1 **Risk stratification for early-onset fetal growth restriction in women with abnormal serum**

2 **biomarkers: a retrospective cohort study.**

3 Ormesher L[1,2], Warrander L.[1,2], Liu, Y.[3], Thomas S.[2], Simcox L.[2], Smith GCS[4], Myers JE.[1,2] &
4 Johnstone ED. [1,2].
5
6 1. Division of Developmental Biology and Medicine, School of Medical Sciences, Faculty of
7 Biology, Medicine and Health, University of Manchester, Manchester Academic Health
8 Science Centre, Manchester, UK
9 2. St Mary's Hospital, Central Manchester University Hospitals NHS Foundation Trust,
10 Oxford Road, Manchester, UK
11 3. Monash University, Scenic Boulevard & Wellington Road, Clayton 3800, Australia
12 4. Department of Obstetrics and Gynaecology, University of Cambridge, Cambridge, UK
13 5. NIHR Cambridge Biomedical Research Centre, Cambridge, UK
14
15 Corresponding author: Professor Edward Johnstone

16 MFHRC, 5th Floor St Mary's Hospital, Central Manchester University Hospitals NHS
17 Foundation Trust, Oxford Road, Manchester M13 9WL.
18 0161 701 6960 / Edward.johnstone@manchester.ac.uk
19
20

Abstract

Abnormal maternal serum biomarkers (AMSB), identified through the aneuploidy screening programme, are frequent incidental findings in pregnancy. They are associated with fetal growth restriction (FGR), but previous studies have not examined whether this association is with early-onset (<34 weeks) or late-onset (>34 weeks) FGR; as a result there is no consensus on management. The aims of this study were to determine the prevalence and phenotype of FGR in women with AMSB and test the predictive value of placental sonographic screening to predict early-onset FGR.

1196 pregnant women with AMSB underwent a 21-24 week "placental screen" comprising fetal and placental size, and uterine artery Doppler. Multivariable regression was used to calculate a predictive model for early-onset FGR (birthweight centile <3rd / <10th with absent umbilical end-diastolic flow, <34 weeks).

FGR prevalence was high (10.3%), however early-onset FGR was uncommon (2.3%). Placental screening effectively identified early-onset (area under the curve (AUC) 0.93, 95% confidence interval (CI) 0.87-1.00), but not late-onset FGR (AUC 0.70, 95% CI 0.64 – 0.75). Internal validation demonstrated robust performance for detection/exclusion of early-onset FGR. In this cohort, utilisation of our proposed algorithm with targeted fetal growth and Doppler surveillance, compared with universal comprehensive surveillance would have avoided 1044 scans, potentiating significant cost-saving for maternity services.

INTRODUCTION

Despite the emergence of cell-free DNA testing in 2012, maternal serum biomarker

measurement remains a part of aneuploidy screening in many healthcare settings(1–3).

"Extreme" values of these maternal serum biomarkers (defined using multiples of the

median) and termed abnormal maternal serum biomarkers (AMSB), are associated with a

range of adverse pregnancy outcomes, particularly fetal growth restriction (FGR)(4–8) .

AMSB lack sufficient sensitivity to be used in isolation as a primary screening tool for

adverse pregnancy outcomes, but evidence-based care pathways for the timing and

frequency of surveillance of women with AMSB remain lacking. Currently, there is no

consensus on which AMSB should trigger surveillance, what the components of monitoring

assessment should be and when and how frequently these assessments should occur.

United Kingdom (UK) and New Zealand guidelines recommend serial ultrasound assessment

from 26-28 weeks' gestation for low pregnancy-associated plasma protein-A (PAPP-A)

only(9,10), whereas other guidelines are less prescriptive(11), advising individualised

surveillance plans(12) or varying scan frequency depending on initial ultrasound

assessment(13). Current guidelines also do not delineate the two different phenotypes of

FGR: early-onset disease, which occurs between 22-34 weeks and is associated with

abnormal maternal and fetal placental perfusion, and late-onset disease, characterised by

slowing fetal growth after 32 weeks and an absence of measurable placental perfusion

defects(14). Early-onset FGR accounts for ~20% of all FGR(15), but without recognition and

intervention, it is associated with a very high stillbirth rate. Although late-onset FGR is also

associated with significant risk of poor perinatal outcome(16)(17), adverse outcomes occur

much later in pregnancy and the overall stillbirth rate is lower. AMSB are associated with

both early- and late-onset FGR(14,15), however information on the relative distribution of

