

1 **Placental Growth Factor Informed Management of Suspected Pre-eclampsia or**
2 **Fetal Growth Restriction: The MAPPLE Cohort Study**

3
4 Andrew SHARP^{1*}, Lucy C. CHAPPELL^{2*}, Gustaaf DEKKER³, Sanja PELLETIER⁴, Yves GARNIER⁴, Onur
5 ZEREN⁴, Katharina M. HILLERER⁵, Thorsten FISCHER⁵, Paul T. SEED², Mark TURNER¹, Andrew H.
6 SHENNAN², Zarko ALFIREVIC¹

7
8 **Affiliations:**

- 9 1. Department of Women's and Children's Health Research, University of Liverpool, United
10 Kingdom
11 2. Women's Health Academic Centre, King's College London, United Kingdom
12 3. Department of Obstetrics and Gynaecology, Lyell McEwin Hospital, University of Adelaide,
13 Australia
14 4. Klinik für Frauenheilkunde und Geburtshilfe, Klinikum Osnabrück, Lehrkrankenhaus der
15 Universität Münster, Germany
16 5. Department of Obstetrics and Gynecology, Paracelsus Medical University, Salzburg, Austria.

17
18 *joint senior authors

19
20 **Correspondence:**

21 Dr Andrew Sharp

22 Department of Women's and Children's Health Research, University of Liverpool, Liverpool
23 Women's Hospital, Crown Street, Liverpool, L8 7SS, United Kingdom.

24 Tel: +44 151 795 9560

25
26 Email: asharp@liv.ac.uk

27

28 **Abstract**

29 **Objectives**

30 Placental Growth Factor (PIGF) has been shown to be beneficial in diagnosing pre-eclampsia. We performed
31 a prospective cohort study of revealed PIGF in standard clinical use in four teaching hospitals in UK,
32 Germany, Austria and Australia.

33

34 **Study Design**

35 Clinical data from women with suspected pre-eclampsia or fetal growth restriction < 35 weeks' gestation
36 with revealed PIGF measurement were collected (MAPPLE study).

37

38 **Main Outcome Measures**

39 Data were compared to the PELICAN study (PIGF concealed). Pre-specified outcomes were compared using
40 standard statistical tests (median difference or Risk Ratio). The results were further categorised by PIGF
41 concentration: i) very low (<12pg/ml), ii) low (12-100pg/ml), iii) normal (>100pg/ml).

42

43 **Results**

44 396 women managed with revealed PIGF (MAPPLE) were compared with 287 women with concealed PIGF
45 (PELICAN). Revealed PIGF led to delivery 1.4 weeks earlier (-2.0 to -0.9, 34.9 weeks vs 36.7 weeks). There
46 were no significant differences in maternal adverse outcomes (11.9% vs 10.1%, Risk Ratio (RR) 1.17, 95%CI
47 0.76-1.82) or caesarean sections (73.8% vs 64.5%; RR 1.14, 95%CI 1.03 to 1.26). Revealed PIGF led to fewer
48 perinatal deaths (2 vs 9; RR 0.16, 95%CI 0.03 to 0.74) and fewer babies with birthweight <3rd centile (28.9%
49 vs 36.1%; RR 0.80, (0.65 to 0.99), but with more neonatal adverse outcomes (30.4% vs 17.1%; RR 1.78, 95%CI
50 1.32 to 2.41).

51

52 **Conclusions**

53 Revealed PIGF may be associated with lower perinatal mortality and birthweight <3rd centile but appears to
54 lead to earlier delivery with more neonatal respiratory morbidity. Randomised trials with adequate power
55 for clinical outcomes are needed.

56

57 **Funding**

58 Financial assistance was received from Alere to support the running of the MAPPLE database. Alere had no
59 access to the information or control over the database itself.

60

61 **Keywords**

62 Placental Growth Factor, Pre-eclampsia, Pregnancy Outcome, Small for Gestational Age Fetus, Stillbirth

63

64 **Highlights**

- 65 • We report PIGF-led management of pregnant women as part of routine clinical care
- 66 • We compared our revealed PIGF cohort to a previous cohort with concealed PIGF results
- 67 • Revealed PIGF leads to earlier delivery by 1.4 weeks
- 68 • Revealed PIGF leads to fewer perinatal deaths and babies <3rd centile at birth
- 69 • Revealed PIGF increased neonatal morbidity, predominantly due to respiratory causes

70

71 **Introduction**

72 Pre-eclampsia is a multisystem disorder affecting 3-5% of pregnancies and is associated with abnormal
73 placentation and placental dysfunction (1). The detection of pre-eclampsia is a major focus of maternity care
74 as it remains a significant cause of maternal and perinatal morbidity and mortality (1). The only treatment
75 for pre-eclampsia currently available is delivery and therefore accurate diagnosis with the aid of a biomarker
76 could allow adjustment to clinical care.

