Placental growth factor testing to assess and diagnose preeclampsia: a stepped wedge randomised controlled trial.

Kate E Duhig, M.R.C.P.[1], Clinical Research Fellow. kate.duhig@kcl.ac.uk

Jenny Myers, Ph.D.[2], NIHR Clinician Scientist, Jenny.Myers@manchester.ac.uk

Paul T Seed, C.Stat.[1], Senior Lecturer in Medical Statistics. Paul.seed@kcl.ac.uk

Rachael M Hunter, MSc [3], Health Economist. r.hunter@ucl.ac.uk

Andrew H Shennan, M.D. [1], Professor of Obstetrics. andrew.shennan@kcl.ac.uk

Lucy C Chappell, Ph. D. [1], NIHR Research Professor in Obstetrics. lucy.chappell@kcl.ac.uk

On behalf of the PARROT trial group

[1]Department of Women and Children's Health, School of Life Course Sciences, King's College London (KED, PTS, AHS, LCC),

[2]The Division of Developmental Biology and Medicine, University of Manchester (JM),

[3]Research Department of Primary care and Population Health, University College London (RMH).

Corresponding author: Professor Lucy Chappell, Department of Women and Children's Health, School of Life Course Sciences, King's College London, Westminster Bridge Road, London, SE1 7EH; lucy.chappell@kcl.ac.uk

Abstract

Background

Previous prospective cohort studies have demonstrated that angiogenic factor measurements have high diagnostic accuracy in women with suspected pre-eclampsia, but the clinical impact of these tests when revealed to clinicians remains uncertain.

Methods

We conducted a multi-centre, pragmatic, stepped-wedge cluster randomised controlled trial in eleven UK maternity units (3000-9000 deliveries per annum). Women who presented with suspected pre-eclampsia between 20^{+0} and 36^{+6} weeks' gestation were invited to participate. Maternity units were randomly assigned to the order of implementation of revealed PlGF measurement, incorporated within a clinical management algorithm; in the usual care arm, PlGF measurement remained concealed. The primary outcome was time from presentation with suspected pre-eclampsia to documented pre-eclampsia. Secondary outcomes included other maternal and perinatal adverse outcomes.

Findings

Between June 2016 and October 2017, 1,023 women with suspected pre-eclampsia were enrolled. Median time to preeclampsia diagnosis decreased from 4·1 days (usual care) to 1·9 days (intervention) (time ratio 0·39 (95% CI 0·17-0·91) by parametric survival analysis). Maternal severe adverse outcomes reduced from 5·4% (usual care group) to 3·8% ((intervention group) adjusted OR 0·32 (95% CI 0·11-0·96) with no evidence of a difference in perinatal adverse outcomes.

Interpretation

PlGF testing has been shown to substantially reduce the time to clinical confirmation of preeclampsia. Where PlGF was implemented there was a reduction in maternal adverse outcomes,

consistent with targeted, enhanced surveillance as recommended in the trial management guidance for clinicians. Adoption of PlGF testing in women with suspected preeclampsia is supported by the results of this study.

Trial Registration Number: ISRCTN 16842031

Introduction

Hypertension affects 10% of pregnant women, with preeclampsia complicating around 3% of singleton pregnancies.[1, 2] Women with preeclampsia are often asymptomatic even with severe disease. Diagnosis is based on clinical features such as hypertension and raised urinary protein excretion, both of which are subject to observer error,[3] heterogeneity in test accuracy,[4, 5] and limited ability to predict important adverse pregnancy outcomes.[6] The presentation of preeclampsia is often clinically ambiguous, and risk stratification of women with suspected preeclampsia is complex. This leads to repeated attendances for antenatal monitoring, increased health resource use,[7] and considerable anxiety for women, while missing at risk cases.[8]

Angiogenic factors are associated with the pathophysiology of preeclampsia.[9, 10] In a diagnostic test accuracy study, low circulating maternal Placental Growth Factor (PlGF) concentrations had high sensitivity (96%; 95% confidence interval 89%-99%) and negative predictive value (98%; 95% CI 93%-99·5%) for diagnosing preeclampsia requiring delivery within 14 days;[11] the area under the receiver operating characteristic curve for low PlGF concentrations in determining preeclampsia was 0·87 (standard error 0·03), greater than all commonly used tests.

Many diagnostic tests enter clinical care without being evaluated in a trial to assess whether the test makes a difference to diagnosing the condition it is intended for, or whether use of the test impacts on downstream outcomes when implemented into practice, and to determine whether diagnostic test performance is maintained in a real-world setting. There is a need to determine if these novel angiogenic factors (such as PlGF) measured in pregnant women could translate into improved diagnosis and care when implemented into clinical practice. The aim of this trial was to evaluate the impact of PlGF measurement as a diagnostic test, integrated with a clinical management algorithm. The main outcome was to determine whether knowledge of PlGF decreased the time for clinicians to

make a preeclampsia diagnosis in women with suspected disease, and whether this reduced subsequent maternal or perinatal adverse outcomes.

Methods

We undertook a multicentre, pragmatic, stepped-wedge cluster randomised controlled trial in eleven UK maternity units (size 3000-9000 deliveries per year). There was no commercial sponsorship for this study. All participants provided individual-level consent. Women aged over 18 years were offered enrolment if they presented with suspected preeclampsia between 20^{+0} and 36^{+6} weeks' gestation, with a live, singleton fetus. Those with a documented diagnosis of preeclampsia at presentation were ineligible. Suspected preeclampsia was defined as a woman having any of the following signs or symptoms: new-onset or worsening of existing hypertension, dipstick proteinuria, epigastric or right upper quadrant pain, headache with visual disturbances, fetal growth restriction, abnormal maternal biochemistry.

