Predictive Ability of The Sflt-1/Plgf Ratio for the Development of Perinatal Complications

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Research Article

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Abstract

Objectives

Hypertensive disorders of pregnancy (HDP) and fetal growth restriction (FGR) of vascular placental origin are two main pregnancy complications associated with an increased incidence of poor outcomes. These conditions are both characterized by vascular dysfunction and syncytiotrophoblast oxidative stress. sFlt-1/PlGF ratio as an index of oxidative stress could be a valid diagnostic tool for predicting adverse perinatal outcomes in high risk population.

Methods

We recruited women affected by HDP, classified according to fetal growth or with isolated FGR. Women with an uneventful pregnancy were recruited as control group. Ultrasound data and sera sample were collected at recruitment. Perinatal complications were the main outcome of this diagnostic study. A survival analysis, a logistic regression model with all covariates and a predictive model based on a Random Forest and a Mean Decrease Gini index were performed.

Results

We recruited 350 consecutive singleton pregnancies. The 90 patients who suffered of perinatal complications had a significantly higher sFlt-1/PlGF ratio (267.2±271.2) at recruitment than those who did not (57±93.5), ($p < 0.001$). Survival curves censored by prevalence of perinatal complications were significantly associated with sFlt-1/PlGF ratio reported risk groups ($p<0.0001$). The logistic regression including all recorded clinical biophysical diagnostic data and sFlt-1/PlGF ratio showed that for each 10-unit increase in the sFlt-1/PlGF ratio the chance of developing perinatal complications increased of 6% (OR 1.006; CI 95% 1.004-1.009; $p < 0.001$). The Predictive Model, using only variables known at the time of recruitment, achieved a sensitivity of 81% and a specificity of 89% ($p < 0.001$), and according to the Mean Decrease Gini index the sFlt-1/PlGF ratio was ranking first.

Conclusion

sFlt-1/PlGF ratio, at the time of recruitment, proved to be a useful tool for predicting perinatal complications in a cohort with all of hypertensive disorders and fetal growth restriction, as a marker of syncytiotrophoblast oxidative stress, independently from the cause of the placental imbalance.

Introduction

Placental dysfunction (PD) is a pregnancy disorder characterized by suboptimal placental activity, which can lead to a spectrum of conditions such as hypertensive disorders (HDP) and fetal growth restriction

(FGR)[1, 2]. HDP and FGR associated with poor placental function share a multifactorial pathogenesis [3], often involving placentation vascular malfunctions or other causes of placental oxidative stress [4–7]. Indeed, these diseases are characterized by an angiogenic imbalance, with an elevation of soluble blocking factors such as soluble fms-like tyrosine kinase 1 (sFlt-1) levels and a decrease in placental growth factor (PlGF) levels [8, 9]. Pregnancies complicated by HDP and/or FGR have higher risks for the fetus to develop perinatal complications, due both to the poor placental function typical of these pathologies and both to the numerous iatrogenic premature deliveries to which these conditions lead. [10]. This longitudinal study was performed on patients with pregnancies complicated by HDP, FGR or both of these conditions, in order to evaluate the possible role of the sFlt-1/PlGF ratio to predict perinatal complications.

Materials And Methods

Study design

This is a longitudinal, observational, multicenter study performed from January 2019 to January 2021. The study participants were recruited at the High Risk Maternity Mangiagalli Centre, Department of Woman, Child and Neonate, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, and at the Unit of Obstetrics, Department of Obstetrics and Gynecology, MBBM Foundation at San Gerardo Hospital, Monza, Italy.

The objective of the study is to create a predictive model for the development of perinatal complications, using sFlt-1/PlGF values and without knowing the delivery gestational age.

All pregnant women admitted for HDP, FGR, or both, were eligible for the present study. Women with an uneventful pregnancy were recruited as control group. Exclusion criteria were: multiple pregnancies, genetic or structural anomalies of the fetus, maternal infections, maternal age less than 18 years old. All patients provided written, informed consent prior to enrolment. The protocol of the study complies with the European Union's Good Clinical Practice standards and the Declaration of Helsinki, and it was approved by the Milan Area 2 Ethics Committee (MATER n° 71_2020 Fondazione IRCCS) and PREBIO STUDY (San Gerardo Hospital).