77
78 Placental Growth Factor (PlGF) is one of several biomarkers which have been shown to have a predictive
79 capacity for the screening and detection of pre-eclampsia (2, 3). PlGF is produced by the syncytiotrophoblast
80 and is identifiable in maternal blood from as early as 12 weeks (4) with concentrations increasing with
81 gestation until around 30 weeks before declining until birth (5). A decline in PlGF appears to represent a
82 negative syncytiotrophoblast stress response to a variety of insults ranging from hypoxia (6), inflammation,
83 oxidative stress(7) and is as such also seen as part of syncytiotrophoblast aging. PlGF concentrations are
84 lower in pre-eclampsia (2), and extremely low in severe early-onset pre-eclampsia (8). Recently it has also
85 been suggested that low PlGF concentrations are associated with fetal growth restriction (FGR) (9) and
86 placental dysfunction (10).

87
88 Currently the National Institute for Health and Care Excellence (NICE) (11) recommends the use of two
89 platforms for PlGF assessment in pregnancy, produced by Alere (2) and Roche (12). The Alere platform uses
90 antibodies against PlGF isoform-1, with some cross-reactivity for isoform-2, and has a moderate body of
91 evidence for its clinical effectiveness at determining pre-eclampsia requiring delivery within 14 days
92 (PELICAN study) (2, 13). The Roche platform, which measures soluble FMS-like tyrosine kinase-1 (sFlt-1)
93 relative to PlGF also has a developing body of evidence (PROGNOSIS study) (12). Both tests have been
94 endorsed by NICE for the investigation of hypertension in pregnancy, to 'rule out' a diagnosis of pre-
95 eclampsia (11). Economic benefits, with savings of approximately £500 per patient, have also been
96 suggested to be achievable if a PlGF based management pathway for women with hypertension in
97 pregnancy is instigated (13).

98
99
100 To date there have not been any published randomised controlled trials of the use of PlGF as a diagnostic
101 test in women with hypertension in pregnancy. The best estimates of cost-effectiveness and clinical utility
102 will come from randomised controlled trials such as the PARROT study (14). However, until these are
103 available comparative cohort studies may offer an insight into the clinical impact of PlGF, when used as a
104 diagnostic test in women presenting with suspected pre-eclampsia. The objective of the MAPPLE study was

105 to report clinical outcomes in women managed with revealed PIGF results and to compare those outcomes
106 with those of the PELICAN study (2) in which clinicians were not informed of the PIGF result. This would
107 identify the potential clinical implications of revealing PIGF results to the clinician.

108

109 **Methods**

110 The Management of pregnancy complications with PIGF testing (MAPPLE) registry was established as a
111 prospective cohort of women managed with revealed PIGF results according to local guidelines as part of
112 clinical service evaluation. Four maternity units agreed to compile data on women with pregnancies
113 complicated by suspected pre-eclampsia or fetal growth restriction managed with revealed PIGF as part of
114 standard maternity care and funded from within maternity budgets. Participating units were located in the
115 United Kingdom (Liverpool), Austria (Salzburg), Germany (Osnabrück) and Australia (Adelaide).

116 A single 2.5ml whole blood sample was taken from each women into bottles containing ethylenediamine
117 tetra-acetic acid. The plasma derived after centrifugation at 3000rpm for 5 mins was tested for PIGF
118 concentration, using the Triage system (Alere, San Diego, CA), according to the manufacturer's instructions.
119 All meters were programmed throughout to produce a revealed PIGF result available immediately to
120 laboratory and clinical staff. The assay uses fluorescently labelled recombinant murine monoclonal
121 antibodies targeted to PIGF, which provide a quantifiable result within the range 12 to 3000pg/mL, within
122 approximately 15 minutes. The manufacturer states a limit of detection of 9-3000pg/ml (11).

123

124 Women presenting prior to 35 weeks' gestation attending their local hospital with suspected pre-eclampsia
125 or fetal growth restriction were offered PIGF testing in line with local hospital policy. No consent was
126 required as PIGF informed management constituted routine care in these units. Clinicians were aware of the
127 PIGF result and were expected to adjust care accordingly. An example of the PIGF guideline used at Liverpool
128 Women's Hospital can be found in Supplementary Text 1.

