A Prediction Model for Short-Term Neonatal Outcomes in Severe Early-Onset IUGR

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BACKGROUND

Severe early-onset fetal growth restriction (FGR) predisposes to fetal death, neonatal death, neonatal morbidity and neurodisability. The use of placental biomarkers has been proposed for risk stratification in pre-eclampsia but they could be equally useful in FGR in order to aid management.

METHODS

This is a secondary analysis of the multicenter, placebo-controlled STRIDER trial of singleton pregnancies with severe early-onset FGR. Women with a pregnancy complicated by FGR between 22^{+0} and 29^{+6} weeks of gestation were randomly assigned to receive either sildenafil 25 mg three times daily or placebo until 32^{+0} weeks' gestation or delivery. We developed prediction models for livebirth, gestation at birth, birth weight, overall survival and neonatal morbidity based upon maternal demographics (age, parity, blood pressure, preeclampsia, gestational hypertension), fetal biometric (estimated fetal weight) and Doppler measurements (Middle Cerebral Artery, Umbilical Artery) and maternal angiogenic biomarkers (PlGf, sEng, sFlt-1 and sFlt-1:PlGF ratio).

RESULTS

A complete data set was available for 105 out 135 randomised women. Multivariable analysis identified estimated fetal weight (EFW) and soluble fms-like tyrosine kinase 1: placental growth factor ratio (sFlt-1:PlGF) as independent predictors of livebirth and overall survival. EFW was a consistent predictor for all outcomes other than gestation at delivery. sFlt-1:PlGF ratio was a consistent predictor for all outcomes other than neonatal morbidity.

CONCLUSIONS

In severe early-onset FGR pregnancies livebirth and overall survival can be predicted using a model involving EFW and sFlt-1:PlGF ratio. This model will allow informed decision making about pregnancy management, especially in cases that may be considered previable.

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Introduction

Severe early-onset fetal growth restriction (FGR) is associated with significant adverse pregnancy outcomes, which includes; fetal and neonatal death [1-3], necrotizing enterocolitis [3], respiratory complications [3], neurodisability [4-7] and lifelong risks to the health of the affected child [8-10]. Currently, there is no effective treatment for FGR with women being offered a choice of; 1) expectant management with intensive surveillance and iatrogenic preterm delivery or 2) termination of pregnancy [11].

We conducted a RCT to test the hypothesis that sildenafil, a phosphodiesterase 5 (PDE5) inhibitor, could prolong gestation improving the blood supply to the placental bed [12]. However, our RCT demonstrated no evidence of benefit in either short term fetal or neonatal outcomes in those women treated with sildenafil [13]. Despite these negative findings the STRIDER RCT does provide valuable clinical and biomarker information for early-onset FGR pregnancies with a more extreme phenotype than other previously published cohorts [1,11].

To date the ability of risk stratification to predict those fetuses that will go on to be severely growth restricted has been poor [14]. With the addition of detailed biomarker assessment in the first trimester, the risk of fetal growth restriction can be modified but remains imprecise [14]. The mainstay of currently advocated prediction models is based on the pathophysiological similarities between preeclampsia and FGR, both of which share similar patterns of placental dysfunction [15].

More useful, and distinctly lacking at present, are large studies to give women and clinicians data on which to base a prognosis for the pregnancy, particularly when diagnosis is made at extremely early gestations where viability is uncertain.

Published FGR cohorts such as the TRUFFLE study provide data on the risk of perinatal mortality and neurological impairment at 2 years of age in pregnancies with moderate to severe FGR [7,11]. The results of this study demonstrated that the risk of fetal demise is very low (<2%) when estimated fetal weight is >500g, Umbilical artery Doppler is abnormal (raised PI or worse) and management is led by a fetal medicine expert with recourse to ultrasound and computerized CTG. Another large cohort of severe early-onset FGR fetuses, classified as previable, showed a perinatal mortality of 52% (111/212, after excluding terminations) and a diagnosis to delivery interval of 8.1 weeks for survivors [1]. Unfortunately, neither of these studies had information on placental biomarkers.