The maternity units (clusters) were randomly allocated to the order in which the intervention (revealed PlGF measurement and management algorithm) was introduced. PlGF measurement was not routinely available in any of the centres prior to participation in the trial, and for the duration of the trial PlGF measurement was not used outside of the study in any of the centres. The centres were randomised by the trial statistician, accounting for the number of deliveries per month, such that the rank correlation between delivery rate and the order of randomisation was zero. All 11 units participated from the beginning of the trial. Prior to intervention implementation, blood samples were processed at each unit on an electronically-masked Triage (Alere, San Diego, CA) instrument, according to the manufacturer's instructions, confirming that the test had been performed but without revealing a result. The subsequent usual care pathway followed local hospital practice,

following the National Institute for Health and Care Excellence (NICE) guidelines for management of hypertension in pregnancy.[12]

The trial was made up of 12 time points, of six-week blocks, with one unit transitioning to the intervention at the start of each block. Each unit was informed six weeks in advance to allow time to plan training. At transition, an unmasked instrument and a training package were provided, which incorporated PlGF measurement into the national (NICE) guidance for the management of hypertensive pregnancies (Figure 1). By the last block, all participating units were using this intervention.

The first and last authors confirm the accuracy and completeness of the data and the fidelity of this report in respect to the trial protocol and statistical analysis plan.

Trial Outcomes

The primary outcome was time in days from trial entry, to a documented diagnosis of preeclampsia in the woman's clinical notes, as defined by the International Society for the Study of Hypertension in Pregnancy 2014 statement.[13] PlGF measurements were not a component of the clinical diagnosis, as this is not included within the ISSHP diagnostic criteria. Every diagnosis was also reviewed by a central adjudication panel, masked to trial allocation. The secondary maternal outcomes were a composite of severe maternal adverse outcomes as defined by the fullPIERS consensus,[14] systolic blood pressure above 160mmHg, progression to severe preeclampsia, placental abruption, mode and onset of delivery, use of medication, test performance in women presenting a) below 35 weeks' gestation and b) between 35^{+0} and 36^{+6} weeks' gestation for clinically-indicated delivery within 14 days of trial entry, proportion of women reaching the diagnostic criteria (irrespective of clinical documentation) for preeclampsia. Secondary perinatal outcomes included a composite of severe perinatal adverse outcomes (number of babies with one or more of the following: intraventricular

haemorrhage, seizures, retinopathy of prematurity, respiratory distress syndrome, bronchopulmonary dysplasia, necrotising enterocolitis stage 2 and 3, stillbirth, early neonatal death and late neonatal death to 28 days), gestation at delivery, preterm birth below 37 weeks gestation, birthweight and birthweight centile,[15] Apgar scores at 5 minutes post birth, neonatal unit admission, perinatal death (stillbirths from 24 weeks gestation to deaths up to seven completed days after birth) and late neonatal death (deaths between 8 and 27 completed days of life). Maternal health care resource use outcomes were outpatient attendances and inpatient nights. Neonatal resource use outcomes were nights in highest level care (intensive and high dependency care),[16] and special care. All outcomes are participant level outcomes.

Statistical Analysis

Sample size calculation: Based on the PELICAN study,[11] and assuming a high intra-cluster correlation (0·3), and at least seven diagnosed preeclampsia cases per unit per time-period, we had over 95% power (by Hemming & Girling's method)[17] to show a 50% reduction in mean time to diagnosis from 14 days (standard deviation 14 days) to seven days, assuming a minimum of seven units. We chose a 50% reduction for time to diagnosis as something that was plausible and important, and likely to affect clinical practice. In the trial, 11 units participated, with corresponding increase in study power. The Statistical Analysis Plan (including dummy tables) was reviewed by the independent oversight committees prior to analysis by allocated arm.

Participants were analysed according to their assigned group, using the intention-to-treat principle. To account for the stepped-wedge design and potential for selection bias, differences in pre-specified, clinically relevant baseline characteristics were tested using logistic regression for binary variables and ordered logistic regression for ordered categorical variables. If there were more than 5% with missing data for the primary outcome, further adjustment would be considered.

All outcomes were adjusted for centre and categorical time effects because of the trial design. Effects were estimated using multiple regression including terms for the intervention with fixed effects using dummy variables at each time in each centre. Centre was considered as a categorical variable and fitted as separate dummy variables for each centre. Calendar time was treated as a single categorical time variable. The primary outcome (time to pre-eclampsia diagnosis) was assessed by parametric survival analysis presented as adjusted time ratios of geometric means. Pre-specified sensitivity analyses were performed using linear regression on all women with a preeclampsia diagnosis by either the clinicians or the trial team, and censoring diagnosis within four weeks from trial entry.

Secondary outcomes were analysed using linear regression, adapting with log transformation where appropriate. All binary outcomes were analysed using a binomial regression model with a log link. Test performance was evaluated using sensitivity, specificity, positive and negative predictive values and positive and negative likelihood ratios. Mixed effects log-normal regression curves were generated for the proportion of women diagnosed relative to time from trial entry. Health care resource use was analysed using generalised linear mixed models (GLMM) with linear time fixed effects and random effects for centre. Suitable family and link functions were chosen based on the Akaike Information Criterion (AIC) to account for non-normally distributed data.
All statistical analyses were undertaken using Stata version 14·2 (StataCorp, College Station, Texas, USA).

Reporting

All results have been reported using the CONSORT extended guideline for cluster trials (2012) [18] (supplementary material).

Role of the Funding Source

The funder of the study did not participate in the design, data collection, analysis or interpretation of the results, or in the preparation of the manuscript. The corresponding author had full access to all of the data and had the final responsibility for the decision to submit for publication.

Results

Enrolment

Between 13 June 2016 and 27 October 2017, 1035 women were enrolled for the trial from 11 maternity units; 12 women were found to be ineligible (Figure 2). Of the 1023 eligible women, 576 were assigned to the intervention group, and 447 to usual care. Outcomes were collected on 1019 (99·6%); three women were lost to follow up, and one withdrew consent to follow-up data collection. No further analyses were needed to account for missing data (0·4%). There was no contamination between trial arms. With usual care, there were nine women at one site whose samples were not processed due to an administrative error, and two women at other sites in whom a sample was not obtained. Participant characteristics are given in Table 1. Recruitment by trial centre is shown in Table S1. The two groups were comparable at trial entry with no significant differences seen in baseline variables.