Patients were recruited at the time of referral at the outpatient high risk clinics, or at admission at the Maternal Fetal Medicine Wards. The visit included a general and obstetrical physical examination, with the assessment of maternal weight gain and the measurement of blood pressure. The diagnosis of HDP was made according to ISSHP guidelines [11], including both gestational hypertension (GH) and chronic hypertension (CH). Patients were evaluated longitudinally during pregnancy and they all underwent an obstetric ultrasound in order to evaluate fetal well-being by the measurement of the fetal biometry, Amniotic Fluid Index (AFI), and Doppler velocimetry of uterine arteries (mean UtA PI), umbilical arteries (UA PI), middle cerebral artery (MCA PI) and the fetal ductus venosus (PIV) when appropriate. The diagnosis of FGR was made according to the Delphi consensus [12].

Placental biomarkers sFlt-1 and PlGF were measured at recruitment. Venous blood was sampled and collected in tubes containing a separating gel, then the tubes were labeled and centrifuged for 10 minutes, within three hours of collection. sFlt-1 and PlGF were analysed by Roche's Elecsys automated method, immunoassays based on electro-chemoluminescence technology. The limits of detection varied between 10 and 8500 pg/ml for sFlt-1 and between 3 and 10000 pg/ml for PlGF.

For the purpose of the study, patients were classified according to the occurrence of perinatal complications. We considered as perinatal complications: intrauterine fetal death (IUFD), neonatal death, preterm delivery (<34 weeks) on maternal indication, newborn's pH <7.1 or BE >-12, Apgar score <7 at 5 minutes, neonatal respiratory distress syndrome (RDS), retinopathy of the premature (ROP), necrotizing enterocolitis (NEC), persistent ductus arteriosus, sepsis, acute renal failure, pneumothorax, and hypoxic-ischemic encephalopathy (HIE).

Statistical analysis

We chose to use the Mann Whitney U-test for scalar variables and Fisher's exact test for categorical variables. Data are expressed as mean and standard deviation for continuous variables and as absolute and relative frequencies for categorical, respectively.

The survey is divided into an initial interpretative analysis of the test population and a subsequent predictive phase.

The first step of our study was a Survival Analysis performed in order to evaluate perinatal complications in relation to gestational age at delivery. The event of interest is the gestational age at the onset of complications. Cumulative incidence curves were built using Kaplan Meier estimates and gestational age at delivery was considered as the time variable. We considered the cumulative incidence of perinatal complications distinguished for the four risk categories established on the basis of the sFlt-1/PlGF ratio values at recruitment (low <38, medium 38-85/38-110, high >85/>110 and very high >655/>201 before and after the 34th week of gestation respectively) [13]. Log rank test was used to compare the curves.

The second step of our analysis was a logistic regression model in order to understand whether sFlt-1/PlGF ratio is among the predictors of perinatal complications and how it influences the outcome. The dependent variable of the model were perinatal complications. The covariates we used were: sFlt-1/PlGF ratio at recruitment, pre-pregnancy BMI, maternal age, aspirin (ASA) or low-molecular-weight heparin (LMWH) during pregnancy, gestational diabetes, mean UtA PI, pre-pregnancy disease, gestational age at recruitment, parity, previous PE/FGR/IUFD, conceive with assisted reproductive technology (ART), and the macro-ethnicity of women divided into North African, Central and South African, Asian, Indian and South American. Odds Ratio were used to interpret the relationship between predictors and perinatal complications, and Wald test was performed in order to assess the significance of predictors.

Finally, **the third step** consisted in a classification analysis for which we used a Random Forest (we specified 500 trees and 3 randomly selected variables for each split) to create a model capable of predicting the occurrence of these complications. The dataset was divided into two groups: 75% of the

data were used to train the model (training set), and 25% of the data were used to test the model (test set). Furthermore, since the number of pregnancies with perinatal complications was much lower than uncomplicated pregnancies, we adopted the Random Over Sampling Examples (R.O.S.E.) algorithm to balance only the training set. Finally, the model for predicting perinatal complications built on the training set was applied to the test set and its classification performances were reported. Mean decrease Gini index was used to evaluate the rank of each variable. Statistical analysis was performed by a statistician using R version 4.0.3 (2020-10-10).

Results

Three hundred and fifty patients, of the 359 recruited, were eligible for the analysis of the study. Five patients were excluded during the study for SARS-COV-2 infection during pregnancy, three were delivered at another hospital and lost at follow-up, one was excluded because of fetal malformations discovered after recruitment.