Various biomarkers have been proposed to aid in the identification of pregnancies at risk of an adverse pregnancy outcome although the definition of adverse outcome is often a mixture of fetal/neonatal death and morbidity related outcomes of varying severity and clinical importance. With regards to prediction of low birth weight, the most effective markers to date appears to be PlGF [16-18]. A panel of angiogenic biomarkers, including PlGF and sFlt-1, taken at 24-28 weeks of gestation appears to be a good predictor of subsequent fetal demise (Relative risk of 29.1) when the biomarkers are grossly abnormal [19]. Furthermore, when PlGF/sFlt-1 ratio at 30-34 weeks of gestation is characterized as grossly abnormal (<0.12 MoM) it appears to be associated with subsequent stillbirth (80% sensitivity, 94% specificity) [20].

Unfortunately, the use of biomarkers to prevent perinatal mortality in RCTs has been limited with only two small studies of oestrogen and human placental lactogen included in a recent Cochrane review, neither of which showed a beneficial effect [21].

In light of the promising data from small studies on biomarker prediction and the significant pathology in our STRIDER cohort, we hypothesized that a prediction model

based upon measurable clinical features on ultrasound and biomarkers for placental disease could be valuable in providing prognostic information to women and clinicians.

Methods

This is a secondary analysis of the association between fetal biometric measurements, Doppler indices and maternal angiogenic biomarkers at the time of diagnosis of severe early-onset FGR with pregnancy outcome from the STRIDER trial [13].

STRIDER was a multicenter randomised controlled trial of sildenafil vs placebo for the treatment of severe early-onset IUGR defined as a singleton pregnancy between 22^{+0} and 29^{+6} weeks of gestation with; i) a fetus with abdominal circumference (AC) or estimated fetal weight (EFW) below the 10^{th} centile and ii) absent or reversed end diastolic flow in the umbilical artery on Doppler velocimetry.

Following informed consent women were randomised to receive sildenafil or placebo (25 mg three times per day) until delivery or 32+0 weeks with decision to deliver determined by the attending clinical team. Doppler, growth and blood pressure were assessed a minimum of weekly by a fetal medicine specialist. Blood samples were taken before treatment and at regular points over the next 2 weeks. There was no change in angiogenic blood parameters over time which is demonstrated by the fitting of longitudinal models and assessing the slope term (data not shown). As there was no change, only blood biomarkers from the time of diagnosis of FGR have been considered for this analysis.

Doppler ultrasound was performed serially in four vessels; the umbilical artery (UA), middle cerebral artery (MCA), ductus venosus (DV) and uterine artery (UtA). In addition to the Pulsatility Index (PI), UA end diastolic flow (EDF), DV a-wave and bilateral UtA notching were recorded. Abnormal Doppler findings were defined as

follows; UA, raised PI, absent EDF, or reversed EDF; for MCA, low PI (<5th centile); for DV a-wave absent or reversed, and for UtA mean PI >1.45 or bilateral notching. Serum samples (≥2 ml) were analysed retrospectively. Soluble fms-like tyrosine kinase 1 (sFlt-1) and placental growth factor PlGF (pg/ml) levels were determined using the automated Elecsys® electro-chemiluminescence immunoassay platform (Roche Cobas) and the sFlt-1:PlGF ratio was calculated. Additional analysis of PlGF was performed on baseline (pretreatment) plasma samples using the Alere™ Triage® system. Maternal serum levels of vascular endothelial growth factor (VEGF) (pg/ml) and soluble endoglin (sEng) (ng/ml) were analyzed using human Quantikine® enzyme-linked immunosorbent assays (R&D Systems).

Statistical Methodology

Clinical covariates at randomization included; gestational age, gestational hypertension, pre-eclampsia, preterm prelabour rupture of membranes (PPROM), EFW, blood pressure, mean arterial pressure (MAP) and parity. Doppler covariates included UA EDF, DV a-wave, MCA and UtA. Biomarker data included PlGF, sFlt-1, sEng and sFlt-1:PlGF ratio.

Analyses were carried out on five clinical outcomes; birth status (alive or stillborn), gestation at delivery, overall survival, neonatal morbidity and birth weight. Overall survival was defined as a hospital discharge of a live child (excluding stillbirths and neonatal deaths). Neonatal morbidity was defined as a liveborn fetus surviving to discharge and experiencing at least one of the following adverse outcomes: necrotising enterocolitis, retinopathy of prematurity, bronchopulmonary dysplasia requiring oxygen therapy, patent ductus arteriosus requiring medical or surgical treatment, the need for vasopressor therapy, neonatal infection, intraventricular hemorrhage within 6 weeks of delivery or a confirmed SAE as defined by the STRIDER protocol [13].