Primary outcome

The median time to preeclampsia diagnosis was reduced in the intervention group compared to usual care (1·9 vs 4·1 days; adjusted time ratio 0·39 (95% CI 0·17-0·91)) (Table 2). The intra-cluster correlation for the primary outcome was 0.035. The total number of women diagnosed with preeclampsia was 35·8% in the intervention group, and 34·8% with usual care. A greater proportion of women were diagnosed within 24 hours of enrolment in the intervention group (20·3%) compared to those with usual care (15·8%; adjusted Odds Ratio (aOR) 3·6 (95% CI 1·16-11·2). Figure 3 shows the mixed-effects lognormal regression curves showing proportion of women diagnosed by time from trial entry showing differences in days (A), and weeks (B) with revealed PlGF testing.

Maternal Outcomes

There was a reduction in severe maternal adverse outcomes[19] in the intervention group compared to usual care (3·8% vs 5·4%; aOR 0·32 (95% CI 0·11-0·96)). In particular, there were five serious events (two eclamptic fits, two strokes and one cardiac arrest in four women) in the usual care group (all with low PlGF concentrations) compared to no such corresponding events in the intervention group (Table 2). A higher proportion of women received transfusion of blood products with usual care (3·1% vs. 1·6%; Table 2 and Table S2). There were no differences in highest mean systolic blood pressure, use of antihypertensive medication or magnesium sulfate. A higher proportion of women received a fetal ultrasound (76·6% in the intervention group vs 69·3% with usual care); higher umbilical artery pulsatility index was seen in the intervention group (15·5%) compared to usual care (8·8% (aOR 2·94 (95% CI 1·07-8·11)). Both groups had similar pre-labour caesarean section rates. Delivery gestation did not differ significantly between the intervention group and usual care (36·6 and 36·8 weeks respectively; mean difference -0·52 (95% CI -0·63 to 0·73).

The percentages of women who met the diagnostic criteria for preeclampsia following adjudication were similar in both groups (44·7% in the intervention group and 44·2% with usual care). In women with preeclampsia by adjudication, diagnosis was reached by the treating clinicians in 80·1% in the intervention group, compared to 78·7% with usual care.

Total antenatal outpatient attendances were 6·14 (standard error (SE) 0·53) visits in the intervention group vs 9·44 (SE 0·81) visits with usual care; however this difference effectively disappears using negative binomial regression adjusted for calendar time (negative binomial -0·04 (-0·23 to 0·16)). Inpatient nights were 7·43 (SE 0·36) in the intervention groups vs 7·26 (SE 0·38) nights with usual care (negative binomial -0·06 (-0·22 to 0·09)).

Perinatal Outcomes

There was no evidence of a difference in the composite adverse perinatal outcome with the intervention (15·0%) compared to usual care (14·1%; aOR 1·45 (95% CI 0·73-2·90). There were no differences in perinatal deaths, preterm delivery, birthweight centiles and neonatal unit admission rates (Table 3, Table S3). Pre-specified Serious Adverse Events are reported in Table 4. There was a reduction in the highest levels of neonatal care use (intensive and high dependency care nights) in the intervention group (15·17 (SE 1·7) nights vs 24·18 (SE 3·8) nights in the concealed testing (usual care) group (mean difference -10·64 (95% CI -20·81 to -0·47)) with no difference seen in admission nights in the special care baby unit.

Test accuracy

In the concealed testing (usual care) group, low PlGF (<100 pg/mL) concentrations had high test accuracy for determining preeclampsia requiring delivery within 14 days with high sensitivity (94·9%) and negative predictive values (98·3%) in women presenting before 35 weeks' gestation (Table 5). In women presenting between 35^{+0} and 36^{+6} weeks' gestation, the sensitivity and negative predictive value for delivery before 37 weeks were 96·2% and 97·1% respectively.

Discussion

This trial has shown that in women presenting with suspected pre-eclampsia, PlGF measurement incorporated into a management algorithm based on national guidelines, significantly reduces (by 60%) the time taken for treating clinicians to diagnose preeclampsia. This improvement was associated with a significant reduction in maternal adverse outcomes, with no detected difference in adverse perinatal outcomes. In addition, there was no increase in neonatal unit admission rates, with a reduction seen in the higher levels of neonatal care use. For over a hundred years,

preeclampsia diagnosis has relied on poorly reproducible clinical signs, (such as blood pressure and proteinuria); PlGF measurement presents a change for antenatal care that impacts positively not just in diagnosis, but on management and pregnancy outcome.

To our knowledge, this is the first multicentre randomised controlled trial of PlGF measurement as a diagnostic test for preeclampsia. Trials to assess the impact of diagnostic tests on clinical care are uncommon. The Patient Centred Outcomes Research Institute recommend that process of care outcomes (such as time to procurement of a definitive diagnosis) should be used to evaluate diagnostic tests, alongside patient centres outcomes such as morbidity or mortality outcomes.[20] Management of women in both arms of the trial followed the national guidelines on the management of hypertension in pregnancy. The difference between the usual care arm and the 'revealed PlGF' arm was PlGF measurement incorporated within management. This was a pragmatic trial, in order to reflect how angiogenic factor measurement may be adopted clinically and realistically within a healthcare service. Simple guidance was provided around the blood test result (as would be given in usual practice), with clinical management decisions of individual pregnant women left to the discretion of the treating clinician, including future assessments and schedules of care. The trial was intentionally designed to evaluate real-world effectiveness of the intervention,[21] rather than efficacy in ideal conditions, by mimicking adoption of the diagnostic test into clinical practice across a number of sites.

