Association between adverse pregnancy outcome and placental biomarkers in the first trimester: A prospective cohort study

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Abstract

Objective: To determine the inter-relationships between five first-trimester biomarkers (pregnancy associated plasma protein A [PAPP-A], alpha-fetoprotein [AFP], beta human chorionic gonadotrophin [beta-hCG], placenta growth factor [PlGF] and soluble fms-like tyrosine kinase receptor-1 [sFlt-1]) and a range of adverse pregnancy outcomes (APOs).

Design: Prospective cohort study of nulliparous singleton pregnancy.

Setting: Cambridge, UK.

Population or Sample: 4056 pregnancy outcome prediction study participants.

Methods: The biomarker concentrations were measured in maternal serum at ~12 weeks of gestation. Univariable analysis of APOs was performed using logistic regression. Multivariable analysis used best subsets logistic regression with cross-validation.

Main outcome measures: Pre-eclampsia (PE), small for gestational age (SGA), including severe SGA (birthweight <3rd), fetal growth restriction (FGR), preterm birth (PTB, both induced and spontaneous [iPTB and sPTB, respectively]), pre-viable loss and stillbirth, plus combinations of outcomes.

Results: Lower values of PAPP-A, PlGF and sFlt-1 and higher values of AFP were associated with FGR (OR for 1 SD higher value 0.59 [95% CI 0.48–0.74], OR 0.56 [95% CI 0.44–0.70], OR 0.71 [95% CI 0.57–0.87] and OR 0.71 [95% CI 0.56–0.90]) and severe SGA (OR 0.59 [95% CI 0.54–0.87] and OR 1.53 [95% CI 1.25–1.88]), severe PE (OR 0.59 [95% CI 0.49–0.72] and OR 0.57 [95% CI 0.47–0.70]), severe SGA (OR 1.41 [95% CI 1.17–1.71]), iPTB (OR 0.72 [95% CI 0.57–0.91], OR 0.62 [95% CI 0.49–0.78] and OR 0.71 [95% CI 0.56–0.90]), sPTB (OR 0.61 [95% CI 0.50–0.73], OR 0.79 [95% CI 0.66–0.96] and OR 1.41 [95% CI 1.18–1.67]) and iPTB (OR 0.72 [95% CI 0.57–0.91], OR 0.62 [95% CI 0.49–0.78], OR 0.71 [95% CI 0.56–0.90] and OR 1.44 [95% CI 1.16–1.78]), respectively. When combinations of biomarkers were assessed, PAPP-A and AFP were independently associated with severe SGA; PAPP-A alone with PE + PTB; PlGF alone with severe PE; PlGF, beta-hCG, AFP and PAPP-A with the combination of PE and SGA; AFP and sFlt-1 with sPTB; and AFP and PlGF with iPTB.

Conclusions: Combinations of first-trimester placental biomarkers are associated with APOs. However, the patterns vary for different types of APO, indicating heterogeneity in the underlying pathophysiological pathways.

KEYWORDS
fetal growth restriction, first trimester, pre-eclampsia, pregnancy, preterm birth, protein biomarkers, stillbirth
1 | INTRODUCTION

Early pregnancy identification of women at increased risk of pregnancy complications has been a standard element of prenatal care for decades and women with high risk features in their medical or obstetric history are directed towards more intensive patterns of care. In the last ~20 years, many studies have identified associations between maternal serum levels of proteins in the first trimester and the risk of adverse pregnancy outcome (APO). These associations highlight that the pathophysiological pathways leading to APOs often have their origins in processes taking place in early pregnancy, such as placental growth and invasion. Moreover, they are also used clinically in identifying women at high risk of conditions such as preterm pre-eclampsia and stillbirth. Among these proteins, pregnancy-associated plasma protein A (PAPP-A), alpha fetotroprotein (AFP), human chorionic gonadotropin (beta-hCG), placental growth factor (PlGF) and soluble fms-like tyrosine kinase 1 (sFlt-1) and their ratios have been associated with APOs at various stages of pregnancy. However, there is limited knowledge of the relative importance of each biomarker association with each APO or combinations of APO in the first trimester of pregnancy. The aim of the present study was to determine optimal combinations of biomarkers that are associated with individual APOs and combinations of APOs. We addressed these aims by clinical grade measurement of first-trimester maternal serum proteins in a large, well-characterised cohort of nulliparous women with a singleton pregnancy conducted in the UK.

