Longitudinal change in the cerebroplacental ratio and the risk of stillbirth

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ABSTRACT

Objectives: To investigate whether the longitudinal Doppler changes in small-for-gestational age (SGA) fetuses improves the prediction of those at risk of intrauterine fetal death (IUFD).

Methods: A longitudinal study using two cohorts of singleton pregnancies (SGA and appropriate for gestational age [AGA]). The inclusion criteria for the SGA cohort were singleton pregnancies at 20 weeks' gestation or beyond and diagnosed with SGA. The AGA fetuses consisted of singleton pregnancies deemed at high-risk of developing SGA which were followed up longitudinally but remained AGA. The last two measurements prior to birth were included in the analysis. Longitudinal models for Doppler variables were developed via linear-mixed models and predictive accuracies were tested with generalized linear models. A Bayesian framework was employed to compare model accuracies.

Results: In total, 1549 AGA and 941 SGA babies were included in the analysis. There were 30 (3.2%) and no IUFD cases in the SGA and AGA group, respectively. Using the last measurements, the best models for the prediction of IUFD were the cerebroplacental ratio (CPR) (accuracy: 75.0%, 95% CI: 72.6-77.2%) and umbilical artery (UA) (accuracy: 71.0%, 95% CI: 68.6-73.4%) models. The posterior probability of the CPR model having a higher accuracy compared to the UA model was 97.2% (magnitude of change (MC): 3.9%, 95% credible intervals (CrI): 0.5 to 7.3%). The predictive accuracies of the UA (accuracy: 71.0% vs. 72.8% using the standard vs. longitudinal model, respectively), middle-cerebral artery (MCA) (accuracy: 64.6% vs. 63.8% using the standard vs. longitudinal model, respectively) and CPR

models (accuracy: 75.0% vs. 74.9% using the standard vs. longitudinal model, respectively) were not significantly altered with longitudinal assessment. The posterior probabilities for accuracy improvement with longitudinal assessment were 50.1% (MC: <0.1%, 95% CrI: -3.3 to 3.3%), 35.2% (MC: -0.1%, 95% CrI: -4.5 to 2.8%) and 82.2% (MC: 1.9%, 95% CrI: -1.5 to 5.3%) for CPR, MCA and UA models, respectively. The change in Doppler parameters did not improve the predictive accuracy for IUFD compared to the last scan measurement.

Conclusion: The change in MCA, UA and CPR with advancing gestation was significantly different between live born AGA and SGA fetuses with less pronounced difference with advancing gestation. Longitudinal assessment of Doppler parameters was not useful in improving the detection of IUFD compared to a single point assessment.

INTRODUCTION

Despite the advances in antenatal care, the search for a test to identify the fetus at risk for intrauterine demise continues. The cerebroplacental ratio (CPR), a marker of brain sparing, is emerging as a predictor of the fetus at risk for adverse perinatal outcome, fetal growth restriction (FGR), neonatal care unit admission, intrapartum fetal compromise, episodes of recurrent reduced fetal movements, postnatal circulatory problems and perinatal death in near term fetuses.[1-18] A low CPR reflects redistribution of the cardiac output to the brain and has been shown to improve the accuracy of predicting adverse outcome compared with middle cerebral artery (MCA) or umbilical artery (UA) Doppler alone.[19-23] A recent Delphi consensus implemented CPR as an adjunct marker for diagnosing FGR though the extent of CPR's utility for improving fetal outcome is still under investigation.[24]

FGR, especially early-onset disease, is characterized by a progressive deterioration in Doppler parameters. The clinical management of these fetuses is usually based upon the last available measurement and the utility of longitudinal assessment is not as well known. Most of the studies which assessed the value of CPR in identifying the fetuses at risk had no longitudinal data. Some argue that the reference ranges used during the serial monitoring of small for gestational age (SGA) fetuses, should be based on studies with a longitudinal design.[25] However, the currently used CPR reference ranges are based on cross-sectional studies, and thus, suitable for single observations and not serial monitoring.[25-28] The CPR level decreases as gestation advances beyond 32 weeks in normal fetuses.[28,29] It is possible that the magnitude of reduction and/or the speed of its change could be useful in identifying the fetus at risk. In a recent study, CPR ≤ 5th and ≤ 10th centile was associated with adverse perinatal outcomes.[30]

Moreover, using the conditional centile of CPR has improved the prediction of adverse perinatal outcome, compared to the use of conventional centile alone.[31] Of note, the defined adverse perinatal outcome in this study was a composite measure including many events which are loosely related (i.e. operative delivery due to fetal distress, neonatal hypoglycemia, etc.).[31] Despite the fact that the use of a composite outcome or a combined variable (any adverse outcome) is an accepted method to improve the statistical power of the study, the list of adverse outcomes is heterogeneous and the clinical significance of each of them differs. Nevertheless, it is yet to be established whether a change in the Doppler variables, in addition to the values at the last scan, improves the prediction of intrauterine fetal demise (IUFD). The main aim of this study was to investigate whether the longitudinal Doppler changes in SGA fetuses improves the prediction of those at risk of IUFD.

METHODS

Study design and population

This was a longitudinal study using prospectively collected data from two cohorts of singleton pregnancies. Cohorts included fetuses at risk of growth disorder or already diagnosed with SGA and live born appropriate for gestational age (AGA) fetuses. The study took place in a single tertiary referral centre over a 14-year period from 2000 to 2013. Pregnancies were identified by searching the electronic database (ViewPoint 5.6.8.428, ViewPoint Bildverarbeitung GmbH, Weßling, Germany) in the Fetal Medicine Unit, St George's Hospital, London. The inclusion criteria were singleton pregnancies at 20 weeks' gestation or beyond, which were at risk of fetal growth disorder or already diagnosed with SGA, available serial monitoring and pregnancy outcome data. The AGA fetuses consisted of singleton pregnancies deemed at high-risk of developing SGA due to several factors (low PAPP-A levels, history of SGA neonate in a previous pregnancy, etc.) and were followed up longitudinally.