The strengths of this study include robust evaluation of a test on both real-world diagnostic performance and clinical impact (beyond demonstrating test accuracy), generalizability of the findings through testing across multiple sites, ethnically and socio-demographically diverse population inclusion, and pragmatic test implementation. The broad inclusion criteria for testing relate to usual antenatal presentations to obstetric triage. The provision of the management algorithm and short training package, with individual patient management left to the discretion of

the treating clinician, reflect how PlGF testing may be utilised if adopted more widely. We anticipate that these findings would be generalisable to similar settings where pregnant women present to physicians with suspected pre-eclampsia for assessment. All diagnoses were reviewed by the trial team, with application of stringent diagnostic criteria, masked to trial allocation. The analysis followed a pre-specified analysis plan. This trial also had some limitations; it was restricted to women with singleton pregnancies before 37 weeks' gestation and the findings may not be generalizable to multi-fetal pregnancies and those presenting with late-onset preeclampsia after 37 weeks' gestation, although the latter group are usually managed with planned delivery rather than surveillance.[22] As the greatest challenges associated with diagnostic uncertainty relate to women presenting prior to 37 weeks' gestation, in whom maternal and perinatal morbidity associated with preeclampsia is greatest, this trial has addressed an important component of clinical preeclampsia management.

Previous studies have used a cohort design to investigate the potential utility of angiogenic factors for preeclampsia diagnosis, rather than randomised trials. We have demonstrated similar test performance statistics in our masked trial arm to those seen in other large cohort studies[11, 23] and clinical evaluation studies.[24, 25] We did not report test performance in the intervention arm to avoid treatment paradox. In this trial we used PlGF testing, rather than the soluble fms-like tyrosine kinase 1/PlGF ratio as used in other studies.[23] As recent evidence has shown that the commercially available tests compare similarly in their prediction of need for delivery within 14 days;[26] we anticipate that these results would be generalizable in similar settings utilising alternative PlGF assays.

Suspected preeclampsia is one of the most frequent presentations to antenatal services, and current methods to risk stratify women are inadequate for accurate prediction of adverse outcomes. This trial has shown that clinical use of PlGF facilitates earlier diagnosis; as a result, more timely management, particularly relating to targeted surveillance of women at increased risk may

contribute to a reduction in maternal adverse events. Low PlGF concentrations have been shown to have high sensitivity and negative predictive values for intrauterine fetal death.[11] In this trial all stillbirths of morphologically normal babies were preceded by low PlGF measurement with 100% sensitivity. However, many of these babies had severe early-onset growth restriction, below a viable birthweight, where delivery was not an option and other interventions do not exist to impact on outcome. For pregnancies complicated by fetal growth restriction with a viable fetus between 26 and 32 weeks' gestation, there is evidence from long-term neurodevelopmental follow-up, that management should be directed by monitoring of the ductus venosus waveform and computerised CTG.[27] Earlier confirmation of placental dysfunction in suspected fetal growth restriction using PlGF has the potential to improve risk stratification and target surveillance. However, given the low numbers of stillbirths in this study, further work is required to investigate the utility of PlGF for the prevention of later stillbirths.

In the intervention group, there was a reduction in the duration of intensive and high dependency care received by infants compared to the concealed testing group. For maternal health care resource there was no difference between intervention and treatment groups. These findings may reflect more appropriate antenatal surveillance in at risk pregnancies, including earlier recognition of fetal compromise and more timely delivery, with more appropriate stratification of those at lower risk.

Previous cohort studies have suggested that test performance of angiogenic markers is highly accurate in ruling out preeclampsia.[11, 23] Angiogenic markers vary throughout gestation, and there is a paucity of evidence regarding acute changes in angiogenic markers in pregnancies with persistent clinical disease suspicion. Our trial did not assess repeat PlGF testing in women with recurrent presentations who remained undiagnosed, and the optimum timing of repeat sampling remains uncertain. Furthermore, whist this trial has evaluated the utility of PlGF using categories based on centile thresholds[11] there may be additional benefit to the use of PlGF as a continuous

measurement, in a similar manner to other clinically-utilised biochemical variables. Lastly, there may also be a role for PlGF measurement in prognostic stratification once pre-eclampsia is confirmed as a diagnosis, particularly at gestations where risk-benefit to mother and baby is difficult to balance.

In conclusion, the findings of this trial provide novel and strong evidence for the adoption of PlGF testing as a diagnostic adjunct in women presenting with suspected pre-eclampsia.

Contributions

All authors were involved in the study conception and in securing funding for the study. Study conduct and data collection were coordinated by KD and LCC. Study analysis was undertaken by KD and PS, supervised by LCC. Health economic analysis was undertaken by RH. The manuscript was written by KD and LCC, with assistance from JM, PS, RH and AS. All authors approved the final version of the manuscript.

Acknowledgements:

PARROT Trial Investigators are:

Rachna Bahl, Gabrielle Bambridge, Sonia Barnfield, Jenie Fetherston, Jo Ficquet, Carolyn Gill, Joanna Girling, Kate Harding, Asma Khalil, Jessica Lowe, Andrew Sharp, Nigel AB Simpson, Derek Tuffnell

We thank the independent Trial Steering Committee; Baskaran Thilaganathan, Christopher Gale, Beth Reeves, Lesley Munns and Kylie Watson, and the independent Data Monitoring Committee; Pollyanna Hardy, Lucy MacKillop and Katherine Tucker. We thank all participants and their obstetricians and midwives involved in trial recruitment; Derek Tuffnell and Jennifer Syson, Bradford Teaching Hospitals NHS Foundation Trust; Jenny Myers and Catherine Chmiel, Central Manchester University Hospitals NHS Foundation Trust; Kate Harding and Jenie Fetherston, Guy's and St Thomas' NHS Foundation Trust; Gabrielle Bambridge and Amisha Chauhan, Kingston Hospital NHS Foundation Trust; Nigel Simpson and Rebecca Hudson, Leeds Teaching Hospitals NHS Trust; Andrew Sharp and Michelle Dower, Liverpool Women's NHS Foundation Trust; Sonia Barnfield and Mary Alvarez, North Bristol NHS Trust; Asma Khalil and Emily Marler, St George's University Hospitals NHS Foundation Trust; Jo Ficquet and Mel Rich, Royal United Hospitals Bath NHS Foundation Trust; Rachna Bahl and Carole Shahin, University Hospitals Bristol NHS Foundation Trust, Joanna Girling and Bernadette Tilley, Chelsea and Westminster University Hospitals NHS Foundation Trust; the sponsors, Guy's and

St Thomas' NHS Foundation Trust and King's College London. Disclosure forms are provided by the authors.