Univariable analyses and multivariable analyses were carried out using a generalized linear modelling approach assuming a Gaussian family with identity link for continuous outcomes and a binomial family with logistic link for categorical outcomes. All terms included were considered as candidate covariates in the multivariable analysis. Selection of terms in multivariate models were performed using a forward stepwise approach evaluated using Akaikes Information Criterion (AIC). A forward approach was chosen over a backwards approach to avoid over parameterized models which included a large number of candidate covariates.

Values of PlGF, sFlt-1, sEng, and sFlt-1:PlGF ratio were included as covariates measured on the log scale. Reported results are presented in terms of odds ratios (95% CI) for categorical data and mean (se) for continuous outcomes. Interval validation of the final model for each outcome is carried out using a bootstrap approach using measures of discrimination and calibration. Graphical summaries present the predicted model results along with all analyses are carried out using the statistical package R (Version 3).

Results

Study population

One hundred and thirty five women were recruited to the STRIDER trial between November 2014 and July 2016 from 18 fetal medicine units within the UK. The study population available for analysis was 105 (77.8%) women (Table One); the data for 30 women from the 135 participants of the STRIDER trial were removed as angiogenic biomarker information was unavailable. 61 (58%) women were recruited before 26^{+0} weeks and 44 (42%) between 26^{+0} and 29^{+6} weeks of gestation. Of the 105 available patients, 70/105 (67%) babies were born alive and 59/105 (56%) were discharged alive. 46/70 (66%) liveborn babies experienced neonatal morbidity. The median (IQR) gestation at delivery was 28.3, (26.9, 29.7) weeks and the median (IQR) birth weight was 590g (480, 769).

Modelling

The results of univariable analysis for each of the five outcomes are included in Table Two. Considering clinical covariates, EFW and gestation at randomization were consistent univariable predictors for all outcomes. Pre-eclampsia was a univariable

indicator of a lower gestational age at delivery (est [se] = -1.06 [0.506]; p-value =0.038) and a higher diastolic blood pressure was a univariable indicator of a greater birth weight (est [se] = 1.46 [0.699]; p-value =0.039). Reversed UA EDF Doppler (est [se] = -1.08 [0.417]; p-value =0.011) was a univariable indicator of gestation at delivery. All four biomarker measures (PlGF, sEng, sFlt and sFlt-1:PlGF ratio) were univariable indicators of gestation at delivery and birth weight. PlGF and the sFlt-1:PlGF ratio were significant univariable indicators of livebirth and overall survival.

The results of univariable modelling selected are included in Table Two. The results of multivariable modelling are included in Table Three and include model intercepts for completeness. The results for each outcome are discussed separately.

Livebirths: As EFW increases, the odds of a live birth also increases [OR: 1.01 (1.008, 1.021); p-value <0.001]. Conversely a lower sFlt-1:PlGF ratio [OR: 0.53 (0.284, 0.994); p-value = 0.048] is associated with a larger probability of overall neonatal survival. The intercept of 0.14 (0.003, 7.39) allows estimation of the probability of a live birth (Figure One). For example; for a fetus with an estimated fetal weight of 400g and a (log) sFlt-1:PlGF ratio of 4, the estimated probability of a live birth is 37% as shown below.

$$logit(p) = \log(0.14) + 400\log(1.01) + 4\log(0.53)$$

$$p = 0.3716$$

Gestation at birth: The presence of pre-eclampsia reduced the gestation at birth by almost a week [Est: -0.97 (-1.8, -0.2); p-value = 0.020] whilst having a later gestational age at randomization delayed the gestation at birth [Est: 0.61 (0.5, 0.7); p-value <0.001]. Regarding Doppler measurement, having reversed EDF in the umbilical artery [Est: -0.97 (-1.6, -0.3) p-value <0.001] resulted in an earlier gestation at delivery

With respect to biomarker data, a higher sFlt-1:PlGF ratio [Est: -0.6 (-0.8, -0.3); p-value < 0.001] led to an earlier gestation at delivery.