65 FGR phenotypes within this population is limited. Serial ultrasound assessment of fetal

66 growth can detect both phenotypes of FGR and trigger iatrogenic delivery, but is resource

67 intensive, particularly if frequent serial scans are performed from 26-28 weeks. Uterine

68 artery Doppler resistance measurements at 21-24 weeks may improve the ability of

69 ultrasound to detect early-onset FGR(18–22), but studies using this in AMSB cohorts are

70 small and the numbers of cases of early-onset FGR relatively few(19). Other investigators

71 have attempted to enhance ultrasound assessment by measuring placental size or

72 volume(19,23–27), but these techniques have not been widely implemented.

73 The aim of this study was to determine whether a 21-24 week "placental screen,"

74 comprising ultrasound assessment of fetal biometry, placental biometry and uterine artery

75 Doppler impedance, could identify the subgroup of women with AMSB who were at

76 significant risk of developing early-onset FGR. We also hypothesised that a negative

77 placental screen would be associated with a low probability of early-onset FGR. We aimed

78 to design a model with a high negative predictive value that could be used as a tool to rule-

79 out early-onset FGR without compromising detection rates and therefore direct ultrasound

80 resources more appropriately.

81 ## RESULTS
82 ### Population pregnancy outcomes
83 Between January 2011 and December 2018, there were 67,065 births at St Mary's Hospital

84 (SMH), Manchester, UK, of which 65,192 (97.2%) had a complete pregnancy outcome with a

85 birth recorded >22 weeks' gestation (Supplementary Table 1). The perinatal death rate for

86 the study period was 6.7/1000 births. SGA affected 12,355 (19.0%) of this population and

87 FGR affected 4491 (6.9%), of whom 427 (0.7%) were born <34 weeks. Over the same time

88 period there were 29,796 pregnancies in which serum screening was performed, of which

89   25,688 (86.2%) had a birth >22 weeks recorded at St Mary's Hospital. Of the 25,688

90   pregnancies, 27.4% had combined screening and 12.0% second trimester screening.

91   Amongst the women with abnormal serum markers (1709/25,688 (6.6%)), the prevalence of

92   FGR and early-onset FGR were 12.8% and 2.2%, respectively; these equate to a 2.2- and 5.6-

93   fold increase, compared with the rest of the population. Standard metrics describing the

94   performance of each of the biomarkers at different thresholds in the population data are

95   shown in Supplementary Figure 1 and Supplementary Table 2.

Cohort characteristics

97   1276/1709 (71.0%) pregnancies with AMSB attended at 21-24 weeks' gestation for a

98   'placental screen'. 80 pregnancies were subsequently excluded from the analysis due to

99   incomplete data (n=74 delivered elsewhere, missing data n=2) or fetal abnormalities (n=4)

100   leaving 1196 included (see Figure 2). Characteristics of the cohort are described in Table 1.

Cohort pregnancy outcomes

102   There was a high rate of SGA (16.4 – 27.7%) and FGR (7.3 – 18.1%) across all AMSB (Figure

103   3), which was comparable to FGR rates in all women with AMSB in the population dataset

104   (28.9% and 12.8%). The majority (96/123, 78.1%) of cases were late FGR, requiring

105   intervention after 34 weeks. There was a low incidence (27/1196, 2.3%) of early-onset FGR

106   in our study population.

Statistical modelling

108   Univariate analysis demonstrated significant associations between early-onset FGR and the

109   following ultrasound parameters: customised estimated fetal weight (EFW) centile, mean

110   umbilical and uterine artery PI and RI, and placental biometry (Supplementary Table 3).

111   Known maternal risk factors for SGA (including ethnicity and parity)(28) were not predictive

112   of early-onset FGR and were therefore not included in the model.

The best model for exclusion of early-onset FGR (n=27/1196; 2.3%) included log (customised

EFW centile) and log (mean uterine artery PI). This model had a positive likelihood ratio

(LR+) of 8.53 and a negative likelihood ratio (LR-) of 0.08 (AUC 0.93, 95% CI 0.87-1.00)). The

logistic regression model to calculate the predicted probability of early-onset FGR is as

follows:

Probability score = (4.386609*log mean uterine artery PI))-(0.7089351*log EFW centile)-2.081191.