Management protocol

Suspected SGA fetuses were managed based on their Doppler measurements. Prior to 30 weeks' gestation, the ductus venosus Doppler was used to determine the need for delivery. After 30 weeks' gestation the umbilical artery (UA) reversed end-diastolic flow (EDF) was an indication for delivery, while the UA absent EDF was an indication for delivery after 32 weeks. After 34 weeks the UA pulsatility index (PI) above 95th percentile was an indication for delivery. After 36 weeks' gestation pregnant women with fetal middle cerebral artery (MCA) PI below the 10th centile were offered delivery. In cases where the Doppler measurements remained within

normal ranges, induction of labor was offered between 38 and 39 weeks' gestation at the discretion of physician. The intervals of repeated examinations were individualized according to the clinical needs, but the follow-up protocol during the study period aimed for weekly ultrasound for Doppler assessment and fetal weight estimation every 2-3 weeks. In the analysis we included only those who had two or more measurements because at least two observations are necessary to address variability at individual level. However, only the last two measurements were included in analysis. SGA was defined as estimated fetal weight (EFW) less than the 10th centile.[32] Pregnancies complicated by fetal abnormality, aneuploidy or genetic syndrome, or those with missing pregnancy outcome data, were excluded from the analysis. Stillbirth was defined as a fetus which was born dead after 24 weeks' gestation.

Ultrasound assessment

The gestational age (GA) was calculated from the crown-rump length measurement at 11-13 weeks.[33] The UA and MCA Doppler waveforms were recorded using color Doppler, and the PI calculated according to a standard protocol.[34,35] In brief, MCA PI values were obtained in the space where the artery passes by the sphenoid wing close to the Circle of Willis, and UA PI values were obtained in free loops of umbilical cord. The measurements were obtained in the absence of fetal movement, and keeping the insonation angle with the examined vessels less than 30°. The CPR was calculated as the simple ratio between the MCA PI and the UA PI.[28] The CPR values and their multiple of median (MoM) or centiles were not available on the Viewpoint

system and to the clinicians as the values were calculated as part of the data analysis for this study.

Statistical Analysis

Explanatory variables were presented as median and interquartile ranges (IQR) for continuous data and as n (%) for categorical data. Categorical variables were compared by X^2-test or Fisher's exact test, while continuous data were compared using either independent samples t-test or Mann-Whitney U test. Longitudinal predicted means were constructed via linear mixed modeling by using two measurements (last measurement and penultimate measurement) per patient. Linear mixed models have two components which are fixed model coefficients and random effect model (REM) intercepts. Fetus level variability (change in Doppler parameters) was addressed by using random-effects term in the model. GA in days was used as an explanatory variable and a quadratic equation was used to describe the association of GA and Doppler parameters. The same approach was followed to construct predicted means for AGA fetuses.

After constructing longitudinal predicted means, Doppler models for predicting stillbirth were developed via two-stage model approach.[36] In the two-stage model, a linear mixed effect model is constructed to predict Doppler measurements across GA range while random-intercepts in the model represent the individual level variability for Doppler measurements extracted for each patient. Models were built with generalized linear regression with a logit link function with

random-intercepts extracted from mixed-models and last measurement for standard and longitudinal assessment. Explanatory variables used in these models were MoM values of each Doppler variable, or the random-intercept for MoM values in the case of longitudinal assessment. Since the available data was heavily imbalanced due to low incidence of stillbirth (<1%), under-sampling was applied. Data were partitioned randomly into balanced subgroups (1:1) and performance measures were averaged across all subgroup models. After obtaining the estimate for each independent variable, the performance measures were tested with confusion matrices and sensitivity, specificity, accuracy, positive predictive value and negative predictive value parameters were obtained. For each model 50% cut-off was used to categorize the predicted outcome probabilities as the subgroups were balanced 1:1. The confidence intervals for accuracy parameter were obtained via bootstrapping.

A Bayesian framework was employed to compare model accuracies due to inability of traditional approaches (receiver operating characteristic curve, De Long's test etc.) to do so when undersampling is used for model building. Details of the Bayesian model can be found in a supplementary appendix (Supplementary Appendix 1). All statistical analyses were performed with R Studio version 1.1.442. The "stats", "lme4" and "caret" package were used to construct logistic regression, random effects model and confusion matrix, respectively.[36-39]

RESULTS

After database screening process using appropriate filters in Viewpoint system, 1549 AGA and 941 SGA babies who had longitudinal assessment with available pregnancy outcome were identified and included in the analysis. There were 30 (3.2%) IUFD cases in the SGA group, whereas none of the fetuses had IUFD in the AGA group. Longitudinal predicted means for the AGA babies were constructed by using the last and penultimate Doppler measurements. All Doppler variables (UA PI, MCA PI and CPR) showed a quadratic relationship with GA in linear mixed models using random-intercepts for individual fetuses (Supplementary Table 1). When categorized as AGA and SGA according to their respective EFW, factor level variability had a significant effect on Doppler variables and interaction with GA in all models ($P<0.001$ for all) (Supplementary Table 1). The effect of fetal weight category on the estimated mean trajectories can be observed in longitudinal predicted means for Doppler variables (Figure 1). The observed difference was more evident for earlier GAs (Figure 1).

There were 941 SGA babies included in the analysis. Longitudinal predicted means for the SGA babies were constructed in the same fashion as AGA babies. A quadratic relationship was also observed for SGA babies for all Doppler parameters (Supplementary Table 1). When categorized according to their outcome status (live born vs. stillborn), factor level variability did not have a significant effect on Doppler variables but showed marginally significant interaction with GA in the UA model only ($P=0.090$) (Supplementary Table 1). This finding is likely due to low number of fetuses in the IUFD group. Visual estimation of predicted mean trajectories showed divergent patterns for CPR, UA PI (Figure 2).

