at 24 months. Planned delivery resulted in a significantly lower mean cost per woman and infant(s) over 24 months (- £2711, 95% confidence interval (CI) - 4840 to - 637), with a mean incremental difference in QALYs of 0.019 (95% CI - 0.039 to 0.063). Short-term and 24-month infant costs were not significantly different between the intervention arms. There is a 99% probability that planned delivery is cost-effective at all thresholds below £37,000 per QALY gained. CONCLUSION: There is a high probability that planned delivery is cost-effective compared to expectant management. These results need to be considered alongside clinical outcomes and in the wider context of maternity care.

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