This combination of log (uterine artery PI) and log (customised EFW) was also predictive of

SGA, delivery and indicated delivery <34 weeks' gestation (Table 2 and Figure 4). Placental

biometry was a significant predictor of early-onset FGR, however inclusion of placental

surface area (PSA; width x width) in the model did not significantly improve its performance,

despite a halving of the negative likelihood ratio (Supplementary Table 4; p=0.06 (DeLong);

LR+ 9.38, LR- 0.04; AUC 0.94 (95% CI 0.88-1.00)). Additionally, use of population centiles or Z

scores for EFW did not improve the model (p=0.63, AUC: 0.92 (95% CI 0.84-1.00) and

p=0.73, AUC 0.93 (95% CI 0.86-1.00), respectively (DeLong)). Since placenta-mediated FGR is

typically asymmetrical, we tested inclusion of a measure of asymmetry (Z score of head

circumference/abdominal circumference divided by the Z score of femur length)(29). This

had inferior performance, compared with customised estimate fetal weight centile (p=0.02,

AUC=0.87 (95% CI 0.79-0.95). The model performance was not different if early-onset FGR

was defined using non-customised centiles (28/1198; either with (AUC 0.89 (95% CI 0.81-

0.98)) or without (AUC 0.89 (0.79-0.87)) customisation of EFW).

The regression model characteristics are summarised in Supplementary Table 5. This model

was significantly better at predicting early rather than late FGR (AUC 0.70 (95% CI 0.64 –

0.75)). Using a threshold of ≥0.03 to define a "positive placental screen" to compare groups,

there was a significant difference in birthweight centiles between the "negative"

137   (1044/1196; 87.3%) and "positive" (152/1196; 12.7%) placental screen groups: median

138   31.56 (interquartile range 45.27) vs. 6.20 (interquartile range 30.32) respectively, p<0.001

139   (Supplementary Table 6 and Supplementary Figure 2). A higher proportion of the "positive"

140   placental screen group delivered before 34 weeks (22.4% compared with 1.6%, p<0.001)

141   and before 36 weeks (32.9% compared with 5.5%, p<0.001), with a significant difference in

142   the median gestational age at delivery between the two groups (p<0.001; Supplementary

143   Figure 3). The model performed well across all AMSB, with false positive rates ranging

144   between 5.6% (βHCG) and 11.8% (PAPP-A). Internal validation of the model did not

145   significantly alter the performance of the model (Table 3).

146   There were a small number (17, 1.6%) of screen-negative women who delivered <34 weeks

147   (Supplementary Table 7). Ten (58.8%) of these were spontaneous preterm births. Two were

148   definite false-negatives with FGR requiring delivery <34 weeks(10). These two cases possibly

149   represented EFW measurement error at the placental screen rather than a failure of the

150   model as both had EFW>15% larger than birthweight, within 3 weeks of delivery.

151   Supplementary table 8 summarises the causes of the stillbirths, for both positive and

152   negative placental screens.

153   Assuming that current common practice would involve three to four weekly scanning from

154   26 to 28 weeks' gestation, a minimum of one scan per negative screen could have been

155   avoided by implementing our mid-trimester model and care pathway (Figure 5). This

156   equates to the avoidance of a minimum of 1044 scans (847 scans per 1000 women with

157   AMSB screened).

158   The proportion of FGR births <38 weeks as a proxy for the antenatal detection of FGR has

159   been suggested as a metric within the Saving Babies Lives Care Bundle version 2. In our

160   population cohort 36% of all FGR pregnancies delivered before 38 weeks, 56.9% in those

161 women who had serum screening performed and 65.9% in those who attended for a

162 placental screen.

DISCUSSION

164 Our study has confirmed the association between low PAPP-A, and increased

165 βHCG/Inhibin/αFP, with SGA (24.5%) and FGR (10.3%) and demonstrated these markers to

166 be useful incidental pregnancy risk factors when identified through combined aneuploidy

167 screening. This confirms the findings of smaller studies which have reported increased risks

168 of placental disease in women with AMSB(30,31).