2 | METHODS

2.1 | Study design

The Pregnancy Outcome Prediction (POP) study was a prospective cohort study of unselected, nulliparous women attending the Rosie Hospital (Cambridge, UK) for their dating scan between January 2008 and July 2012 who had a viable singleton pregnancy, as previously described. Briefly, women with a viable singleton pregnancy were eligible. Gestational age (GA) was defined by ultrasound at the time of the dating scan at ~12 weeks of gestational age (wkGA) and a blood sample was obtained. The study participants attended the National Institute for Health Research (NIHR) Cambridge Clinical Research Facility at ~20, ~28 and ~36 wkGA for further blood sampling and ultrasound scans. Circulating concentrations of protein biomarkers measured from maternal serum samples from the visit at ~12 wkGA were used in the present study. Maternal age was recorded at recruitment, weight was measured at the dating scan appointment, and height was measured at the 20-week appointment. Other maternal characteristics, pregnancy and birth outcome data were collected through a questionnaire at ~20 wkGA, from examination of the clinical case record, or through linkage to the hospital’s electronic databases. All participants provided written informed consent. The present study is a secondary analysis of the POP study data. There was no patient or public involvement, or a core outcome set for the present study.

2.2 | Exclusions

Participants who withdrew, were lost to follow-up, had a therapeutic termination of pregnancy or did not have outcome data available were excluded from the analysis. Also, participants without information on one or more of the five protein biomarkers at ~12 wkGA were excluded.

2.3 | Samples and assays

Serum samples were collected and stored at ~80°C. They had not previously been thawed before the day of analysis. Researchers performing the assays were blinded to the patients’ clinical information and pregnancy outcome. Maternal serum concentrations of PAPP-A, AFP, beta-hCG, PlGF and sFlt-1 were measured using Roche Elecsys assays on the electrochemiluminescence immunoassay platform, Cobas e411 (Roche Diagnostics).

2.4 | Outcome data

The APOs included fetal growth restriction (FGR), severe SGA, PE with PTB, severe PE, PE with SGA, spontaneous preterm birth (sPTB), iatrogenic (medically indicated) preterm birth (iPTB), pre-viable loss and stillbirth. These APOs were defined in a previous publication. Briefly, FGR was defined as birthweight <10th UK population percentile (= SGA) with (i) non-anomalous perinatal death, (ii) any neonatal morbidity or (iii) PE. Severe SGA was defined as birthweight <3rd population percentile. PE was defined according to the 2013 American College of Obstetricians and Gynecologists (ACOG) guidelines. PTB was defined as delivery ≥24 and <37 wkGA. Pre-viable loss was defined as delivery of an infant with no signs of life at <24 wkGA, and stillbirth was defined as delivery of an infant with no signs of life ≥24 wkGA.

2.5 | Statistical analysis

Descriptive analysis of the concentrations of the protein biomarkers was performed by the APO status (at least one APO present versus APO absent). The distributions of the concentrations were compared using the Wilcoxon rank-sum test. For further analysis, multiples of the medians (MoMs) were calculated for each protein biomarker. These were adjusted for GA and maternal weight at the 12-week appointment, and for sample storage time at the time of sample processing, applying a log-linear regression procedure. The log-transformed, adjusted MoMs were transformed into
z-scores, referent to all POP study participants who had the biomarker measurement available. Spearman rank correlations between the biomarkers were calculated in the whole population and by APO status. Odds ratios for each APO were estimated for a one standard deviation (SD) higher biomarker value using logistic regression. Best subsets variable selection including the five biomarkers was then applied on each APO, using the STATA user-written ‘gsselect’ command with logistic as the estimation command. This method is described in detail elsewhere.11 In brief, it performs an exhaustive search of all possible combinations of explanatory variables (in this case biomarkers) and identifies the best performing model for a given number of biomarkers. For the best 1–5 biomarker models, Bayesian information criterion (BIC), Akaike information criterion (AIC) and area under the receiver operating characteristic curve (AUC) were calculated. Lower levels of AIC and BIC and higher levels of AUC are indicative of better performance.12,13 In the 2–5 biomarker models, the AUC was corrected for optimism using 10-fold cross-validation with 100 replications to minimize overfitting.14,15 Statistical analyses were performed using STATA version 17.0 (StataCorp LLC).