One hundred and ninety-one patients developed HDP, among whom 90 were associated with FGR. One hundred and eighteen pregnant patients suffered of FGR without clinical evidence of hypertension. Forty-one patients, among those referred to Maternal Fetal Medicine clinics, had an uneventful pregnancy. The population was then divided according to the perinatal complications into 90 complicated cases and 260 uneventful cases. Figure 1 shows recruitment, selection population and the prevalence of maternal complications into clinical groups.

Interpretative analysis

Table 1 shows maternal demographic and clinical features, delivery data and neonatal outcome of patients included in this analysis. We observed a significant higher prevalence of positive medical history, previous obstetric complications, and gestational diabetes in pregnant with perinatal complications. Of interest, the percentage of smokers during pregnancy was higher in the group without complications, even though all women reported a major reduction in the number of daily cigarettes compared with the pre-pregnancy period. Finally, the group that developed perinatal complications showed significantly lower average neonatal weight and gestational age at delivery than the uncomplicated group.

Table 1
Maternal demographic and clinical features, delivery data and neonatal outcome of all groups under examination. Values are expressed as percentage of total patients in each group or as mean and standard deviation. In bold: p value <0.05 compared with the group without complications, calculated by Fisher's exact test for categorical variables and by Mann-Whitney U-test for scalar variables.

Variable	PERINATAL COMPLICATIONS		p-value
	YES (N= 90)	NO (N=260)	
Maternal Age (years)	34.6 (6)	33.5 (5.9)	0.120
Multiparous women	43.8% (39)	37.2% (96)	0.313
Caucasian ethnicity	75.6% (68)	78.8% (204)	0.556
Pre-pregnancy BMI (kg/m^2)	23.9 (5.3)	24.3 (5.9)	0.842
Smokers during pregnancy	2.2% (2)	8.8% (23)	**0.034**
Previous PE/FGR	27.8% (25)	10.4% (27)	**<0.001**
Pre-pregnancy disease	24.4% (22)	8.5% (22)	**<0.001**
Conceived with ART	16.7% (15)	10% (26)	0.126
Gestational diabetes	5.6% (5)	15% (39)	**0.025**
ASA during pregnancy	46.6% (42)	30% (78)	**0.004**
LMWH during pregnancy	11.1% (10)	4.6% (12)	**0.029**
Antihypertensive therapy	13.3% (12)	13.1% (34)	1.0
Gestational age at first examination (weeks)	29.5 (4.1)	33.1 (4.9)	**<0.001**
Gestational Age at Delivery (weeks)	32 (3.9)	38.1 (1.6)	**<0.001**
Caesarean section rate	82.2% (74)	40.8% (106)	**<0.001**
Neonatal weight (gr)	1478.4 (698.8)	2783.3 (625.7)	**0.001**
FGR	80% (72)	51.5% (134)	**<0.001**
NICU	82.6% (71)	6.5% (17)	**<0.001**

Table 2 shows data regarding the biochemical profile. The sFlt-1/PlGF ratio values have been divided into four risk categories, as suggested by *Stepan et al* [13]. The mean value of the sFlt-1/PlGF ratio at recruitment in patients developing perinatal complications was much higher than the group without complications. Among women who developed perinatal complications only 18.9% fell into the low-risk profile, a much lower percentage than the 60.4% of patients without complications ($p < 0.001$). Even in the medium risk the percentage of patients without perinatal complications is higher, while it is possible to see

an increase of the number of cases distributed in the high risk among patients with perinatal complications ($p < 0.001$).

Table 2
Distribution of the sFlt/PlGF ratio categorized in risk classes for all groups under examination. Values are expressed as percentage of total patients in each group or as mean and standard deviation. In bold: p-value <0.05 compared with the group without complications, calculated by Fisher's exact test for categorical variables and by Mann-Whitney U-test for scalar variables.

Variable	PERINATAL COMPLICATIONS		p-value
	YES (N=90)	NO (N=260)	
sFlt-1/PlGF ratio at recruitment	267.2 (271.2)	57 (93.5)	**<0.001**
Low risk (ratio <38)	18.9% (17)	60.4% (157)	**<0.001**
Medium risk (38<ratio≤85/110)	11.1% (10)	23.5% (61)	**0.014**
High risk (85/110<ratio≤655/201)	57.8% (52)	10.8% (28)	**<0.001**
Very high risk (ratio >655/201)	12.2% (11)	5.4% (14)	0.054

Figure 2 shows the results of the Survival Analysis as the cumulative incidence of perinatal complications in the four risk groups (reported in Table 2) according to sFlt-1/PlGF values at recruitment. Patients with sFlt-1/PlGF ratio within the high and very high risk values developed more perinatal complications at an earlier gestational age than the low and medium risk patients ($p <0.0001$).