Baseline differences between live born and stillborn SGA fetuses are outlined in Table 1. Mothers who delivered stillborn SGA fetuses had significantly higher BMI (P<0.001). Stillborn fetuses had significantly shorter scan interval (P=0.015), lower GA at penultimate (P<0.001) and last scan (P<0.001) which reflects the early-onset growth restriction nature of IUFD group. The birthweight centiles were also lower in the IUFD group (<0.001). Significant differences were also observed between the groups regarding Doppler parameters. Stillborn fetuses had higher UA PI MoM (P<0.001), lower MCA PI MoM (P<0.001) and CPR MoM (P<0.001). The change in the Doppler parameters was calculated as difference between the last scan and penultimate scan, which is then normalized by scan interval. The velocity of change in UA PI MoM was significantly different between live born and stillborn fetuses (P=0.001), whereas the change in MCA PI MoM (P=0.950) and CPR MoM (P=0.086) did not attain statistical significance.

The utility of last Doppler measurement and longitudinal assessment for the prediction of IUFD was modeled using the last Doppler measurement and random-intercept from linear mixed models as variables. Due to the heavily imbalanced outcome measure, multiple balanced models (1:1) were constructed and estimates were averaged across all models. Using the last measurements, the best models for the prediction of IUFD were the CPR MoM (accuracy: 75.0%, 95% CI: 72.6-77.2%) and UA PI MoM (accuracy: 71.0%, 95% CI: 68.6-73.4%) models (Table 2). The posterior probability of the CPR model having a higher accuracy compared to the UA model was 97.4% (magnitude of change: 3.9%, 95% credible intervals: 0.6 to 7.3%) (Table 3). Although that the CPR model offered slightly higher overall accuracy, the positive predictive value of the UA model was higher (81.9% vs. 73.1%), whilst having lower negative predictive value (67.9% vs. 83.6%) compared to the CPR model (Table 2). The predictive accuracies of

the UA PI (accuracy: 71.0% vs. 72.8% using the standard vs. REM model, respectively), the MCA PI (accuracy: 64.6% vs. 63.8% using the standard vs. REM model respectively) and CPR models (accuracy: 75.0% vs. 74.9% using the standard vs. REM model respectively) were not significantly altered with longitudinal assessment (Table 3). The posterior probabilities for accuracy improvement with longitudinal assessment were 50.1% (magnitude of change (MC): <0.1%, 95% credible intervals (CrI): -3.3 to 3.3%), 35.2% (MC: -0.1%, 95% CrI: -4.5 to 2.8%), 82.2% (MC: 1.9%, 95% CrI: -1.5 to 5.3%) for CPR, MCA PI and UA PI models, respectively (Table 3). The velocity of change in Doppler parameters did not improve the predictive accuracy for IUFD compared to the last scan measurement.

DISCUSSION

Summary of *study findings*

In this study we evaluated the utility of longitudinal assessment of fetal Doppler parameters by using the last and the penultimate scan findings. Live born AGA and SGA fetuses had significantly different mean trajectories for UA PI, MCA PI and CPR values across GA range but the significantly different mean trajectories were not observed for live born and stillborn SGA babies. IUFD occurred mainly in early-onset growth restricted fetuses and longitudinal assessment was not helpful in improving the predictive performance of any Doppler measure. Despite the fact that the last measurement and longitudinal assessment models performed similarly, the CPR models showed slightly higher overall accuracy, higher specificity and lower sensitivity compared to the UA models. However, it should be kept in mind that a statistically increased accuracy of CPR model over UA model may not indicate increased clinically utility. Our results suggest that longitudinal assessment may not be helpful for detecting IUFD cases among early-onset growth restricted fetuses.

Strengths and limitations

Our study has several strengths, including using a large cohort of SGA pregnancies, employing robust analysis methodology and providing predicted means for AGA and SGA fetuses. However, our study has some limitations. Firstly, we cannot exclude a possible effect of intervention bias on the results we have obtained. Deviations from the management protocol may mask the beneficial effect of longitudinal assessment in some cases if physicians were to act on perceived deterioration of Doppler parameters, especially in late-onset FGR. On the

other hand, our results could also be interpreted as longitudinal assessment would not have been helpful for preventing IUFD cases in early-onset growth restricted fetuses, which are often considered as monitoring failures. Secondly, we did not have a regular scanning interval for all the fetuses in the study as scans were individualized according to clinical judgment. Despite the fact that irregular intervals may decrease the efficiency of longitudinal modeling, it also represents real life clinical practice which makes study results more relatable to practicing physicians. Thirdly, the investigated outcome was extremely rare in the study population and it was mainly due to early-onset FGR as expected. Due to the low number of pregnancies in the IUFD group, we could not use multivariable regression to test additional models with interaction terms. However, we used under-sampling to ensure that imbalanced data did not produce biased estimates.

Interpretation of study findings and comparison with published literature

The utility of longitudinal Doppler assessment for improving the outcomes in FGR has been scarcely evaluated in the literature. Longitudinal change of Doppler parameters or other indices and also their association with perinatal outcomes have been subject to more research in early-onset FGR compared to late-onset FGR.[41-45] Although the pattern of change in Doppler parameters have been previously described, whether the rate of change is helpful is discerning at risk fetuses is yet to be determined.[41,46] Our results suggest that SGA and AGA babies have different change trajectories for all Doppler parameter for all gestational ages, whereas previously a longitudinal change was only implied for the CPR and MCA but not for the UA Doppler.[41] Ebbing *et al* have suggested that longitudinal reference ranges may be more appropriate than cross-sectional reference ranges for evaluating FGR as the follow-up protocol

requires repeat measurements.[29] In a more recent study, the same research group have suggested that conditional centiles of CPR values offer better prediction for operative delivery for presumed fetal compromise or neonatal care unit admission.[30] Moreover, similar positive findings have been reported for conditional centiles of EFW though these findings are contested by more recent studies.[11,31,47] The relationship of longitudinal changes with perinatal outcome in early-onset FGR is sparsely reported.[48-50] Some studies suggested a worse outcome in early-onset growth restricted fetuses with resolution of cerebral redistribution.[49] Blood levels of soluble fms-like tyrosine kinase 1 (sFlt-1) are correlated with the development of early-onset FGR and abnormal Doppler parameters.[51,52] Herraiz *et al* have investigated the utility of repeat sFlt-1 measurements in predicting perinatal outcomes in early-onset FGR cases.[50] The results have shown limited value of longitudinal assessment for predicting adverse outcomes.[50] Our results are in agreement with the findings of Herraiz *et al* though the method of assessment differed between the two studies (sFlt-1 versus Doppler). Moreover, contrary to the findings of Yeniel *et al*, we could not replicate a benefit of longitudinal assessment of MCA PI.[49]