3 | RESULTS

In total, 8028 eligible women were approached and 4512 were recruited to the POP study. The recruited and non-recruited groups had previously been compared and found to be broadly comparable.16 Of the 4512 recruited participants, 4212 (93%) completed the study. Of these, 4056 (96%) had data on all five biomarkers at 12 wkGA and outcome data available for analysis. We did not make any exclusions based on reported use of medication as this information was not obtained at the 12-week visit. Only 21 participants (three with and 18 without an APO) reported aspirin use at the time of 20-week follow-up and these were included in the analysis. There were 416 participants with one or more APO: 74 FGR, 94 severe SGA, 29 PE + PTB, 129 severe PE, 32 PE + SGA, 111 sPTB, 71 iPTB, 13 pre-viable loss and 11 stillbirth. The overlaps between the APOs have been described previously.6 Maternal characteristics and birth outcomes of the participants have been previously tabulated by APO status.6 Most of the maternal characteristics were comparable between the two groups. The participants with APO had a higher proportion of self-reported smoking and their babies were born on average 2 weeks earlier with a birthweight approximately 800 g lower. The distributions of the biomarker concentrations are presented in Table 1 by APO status, expressed as absolute concentrations and additionally as z-scores adjusted only for GA at measurement. Among the 416 (10.3%) participants who had one or more APO, PAPP-A, PlGF and sFlt-1 concentrations were lower, whereas AFP concentrations were higher than the levels observed in pregnancies without adverse outcomes. The beta-hCG concentrations were similar between the groups. The median GA at measurement was 12 weeks in both groups.

Odds ratios and 95% confidence intervals (CI) for each biomarker in relation to each APO are presented for 1 SD higher biomarker value, adjusted for GA, maternal weight and sample storage time (Figure 1). Lower values of PAPP-A, PlGF and sFlt-1 and higher values of AFP were associated with FGR (OR 0.59 [95% CI 0.48–0.74], OR 0.56 [95% CI 0.44–0.70], OR 0.68 [95% CI 0.54–0.87] and OR 1.53 [95% CI 1.25–1.88]) and severe SGA (OR 0.59 [95% CI 0.49–0.72], OR 0.71 [95% CI 0.57–0.87], OR 0.74 [95% CI 0.60–0.91] and OR 1.41 [95% CI 1.17–1.71], respectively. The patterns were similar for severe PE (and for PE + PTB with more uncertainty)

| Table 1 | Circulating concentrations of maternal serum proteins and gestational age at measurement in the study cohort by presence or absence of APO (n = 4056). |
|-----------------|-----------------|-----------------|-----------------|
| Protein biomarker | APO absent | APO present | P-value |
| n (%) | n (%) | n (%) | n (%) |
| PAPP-A, IU/ml | 3640 (89.7%) | 416 (10.3%) | <0.0001 |
| AFP, IU/ml | 3674 (2412 to 5466) | 2924 (1752 to 4513) | <0.0001 |
| beta-hCG, mIU/ml | 14.33 (9.82 to 20.60) | 16.51 (11.46 to 23.50) | <0.0001 |
| PlGF, pg/ml | 46.26 (35.42 to 60.33) | 39.14 (28.50 to 55.88) | <0.0001 |
| sFlt-1, pg/ml | 1442 (1106 to 1888) | 1199 (934.4 to 1616) | <0.0001 |
| GA at measurement, weeks | 12.7 (12.1 to 13.1) | 12.7 (12.1 to 13.3) | 0.90 |
| PAPP-A, GA adjusted z-score | 0.07 (−0.58 to 0.71) | −0.34 (−1.23 to 0.39) | <0.0001 |
| AFP, GA adjusted z-score | −0.09 (−0.71 to 0.60) | 0.21 (−0.48 to 0.92) | <0.0001 |
| beta-hCG, GA adjusted z-score | 0.02 (−0.62 to 0.66) | −0.02 (−0.71 to 0.65) | 0.42 |
| PlGF, GA adjusted z-score | 0.02 (−0.59 to 0.66) | −0.40 (−1.12 to 0.48) | <0.0001 |
| sFlt-1, GA adjusted z-score | 0.03 (−0.63 to 0.71) | −0.44 (−1.07 to 0.33) | <0.0001 |

Note: The values are expressed in medians and interquartile ranges. Distributions of the biomarker concentrations were compared using the Wilcoxon rank-sum test. The APOs included FGR, severe SGA, PE with PTB, severe PE, PE without SGA, sPTB, iPTB, pre-viable loss and stillbirth.