Table 3 reports the results of the logistic regression analysis for all variables that might be associated with perinatal complications. Variables significantly associated with complications were: mean UtA PI and sFlt-1/PlGF ratio at recruitment, gestational diabetes, pre-pregnancy disease and gestational age at recruitment. This logistic regression analysis showed how a unit increase of the sFlt-1/PlGF ratio induced an increase (OR>1) in perinatal complications of (1.006-1) * 100 = 0.6%.

Table 3
Logistic model for perinatal complications with gestational age at recruitment. Odds Ratio are used to interpret the relationship between predictors and perinatal complications. In bold: p-value < 0.05 calculated by Wald test.

	ODDS RATIO	2,5%	97,5%	p-value
Intercept	0.9879394	0.0310129	30.3525938	0.9945
sFlt-1/PlGF at recruitment	1.006	1.004	1.009	**<0.001**
Pre-pregnancy BMI	1.001	0.939	1.063	0.963
Maternal age	0.990	0.930	1.053	0.755
ASA or LMWH during pregnancy	1.323	0.619	2.789	0.463
Gestational diabetes	0.209	0.047	0.741	**0.025**
Mean UtA PI	4.654	1.986	11.564	**<0.001**
Pre-pregnancy disease	5.516	2.262	13.598	**<0.001**
Gestational age at recruitment	0.884	0.821	0.949	**<0.001**
Parity	1.435	0.690	2.987	0.332
Previous PE/FGR/IUFD	1.982	0.705	5.414	0.186
Conceive with ART	1.988	0.727	5.332	0.174
North African ethnic group	1.315	0.140	8.324	0.788
Asian ethnic group	1.429	0.240	6.567	0.700
Indian ethnic group	0.937	0.197	3.959	0.931
Central and South African ethnic group	5.351	0.252	59.608	0.199
South American ethnic group	1.716	0.424	6.035	0.419

Predictive analysis

We developed two different predictive models, one including the gestational age at delivery, an extremely strong predictor for the development of complications, and the other one based on gestational age at admission. Then, we compared the performances obtained by these two models (Table 4*)*. The first model achieved a sensitivity of 88%, a specificity of 90% and an area under the curve (AUC) of 89%; the second model reached a similar diagnostic accuracy, but unknown the gestational age of delivery.

Table 4
Performance of the model built for predicting perinatal complications with and without gestational age at delivery. The Mc-Nemar test shows how all models have no class preference, while the p-value [Acc>NIR] column shows that for all models the accuracy exceeds the no information rate by a statistically significant amount. All the performances reported refer to the model applied on the test set.

	Accuracy	Sensitivity	Specificity	AUC	PPV	NPV	Mcnemar's Test p-value	P-value [Acc > NIR]
Perinatal complications with delivery GA	0.90	0.88	0.90	0.89	0.80	0.95	0.50	<0.001
Perinatal complications without delivery GA	0.86	0.81	0.89	0.85	0.75	0.92	0.77	<0.001

The Random Forest adopted to construct the predictive models also allows us to obtain an index of the importance of each variable included in the model: the Mean Decreased Gini. Results are shown in *Figure 3*. In the first predictive model gestational age at delivery is the variable with the highest prediction weight, but when the gestational age at delivery is replaced by the gestational age at recruitment the sFlt-1/PlGF ratio and the mean UtA PI measured at recruitment become the two most important variables for the prediction of perinatal complications.

Discussion

Our analysis shows that sFlt/PlGF ratio measured at the time of recruitment is a very useful parameter for predicting the possible onset of perinatal complications, especially in pregnancies with HDP or FGR.