Overall survival: As EFW increases, the odds of overall survival increase [OR: 1.01 (1.006, 1.015); p-value <0.001]. A lower sFlt-1:PlGF ratio [OR: 0.51 (0.286, 0.904); p-value = 0.021] is also associated with a larger probability of overall neonatal survival. Figure Two shows the relationship between EFW and sFlt-1:PlGF ratio at diagnosis and neonatal survival. A graphical representation of the model results is also provided to give predicted probabilities of overall neonatal survival based on EFW and sFlt-1:PlGF ratio (Figure Two).

Neonatal Morbidity: The only covariate chosen for inclusion in the multivariate model of neonatal morbidity was EFW. As EFW increases the probability of neonatal morbidity decreases [Est: 0.99 (0.994, 0.999); p-value = 0.002].

Birth Weight: The birth weight was greater if the EFW [Est: 1.38 (1.14, 1.61); p-value <0.001] at first scan was larger. However, if the gestation at first scan was higher this had a negative impact on birth weight [Est: -26.62 (-49.64, -3.61); p-value = 0.026]. Considering clinical characteristics, primiparity was associated with a greater birth weight [Est: 66.36 (15.67, 117.05); p-value = 0.012]. Considering biomarker covariates, an increased level of sEng [Est: 61.94 (12.72, 111.15); p-value = 0.015] was associated with greater birth weight whereas an increased sFlt-1:PlGF ratio [Est: -119.43 (-151.94, 86.93); p-value < 0.001] was associated with lower birth weight.

Recognising that gestational age is an important predictor of long term neonatal

outcome, model investigations were performed replacing EFW at randomization with gestation at randomization. Comparison of the two models is given in supplementary Table One. This shows that a model including gestational age at randomization has both a larger model deviance (104.9 compared to 89.0) and a smaller measure of concordance (c-statistic) (0.88 compared to 0.83) showing better model fit for the model that includes EFW rather than gestational age at randomization. The impact of the sFlt-1:PlGF ratio did not materially change between the two models. A further summary of the internal validation used to assess the performance of each model is included in the supplementary information.

DISCUSSION

Our study has confirmed that the combination of clinical biometric data routinely recorded in cases of early-onset FGR with the addition of sFlt-1:PlGF ratio can predict pregnancy outcome for both livebirth, gestation at delivery, birthweight and overall survival. Other covariates also showed benefit in predicting gestation at delivery and birth weight. EFW was a consistent predictor for all outcomes other than gestation at delivery. sFlt-1:PlGF ratio was a consistent predictor for all outcomes other than neonatal morbidity.

To date the majority of published data have demonstrated that a low PlGF or raised sFlt-1:PlGF ratio are associated with a greater likelihood of stillbirth with very few stillbirths when results are normal [18,22,23] [23-25]. Furthermore, an abnormal PlGF appears to more than double the risk of adverse pregnancy outcome [26] and is associated with critical fetal growth restriction [2,27-31] and placental pathology [18]. A recent Cochrane Diagnostic Test Accuracy Review on the effectiveness of biomarkers to predict

stillbirth [32] calculated that an abnormal PlGF or sFlt-1/PlGF ratio have a diagnostic odds ratio of 49.2 for subsequent stillbirth.

The strength of our model is that it combines the diagnostic sensitivity of the sFlt-1:PlGF ratio with the routinely collected clinical covariates of EFW and gestational age to determine likelihood of livebirth and overall survival. We feel that the predictive model for livebirth and overall survival using EFW and sFlt-1/PlGF ratio is the most likely to be of clinical benefit to both clinicians and parents when planning the management of pregnancies affected by severe early-onset IUGR. It may aid in the planning of fetal monitoring, timing of delivery, place of birth and neonatal services.

Further large cohort studies will be required to confirm the benefits of this prediction model in severe early-onset FGR and as a predictive test for adverse pregnancy outcome.

Limitations

Some covariates (PPROM, DV A-vave, UA) were not considered for inclusion in the modelling as the distribution of patients in these groups would not allow for reliable model estimates.

We were unable to assess some clinical covariates within our univariate model due to a limited number of cases with this outcome in our cohort. Further prospective sampling will be able to improve the model fit.

Interval validation has been performed but independent prospective data collection would ideally be available in another similar cohort to confirm our models findings.