Abbreviations: AFP, alpha fetoprotein; APO, adverse pregnancy outcome; beta-hCG, human chorionic gonadotropin; FGR, fetal growth restriction; GA, gestational age; iPTB, iatrogenic preterm birth; PAPP-A, pregnancy-associated plasma protein A; PE, pre-eclampsia; PlGF, placental growth factor; PTB, preterm birth; sFlt-1, soluble fms-like tyrosine kinase 1; SGA, small for gestational age; sPTB, spontaneous preterm birth.
but the associations were weaker. Additionally, beta-hCG had a positive association with the combination of PE and SGA (OR 1.68 [95% CI 1.15–2.45]). Lower PAPP-A, PlGF and sFlt-1 and higher AFP were also associated with sPTB (OR 0.61 [95% CI 0.50–0.73], OR 0.79 [95% CI 0.66–0.96], OR 0.57 [95% CI 0.47–0.70] and OR 1.41 [95% CI 1.18–1.67]) and iPTB (OR 0.72 [95% CI 0.57–0.91], OR 0.62 [95% CI 0.49–0.78], OR 0.71 [95% CI 0.56–0.90] and OR 1.44 [95% CI 1.16–1.78]), respectively. Compared with PlGF, sFlt-1 was more strongly inversely associated with sPTB but this was not the case for iPTB. Higher AFP values appeared to be associated with both pre-viable loss and stillbirth; however, the confidence intervals were wide for both APOs due to the small numbers of cases. Nearly all associations remained similar when the biomarkers were adjusted only for GA (Figure S1).

The associations between the biomarkers and APOs were then compared with published results from the Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-Be (nuMoM2b) (Figure S2), which analysed all SGA, PE, PE/gestational hypertension (GH) with PTB, all PTB, sPTB, iPTB and stillbirth as APOs and adjusted protein levels only for the GA of measurement. For SGA and PE, the associations were in the same direction in both cohorts (only severe cases were included in the POP study). For the associations with PE/GH + PTB, the CIs were much narrower in the nuMoM2b, which included preterm GH cases in addition to PE. The main differences between the cohorts were that beta-hCG had weak, inverse associations with all PE and PTB outcomes in nuMoM2b, but there was no association with these APOs in the POP study. There was an inverse association between PAPP-A and sPTB in the POP study but not in the nuMoM2b. The inverse association with sFlt-1 was weaker in the nuMoM2b than in the POP study. PlGF was inversely associated with sPTB in the POP study but positively associated in the nuMoM2b, although both associations were weak.

The Spearman rank correlations were similar in the presence and absence of APO (Figure 2). The strongest correlation was observed between PAPP-A and sFlt-1 (Spearman rho = 0.7). The other correlations were modest or weak.
There was no significant association between AFP and any of the other four proteins. Beta-hCG was weakly positively correlated with levels of PAPP-A and sFlt-1 but not PlGF.

Best subsets selection in the POP study (Figure 3, Panel S1) indicated that FGR was independently associated with three biomarkers, AFP, PlGF and PAPP-A (BIC = 727.7; AIC = 702.5; AUC = 69.1%), resulting in the highest AUC. The best combination for severe SGA included only PAPP-A and AFP (BIC = 879.7; AIC = 860.8; AUC = 64.9%). The most strongly associated biomarker with PE + PTB was PAPP-A on its own (AUC = 57.9%) and with severe PE it was PlGF on its own (AUC = 62.3%). The combination of PE and SGA was associated independently with four biomarkers, PlGF, beta-hCG, AFP and PAPP-A (BIC = 374.6; AIC = 343.1; AUC = 77.9%). The best combination of biomarkers for sPTB was AFP and sFlt-1 (BIC = 994.7; AIC = 975.8; AUC = 67.7%).