129

130 Anonymised clinical data were entered onto a dedicated study case report form. A data transfer agreement
131 was in place at each site before uploading to a secure database (Simplified Clinical Data Systems,
132 Portsmouth, NH). The uploaded data were assessed for completeness by the lead author. Ethical permission
133 was not required as no identifiable patient data were used.

134

135 Data for clinical outcomes were compared, where possible, between revealed (MAPPLE) and concealed
136 (PELICAN) cohorts (2) using median differences or risk ratios. Only the initial PIGF assessment was used even
137 if more than one sample was taken to maintain consistency with the PELICAN study.

138

139 The study is essentially a comparison of two cohorts of pregnant women, selected under different
140 circumstances and for different reasons. Accordingly, we decided to conduct an unadjusted comparison
141 between the studies, which reported on all the important measures, and estimated the size of the
142 differences and then to adjust comparisons for the principal differences between the women prior to PIGF
143 testing. Adjustment was made for maternal age, BMI, nulliparity, and proteinuria. For the adjusted analysis,
144 women with twin pregnancies were excluded, as were women where key predictors were missing.
145 When comparing event rates (e.g. perinatal deaths, perinatal adverse outcomes, results were expressed as
146 odds ratios, with 95% confidence intervals. For the main continuous measures birthweight and gestational
147 age at delivery, differences in the mean were calculated. For additional measures, either means (with SD) or
148 medians (with quartiles) were presented. Data are presented in the previously derived ranges of <12pg/ml
149 (very low), 12-100pg/ml (low; representing <5th percentile of normal) and >100pg/ml (normal) (2, 10).
150 Birthweights are presented as customised fetal weight centiles (15). We examined whether apparent
151 differences in infant outcomes could be due to confounding at baseline (maternal age, singleton pregnancy,
152 ethnicity, pre-gestational diabetes, APS/SLE, previous pregnancy complications, new hypertension,
153 suspected FGR and proteinuria) using multiple regression. We also compared the unadjusted and adjusted
154 impact of revealed PIGF on management of pregnant women (antenatal steroid use, induction of labour,
155 Caesarean section) using an interaction test.

156

157 **Results**

158 Between April 2014 and March 2016, clinical outcomes were obtained from 396 women presenting prior to
159 35 weeks' gestation with a known PIGF result and complete outcome dataset. The clinical datasets included
160 for analysis came from Liverpool: 241 women; Osnabrück: 115 women; Salzburg: 26 women; Adelaide 14
161 women.

162

163 The MAPPLE cohort varied from the PELICAN cohort in a number of demographic features (maternal age,
164 twin status, ethnicity, pre-gestational diabetes, APS/SLE, and complications of previous pregnancies) as
165 shown in Table 1. The distribution of PIGF sub-groups at first sampling were similar.

166

167 There were no significant differences in maternal adverse outcomes between women in the MAPPLE cohort
168 compared to those in the PELICAN study (11.9% vs 10.1%, Risk Ratio 1.17; 95% confidence intervals 0.76 to
169 1.82) with the majority of complications related to hepatic and renal dysfunction (Table 2).

170

171 There were 433 babies in the MAPPLE cohort and 299 in PELICAN (Table 2). There was a single stillbirth
172 within the MAPPLE cohort, in a woman with chronic hypertension with superimposed pre-eclampsia and

173 severe early-onset FGR who withdrew from clinical care before presenting two weeks later with an
174 intrauterine fetal death. There were significantly fewer perinatal deaths in the MAPPLE cohort (n=2, 0.5%)
175 compared to those in the PELICAN study (n=9; 3.0%; Odds Ratio 0.16 (0.03 to 0.74). More babies
176 experienced a composite perinatal adverse outcome in MAPPLE (n=133, 30.7%) than in PELICAN (n=61;
177 20.4%; Risk Ratio 1.51 (1.15 to 1.98), Neonatal adverse outcomes were more common in the MAPPLE cohort
178 (n=131; 30.4% vs. n=51; 17.1%; Risk Ratio 1.78 (1.32 to 2.41); these were dominated by respiratory
179 morbidity including respiratory distress syndrome (RDS) and bronchopulmonary dysplasia (BPD). A higher
180 proportion of babies in the MAPPLE cohort were admitted to the neonatal unit compared to those in the
181 PELICAN study (n=190; 45.5% vs n=117; 39.8%; Risk Ratio 1.14 (0.95 to 1.37).

182

183 The time between first PIGF test and delivery was shorter when PIGF result was revealed to the clinician with
184 a mean difference of 6 days (-2.0 to -10.0; 24 days vs 29 days) (Table 3). A greater proportion of women with
185 revealed PIGF (n=236; 59.9%) received antenatal steroids for fetal lung maturation compared to PELICAN
186 (n=88; 30.1%; Risk Ratio 1.95; 1.61-2.37).