Clinical and research implications

Although we could not show a benefit of longitudinal assessment for the prediction of IUFD in SGA fetuses, more research is needed. Our results apply mainly to early-onset FGR as IUFD was otherwise rare in late-onset cases. The CPR models showed a slight gain in accuracy over UA PI models which is an interesting finding as the CPR is usually not taken into account in the management of early-onset FGR cases. Post-hoc analyses of large randomized trials such as the TRUFFLE may provide more information on this subject. Furthermore, we have observed marked differences in the velocity of change in Doppler parameters, and therefore, a

prospective study with regular scanning intervals may yield different results. Considering the conflicted nature of literature on this subject with late-onset FGR fetuses, more research is warranted. However, the method of longitudinal assessment must be carefully chosen. The external applicability of two-stage modeling is doubtful due to difficulty in using random-intercepts for predicting outcome in an external cohort. Simpler modeling approaches such as change velocity may be more applicable in routine clinical practice.

Conclusion

The change in MCA, UA and CPR PI was significantly different between liveborn AGA and SGA fetuses with less pronounced difference with advancing gestation. Longitudinal assessment of Doppler parameters was not useful in improving the detection of IUFD in early-onset FGR, compared to a single point assessment. Single last measurement of CPR and UA were moderately predictive of the risk of IUFD in SGA fetuses. Therefore, no need for complex velocity assessments of Doppler indices.

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Table 1. Comparison of antenatal and ultrasound variables between live births and intrauterine deaths in small-for-gestational age fetuses

	Live Births (n=911)	**Stillbirths (n= 30)**	**P value***
Antenatal variables			
Maternal age in years, median (IQR)	30.00 (25.00-34.00)	31.00 (26.25-36.00)	0.199
Body mass index in kg/m2, median (IQR)	23.00 (21.10-26.90)	28.05 (24.50-31.10)	<0.001
Assisted conception, n (%)	83 (9.1)	1 (3.3)	0.506
Multiparous, n (%)	311 (34.1)	10 (30.0)	0.999
Self reported ethnicity, n (%)			0.065
- Caucasian	356 (39.1)	15 (50.0)	
- Asian	299 (32.8)	5 (16.7)	
- Black	170 (18.7)	10 (33.0)	
- Mixed	23 (2.5)	0 (0.0)	
- Other, not reported	63 (6.9)	0 (0.0)	
Smoker, n (%)	77 (8.5)	5 (16.7)	0.174
Ultrasound and delivery variables			
GA at delivery in weeks, median (IQR)	37.57 (34.57-39.14)	28.64 (26.18-32.57)	<0.001
GA at penultimate ultrasound scan in weeks, median (IQR)	32.00 (29.14-34.29)	27.14 (25.79-28.14)	<0.001
GA at last ultrasound scan in weeks,	35.29 (32.57-37.00)	28.57 (27.57-30.00)	<0.001

median (IQR)			
Interval between ultrasound scans in weeks, median (IQR)	2.29 (1.14-4.14)	1.21 (0.71-2.29)	0.015
- Within 1 week, n (%)	211 (23.2)	14 (46.7)	
- Within 1-2 weeks, n (%)	197 (21.6)	5 (16.7)	
- Within 2-4 weeks, n (%)	255 (28.0)	7 (23.3)	
- More than a month, n (%)	248 (27.2)	4 (13.3)	
Birth weight centile, median (IQR)	2.12 (0.50-6.16)	0.36 (0.01-1.05)	<0.001
Umbilical artery PI MoM at last scan, median (IQR)	1.32 (1.11-1.60)	2.60 (1.98-3.39)	<0.001
Umbilical artery PI MoM change velocity, median (IQR) †	0.012 (-0.11 – 0.13)	0.29 (-0.11 – 0.92)	0.001
Middle cerebral artery PI MoM at last scan, median (IQR)	0.91 (0.74-1.05)	0.69 (0.54-0.85)	<0.001
Middle cerebral artery PI MoM change velocity, median (IQR) †	-0.01 (-0.09 – 0.05)	-0.03 (-0.11 – 0.11)	0.950
Cerebroplacental ratio MoM at last scan, median (IQR)	0.42 (0.28-0.54)	0.12 (0.10-0.22)	<0.001
Cerebroplacental ratio MoM change velocity, median (IQR) †	0.00 (-0.04 – 0.05)	-0.01 (-0.06 – 0.01)	0.086

*Group comparison with Wilcoxon rank sum test or Fisher's exact test

† Change calculated as the last scan MoM value subtracted by the penultimate MoM value and normalized by scan interval in weeks

GA: gestational age; PI: pulsatility index; MoM: multiples of median; IQR: interquartile range

Table 2. Predictive accuracy parameters of standard (last measurement) and longitudinal (random-effects model) Doppler models for the prediction of intrauterine death in small-for-gestational age babies.

Models	**Accuracy (%)***	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**
CPR MoM (REM)	74.9 (72.6-77.2)	81.5 (66.7-90.0)	72.7 (70.3-75.1)	75.0 (72.2-77.7)	79.7 (75.2-83.5)
MCA PI MoM (REM)	63.8 (61.2-66.3)	65.4 (53.3-80.0)	66.0 (63.3-68.5)	65.9 (62.6-68.9)	65.7 (61.3-70.0)
UA PI MoM (REM)	72.8 (70.5-75.2)	75.8 (63.3-90.0)	74.2 (71.8-76.6)	74.8 (72.1-77.5)	75.5 (71.1-80.2)
CPR MoM (Standard)	75.0 (72.6-77.2)	87.2 (76.7-96.7)	66.9 (64.3-69.4)	73.1 (70.3-75.9)	83.6 (80.0-86.9)
MCA PI MoM (Standard)	64.6 (62.1-67.2)	73.1 (60.0-86.7)	59.6 (57.0-62.2)	65.1 (61.8-68.5)	68.2 (64.1-72.1)
UA PI MoM (Standard)	71.0 (68.6-73.4)	60.1 (46.7-73.3)	86.4 (84.5-88.3)	81.9 (79.6-84.1)	67.9 (61.0-74.3)

CPR: cerebroplacental ratio, MCA: middle cerebral artery, UA: umbilical artery, PI: pulsatility index, REM: random-effects model, MoM: multiple of median, PPV: positive predictive value, NPV: negative predictive value

Values are provided as mean and 95 confidence intervals within the brackets for accuracy

*95 confidence intervals were calculated with 100.000 bootstrapped replicates

Table 3. Comparison of different models of Doppler parameters for predicting intrauterine demise in small for gestational age fetuses.