STRIDER study group

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DISCLAIMER

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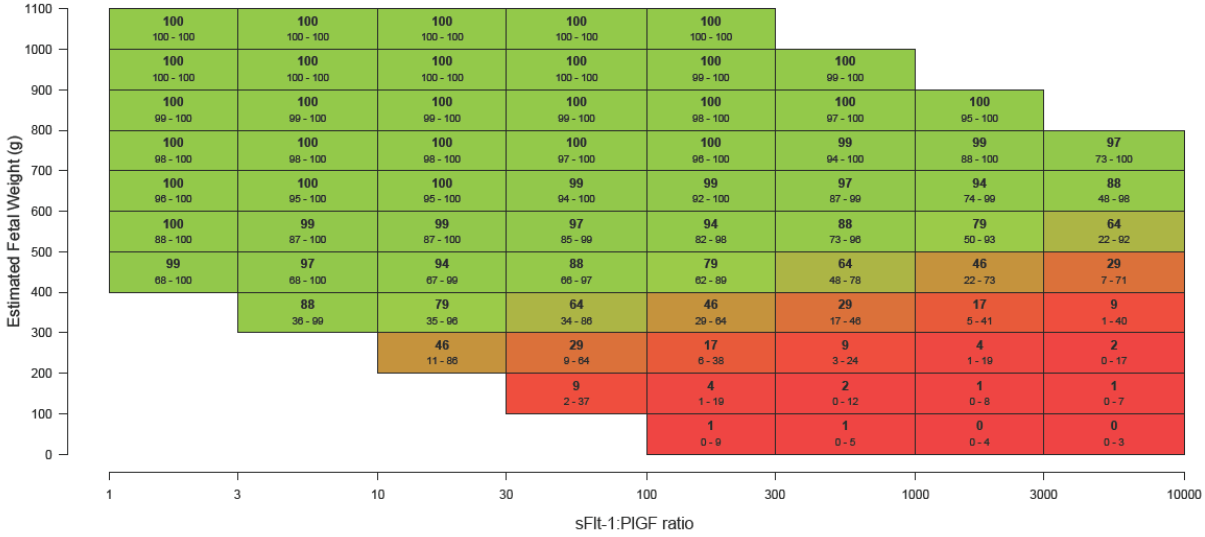