Declaration of Interests

KD, LCC, PS, JM and AS have no conflicts of interest. RH has received writing fees from Alere for previous work.

Acknowledgements

This trial was supported by grants from the National Institute for Health Research, Research for Patient Benefit Programme (PB-PG-0214-33054) and National Institute for Health Research Professorship (Chappell RP-2014-05-019). The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health. We thank all women who participated in the PARROT Trial.

The trial was approved by the London South East Research Ethics Committee (ref. 15/LO/2058).

Data sharing: The dataset will be available to appropriate academic parties on request from the corresponding author in accordance with the data sharing policies of King's College London, with input from the Co-investigator group where applicable, subject to submission of a suitable study protocol and analysis plan.

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Table 1

Participant Demographics and Clinical Characteristics at Enrolment

	Revealed (intervention) N= 576	**Usual Care (non-intervention) N= 446**	**P***
Age (years) Mean (SD)	31·87 (5·92)	31·49 (5·98)	0·66
Ethnicity n (%)			
White	378 (66·0%)	292 (65·8%)	0·46
Black	76 (13·3%)	63 (14·2%)	
Asian	67 (11·7%)	52 (11·7%)	
Mixed	13 (2·3%)	11 (2·5%)	
Other (including Chinese)	39 (6·8%)	26 (5·9%)	
Body Mass Index (kg/m^2) Median (IQR)	27·9 (23·9, 33·1)	28·4 (24·2, 34·1)	0·86
Parity n (%)			0·32
0	317 (55·0%)	211 (47·2%)	
1	133 (23·1%)	120 (26·8%)	
2	59 (10·2%)	65 (14·5%)	
>2	67 (11·6%)	51 (11·4%)	
Previous pregnancies < 24 weeks n (%)			
0	449 (80·3%)	318 (71·9%)	
1	65 (11·6%)	81 (18·3%)	
≥2	45 (8·1%)	47 (10·5%)	
Previous preeclampsia (multiparous women) n (%)	99 (38·2%)	92 (39·1%)	0·46
Pre-existing chronic hypertension	87 (15·1%)	70 (15·7%)	
Pre-existing renal disease	24 (4·2%)	17 (3·8%)	

Pre-pregnancy diabetes	31 (5·4%)	26 (5·8%)	
Blood pressure at booking (mmHg)			
Systolic mean (SD)	120 (14·5)	120 (15·6)	
Diastolic mean (SD)	74 (10·8)	72 (11·7)	
Prophylactic aspirin prescribed n (%)	235 (41·1%)	178 (39·9%)	
Gestational Diabetes n (%)	71 (12·4%)	53 (11·9%)	
Presenting signs and symptoms (non-exclusive) n (%)			
New onset hypertension	299 (51·9%)	209 (46·9%)	0·11
Worsening of existing hypertension	100 (17·4%)	79 (17·7%)	-
New onset proteinuria	341 (59·2%)	263 (59·0%)	0·94
Epigastric/right upper quadrant pain	47 (8·2%)	47 (10·5%)	-
Neurological Symptoms	187 (32·5%)	150 (33·6%)	-
Suspected fetal growth restriction	103 (17·9%)	62 (13·9%)	0·09
Abnormal blood results	19 (3·3%)	8 (1·8%)	-
Reduced fetal movements	6 (1·0%)	5 (1·1%)	-
Gestation at enrolment, weeks (SD)	32·3 (3·8)	32·7 (3·9)	0·07
Highest blood pressure in 48 hours prior to study entry (mmHg)			
Systolic mean (SD)	144 (20)	143 (20)	0·42
Diastolic mean (SD)	91 (14)	91 (13)	0·54
Highest dipstick proteinuria in 48 hours prior to study entry n (%)			
None	207 (36·5%)	170 (38·1%)	-
Trace	60 (10·6%)	57 (12·8%)	-
+1	153 (27·0%)	108 (24·2%)	-

≥+2	147 (25·9%)	111 (24·9%)	0·70
Placental Growth Factor (PlGF) (pg/mL)			
Mean (SD)	185·87 (277)	202 (355)	
Median (IQR)	55·3 (13, 235)	39·3 (12·4, 236)	
PlGF (pg/mL) n (%)			
<12	130 (22·7%)	106 (23·8%)	
12-100	213 (37·2%)	173 (38·8%)	
>100	230 (40·1%)	167 (37·4%)	

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469 * P values were only calculated for pre-specified baseline variables to avoid multiple testing.

470

471 **Table 2.**

472 **Primary and Secondary Maternal Outcomes.**

	Revealed (intervention) N = 573	**Usual Care (non-intervention)** N = 446	**Effect size**
Primary Outcome			
Number of women diagnosed with preeclampsia n (%)	**N= 205 (35·8%)**	**N= 155 (34·8%)**	
Time to diagnosis of preeclampsia (for those diagnosed) (days) Median (IQR)	1·9 (0·5, 9·2)	4·1 (0·8, 14·7)	Time ratio 0·39 (0·17-0·91)
Secondary Maternal Outcomes			
Maternal adverse outcomes n (%)* **(non-exclusive)**	22 (3·8%)	24 (5·4%)	OR 0·32 (0·11-0·96)
Central nervous system n (%)			
Eclampsia	0 (0·0%)	2 (0·4%)	
Stroke	0 (0·0%)	2 (0·4%)	
Cardiovascular/ respiratory n (%)			
Myocardial infarction	0 (0·0%)	1 (0·02%)	
Intubation (other than for caesarean section)	0 (0·0%)	1‡ (0·02%)	
Pulmonary oedema	2 (0·3%)	0 (0·0%)	
Blood oxygen saturations <90%	1 (0·02%)	1 (0·02%)	
Infusion of third parenteral antihypertensive	1 (0·02%)	3 (0·07%)	
Haematological n (%)			
Platelets $<50\times10^9$/L	4 (0·7%)	4 (0·9%)	