The posterior probability for accuracy improvement is provided as percentage, whereas the magnitude of improvement is provided as mean and 95 credible intervals within the brackets. A high posterior probability (>95.0) indicates that the base model (vertical column) is highly likely to be superior to the compared model (horizontal column).

Compared to / Base Model	CPR MoM (REM)	MCA PI MoM (REM)	UA PI MoM (REM)	CPR MoM (Standard)	MCA PI MoM (Standard)	UAPI MoM (Standard)
CPR MoM (REM)	NA	PP: >99.9 MC: 11.1 (7.6 to 14.5)	PP: 84.2 MC: 2.0 (-1.3 to 5.3)	PP: 50.1 MC: <0.1 (-3.3 to 3.3)	PP: >99.9 MC: 10.2 (6.8 to 13.7)	PP: 97.4 MC: 3.9 (0.6 to 7.3)
MCA PI MoM (REM)		NA	PP: <0.01 MC: -9.1 (-12.6 to -5.5)	PP: <0.01 MC: -11.0 (-14.5 to -7.6)	PP: 35.2 MC: -0.1 (-4.5 to 2.8)	PP: <0.01 MC: -7.1 (-10.7 to -3.6)
UA PI MoM (REM)			NA	PP: 16.1 MC: -2.0 (--5.3 to 1.3)	PP: 99.9 MC: 8.2 (4.7 to 11.7)	PP: 82.2 MC: 1.9 (-1.5 to 5.3)
CPR MoM (Standard)				NA	PP: >99.9 MC: 10.2 (6.7 to 13.6)	PP: 97.2 MC: 3.9 (0.5 to 7.3)
MCA PI MoM (Standard)					NA	PP: 0.2 MC: -6.3 (-9.8 to -2.7)
UAPI MoM (Standard)						NA

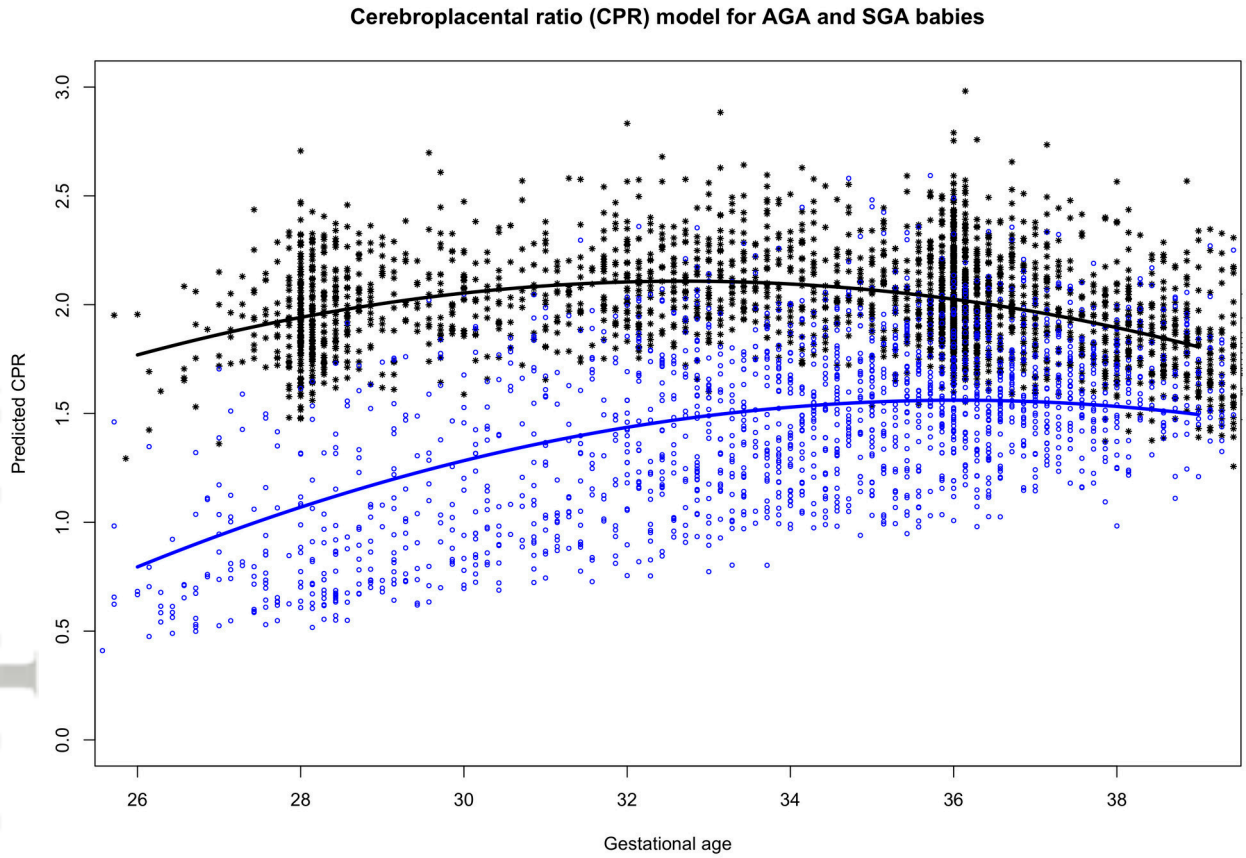
PP: posterior probability, MI: Magnitude of change in accuracy, UA: umbilical artery, MCA: middle cerebral artery, CPR: cerebroplacental ratio, PI: pulsatility index, MoM: multiple of median, REM: random-effects model, NA: not-applicable

Figure 1. Predicted Doppler parameters (cerebroplacental ratio (a), middle cerebral artery (b), umbilical artery (c)) according to the linear mixed models for live born small-for-gestational age (SGA) and appropriate-for-gestational age (AGA) fetuses

Stars and hollow circles represent AGA and SGA fetuses, respectively. The black and blue lines represent the estimated population means for AGA and SGA fetuses, respectively according to the marginal effects model. For all models the effect of estimated fetal weight category (AGA vs SGA) and its interaction with gestational age were significant (P<0.001 for all).