169 Current Royal College of Obstetricians and Gynaecologists (RCOG) guidance highlights PAPP-

170 A <0·415 MoM as a risk factor for SGA(28), but in the current cohort we have confirmed that

171 the risk of FGR was similarly increased for abnormal levels of αFP, inhibin and βHCG. The

172 absence of guidance from current care pathways regarding these additional markers could

173 result in cases of FGR remaining undetected. Given the significantly increased rate of FGR in

174 women with AMSB, third trimester fetal surveillance is justified with the aim of preventing

175 avoidable stillbirths attributable to placental insufficiency through obstetric

176 intervention(11). We have demonstrated that a combination of two continuous variables

177 (EFW centile and mean uterine artery PI) at 21-24 weeks can effectively rule-out FGR

178 requiring intervention before 34 weeks (NPV 99.8%); a serious, but rare adverse outcome in

179 women with AMSB (2.3% in our cohort) whilst correctly identifying 93% of cases. Uterine

180 artery Doppler PI and EFW centile were the strongest predictors of early-onset FGR in our

181 cohort in agreement with previous findings(32). Consistent with a recent review by Kingdom

182 et al.(27), placental biometry was a significant predictor of early-onset FGR, however

183 addition of this to the model did not significantly increase the performance.

184 Using the combined "placental screen" we suggest that subsequent third trimester

185 ultrasound surveillance can be effectively triaged, such that fetal growth assessment can be

186 safely deferred until after 34 weeks in women with a "negative screen". In this way, care

187 can be effectively triaged and unnecessary intervention potentially reduced(29). We have

188 developed an online risk calculator, derived from the internally validated regression model

189 in this study, to simplify decision making at the time of the placental screen:

190 https://drive.google.com/open?id=1v2woSTq7KHNmNDNQ1jHJjv2yUkQ0O7sqfav_NkI_g9Y

191 This model, derived from easily attainable 2-dimensional ultrasound measurements,

192 identifies women at risk of FGR requiring intervention before 34 weeks. By adopting the

193 proposed model and care pathway, scan frequency could be reduced for the majority of

194 women (87% had a negative screen in this cohort), with significant cost and time-saving

195 implications for clinicians and patients. Additionally, amongst those with a positive screen,

196 34 (22%) required delivery <34 weeks. Without routine surveillance, these pregnancies

197 would have been at very high risk of ending in stillbirth.

198 This study used previously published thresholds of AMSB to identify a high-risk cohort. The

199 data collated for this study has demonstrated that the cut-offs applied are applicable to our

200 local population in terms of overall screening performance for the detection of FGR. Review

201 of the distribution of PAPP-A measurements, however, would suggest that in our population

202 lowering the cut-off to 0.39 (representing the 5th centile for the SMH population) would

203 increase specificity without compromising sensitivity. Using this threshold requires 51

204 "placental screens" to be performed per early FGR case detected (see Supplementary Table

205 2). The thresholds used in our cohort for screening Inhibin and αFP AMSB are more

206 stringent than those applied to PAPP-A and consequently have higher positive predictive

207 values with only 29 and 14 screens being performed per early FGR case detected. Further

208   refining of the population to whom the screen is applied by lowering the threshold at which

209   we offer "placental screens" in this group of women so that equivalent numbers of screens

210   are performed per case detected should be associated with an overall improvement in

211   detection.

212   Model performance overall will also be influenced by the background prevalence of FGR. In

213   our local population, the prevalence of FGR was 7% and SGA 19%; higher than might be

214   expected and perhaps reflecting the high level of deprivation in our local population.

215   However, FGR and SGA in our hospital population dataset were classified without maternal

216   characteristic customisation due to missing data. As customisation amongst Asian women

217   under classifies SGA, relative to population centiles(33), it is likely that the prevalence would

218   be lower if customisation were applied.

219   Study strengths include prospective data collection, exclusion of aneuploid pregnancies,

220   internal validation of the model and a sample size sufficient to assess FGR (<3rd centile /

221   <10th centile with absent EDF) rather than SGA (<10th centile). Despite this being the largest

222   study investigating AMSB in early-onset FGR to date, the most significant limitation of our

223   study was the low primary event rate which reflects the rarity of early-onset FGR. Our

224   model will be inevitably over-fitted to the current cohort, but to minimise the risk of over

225   interpretation we limited the number of included variables to two and performed internal

226   validation, which did not demonstrate a significant shift in model performance. A further

227   limitation is that the clinicians managing the cases were not blinded to the placental screen

228   and local protocol-driven management, based on AMSB, could have altered observed