I. The survival analysis performed in order to evaluate perinatal complications in relation to gestational age at delivery, obtained by dividing sFlt-1/PlGF values into four risk classes according to reported clinical criteria [13], showed that the majority of patients who subsequently developed complications fell into the high and very high risk sFlt-1/PlGF ratio groups, and only a very small percentage into the low and medium risk groups ($p < 0.001$).
II. The logistic regression analysis that included all the variable associated with perinatal complications proved that sFlt-1/PlGF ratio was among the significant variable independently associated with perinatal complications, and that for every 10-point increase in the ratio, the risk of developing perinatal complications increased by approximately 6%.
III. After interpreting the predictors of perinatal complications, our goal was to build a model capable of predicting the onset of these. The Random Forest model adopted to assess the predictive value of sFlt-1/PlGF ratio which excluded gestational age at delivery from the possible covariates, proved that this ratio in pregnancies affected by HDP and/or FGR, measured at the time of clinical diagnosis and recruitment, significantly predicted the later development of perinatal complications. The AUC of the

sFlt-1/PlGF ratio was as high as 85% in predicting perinatal complications. Of interest, the inclusion into the model of gestational age at delivery, obviously related to the onset of perinatal complications, did not significantly improved the outcome of the model. According to the Mean Decreased Gini criteria the two most important variables were sFlt-1/PlGF and mean UtA PI at recruitment. This finding further underlies the independent predicting value and strength of sFlt-1/PlGF ratio.

With regard to perinatal complications, most surveys [14-16] identified different cut-offs for the sFlt-1/PlGF ratio in order to define its predictive ability. The study by Bednarek-Jędrzejek M et al. [14] assessed neonatal outcomes by dividing patients into three risk classes: sFlt-1/PlGF ratio <38, between 38 and 85, and >85. The survey showed that perinatal outcomes were significantly worse in the group with sFlt-1/PlGF >85, in which there was a lower birth weight, a shorter duration of gestation and a lower pH of cord blood. Similar findings were observed by Chang YS et al. [15] that used sFlt-1/PlGF values >85 to distinguish high risk from low risk group, and they showed that surviving infants in the high-risk group had a higher incidence of preterm birth, lower birth weight, higher incidence of respiratory distress syndrome and bronchopulmonary dysplasia. Our survey assessed similar correlations in patients belonging to the high and very-high risk sFlt-1/PlGF ratio groups, which had a higher incidence of premature births and thereby developed more perinatal complications at an earlier gestational age.

Finally, according to Zhu X et al. [16] the sFlt-1/PlGF ratio can be useful to predict birth weight, indeed there is an inversely proportional correlation between placental biomarkers values and neonatal weight. Also our analysis showed that infants who developed perinatal complications, and who had higher biomarkers values, also had on average a lower birth weight than infants without complications and with normal biomarkers values.

A recent meta-analysis [17] confirmed these findings on six studies that assessed the sFlt-1/PlGF ratio predictive ability on both maternal and perinatal complications with a sensitivity of 68% (59-75%), specificity 86% (74-93%) and AUC 79% (75-82%). To our knowledge our survey is the first longitudinal study, using placental biomarkers values sampled at recruitment, able to create a predictive model on the development of isolated perinatal complications at delivery.

Strengths and limitations of the study

The main strength of our study is its reproducibility. In fact, we only used sFlt-1/PlGF ratio continuous values without manipulating the data by the use of thresholds. Additionally, in our analysis the predictive model was constructed using Random Forest, only after dividing our population of 350 patients into a training set and a test set: this means that performances reported in our study always refer to the prediction of complications on data from a set external to the one used to build the model, thus excluding the possibility of overfitting that can occur when the model is applied to the data on which it was built. The adoption of this robust procedure allowed us to obtain a more realistic performance, equivalent to that which would be obtained by recruiting a new cohort from scratch or estimating the risk of a single patient. Finally, to the best of our knowledge, our study is the first one using placental biomarkers sampled at recruitment to predict the development of perinatal complications at delivery.

Unfortunately, due to real-life clinical setting of the study, the recruitment of patients did not take place within a precise pre-established gestational age window, but at the time of diagnosis of HDP and/or FGR. The dataset was also collected on population with a predominance of women of South European ancestry and only a minority of different ethnic groups.

Conclusions

Our study proved that in a cohort of patients with HDP and/or FGR the majority of patients who subsequently developed complications fell into the high and very high risk sFlt-1/PlGF ratio groups. The sFlt-1/PlGF ratio in combination with clinical and biophysical assessment of fetal growth and uterine Doppler velocimetry, on a scale of continuous values and without the use of cut-offs, was useful for predicting the development of perinatal complications on cases affected by HDP and/or FGR. The sFlt-1/PlGF ratio, as a marker of oxidative stress of syncytiotrophoblast independent of the cause of stress, was superior to Doppler velocimetry of the Uterine arteries, an index strictly related to placental vascular insufficiency [18] and high vascular peripheral resistance of the mother [19].