Figure 2. Predicted Doppler parameters (cerebroplacental ratio (a), middle cerebral artery (b), umbilical artery (c)) according to the linear mixed models for live born and stillborn small-for-gestational age fetuses (SGA)

Stars and hollow circles represent live born and stillborn SGA fetuses, respectively. The black and blue lines represent the estimated population means for live born and stillborn SGA fetuses, respectively according to the marginal effects model. The effect of stillbirth had marginally significant interaction with gestational age (P=0.090) in the umbilical artery model only. Predicted mean trajectories for stillborn fetuses were truncated at 32 weeks as there were few measurements after 32 weeks' gestation to allow curve extrapolation.



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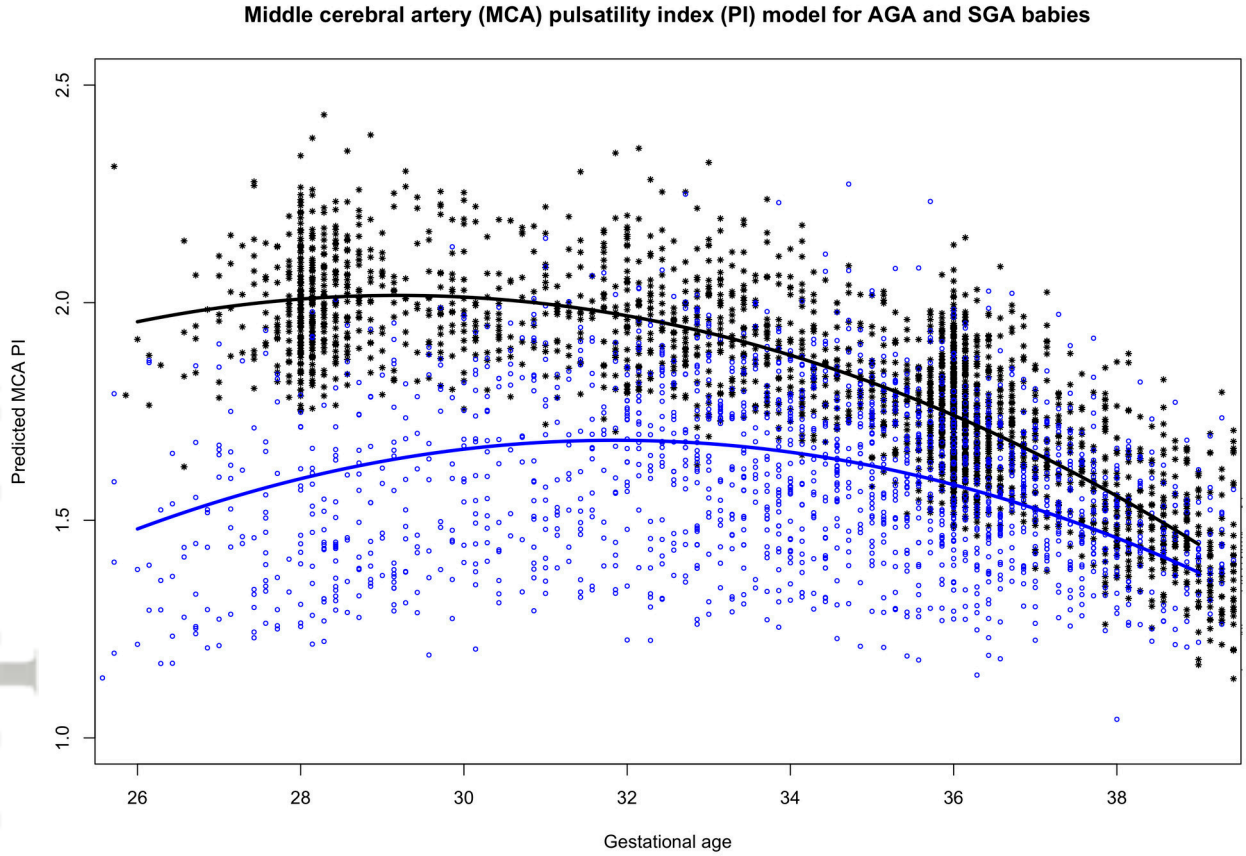