187

188 Fewer women had fetal ultrasound assessment performed after PIGF sampling when PIGF was revealed
189 (89.1% vs 98.7%; Risk ratio 0.90; 0.87 to 0.94) but the proportion of women with estimated fetal weight
190 (EFW) <10th centile or abnormal fetal Doppler (absent or reversed end diastolic flow in the umbilical artery)
191 was similar in both studies. There was no evidence of revealed PIGF testing affecting decisions to give
192 steroids (p=0.09), induction of labour (0.13) or Caesarean section (0.18) assessed using interaction tests.
193 Women with revealed PIGF results were delivered at an earlier gestation with a mean difference of 1.4
194 weeks (-2.0 to -0.9, 34.9 weeks vs 36.7 weeks). There was an increased likelihood of the fetus being
195 delivered by caesarean section in the MAPPLE cohort compared to the PELICAN cohort (73.8% vs 64.5%; Risk
196 Ratio 1.14, 1.03 to 1.26). In women managed with revealed PIGF results, there was a significantly lower risk
197 of women delivering a small for gestational age (SGA) infant <3rd centile (Risk Ratio 0.80; 0.65 to 0.99)
198 compared to those managed with concealed PIGF results.

199

200 Evaluation of principal outcomes in women with a singleton pregnancy (n=356 in MAPPLE; n=275 in
201 PELICAN) with adjustment for baseline confounders did not substantially change the findings: mean
202 gestation at delivery 34.4 (SD 3.6) vs. 36.0 (3.8) weeks; unadjusted median difference -1.33 (-1.89 to -0.77)
203 and adjusted median difference -0.95 (-1.60 to -0.31) weeks; perinatal adverse outcomes 28.4% vs. 18.9%;
204 uOR 1.74 (1.20 to 2.51) and aOR 1.51 (0.93 to 2.43). When analysis was restricted to singleton pregnancies,
205 the increase in Caesarean sections was of borderline significance (uOR 1.39; 1.00 to 1.95) and the odds

206 reduced (and not significant) when adjusted for baseline confounders between the cohorts (aOR 1.33; 0.85
207 to 2.07).

208

209 Tables 4 and 5 report maternal and perinatal outcomes for women managed with revealed and concealed
210 testing by PIGF sub-group (<12, 12-100 and >100pg/ml). A greater proportion of women in the very low PIGF
211 group in both cohorts had maternal adverse outcomes (compared to the other groups) and the interval from
212 sampling to delivery was shortest in this group. As these two cohorts are not from a randomised
213 comparison, and the cohort has been further divided, further statistical testing has not been undertaken.
214 All stillbirths and perinatal deaths in revealed and concealed cohorts occurred in singleton pregnancies with
215 abnormal PIGF concentrations (low or very low) (Table 5). Gestation at delivery was earliest in women with
216 lowest PIGF concentrations, whether the result was revealed or concealed.

217

218 **Discussion**

219 In women managed with revealed PIGF results, there were fewer perinatal deaths; this may be due to
220 modifications in surveillance and monitoring of these pregnancies than if the PIGF result were unknown.
221 Previous observational cohorts have demonstrated a correlation between low PIGF concentrations at 19-24
222 weeks' gestation and subsequent stillbirth (16). Whilst around 25% of fetuses in both cohorts were identified
223 as having an estimated fetal weight <10th centile on ultrasound at presentation, there were significantly
224 fewer infants born small for gestational age (<3rd centile) in those managed with revealed PIGF results, even
225 after adjustment for baseline predictors, suggesting that earlier delivery due to revealed PIGF may have
226 prevented a slowing of fetal growth in utero. Revealing PIGF was associated with a shorter diagnosis to
227 delivery interval and an earlier gestation at delivery. We observed a similar rate of antenatal diagnosis of
228 SGA as the 15% observed in the sFlt1:PIGF study by Zeisler et al. (12).

229

230 The revealing of PLGF to the clinical team was associated with a significant reduction in perinatal mortality.
231 Not surprisingly this gain comes at the cost of increased neonatal unit admissions and perinatal morbidity, in
232 particular respiratory complications. This higher prevalence of respiratory morbidity in the MAPPLE cohort
233 may be related to the earlier gestation at delivery or increased use of caesarean delivery and was not
234 ameliorated by an increased use of antenatal steroids. Diagnosis of respiratory distress syndrome and
235 bronchopulmonary dysplasia was similar across centres within the MAPPLE study; it was higher than that in
236 the PELICAN study and the 10% observed in the TRUFFLE cohort of growth restricted fetuses (who share
237 many features with women in the PIGF <12pg/ml subgroup) (17).