Declarations

FUNDING: *The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.*

CONFLICTS OF INTEREST: *The authors have no relevant financial or non-financial interests to disclose.*

AVAILABILITY OF DATA AND MATERIAL: *The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.*

AUTHOR CONTRIBUTIONS: *All authors contributed to the study conception and design. Conception of the project, design study, supervision and correction the draft manuscript, corresponding author by Daniela Di Martino; material preparation, data collection and literature analysis were performed by Daniela Di Martino, Elisa Sabattini, Valentina Giardini, Vittoria Sterpi; statistical analysis was performed by Gabriele Tinè. The first draft of the manuscript was written by Elisa Sabattini and Daniela Di Martino, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.*

ETHICS APPROVAL: *The protocol of the study complies with the European Union's Good Clinical Practice standards and the Declaration of Helsinki, and it was approved by the Milan Area 2 Ethics Committee (MATER n° 71_2020 Fondazione IRCCS) and PREBIO STUDY (San Gerardo Hospital).*

CONSENT TO PARTECIPATE: *Informed consent was obtained from all individual participants included in the study.*

CONSENT FOR PUBLICATION: *Not applicable.*

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Supplements

***S1**. Distribution of the sFlt-1/PlGF ratio categorized in risk classes for groups divided into: controls, HDP, HDP-FGR, FGR. Values are expressed as percentage of total patients in each group or as media and standard deviation. In bold: p value <0.05 compared between the four groups, calculated by ANOVA of Kruskall-Wallis or Marascuilo procedure as appropriate. Dunnett's post hoc test or the Marascuilo procedure post hoc test, as appropriate, was used to calculate the following significant correlations:*

† p-value<0.05 for FGR vs controls

‡ p-value<0.05 for HDP-FGR vs controls

• p-value<0.05 for HDP vs controls

¶ p-value<0.05 for FGR vs HDP

§ p-value<0.05 for FGR vs HDP-FGR

** p-value<0.05 for HDP vs HDP-FGR*

Variable	Controls (N=41)	HDP (N=101)	HDP-FGR (N=90)	FGR (N=118)	p-value	Post hoc test
sFlt-1/PlGF ratio at recruitment	3.8 (3.1)	83.5 (123.1)	265.7 (263.6)	53.9 (91.7)	**<0.001**	† ‡ • ¶ § *
Low risk (ratio <38)	100% (41)	45.5% (46)	12.2% (11)	64.4% (76)	**<0.001**	† ‡ • ¶ § *
Medium risk (38<ratio≤85/110)	0% (0)	30.7% (31)	17.8% (16)	20.3% (24)	**<0.001**	† ‡ •
High risk (85/110<ratio≤655/201)	0% (0)	19.8% (20)	47.8% (43)	14.4% (17)	**<0.001**	† ‡ • § *
Very high risk (ratio >655/201)	0% (0)	4% (4)	22.2% (20)	0.8% (1)	**<0.001**	‡ § *