Hepatic n (%)			
Acute fatty liver of pregnancy	1 (0·2%)	0 (0·0%)	
Renal n (%)			
Severe acute kidney injury	7 (1·2%)	6 (1·3%)	
Dialysis	0 (0·0%)	1 (0·02%)	
Other adverse events n (%)			
Transfusion of blood products	9 (1·6%)	14 (3·1%)	
Maternal death n (%)	0 (0·0%)	0 (0·0%)	
Primary Diagnosis (exclusive) n (%)			
All preeclampsia			
Preeclampsia	175 (30·5%)	126 (28·3%)	
Superimposed preeclampsia	30 (5·2%)	29 (6·5%)	
All other diagnoses			
Gestational hypertension	100 (17·5%)	77 (17·3%)	
Gestational Proteinuria	29 (5·1%)	20 (4·5%)	
Isolated Small for Gestational Age infant	32 (5·6%)	28 (6·3%)	
Chronic hypertension only	37 (6·5%)	28 (6·3%)	
Chronic hypertension with Small for Gestational Age	11 (1·9%)	9 (2·0%)	
infant	7 (1·2%)	4 (0·9%)	
Renal Disease	94 (16·4%)	63 (14·1%)	
Normal	8 (1·4%)	20 (4·5%)	
Transient hypertension			
Adjudicated diagnosis	50 (8·7%)	42 (9·4%)	
Diagnosis of preeclampsia by adjudication team			
Total number of women with preeclampsia n (%)	256 (44·7%)	197 (44·2%)	

Severe preeclampsia n (%)	98 (17·1%)	67 (15·0%)	
Time to diagnosis 0-23.9 hours n (%)	52 (20·3%)	31 (15·8%)	OR 3·6 (1·16-11·2)
Gestation at preeclampsia diagnosis (weeks)			
Mean (SD)	33·7 (3·6)	34·6 (3·4)	
Pre-eclampsia diagnosed within 4 weeks of trial entry n (%)	186 (90·1%)	133 (85·8%)	
Time to diagnosis of preeclampsia (of those diagnosed within 4 weeks of trial entry) (days)			Time ratio
Median (IQR)	1·3 (0·3, 6·0)	2·7 (0·7, 8·9)	0·37 (0·15-0·90)
Fetal growth abnormalities on ultrasound (non-exclusive) n (%)			
Any of the following:			OR
Scanned	438 (76·6%)	307 (69·3%)	-
Any growth abnormality identified	142 (32·4%)	67 (21·8%)	1·74 (0·87 to 3·47)
Abdominal circumference <10th centile	86 (19·6%)	41 (13·4%)	-
Estimated fetal weight <10th centile	117 (26·7%)	62 (20·2%)	1·49 (0·70 to 3·15)
Umbilical artery pulsatility index >95th	66 (15·1%)	27 (8·8%)	2·94 (1·07 to 8·11)
Absent or reversed end diastolic flow	43 (9·8%)	16 (5·2%)	-
Amniotic fluid index <5th centile	28 (6·4%)	15 (4·9%)	-
Use of antihypertensives (%)	347 (60·6%)	270 (60·5%)	OR 0·91 (0·56 to 1·47)
Use of magnesium sulfate n (%)	72 (12·6%)	64 (14·3%)	OR 0·95 (0·46 to 1·95)
Use of antenatal corticosteroids for fetal lung maturity n (%)	200 (34·9%)	132 (29·6%)	OR 1·26 (0·75 to 2·11)
Systolic blood pressure > or = 160mmHg n (%)	43 (7·5%)	41 (9·2%)	
Placental Abruption n (%)	4 (0·7%)	5 (1·1%)	

Labour onset n (%)			
Spontaneous	79 (13·8%)	78 (17·5%)	
Induced	263 (46·0%)	210 (47·1%)	
Pre-labour Caesarean section	230 (40·2%)	158 (35·4%)	
Gestation at delivery, weeks			Mean difference
Mean (SD)	36·6 (3·03)	36·8 (3·03)	-0·52 (-0·63 to 0·73)
Time to delivery (all diagnoses), days			Ratio of means
Geometric mean (SD)	19·0 (3·1)	17·8 (3·1)	1·10 (0·99-1·24)
Preterm delivery <37 weeks n (%)	234 (40·8%)	167 (37·4%)	OR 1·00 (0·61 to 1·63)
Mode of labour onset n (%)			
Spontaneous	79 (13·8%)	78 (17·5%)	
Induced	263 (46·0%)	210 (47·1%)	
Pre-labour Caesarean	230 (40·2%)	158 (35·4%)	
Mode of delivery n (%)			
Spontaneous vaginal cephalic	210 (36·6%)	182 (40·8%)	OR 1·04 (0·59 to 1·86)
Assisted vaginal (forceps or vacuum)	42 (7·3%)	38 (8·5%)	-
Vaginal breech	1 (0·2%)	2 (0·4%)	-
Pre-labour Caesarean section	170 (29·7%)	130 (29·1%)	OR 0·95 (0·58 to 1·55)
In labour Caesarean section	150 (26·2%)	94 (21·1%)	-
Obstetric			
Major postpartum haemorrhage, n (%)	49 (8·5%)	48 (10·8%)	
Maternal Health resource Use			
Outpatient attendances (visits) mean (SE)	6·14 (0·53)	9·44 (0·81)	Negative Binomial -0·04 (-0·23 to 0·16)
	7·43 (0·36)	7·26 (0·38)	Negative Binomial

Total inpatient nights mean (SE)			-0·06 (-0·22 to 0·09)

473 *Only components with an outcome are included here. Full details in supplementary Table 1.