238

239 Around 10% of women in both cohorts had maternal adverse outcomes, similar to previous observations (2),
240 with the majority of adverse outcomes other than abnormal biochemistry in women with very low PIGF
241 concentrations. There was less preeclampsia in the revealed cohort perhaps suggesting that earlier
242 intervention prevented a worsening of the maternal condition. However, women managed with revealed
243 PIGF results required frequent attendance at antenatal clinic and admission, possibly due to the persistence
244 of hypertension and other risk factors.

245

246 This is the largest cohort study to date assessing the impact of PIGF informed care on pregnancy outcome
247 and provides generalisable 'real life' data applicable across healthcare systems. At present these data
248 provide the best information about the consequences of PIGF results in pregnancy. Outcomes have been
249 compared between women managed with revealed results (MAPPLE) and those managed with concealed
250 results (PELICAN) and variation in practice, differences in multiple pregnancy numbers or ethnicity between
251 different countries could influence some of the outcomes. Statistical comparison was limited to those least
252 influenced by possible variations in practice.

253

254 Our findings are confirmed by the much smaller study by Cetin et al. (18), which assessed just 57 women
255 with pre-eclampsia and 16 with fetal growth restriction.

256

257 **Conclusion**

258 Implication for practice

259 Our data demonstrate that PIGF-informed management of high-risk pregnancies is feasible within standard
260 clinical care. This study was not designed to demonstrate cost-effectiveness or perform an economic analysis
261 of the use of PIGF, but previous assessments have suggested cost savings with PIGF use. Overall, our study
262 suggests that early intervention with PIGF-led management may prevent worsening of fetal health but at the
263 expense of earlier delivery and increased neonatal complications, almost exclusively due to respiratory
264 morbidity, despite increased use of antenatal steroids. This may be offset by lower perinatal mortality and
265 fewer small for gestational age babies.

266

267 The statistically significant reduction in stillbirths between revealed and concealed PIGF led care is of interest
268 but there should be caution in interpreting these data in light of the methodological differences between
269 these two cohorts. Further evidence from randomised controlled trials will assist in interpretation of these
270 findings. However, studies powered for stillbirth and perinatal death as an outcome are difficult to perform.
271 The pattern of earlier delivery suggests that clinicians consider optimal management and timing of delivery
272 in response to the knowledge of PIGF. However, earlier delivery (by six days) was also associated with

273 worsened short-term neonatal outcomes; this may have been influenced by a lower gestation at enrolment
274 in the revealed cohort and by the overall earlier gestation at delivery of 1.4 weeks. Education of obstetric
275 teams and increased confidence in PIGF assessment over time to ensure that PIGF use leads to increased
276 surveillance rather than precipitating delivery may optimise the benefit (i.e. reduced perinatal death) while
277 limiting iatrogenic delivery. Likewise, the mode of delivery should be determined by accepted obstetrical
278 indications rather than PIGF result alone. This should be considered when planning to introduce a new tests
279 in a high risk population.

280

281 Implications for research

282 The nature of this study, with different cohorts, precludes more detailed interpretation of the results in table
283 4 and 5. The true picture of potential clinical benefit or harm from PIGF-led management will only come
284 from further randomised studies of its use as well as full cost-effectiveness assessment. Until the results of
285 these studies are available, caution should be exercised before moving to PIGF-led management for all high-
286 risk women. Ongoing and future randomised studies should have adequate power to confirm or refute our
287 findings.

288

289 **Disclosure of Interests**

290 A Sharp and Z Alfirevic received financial assistance from Alere to support the running of the MAPPLE
291 database. Alere had no access to the information or control over the database itself.

292 A Shennan has been paid as a consultant for and received honoraria from Alere and has also been paid as a
293 consultant for Roche and Perkin Elmer.

294 All other authors declare no conflict of interests.

295

296 **Contribution to authorship**

297 A Sharp and ZA conceived the idea and performed the analysis and wrote the manuscript. LC and A Shennan
298 provided data from the PELICAN study and wrote the manuscript. PS performed statistical analysis. TF, KH,
299 SP, ZO, YG, MT and GD all provided data and reviewed the manuscript.

300

301 **Ethics approval**

302 Ethical permission was not required as no identifiable patient data were used.

303

304 **Funding**

305 This study was funded by financial assistance from Alere to support the running of the MAPPLE database.

306 Alere had no access to the information or control over the database itself.

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Table 1: Demographic data and clinical characteristics at enrolment for women in MAPPLE (revealed PIGF testing) and PELICAN (concealed PIGF testing) cohort studies presenting prior to 35 weeks' gestation.