Figures

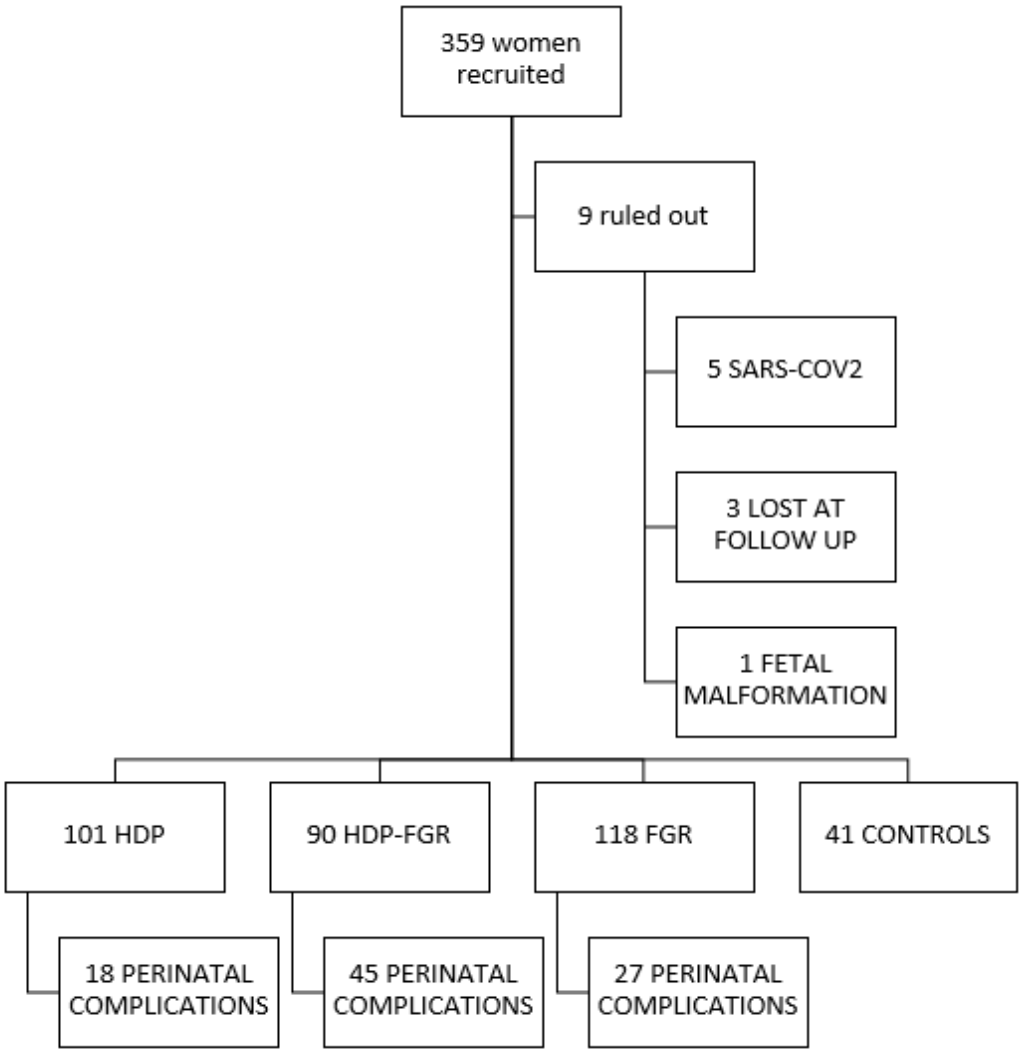

Figure 1

Recruitment, selection population and prevalence of perinatal complications.