229   outcomes in this cohort. The severity of AMSB or abnormal ultrasound findings may have

230   impacted on surveillance frequency and therefore timing of delivery. However, we would

231   argue that in practice, knowledge of the placental screen would be unlikely to influence the

232   decision for an indicated preterm delivery, as this was dictated by standard fetal

233   assessments immediately prior to delivery. Furthermore, a placental screen was only

234   performed in pregnancies where AMSB were identified through combined screening and

235   therefore the population studied is limited to those women who chose aneuploidy

236   screening (just under half of the population in this hospital). Whilst there is no indication

237   that the performance of AMSB and a placental screen would be different in a wider

238   obstetric population, it was not possible to confirm this in the current study. The lack of

239   routine placental histology in this cohort limits our ability to correlate the placental screen

240   with distinct placental causes of FGR (i.e. maternal vascular malperfusion (MVM) versus

241   alternative abnormalities (e.g. chronic histiocytic intervillositis) associated with normal

242   uterine artery Dopplers(34)). A positive placental screen and subsequent ultrasound

243   surveillance has the potential to improve perinatal outcomes in early-onset FGR cases

244   through altered obstetric management, highlighted by the fact that 77% (n=24) of iatrogenic

245   deliveries <34 weeks indicated for placental disease had a positive screen. In addition, there

246   was a high prevalence of FGR (25%, n=32) and preterm birth before 37 weeks (28%, n=36)

247   amongst those with a positive screen, indicating that those with an abnormal assessment at

248   21-24 weeks are a high-risk group that would benefit from increased surveillance. This study

249   has also highlighted the limitations of second trimester ultrasound in predicting FGR

250   developing near term and emphasised the importance of continued efforts to improve the

251   detection and management of late FGR in high risk women. In our cohort, whilst the

252   detection of FGR (assessed by the number of pregnancies delivered by 38 weeks) was

253   increased in women who had a placental screen in comparison to the SMH population (66%

254   vs 36%), despite ultrasound surveillance, a significant proportion of FGR pregnancies

255   remained undetected.

256   Placental production of angiogenic markers (including placental growth factor(PlGF) and

257   soluble fms-like tyrosine kinase-1 (sFlt)) is dysregulated in the context of placental

258   dysfunction(35). For this reason, they are increasingly recognised as diagnostic adjuncts for

259   pre-eclampsia and FGR(36,37). Additionally, there is evidence to support their predictive

260   role in placental FGR(38,39), indicating that angiogenic markers could be a useful adjunct to

261   the placental screen. This is beyond the scope of this study, but would be worth

262   investigating in the future, along with newer placental biomarkers(40,41) with a view to

263   further refining the model.

264   In conclusion, AMSB are significant risk factors for FGR and monitoring fetal growth in the

265   third trimester is justified with the aim of avoiding preventable stillbirths through earlier

266   obstetric intervention. The majority of FGR in women with AMSB however does not require

267   intervention before 34 weeks; therefore, a "placental screen" at 21-24 weeks can safely

268   reduce scan frequency by ruling out the risk of early-onset FGR in this cohort. A suggested

269   screening model to guide the frequency of fetal surveillance for all AMSB is presented in

270   Figure 5. By adopting the proposed model and care pathway, scan frequency could be

271   reduced for the majority of women (87% had a negative screen in this cohort). These

272   findings have significant cost and time-saving implications for health services.

273   ## METHODS
274   This retrospective observational cohort study was performed in a single tertiary UK centre

275   between June 2010 and December 2018 using prospectively collected maternal

276   demographic and ultrasound data. Comparison biomarker screening data and birth outcome

277   data for the study period was extracted from the electronic records for pregnancies over the

278   same time period (estimated delivery dates January 2011 - December 2018). Only

279   pregnancies with a complete pregnancy outcome, >22 weeks' gestation were included in

280 the analysis. Analysis of routinely collected data without the need for individual consent or

281 ethical committee review was nationally approved by the Health Research Authority (HRA;

282 19/HRA/2047) and locally by Manchester University NHS Foundation Trust (MFT) Research

283 and Innovation. The study has been reported in line with the STROBE guidance for reporting

284 in observational studies(42). Biomarker measurements were performed as part of routine

285 fetal chromosomal abnormality screening between 11 and 13+6 weeks' gestation (PAPP-A),

286 and 14 and 17+6 weeks' gestation (beta human chorionic gonadotropin (βHCG), inhibin, and

287 alpha fetoprotein (αFP)). Biomarker concentrations were reported by the laboratory as

288 standard multiples-of-median (MoM) corrected for gestational age(43).