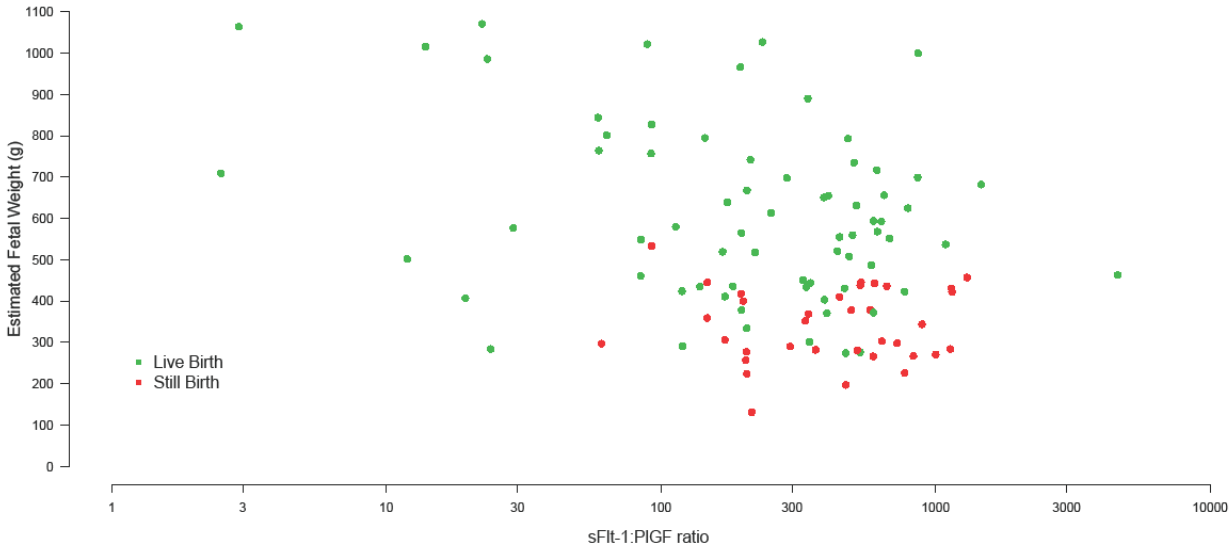
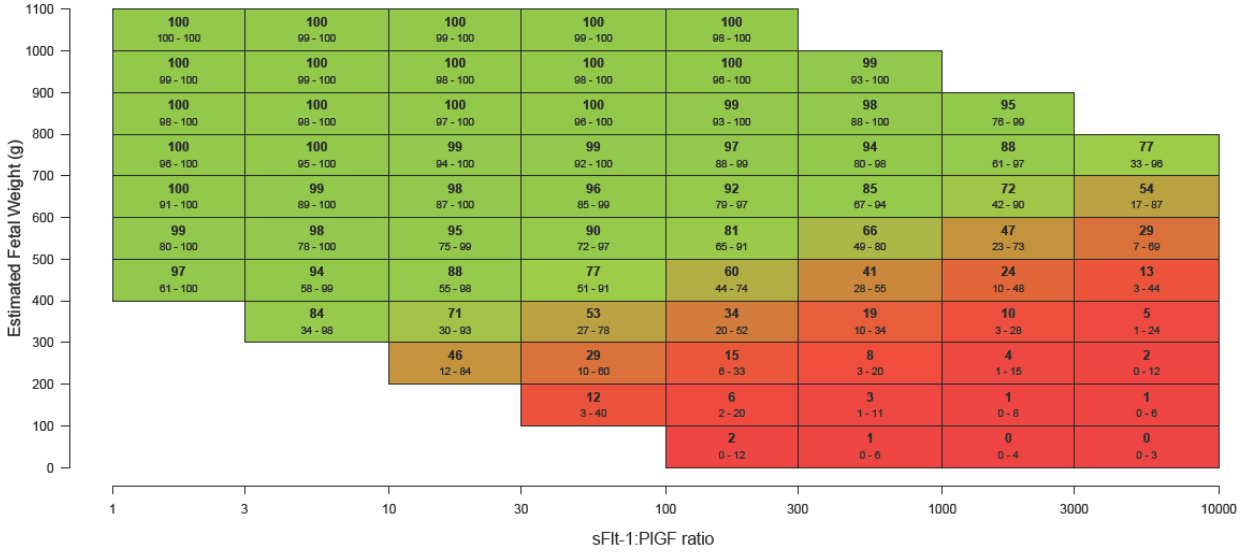


Figure 1: Predicted probability of Livebirth based on both the estimated fetal weight and the sFlt-1:PlGF ratio



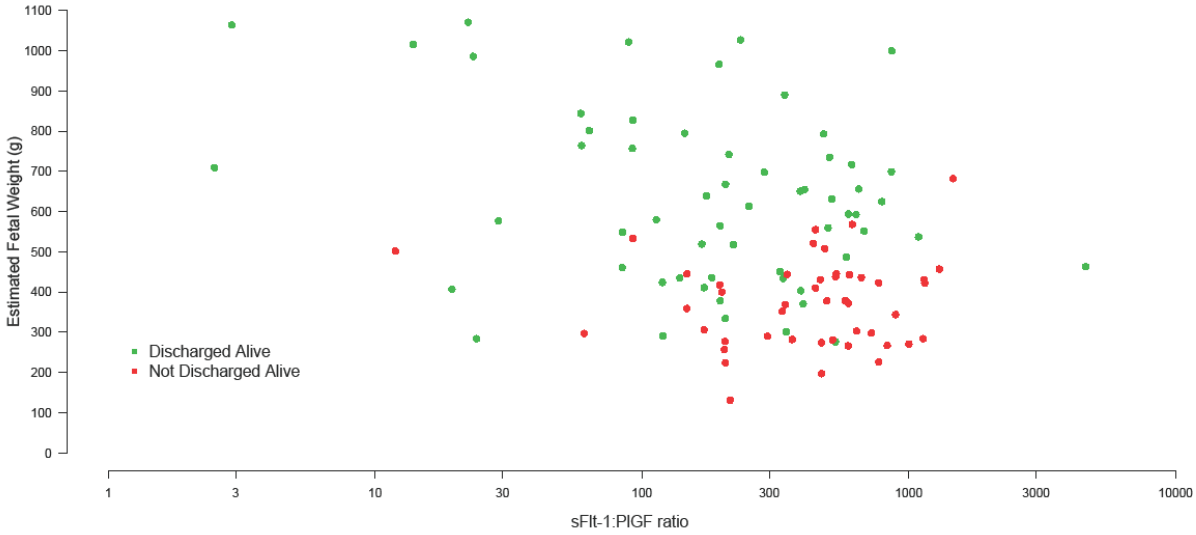


Figure 2: Predicted probability of overall survival based on both the estimated fetal weight and the sFlt-1:PlGF ratio