**Figure 2** Spearman correlations between the first-trimester protein measurements (A) in the whole study population (n = 4056), (B) in the presence of APO (n = 416) and (C) in the absence of APO (n = 3640). The proteins were analysed as multiples of the medians (MoMs), corrected for the exact gestational age and maternal weight at measurement and sample storage time. The total number of cases and controls was 4056. APO, adverse pregnancy outcome; PAPP-A, pregnancy-associated plasma protein A; AFP, alpha fetoprotein; beta-hCG, human chorionic gonadotropin; PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase 1.
FIGURE 3  
Performance of the models from the best subsets selection. The APOs with at least 30 events included FGR, severe SGA, severe PE, PE + SGA, sPTB and iPTB. AIC, Akaike information criterion; APO, adverse pregnancy outcome; AUC, area under the receiver operating characteristic curve; BIC, Bayesian information criterion; FGR, fetal growth restriction; iPTB, iatrogenic preterm birth; PE, pre-eclampsia; PTB, preterm birth; SGA, small for gestational age; sPTB, spontaneous preterm birth.
and for iPTB the best combination was AFP and PlGF (BIC = 712.4; AIC = 693.6; AUC = 63.0%).

4 | DISCUSSION

4.1 | Main findings

This study of a prospective pregnancy cohort identified associations between five first-trimester protein biomarkers (PAPP-A, AFP, beta-hCG, PlGF and sFlt-1) measured in maternal serum and multiple APOs. The pattern of association between biomarkers differed in relation to different types of APO, indicating heterogeneity in the underlying pathophysiological pathways. The inclusion of two or three biomarkers in the model was optimal in most cases. The optimism-corrected AUC for the best models varied between 62% and 77%. This suggests that even combinations of biomarkers are of limited predictive value; however, they may be clinically useful when combined with other variables.

4.2 | Clinical implications

We found that, in general, a given protein tended to have the same direction of association with all APOs. First-trimester PAPP-A, PlGF and sFlt-1 tended to be lower in pregnancies with one or more adverse outcomes, whereas AFP tended to be higher. This is consistent with the view that the major complications of pregnancy, sometimes referred to as the Great Obstetrical Syndromes, have shared pathophysiological pathways in disordered placenta. Hence high or low levels of a given protein may indicate that the function or number of a population of placental cells is dysregulated in some way. Analyses of the correlation matrices helped explain some of the results. AFP was not correlated with any of the other proteins and was frequently selected in the optimal model. This suggests that maternal serum levels of AFP yield information on some element of early placenta which is not captured by the other proteins. Conversely, we observed strong correlations between sFlt-1 and PAPP-A, and it is noteworthy that none of the models for complications in the third trimester included both of these proteins. This suggests that maternal serum levels of these proteins provide information on the same or related underlying processes and, hence, measuring both has limited potential to improve diagnostic performance.

Of the five proteins studied, only levels of beta-hCG did not vary overall between cases and controls. The only significant association was that levels of beta-hCG were higher in women who went on to experience PE combined with SGA, but did not differ comparing either outcome on its own or with any of the other APOs. The only case where a given protein appeared to exhibit different directions of association with different APOs was sFlt-1, which showed a strong trend to higher values being associated with pre-viable loss in contrast to the reduced risk of other APOs. However, this observation is consistent with previous work. We first demonstrated in 2007 that sFlt-1 is negatively associated with the risk of complications when measured in the first trimester, although other studies have demonstrated that it is positively associated with the risk of complications – pre-eclampsia in particular – when measured in the third trimester. The latter association is thought to be due to the stimulation of release of sFlt-1 by the stressed placenta. In pregnancies resulting in pre-viable loss, increased sFlt-1 levels were observed quite close to the manifestation of the disease, whereas for most of the other APOs the given complication was manifested many months after the first-trimester measurement. Hence, although high sFlt-1 in early pregnancy is usually protective against APOs occurring late in pregnancy, it is possible that a pathological rise occurs in early pregnancy in cases which end in a pre-viable loss, where the outcome is more proximal to the time of measurement.

4.3 | Interpretation

When we compared our univariable associations with those previously described in a cohort of nulliparous women in the USA (the nuMoM2b), overall, associations appeared similar. However, there were a number of apparent differences. First, beta-hCG was negatively associated with multiple APOs in the nuMoM2b cohort but was positively associated with the combination of PE and SGA in the POP study and was not associated with any of the other APOs. Secondly, the associations with sPTB were markedly different comparing the two studies: associations with PlGF were in the opposite direction, PAPP-A was negatively associated in the POP study but not associated in nuMoM2b, and sFlt-1 was strongly negatively associated in the POP study and only weakly negatively associated in nuMoM2b.