289 As per local guidance (Figure 1), women at increased risk of FGR were referred to the

290 Placenta Clinic and Manchester Antenatal Vascular Service (MAViS Clinic), specialist

291 translational research clinics (LREC No. 08/H1010/55+5; 15/NW/0929; 11/NW/0426).

292 Referral criteria include an incidental finding of AMSB (PAPP-A≤0.415 MoM (5th

293 centile)(10,12,44), βHCG ≥4.0 MoM(12,44,45), inhibin ≥2.0 MoM(4,12,44) and αFP ≥2.2

294 MoM(4,12,44)). In this clinic, women undergo a 21-24 week placental screen, in which

295 liquor volume (amniotic fluid index and maximum pool depth), placental and fetal biometry,

296 and umbilical and uterine artery Dopplers are measured. During the study period, the scan

297 at 21-24 weeks did not trigger intervention or alter the frequency of surveillance although

298 the findings were reported to the clinicians.

299 Placental biometry was measured using the following method(26): the longest plane of the

300 placenta was identified using 2-dimensional ultrasound. The placental diameter was then

301 measured (end-to-end) using one or two adjoining straight lines. Placental depth was

302 measured at the deepest point, perpendicular to its diameter. Following 90° rotation of the

303   ultrasound probe, the second diameter was measured (end-to-end, using one or two

304   adjoining straight lines).

305   As per our routine clinical practice, customised birthweight centiles(46) were used to

306   calculate both the EFW centile and final birthweight centile in the cohort study. A sensitivity

307   analysis included performance of the model for early-onset FGR defined using non-

308   customised centile. SGA was defined as <10th centile birthweight and FGR was defined as

309   <3rd centile birthweight / <10th with absent end-diastolic flow (EDF). Early-onset FGR was

310   defined as an fetus requiring delivery before 34 weeks' gestation with birthweight <3rd

311   centile or <10th centile with absent EDF. Due to missing data for maternal ethnicity, parity

312   and body mass index in the hospital electronic records, birthweight centiles in the

313   population dataset were calculated without customisation (using Hadlock).

Statistical methods

315   The distribution of continuous variables was assessed for normality using the Jarque-Bera

316   skewness-kurtosis test and data appropriately transformed. Chi-squared test was used to

317   compare categorical variables between the two groups. The association between each of

318   the ultrasound variables and FGR was assessed using univariate comparisons. STATA version

319   14.2 was used to derive a logistic regression model restricted to three variables (to avoid

320   overfitting) to determine the accuracy of prediction for early-onset (<34 weeks') FGR.

321   Different combinations of variables were included in the model; the performance of each

322   model was then determined using receiver operator characteristics (ROC) curve analyses.

323   These areas were compared using DeLong method to determine the best model. Due to

324   non-normality of uterine artery PI and EFW, these variables were log transformed.

325   Continuous variables were compared between test-positive and test-negative women using

326   t test / Mann-Whitney as appropriate. Varying probability cut-offs were tested to determine

327   the optimum positive and negative likelihood ratios for the regression model. The models

328   were subjected to a bootstrapping sample, with replacement from the same dataset with

329   1000 replications. Model performance (AUC, 95% CI) was compared between the original

330   and bootstrap samples. The coefficients for each variable in the final regression model were

331   used to create a web-based risk prediction calculator.

332

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495   **Competing Interests**

496   None of the author has conflicting interests to declare with regard to this study.

497   **Contributions of authors**

498   LO, LW, YL, JM, LS and EDJ were responsible for data analysis and writing the paper. GS

499   advised on statistical analysis and contributed to the writing of the paper and data

500   presentation. EDJ supervised the project and led the team that collected the data along with

501   ST.

502

503 **Figure 1: Manchester University NHS Foundation Trust (MFT) Placenta Clinic referral**

504 **pathway.**

505 **Figure 2: Consort diagram.**

506 **Figure 3: The risk of adverse pregnancy outcomes <34 weeks associated with different**

507 **abnormal serum biomarkers. The red horizontal lines indicate the background incidence**