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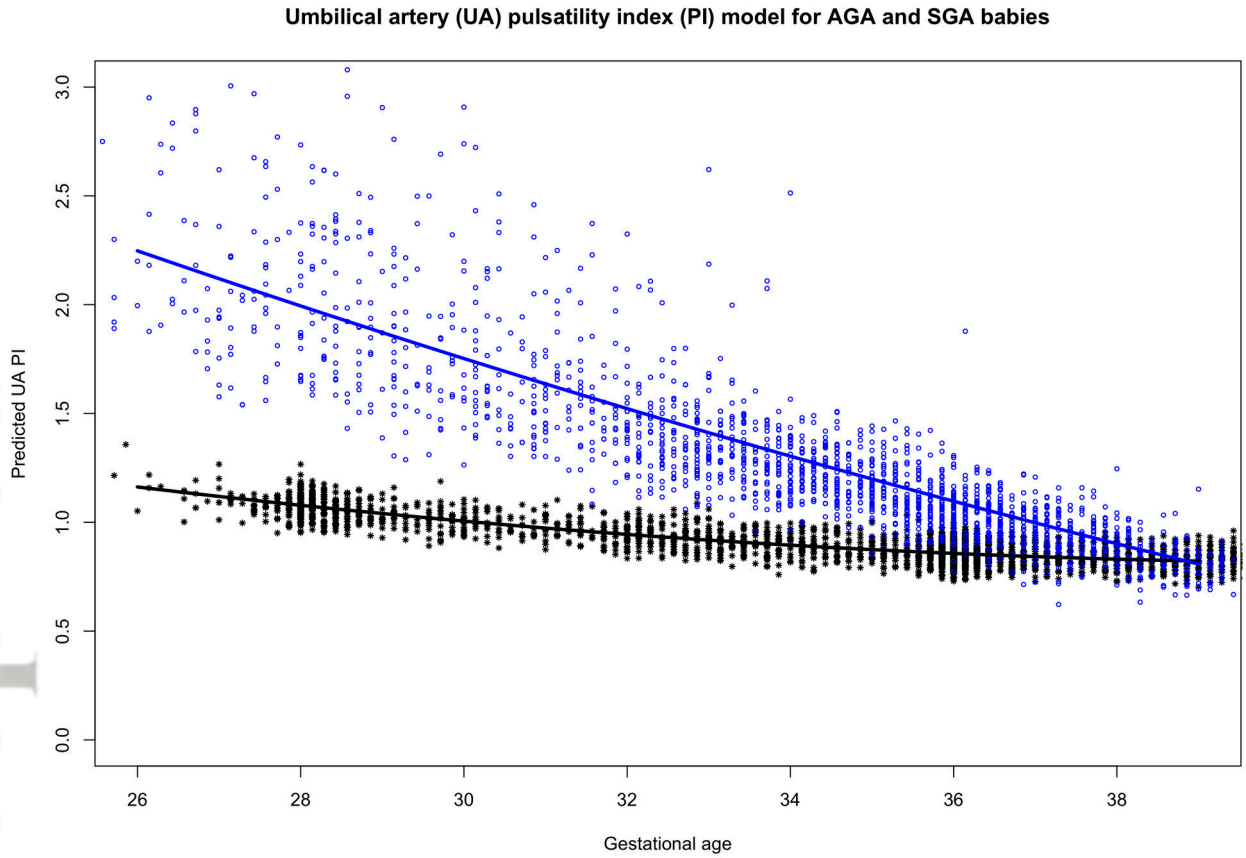

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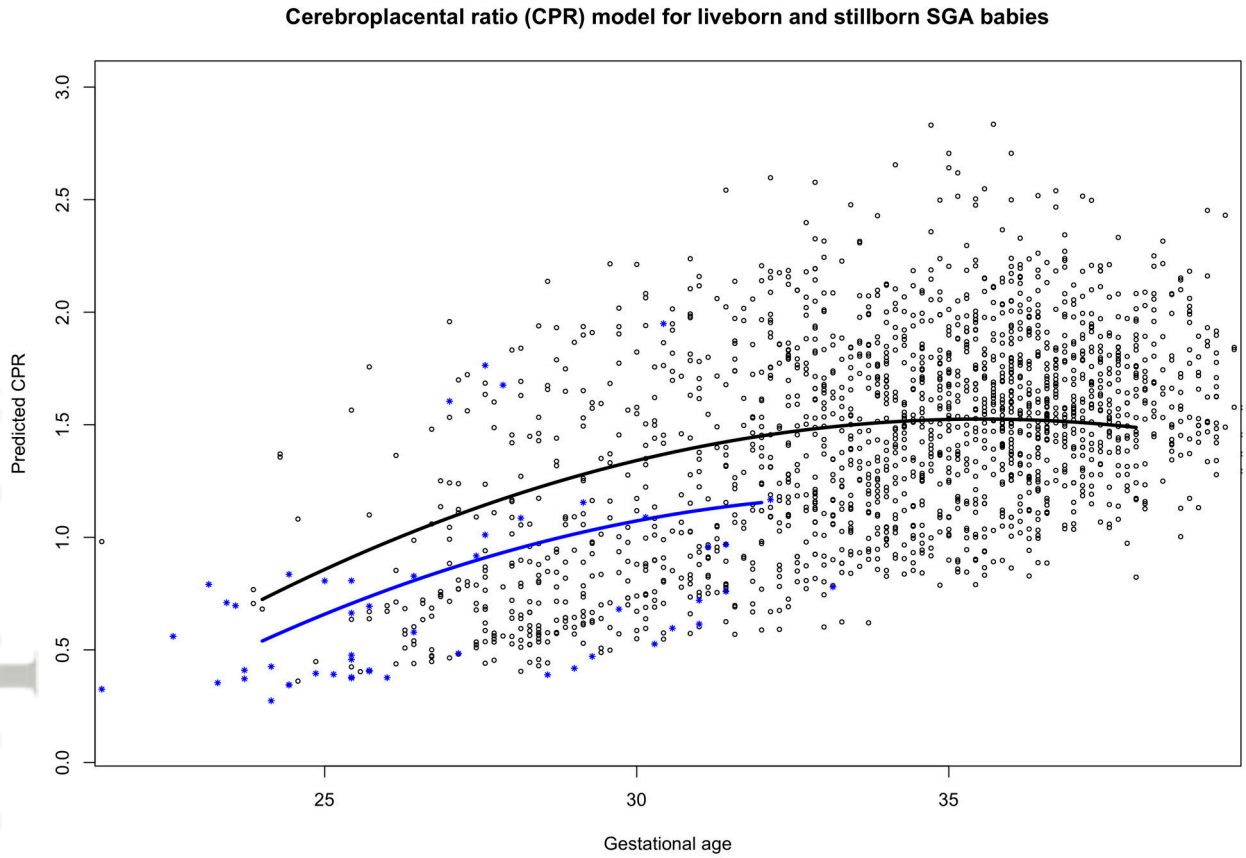