	MAPPLE (revealed PIGF testing)	PELICAN (concealed PIGF testing)	Risk Ratio
	n=396	n=287	
Age (years; median, quartiles)	31 (27-35)	32 (27-36)	-1.3 (-0.4 to -2.3)
BMI (kg/m ² ; median, quartiles)	27 (24-32)	29 (24-34)	-0.8 (-0.1 to -1.8)
Nulliparous	208 (52.7)	164 (57.1)	0.92 (0.80 to 1.06)
Singleton pregnancy	360 (90.9)	275 (95.8)	0.95 (0.91 to 0.99)
Current Smoking	43 (11.3)	24 (8.6)	1.32 (0.82 to 2.12)
Ethnicity: White	357 (91.1%)	187 (65.6%)	
Ethnicity: Black	12 (3.1%)	70 (24.6%)	0.12 (0.07 to 0.22)
Ethnicity: Asian	8 (2.0%)	19 (6.7%)	0.24 (0.11 to 0.53)
Ethnicity: Other	19 (4.8%)	11 (3.8%)	
Previous Medical History			
Previous Preeclampsia	87 (22.0)	55 (19.2)	1.15 (0.85 to 1.55)
Chronic Hypertension	55 (14.4)	45 (15.7)	0.83 (0.58 to 1.19)
Systemic Lupus Erythematosus/ Antiphospholipid syndrome	6 (1.5)	12 (4.2)	0.34 (0.13 to 0.89)
Pre-gestational diabetes	37 (9.3)	6 (2.2)	4.19 (1.79 to 9.79)
Renal Disease	14 (3.5)	19 (6.6)	0.50 (0.26 to 0.98)
Previous hypertensive disorder of pregnancy (excluding preeclampsia)	7 (1.8)	15 (5.6)	0.32 (0.13 to 0.77)
Indication for PIGF testing (non-exclusive)			
New onset of hypertension	314 (79.5)	155 (54.0)	1.47 (1.31 to 1.66)
Persistent epigastric/ right upper quadrant pain	12 (3.0)	18 (6.3)	0.48 (0.24 to 0.99)
Suspected fetal growth restriction	66 (16.7)	25 (8.7)	1.92 (1.24 to 2.96)
Proteinuria	59 (14.9)	161 (56.1)	0.27 (0.21 to 0.34)
Gestational age at sampling, (weeks; median, quartiles)	30.7 (27.7-33.1)	31.0 (27.9-33.4)	-0.1 (0.3 to -0.7)
PIGF result at first testing			
PIGF <12	117 (29.5)	69 (24.0)	
PIGF 12-100	136 (34.3)	97 (33.8)	
PIGF >100	144 (36.3)	121 (42.2)	

311
312

313 **Table 2: Maternal and perinatal adverse outcomes for women in MAPPLE (revealed PIGF testing) and**
 314 **PELICAN (concealed PIGF testing) cohort studies presenting prior to 35 weeks' gestation with comparisons**
 315 **for major outcomes.**

	MAPPLE (revealed PIGF testing)	PELICAN (concealed PIGF testing);	Risk ratio
	n=396	n=287	
Final diagnosis of pre-eclampsia (n, %)	193 (52.9)	176 (61.3)	0.86 (0.75 to 0.99)
Women with maternal adverse outcomes (n, %)	47 (11.9)	29 (10.1)	1.17 (0.76 to 1.82)
Maternal adverse outcomes (non-exclusive) (n)	55	36	-
Maternal death	0	0	-
Central nervous system			
Eclampsia	0	1	-
Stroke; hypertensive encephalopathy	0	0	-
Cortical blindness or retinal detachment	0	0	-
Cardiovascular/ respiratory			
Myocardial infarction	0	0	-
Intubation (other than for caesarean section)	0	1	-
Pulmonary oedema	2	2	-
Haematological			
Platelets <50×10 ⁹ /L (without transfusion)	2	2	-
Disseminated intravascular coagulation	1	1	-
Thrombotic thrombocytopenic purpura/ haemolytic uraemic syndrome	0	0	-
Hepatic			
Dysfunction (Alanine transaminase ≥70IU/L)	38	23	
Haematoma; rupture; acute fatty liver of pregnancy	1	0	-
Renal			
Creatinine >150 µmol/L	7	2	-
Dialysis	2	0	-
Obstetric			
Placental abruption	1	4	-
Number of infants	n=433	n=299	Risk Ratio
Infants with composite perinatal adverse outcome (perinatal death or neonatal adverse outcome) (n, %)	131 (30.4)	60 (20.1)	1.51 (1.15 to 1.98)
Perinatal death (n, %)	2 (0.5)	9 (3.0)	0.16 (0.03 to 0.74)
Stillbirth (n, %)	1 (0.2)	7 (2.3)	-
Early neonatal death (n, %)	1 (0.2)	2 (0.7)	-
Infants with neonatal adverse outcomes (n, %)	131 (30.4)	51 (17.1)	1.78 (1.32 to 2.41)
Neonatal adverse outcomes (non-exclusive) (n)	178	62	-
Respiratory distress syndrome (n)	128 (30.5)	46 (15.4)	-