508 **of each outcome.**

509 *Background prevalence of iatrogenic delivery <34 weeks and stillbirths without congenital
510 anomaly were not reliably coded in electronic health records and therefore has not been
511 included. Illustrated as proportions and 95% confidence intervals.
512
513 **Figure 4: Receiver operating characteristic curve (ROC) analysis of log (mean uterine artery**

514 **PI) and log (customised EFW centile) to predict adverse pregnancy outcomes <34 weeks**

515 **gestation. The vertical lines indicate the threshold for a positive screen.**

516
517 **Figure 5: Suggested care algorithm for women with abnormal serum biomarkers (PAPP-**

518 **A≤0.415 MoM, βHCG ≥4.0, MoM, inhibin ≥2.0 MoM and αFP ≥2.2 MoM).**

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Table 1: General characteristics of the study group (n=1196)

Gestation at assessment* (weeks + days)	23+2 (21+0 – 24+0)
Gestation at delivery* (weeks + days)	39+1 (22+6 – 42+3)
Ethnicity, N (%)	
White	692 (57.9%)
Black	159 (13.3%)
Asian	211 (17.6%)
Other	134 (11.2%)
BMI (kg/cm^2)*	25.28 (16.46– 54.67)
Delivered <34 weeks, N (%)	51 (4.3%)
Birthweight* (grams)	3145 (300 – 5119)
Birthweight centile*	29.05 (0·00 – 100·00)
Birthweight <10th centile N (%)	293 (24.5%)
Birthweight <3rd centile N (%)	123 (10.3%)
Early-onset (<34 weeks) FGR (<3rd centile / <10th centile with AEDF) N (%)	27 (2.3%)
Stillbirth, N (%)	12 (1.0%)
Stillbirth <34 weeks, N (%)	9 (0.8%)

BMI, body mass index; FGR, fetal growth restriction; AEDF, absent end-diastolic flow.

*Median (range) quoted for continuous non-parametric data

Table 2: 21-24 week placental screen test performance for adverse pregnancy outcomes before 34 weeks gestation.

Adverse pregnancy outcome <34 weeks	True +ve/ False -ve	False +ve / True -ve	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)	DOR (95% CI)
FGR (<3rd centile / <10th centile with AEDF)	25/2	127/1042	92.6 (76.6-97.9)	89.1 (87.2-90.8)	8.53 (7.01-10.37	0.08 (0.02-0.32)	102.56 (24.01-438.10)
SGA (<10th centile)	30/4	184/978	88.2 (73.4-95.3)	84.2 (82.0-86.1)	5.57 (4.65-6.68)	0.14 (0.06-0.35)	39.86 (13.88-114.50)
Delivery <34 weeks	39/12	394/751	76.5 (63.2-86.0)	65.7 (62.8-68.3)	2.22 (1.87-2.64)	0.36 (0.22-0.59)	6.20 (3.21-11.97)
Iatrogenic delivery / stillbirth <34 weeks	29/3	363/801	90.6 (75.8-96.8)	68.8 (66.1-71.4)	2.91 (2.53-3.34)	0.14 (0.05-0.40)	21.33 (6.46-70.48)

+ve, positive; -ve, negative; CI, confidence interval; LR+, positive likelihood ratio, LR-, negative likelihood ratio; DOR, diagnostic odds ratio; FGR, fetal growth restriction; AEDF, absent end-diastolic flow; SGA, small for gestational age.

Table 3: Observer area under the curve (AUC) and optimism adjusted AUC after 1000-fold bootstrapping for adverse outcomes before 34 weeks' gestation.

Adverse pregnancy outcome <34 weeks	Original sample			Bootstrapped sample		
	AUC	SE	95% C.I.	AUC	SE	95% C.I.
FGR (3rd centile)	0.934	0.033	0.867 – 1.000	0.950	0.013	0.924 – 0.976
SGA (<10th centile)	0.904	0.035	0.835 – 0.973	0.922	0.018	0.886 – 0.958
Delivery <34 weeks	0.816	0.039	0.740 – 0.892	0.834	0.026	0.784 – 0.884
Iatrogenic delivery / stillbirth <34 weeks	0.869	0.040	0.790 – 0.948	0.841	0.030	0.783 – 0.899

AUC, area under curve; SE, standard error; CI, confidence interval; FGR, fetal growth restriction; SGA small for gestational age.