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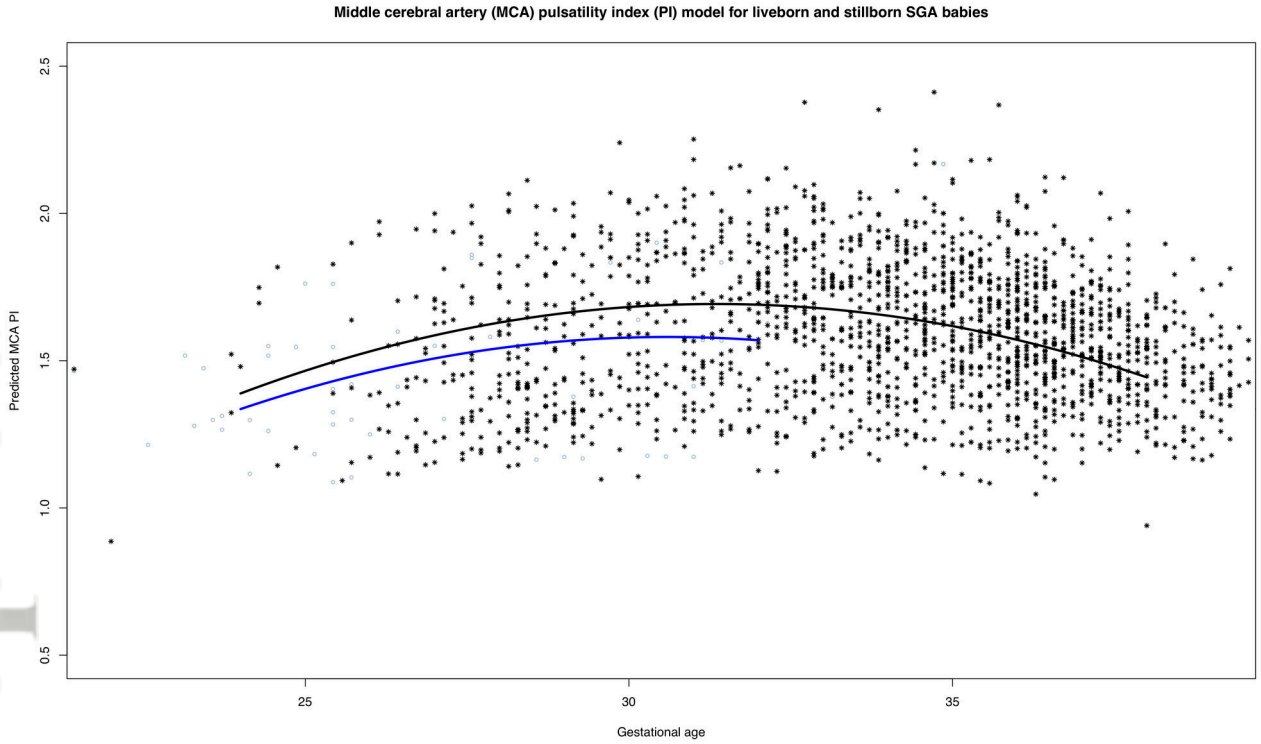

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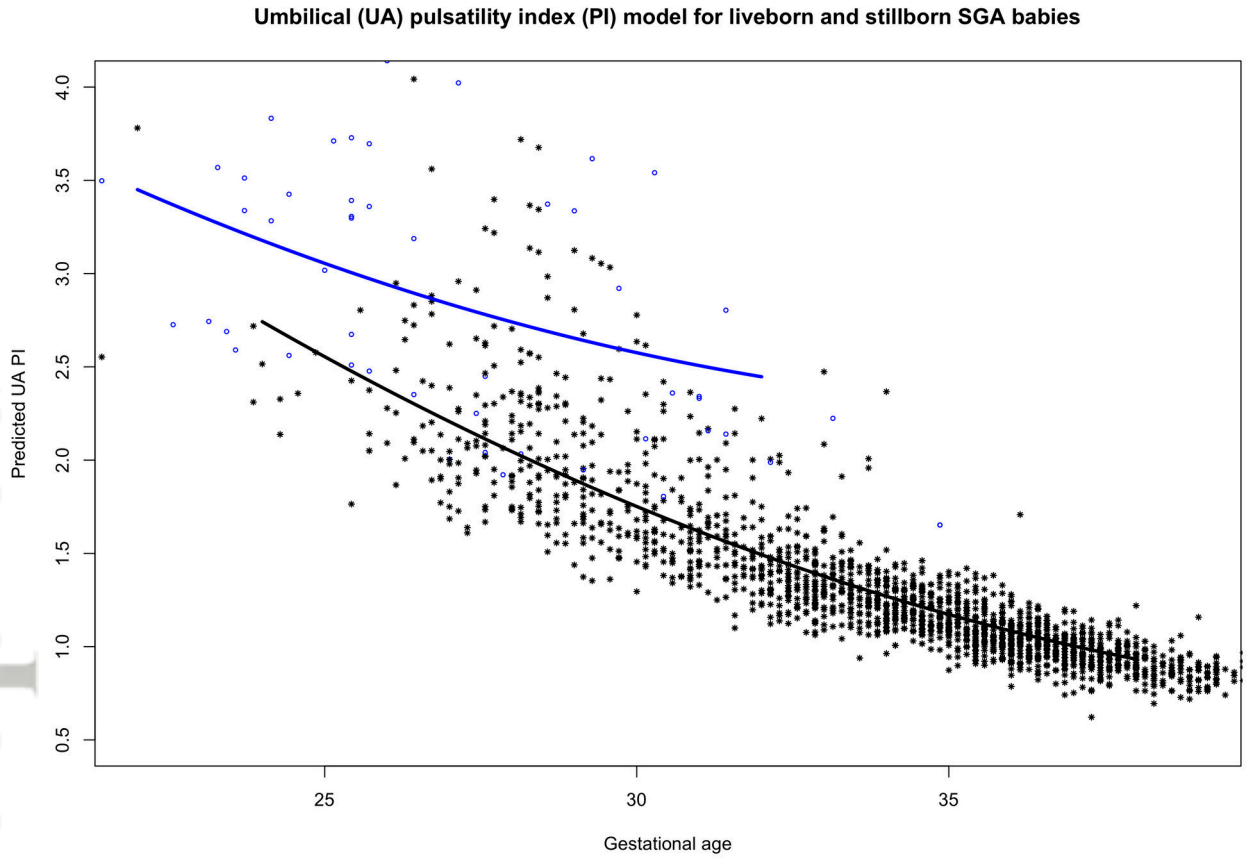

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