474

475 **Table 3**

476 Secondary Perinatal Outcomes

477

	Revealed (intervention) N = 573	**Usual Care (non-intervention)** N = 446	**P***
Secondary Perinatal Outcomes			
Status at Birth n (%)			
Livebirth	567 (99·0%)	440 (98·9%)	
Intrauterine fetal death	7 (1·2%)	6 (1·3%)	
Perinatal adverse outcome*, n (%)	86 (15·0%)	63 (14·1%)	OR 1·45 (0·73 to 2·90)
Perinatal adverse outcomes (composite; non-exclusive) n (%)			
Central nervous system:			
Intraventricular haemorrhage (any grade)	7 (1·3%)	11 (2·5%)	
Seizure	0 (0·0%)	2 (0·4%)	
Retinopathy of prematurity (any grade)	9 (1·6%)	9 (2·1%)	
Respiratory:			
Respiratory distress syndrome	78 (14·2%)	54 (12·2%)	
Bronchopulmonary dysplasia	5 (0·9%)	3 (0·7%)	
Gastrointestinal:			
Necrotising enterocolitis (stage 2 or 3)	7 (1·2%)	7 (1·6%)	
Perinatal death n (%)	6 (1·0%)	4 (0·9%)	
Late neonatal death (%)	3 (0·5%)	1 (0·2%)	
Neonatal unit admission n (%)	195 (34·5%)	146 (33·0%)	OR 1·09 (0·66 to 1·80)

Birthweight (grams) Mean (SD)	 2657 (887)	 2720 (858)	Mean Difference 9 (-188 to 206)
Birthweight centile Mean (SD)	 42·8 (33·0)	 43·4 (33·1)	Mean Difference 0·58 (-0·59 to 0·50)
Birthweight < 10th centile	124 (21·8%)	98 (22·1%)	OR 0·82 (0·46 to 1·44)
Birthweight < 3rd centile	58 (10·2%)	43 (9·7%)	OR 0·89 (0·40 to 2·00)
Apgar at 5 minutes after delivery mean (SD)	9·14 (1·52)	9·24 (1·41)	
Umbilical arterial pH at birth	7·25 (0·11)	7·23 (0·09)	
Perinatal Health Resource Use (for those admitted)			
 Inpatient neonatal unit nights mean (SE) Intensive Care Unit/ High Dependency Unit Special Care Baby Unit	 22·07 (25·88) 15·17 (1·7) 14·70 (14·41)	 24·62 (35·19) 24·18 (3·8) 13·09 (12·58)	Mean Difference - -10·64 (-20·81 to 0·47) 1·64 (-3·22 to 6·51)

478 *Only components with an outcome are included here. Full details in supplementary Table 2.

479

480 **Table 4**

481 **Serious Adverse events (pre-specified as reportable)**

	Total	**Revealed (intervention) N= 9**	***PlGF <5th Centile***	**Usual care (non-intervention) N= 9**	***PlGF <5th Centile***
Maternal Serious Adverse Events number of women	4	0		4	
Maternal death	0	0		0	
Maternal stroke	2	0		2	*2*
Maternal Cardiac Arrest	1	0		1*	*1*
Eclampsia	2	0		2	*2*
Perinatal Serious Adverse Events number of babies	17	10		7	
Intrauterine fetal death					
Pre-viable**	6	3	*2*	3	*3*
Viable (no dysmorphism)	4	1	*1*	3	*2 (1 not processed)*
Viable (dysmorphism noted)	3	3	*1*	0	*0*
Neonatal death	4	3	*3*	1	*1*

482 *This cardiac arrest occurred as an additional event to a stroke.

483 ** Defined as < 24 weeks' gestation or < 500 grams

484

Table 5

Test performance statistics in women allocated to usual care (concealed testing) for low Placental Growth Factor in prediction of preeclampsia

	Enrolled <35 weeks' gestation N=265	**Enrolled 35-36^{+6} weeks' gestation N= 170**
	Preeclampsia requiring delivery within 14 days	Preeclampsia requiring delivery before 37 weeks
PlGF <100 pg/mL		
Sensitivity (%; 95% CI) n/N	94·9 (82·7 to 99·4) 37/39	96·3 (81·0 to 99·9) 25/27
Specificity (%; 95% CI) n/N	52·7 (45·9 to 59·3) 119/226	23·8 (17·1 to 31·6) 34/143
Positive predictive value (%; 95% CI) n/N	25·7 (18·8 to 33·6) 37/144	19·3 (13·0 to 26·9) 26/135
Negative predictive value (%; 95% CI) n/N	98·3 (94·2 to 99·8) 119/121	97·1 (85·1 to 99·9) 34/35
Positive likelihood ratio (95% CI)	2·00 (1·71 to 2·34)	1·26 (1·12 to 1·42)
Negative likelihood ratio (95% CI)	0·10 (0·03 to 0·38)	0·16 (0·02 to 1·09)
PlGF <12 pg/mL		
Sensitivity (%; 95% CI) n/N	74·4 (57·9 to 87·0) 29/39	37·0 (19·4 to 57·6) 10/27
Specificity (%; 95% CI) n/N	84·1 (78·6 to 88·6) 190/226	78·3 (70·7 to 84·8) 12/143

Positive predictive value (%; 95% CI) n/N	44·6 (32·3 to 57·5) 29/65	24·4 (12·4 to 40·3) 10/41
Negative predictive value (%; 95% CI) n/N	95·0 (91·0 to 97·6) 190/200	86·8 (79·7 to 92·1) 112/129
Positive likelihood ratio (95% CI)	4·67 (3·28 to 6·64)	1·71 (0·95 to 3·06)
Negative likelihood ratio (95% CI)	0·30 (0·18 to 0·52)	0·80 (0·59 to 1·09)