Bronchopulmonary dysplasia (n)	28 (6.7)	6 (2.0)	-
Intraventricular haemorrhage (Grade 3 or 4) (n)	4 (0.9)	0 (0.0)	-
Necrotising enterocolitis (n)	7 (1.7)	4 (1.3)	-
Retinopathy of prematurity (n)	11 (2.6)	6 (2.0)	-
Infants admitted to neonatal unit (n, %)	190 (45.5)	117 (39.8)	1.14 (0.95 to 1.37)

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317

318 **Table 3: Impact of PLGF testing of the pregnancy management in women in MAPPLE (revealed PIGF**
 319 **testing) and PELICAN (concealed PIGF testing) cohort studies presenting prior to 35 weeks' gestation**

	MAPPLE (revealed PIGF testing)	PELICAN (concealed PIGF testing)	Median Difference/ Risk Ratio
Maternal	n=397	n=287	
Interval from first test to delivery (days; median, quartiles)	24 (4 to 52)	29 (11 to 59)	-6.0 (-2.0 to -10.0)
Antenatal steroids (n, %)	236 (59.9)	88 (30.7)	1.95 (1.61 to 2.37)
Induction of labour (n, %)	97 (24.5)	108 (37.6)	0.66 (0.52 to 0.82)
Fetal	n=433	n=299	
Ultrasound scans (n, %)	384 (89.1)	295 (98.7)	0.90 (0.87 to 0.94)
Estimated fetal weight <10th centile (n/N, %)	80/375 (21.3)	83/285 (29.1)	0.73 (0.56 to 0.96)
Absent or reduced end diastolic flow (umbilical artery Doppler (n/N, %))	52/384 (13.5)	37/285 (13.1)	1.04 (0.70 to 1.54)
Perinatal	n=433	n=299	
Gestational age at delivery (weeks; median, quartiles)	34.9 (32.0-37.1)	36.7 (33.6–38.6)	-1.4 (-0.9 to -2.0)
Caesarean section (n, %)	318 (73.8)	193 (64.5)	1.14 (1.03 to 1.26)
Birthweight (grams; median, quartiles)	2280 (1490-2960)	2420 (1620–3125)	-160 (-15 to -310)
Small for gestational age infant <10th centile (n, %)	181 (42.2)	145 (48.5)	0.87 (0.74 to 1.02)
Small for gestational age infant <3rd centile (n, %)	124 (28.9)	108 (36.1)	0.80 (0.65 to 0.99)

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Table 4: Maternal and fetal outcomes in women in MAPPLE (revealed PIGF testing) and PELICAN (concealed PIGF testing) cohort studies presenting prior to 35 weeks' gestation presented by PIGF results at enrolment.