1.1 TABLE 1: PATIENT DEMOGRAPHICS

Covariate	Level	Total n=105
Age	Median (IQR)	30 (27, 35)
Previous Pregnancy	No	54
	Yes	51
Gestational Hypertension	No	81
	Yes	24
Pre-Eclampsia	No	87
	Yes	18
Diastolic Blood Pressure	Median (IQR)	88.5 (79.5, 95.5)
Systolic Blood Pressure	Median (IQR)	134.5 (124.5, 144.5)
Mean Arterial Pressure	Median (IQR)	104.167 (93.5, 111.667)
PPROM	No	104
	Yes	1
Estimated Fetal Weight	Median (IQR)	451 (369, 651)
Gestation at Randomization	Median (IQR)	25.286 (24.143, 27.429)
EDF	Absent	74
	Reversed	29
DV a-wave	A wave Positive	93
	A wave Reversed	7
MCA	Abnormal	53
	Normal	42
UA	No Notch (<1.45)	13
	No Notch (≥1.45)	7
	Notch	73
Birth Status	Stillbirth	35
	Livebirth	70
Gestation at Delivery	Median (IQR)	28.286 (26.857, 29.714)
Neonatal Outcome	Died (SB/NND)	46
	Survived	59
Neonatal Morbidity	No	24
	Yes	46
Birthweight	Median (IQR)	590 (480, 769)
PlGF	Median (IQR)	22 (13, 42)
sEng	Median (IQR)	33.61 (20.36, 57.82)
sFlt-1	Median (IQR)	6894 (5025, 10380)
sFlt-1/PlGF	Median (IQR)	343.9 (167.2, 591.6)