488

489

Figure 1

Clinical Management Algorithm

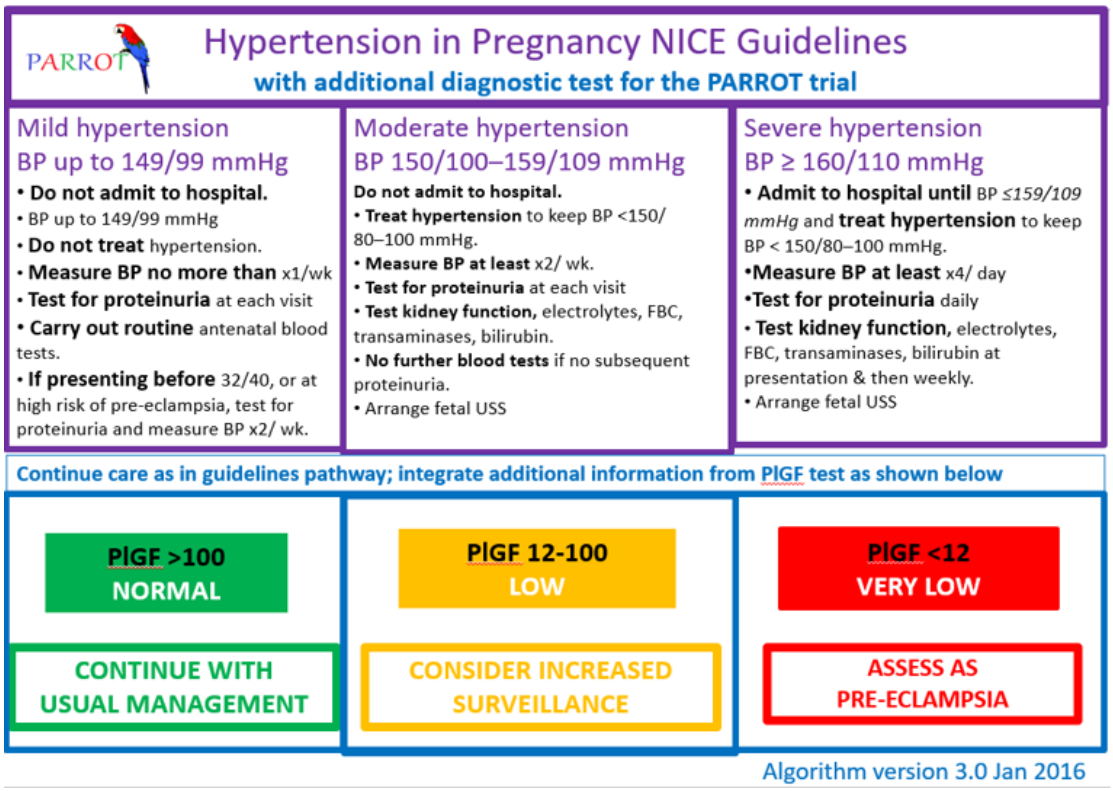

Figure 2

Consort Diagram

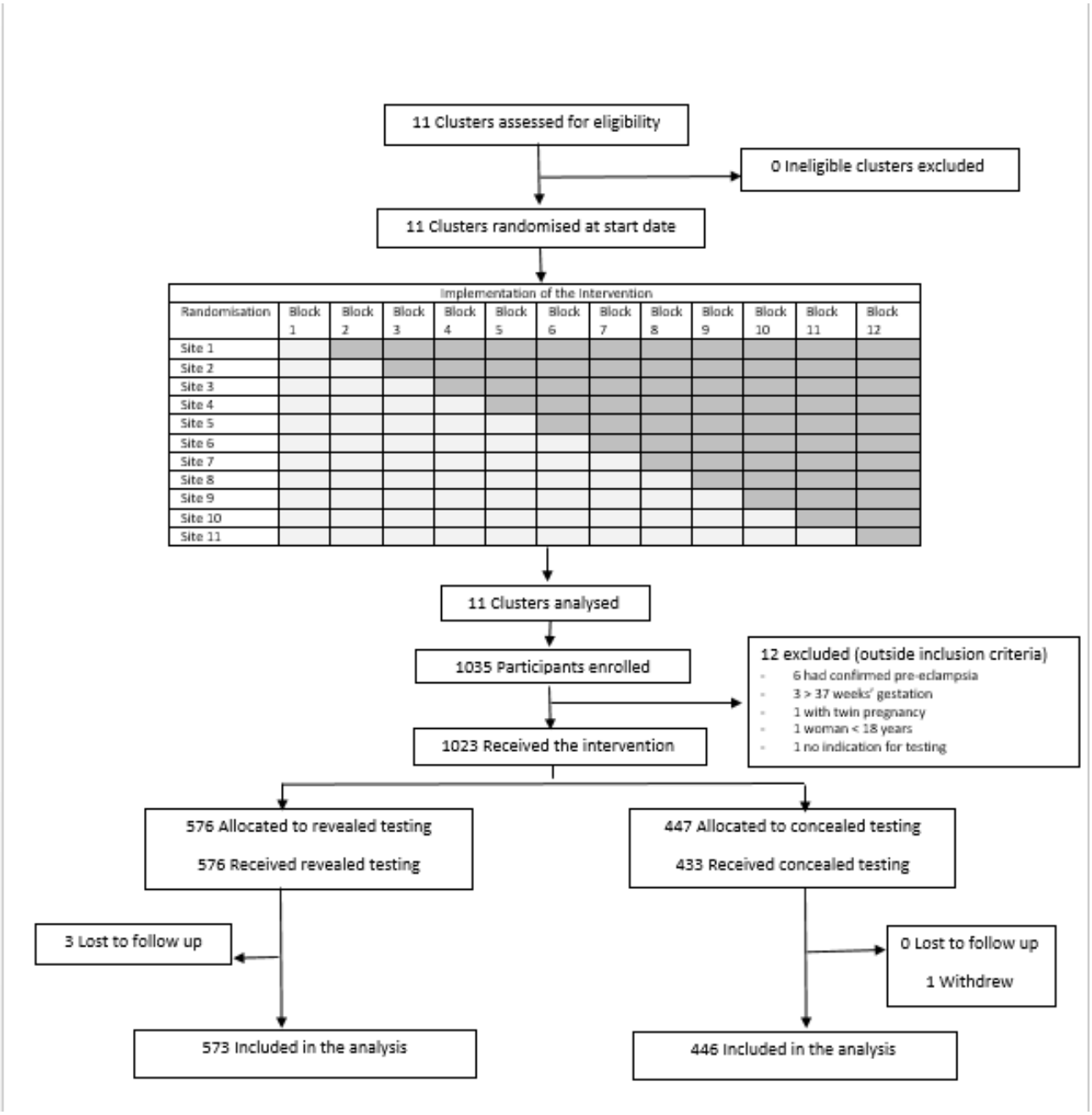

Figure 3

Proportion of women diagnosed with preeclampsia over time; mixed-effects lognormal regression curves showing proportion of women diagnosed by time from trial entry showing differences in days (A), and weeks (B) with revealed PlGF testing