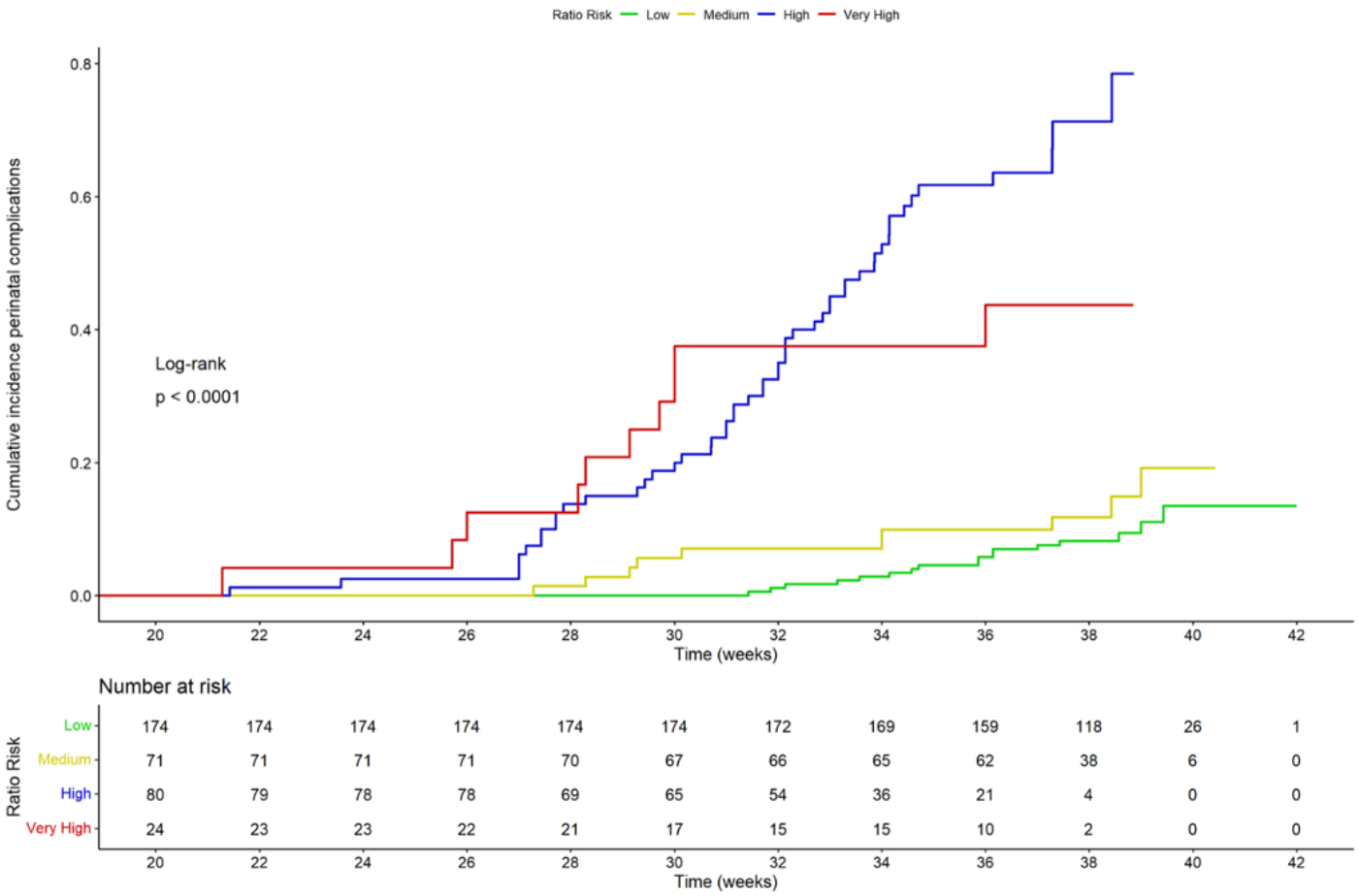

Figure 2

Cumulative incidence curves of perinatal complications in risk groups divided according to sFlt-1/PlGF ratio levels. The y-axis shows the cumulative incidence of complications, while the x-axis shows the gestational age at the time of occurrence of complication. Each step indicates the onset of a new complication.

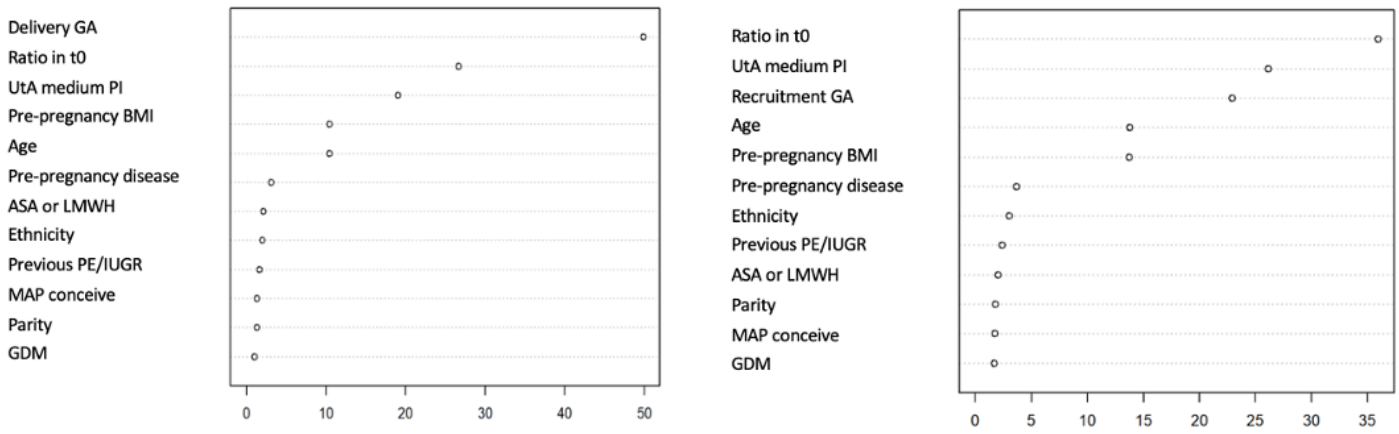

Figure 3

Representation of the variables importance in the predictive model of perinatal complications, with and without gestational age respectively. The y-axis shows variables considered for the predictive model, while the x-axis shows the Mean Decrease Gini index.