There are a number of possible explanations for these observed differences. First, the mean GA in the cases used in nuMoM2b was 11+6 weeks and the SD was 1.5 weeks. In contrast, the mean GA in POP study was 12+3 weeks, and the SD was 0.9 weeks. Hence, it is possible that different associations may have been observed due to different GAs of sampling. Secondly, differences in the definitions of APOs between the two cohorts could have played a role. Thirdly, the different pattern in relation to sPTB could reflect different pathophysiological processes leading to this APO. sPTB is the endpoint of multiple pathways and it is possible that the proportion of cases caused by early pregnancy dysfunction differs between nulliparous women in the USA and UK; this possibility is supported by epidemiological studies.

4.4 | Strengths and limitations

Our study has several strengths. It was performed in a large, low-risk nulliparous cohort of singleton pregnancies. A high proportion of the women who were recruited to the study completed it and donated first-trimester blood samples.
The protein biomarkers measured for this study were analysed only after the outcome collection, and therefore their levels did not have an impact on the management of the pregnancy. The measurement of biomarkers was performed using clinical grade (CE marked) equipment and reagents. The statistical analysis was similarly rigorous: the impact of different levels of adjustments to the measurements was studied and correction for over-fitting was used in the evaluation of the performance of the models. In several cases the optimism-corrected AUC declined as additional biomarkers were added, which indicates the success of cross-validation in accounting for over-fitting; non-cross-validated models would have exhibited a progressive rise in AUC as additional biomarkers were added.

In terms of limitations, the POP study cohort was recruited from a single centre in Cambridge, UK, and the population is predominantly of European ancestry. However, comparison between the POP study results and published results from the demographically highly dissimilar nuMoM2b study suggested that many of the associations were consistently observed across the two populations. Finally, both studies only included nulliparous women and the generalisability of these findings to parous women is unclear. However, parous women necessarily have a past obstetric history and the presence or absence of complications in preceding pregnancies is one of the best predictors of risk in a current pregnancy, hence there is a particular need for early pregnancy predictors in the nulliparous populaition.22–24

4.5 | Research implications

Future work could focus on evaluating a more diverse set of potential markers. Most of the markers evaluated in this and previous studies were identified through secondary analyses of studies screening for the risk of the baby being affected by Down syndrome. Hence, these studies have not been purposeful, based on known pathways, but opportunistic, being based on what data were available. Moreover, we currently lack mechanistic understanding of the causes of APOs. Hence, the challenge in measuring potential biomarkers targeting specific pathways is that we do not know all of the pathways which might be involved. Collectively, these findings underline the potential utility of untargeted analysis of the relationship between protein levels and APOs using proteomics.25

5 | CONCLUSIONS

We found that among women who subsequently experienced APOs, first-trimester levels of PAPP-A, PlGF and sFlt-1 were lower, AFP levels were higher, and there was no difference in beta-hCG levels. Exceptions to this pattern were that high first-trimester levels of beta-hCG were specifically associated with the combination of PE and SGA, and high sFlt-1 was associated with pre-viable loss. In multivariable analysis we found that optimal models included two or three proteins but the combination of proteins differed for different conditions, pointing to heterogeneity in the early placental pathophysiology underlying these serious complications of pregnancy.

AUTHOR CONTRIBUTIONS

Study concept and design: GCSS, DSC-J. Laboratory experiments: FG, EC. Statistical analysis of data: US. Interpretation of data: GCSS, DSC-J, US. Drafting of the paper: GCSS, US. Critical revision of the paper for important intellectual content and final approval of the version to be published: all authors.

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CONFLICT OF INTEREST STATEMENT

Performing the assays for the present analysis was supported by Roche Diagnostics Ltd. We have the following disclosures outside the area of the submitted work. GCSS and DSC-J have received research support from Roche Diagnostics Ltd, Illumina, Pfizer and Sera Prognostics (fetal growth restriction, pre-eclampsia, group B streptococcus and preterm birth). GCSS's department has received payment from Roche for a talk given by GCSS (fetal growth restriction). GCSS has been a paid consultant to GSK (preterm birth) and is a member of a Data Monitoring Committee for GSK trials of RSV vaccination in pregnancy. The remaining authors report no conflict of interest.

DATA AVAILABILITY STATEMENT

Restrictions apply to the availability of data generated or analysed during this study to preserve patient confidentiality or because they were used under license. The corresponding
authors will on request detail the restrictions and any conditions under which access to some data may be provided. Data requests can be made to the corresponding authors.

ETHICS APPROVAL

Ethical approval was given by the Cambridgeshire 2 Research Ethics Committee (reference number 07/H0308/163) on 16 November 2007.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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