	MAPPLE (revealed)	PELICAN (concealed)	MAPPLE (revealed)	PELICAN (concealed)	MAPPLE (revealed)	PELICAN (concealed)
	PIGF <12	PIGF <12	PIGF 12-100	PIGF 12-100	PIGF >100	PIGF >100
Maternal	n=116	n=69	n=137	n=97	n=143	n=121
Final diagnosis of pre-eclampsia (n, %)	51 (48.6)	67 (97.1)	69 (53.1)	72 (74.2)	73 (56.2)	37 (30.6)
Women with any maternal adverse outcome (n, %)	25 (21.6)	12 (17.4)	16 (11.7)	8 (8.2)	6 (4.2)	9 (7.4)
Eclampsia	0	0	0	1	0	0
Intubation	0	1	0	0	0	0
Pulmonary oedema	1	2	1	0	0	0
Platelets <50×10 ⁹ /L	2	1	1	0	0	1
Disseminated intravascular coagulation	1	1	0	0	0	0
Dysfunction (Alanine transaminase ≥70IU/L)	23	9	11	7	4	7
Creatinine >150 µmol/L	1	2	4	0	2	0
Dialysis	0	0	1	0	1	0
Placental abruption	1	3	0	0	0	1
Interval from first test to delivery (median, quartiles)	3 (1 to 13)	9 (3 to 16)	19 (6 to 43)	23 (11 to 40)	48 (32 to 69)	61 (37 to 90)
Antenatal steroids for fetal lung maturity (n, %)	103 (89.6)	41 (59.4)	81 (59.6)	34 (35.1)	52 (36.4)	13 (10.7)
Induction of labour (n, %)	10 (8.6)	13 (18.8)	35 (25.5)	44 (45.4)	52 (36.4)	51 (42.1)
Antenatal clinic or assessment unit visits (mean, SD)	2.5 (5.5)	N/A	3.7 (5.3)	N/A	5.2 (5.5)	N/A
Antenatal inpatient nights (mean, SD)	2.3 (4.8)	N/A	2.4 (5.8)	N/A	3.8 (5.7)	N/A
Fetal	n=122	n=69	n=158	n=105	n=151	n=125
Number with ultrasound scans (n, %)	111 (91.0)	68 (98.6)	146 (92.4)	104 (98.4)	127 (84.1)	123 (90.6)
Estimated fetal weight <10th centile (n/N, %)	50/109 (45.9)	43/68 (63.2)	17/142 (12.0)	28/99 (28.3)	13/124 (10.5)	12/118 (10.2)
Absent or reduced end diastolic flow in umbilical artery - Doppler (n/N, %)	36/111 (32.4)	24/68 (35.3)	12/146 (8.2)	9/99 (9.1)	4/127 (3.1)	4/118 (3.4)

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Table 5: Perinatal outcomes in MAPPLE (revealed PIGF testing) and PELICAN (concealed PIGF testing) cohort studies presenting prior to 35 weeks' gestation presented by PIGF results at enrolment.

	MAPPLE (revealed)	PELICAN (concealed)	MAPPLE (revealed)	PELICAN (concealed)	MAPPLE (revealed)	PELICAN (concealed)
	PIGF <12	PIGF <12	PIGF 12-100	PIGF 12-100	PIGF >100	PIGF >100
Perinatal	n=124	n=69	n=158	n=105	n=151	n=125
Stillbirth (n, %)	1 (0.8)	4 (5.8)	0	3 (2.9)	0	0
Neonatal death (n, %)	1 (0.8)	2 (2.9)	0	0	0	0
Gestational age at delivery (weeks; median, quartiles)	31.2 (29.0-33.4)	31.9 (29.3-34.1)	35.0 (33.3-36.8)	35.7 (34.1-37.9)	37.4 (36.1-38.4)	38.4 (37-39.9)
Delivery <37 weeks (n, %)	120 (100)	65 (94.2)	126 (79.7)	64 (60.1)	58 (38.4)	29 (23.2)
Delivery <34 weeks (n, %)	97 (80.8)	50 (72.5)	48 (30.4)	23 (21.9)	22 (14.6)	10 (8.0)
Caesarean section (n, %)	115 (94.3)	57 (82.6)	120 (75.9)	74 (70.5)	83 (55.0)	62 (49.6)
Birthweight (grams; mean, SD)	1360 (970-1650)	1280 (862-1678)	2290 (1810-2740)	2270 (1757-2830)	2990 (2590-3355)	3100 (2672-3505)
Small for gestational age infant <10th centile (n, %)	92 (76.7)	57 (82.6)	65 (41.1)	59 (56.2)	24 (15.9)	29 (23.2)
Small for gestational age infant <3rd centile (n, %)	71 (59.2)	50 (72.5)	44 (27.8)	46 (43.8)	9 (6.0)	12 (9.6)
Neonatal unit admission (n, %)	94 (81.7)	53 (82.8)	71 (46.4)	46 (43.8)	25 (16.7)	18 (14.4)
Infants with neonatal adverse outcomes (n, %)	74 (60.7)	27 (39.1)	37 (23.4)	14 (13.3)	20 (13.2)	10 (8.0)
Respiratory distress syndrome (n, %)	72 (62.1)	23 (33.3)	36 (23.4)	14 (13.3)	20 (13.3)	9 (7.2)
Bronchopulmonary dysplasia (n, %)	19 (16.4)	6 (8.7)	4 (2.6)	0	5 (3.3)	0
Intraventricular haemorrhage (Grade 3/4) (n, %)	2 (1.6)	0	2 (1.3)	0	0	0
Necrotising enterocolitis (n, %)	4 (3.4)	3 (4.3)	2 (1.3)	0	1 (0.7)	1 (0.8)
Retinopathy of prematurity (n, %)	7 (6.0)	5 (7.2)	3 (1.9)	1 (1.0)	1 (0.7)	0

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