Table 1: Patient Demographics for the whole Strider Cohort

1.1 TABLE 2: UNIVARIATE ANALYSIS

Covariate	Level	Livebirth		Gestation at Birth		Overall Survival		Neonatal Morbidity		Birth Weight	
		Est	P	Est	P	Est	P	Est	P	Est	P
Allocation	Placebo										
	Sildenafil	1.19 (0.578, 2.464)	0.632	-0.42 (0.392)	0.285	1.01 (0.514, 1.999)	0.969	1.81 (0.75, 4.369)	0.187	-13.41 (56.726)	0.813
Age		0.97 (0.911, 1.039)	0.411	-0.02 (0.035)	0.615	0.98 (0.925, 1.045)	0.587	1.01 (0.932, 1.089)	0.852	0.28 (5.101)	0.956
Previous pregnancy	No										
	Yes	1.02 (0.49, 2.105)	0.967	0.29 (0.395)	0.471	0.85 (0.43, 1.684)	0.642	1.32 (0.544, 3.193)	0.54	71.91 (56.71)	0.207
Gestational Hypertension	No										
	Yes	1.23 (0.53, 2.862)	0.629	-0.22 (0.449)	0.623	0.93 (0.431, 2.022)	0.861	0.64 (0.245, 1.661)	0.357	1.56 (64.691)	0.981
Pre-Eclampsia	No										
	Yes	1.5 (0.549, 4.097)	0.429	-1.06 (0.506)	0.038	0.93 (0.385, 2.266)	0.88	2.87 (0.76, 10.827)	0.119	-73.44 (73.876)	0.322
Diastolic Blood Pressure		1.01 (0.984, 1.032)	0.532	0.01 (0.005)	0.142	1.01 (0.988, 1.025)	0.471	0.98 (0.942, 1.019)	0.298	1.46 (0.699)	0.039
Systolic Blood Pressure		1 (0.973, 1.019)	0.711	-0.02 (0.012)	0.079	0.99 (0.969, 1.012)	0.394	1 (0.972PlGF and t, 1.033)	0.897	-1.54 (1.801)	0.395
Mean Arterial Pressure		1.01 (0.987, 1.026)	0.54	0.01 (0.007)	0.288	1.01 (0.99, 1.021)	0.513	0.99 (0.958, 1.013)	0.299	1.81 (1.00)	0.072
Estimated Fetal Weight		1.02 (1.01, 1.022)	<0.001	0.01 (0.001)	<0.001	1.01 (1.007, 1.015)	<0.001	1 (0.994, 0.999)	0.002	1.31 (0.066)	<0.001
Gestation at Randomization		2.16 (1.623, 2.874)	<0.001	0.68 (0.067)	<0.001	2 (1.566, 2.542)	<0.001	0.63 (0.485, 0.824)	0.001	103.23 (9.276)	<0.001
EDF	Absent										
	Reversed	0.8 (0.37, 1.732)	0.571	-1.08 (0.417)	0.011	0.65 (0.313, 1.359)	0.254	1.64 (0.603, 4.475)	0.331	-57.29 (61.465)	0.353
MCA	Abnormal										
	Normal	1.42 (0.653, 3.081)	0.377	0.56 (0.427)	0.192	1.05 (0.511, 2.148)	0.9	0.93 (0.372, 2.341)	0.883	28.44 (61.676)	0.646
UA	No Notch (<1.45)										
	No Notch (≥1.45)	0.43 (0.08, 2.308)	0.324	0.84 (0.138, 5.07)	0.847	0.64 (0.134, 3.029)	0.57	0.28 (0.037, 2.092)	0.214	-16.7 (129.571)	0.898
	Notch	0.48 (0.146, 1.574)	0.225	0.33 (0.102, 1.079)	0.069	0.62 (0.222, 1.749)	0.368	1.42 (0.413, 4.902)	0.576	-181.21 (84.746)	0.035
PlGF		3.89 (1.9, 7.956)	<0.001	1.4 (0.219)	<0.001	3.67 (1.903, 7.058)	<0.001	0.59 (0.336, 1.04)	0.068	262.6 (28.438)	<0.001
sEng		0.77 (0.455, 1.303)	0.331	-0.67 (0.274)	0.015	0.63 (0.381, 1.045)	0.073	1.22 (0.672, 2.227)	0.509	-115.58 (40.862)	0.006
sFlt-1		1.12 (0.611, 2.036)	0.722	-0.95 (0.329)	0.005	0.88 (0.49, 1.564)	0.653	1.53 (0.769, 3.046)	0.226	-124.97 (49.403)	0.013
sFlt-1/PlGF		0.56 (0.355, 0.872)	0.011	-0.99 (0.157)	<0.001	0.51 (0.327, 0.782)	0.002	1.42 (0.978, 2.075)	0.065	-169.72 (21.821)	<0.001

Table 2: Clinical covariates included for univariate analysis

Covariate	Level	Livebirth		Gestation at Birth		Overall Survival		Neonatal Morbidity		Birth Weight	
		OR (95 % CI)	P	Est (95 % CI)	P	OR (95% CI)	P	OR (95 % CI)	P	Est (95% CI)	P
Intercept		0.14 (0.003 , 7.39)	0.33	16.67 (12.5, 20.9)	<0.00 1	0.43 (0.013, 14.798)	0.641	21.72 (4.275 , 110.3)	<0.00 1	1050.38 (544.26, 1556.51)	<0.00 1
Pre-Eclampsia	No										
	Yes			-0.97 (-1.8, -0.2)	0.020						
EDF	Absent										
	Reverse d			-0.97 (-1.6, -0.3)	<0.00 1						
Estimated Fetal Weight	median (IQR)	1.01 (1.008 , 1.021)	<0.00 1			1.01 (1.006, 1.015)	<0.00 1	0.99 (0.994 , 0.999)	0.002	1.38 (1.14, 1.61)	<0.00 1
	Yes										

Previous Pregnancy	No									66.36 (15.67, 117.05)	0.012
Gestation at Randomization	median (IQR)			0.61 (0.5, 0.7)	<0.001					-26.62 (-49.64, -3.61)	0.026
sEng	median (IQR)									61.94 (12.72, 111.15)	0.015
sFlt-1/PlGF	median (IQR)	0.53 (0.284, 0.994)	0.048	-0.6 (-0.8, -0.3)	<0.001	0.51 (0.286, 0.904)	0.021			-119.43 (-151.94, 86.93)	<0.001

Table 3: Multivariate analysis of significant covariates for main outcome measures