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Feasibility of Predicting Rare Adverse Outcomes of Pregnancy Using Machine Learning: Can an Algorithm Use Fetal to Placental Weight Ratios to Predict Which Pregnancies End In Stillbirth?

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2016

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An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
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in Epidemiology
2023

Abstract

Feasibility of Predicting Rare Adverse Outcomes of Pregnancy Using Machine Learning: Can an Algorithm Use Fetal to Placental Weight Ratios to Predict Which Pregnancies End In Stillbirth?
`By Mundayi V. Nlandu

Stillbirth, a rare adverse pregnancy outcome, continues to negatively impact families worldwide. However, the etiology of many stillbirths is uncertain, and novel prevention strategies are needed. Some evidence suggests abnormal fetal to placental weight ratios are associated with increased risk of stillbirth. Although a method exists to estimate placental volume (EPV) during pregnancy, this tool has not yet been studied for stillbirth prevention. Given the challenges of conducting a prospective study for this rare outcome, we used machine learning to develop algorithms to predict stillbirth and evaluate the role of fetal to placental weight ratios in predictive accuracy.

We used Medical Birth Registry data from Norway for approximately 1 million women with singleton pregnancies ($\geq$ 24 weeks). We created a dataset with stillbirth as the outcome, fetal to placental weight ratio as the main covariate of interest and multiple additional covariates to potentially improve predictive accuracy. We used a stacking algorithm, Super Learner, that combines several standard regression and machine learning algorithms into one, via a 5-fold cross validation. We used a 70:30 train:test data split to fit 3 models for predicting stillbirth: one with basic covariates only, one with EPV only, and a third with all variables included. Specificities and sensitivities were calculated, using the test dataset, to develop receiver operating characteristic (ROC) curves with which we assessed the area under the curve (AUC). We evaluated concordance measures for each algorithm.

While results are pending application of our programs to the Norway Medical Birth Registry data by our Norway colleagues, we expect to receive outputs from the three models that estimate predictive accuracy and intend to evaluate these results in two dimensions: absolute performance (how well each algorithm predicts stillbirth) and relative performance (how each algorithm compares to the other).

Overall, stillbirth remains a pregnancy issue requiring greater awareness and research efforts. Hence, prediction studies, such as this, can provide insight into how future studies may be constructed to predict stillbirth, and other rare adverse health outcomes.

Key words: stillbirth, fetal to placental weight ratio, machine learning, estimated placental volume, Super Learner, prediction, receiver operating characteristic curves, area under the curve.

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Introduction

Stillbirth, one of the most common yet least studied adverse pregnancy outcomes, continues to devastate numerous families worldwide. Each year, there are approximately 2 million stillbirths.[1] In 2019, the stillbirth rate was 13.9 stillbirths per 1,000 total births, with stillbirth defined as a baby without signs of life at 28 weeks' gestation or later. [1,2] These statistics are just a glimpse of the data on stillbirth, as prevalence is frequently under-reported, and dependent on the geographical context, missing data, and variation of stillbirth definition. [1]

Risk factors associated with stillbirth include pre-eclampsia, diabetes mellitus, primiparity, obesity, hypertension, smoking and lack of access to healthcare. [3–6] However, there is still much ambiguity surrounding etiology, and prevention strategies for stillbirth. [4] Progress in reducing stillbirth rates will remain stagnant without effective prevention strategies.

Current modalities of stillbirth prevention include antenatal care, nutrition interventions to improve diet and address pre-pregnancy conditions, and maternal immunizations. [7,8] It is recommended that prevention strategies focus on equitable healthcare for maternal care, improved data collection, access to fetal autopsy, placental examination, improved antenatal detection of fetal growth restriction, and updated clinical guidance on reduced fetal movement. [2,6,7,9,10]

Some evidence suggests that abnormal placenta size is associated with increased likelihood of stillbirth and other adverse pregnancy outcomes.[11–13] Moreover, evidence shows that, with respect to placental size, the fetuses at greatest risk of stillbirth are those with large fetal to placental weight ratios (i.e., the fetuses are much larger than their placenta). [13–15] Given the critical role that the placenta plays in providing the fetus with oxygen and nutrients especially

as the demand increases throughout the progress of the pregnancy, the combination of a large fetus with a small placenta could result in a reduced supply of oxygen and nutrition to fetus leading to critical compromise and hypoxic episode while in utero. [15,16] Despite the known association between small placentas and stillbirth, it is unknown whether the ratio of fetal to placental weight can be used to predict pregnancy outcomes. This is an important question, as there is a method available to estimate placental volume during pregnancy, which could be used as a method to detect pregnancies at an increased risk of stillbirth. To obtain an estimated placental volume (EPV), healthcare providers can take three measurements using a standard two-dimensional ultrasound and use the *Merwin's Calculator* application, to obtain the estimate. [17–19]

Due to the large sample required for a prospective study, it has not been feasible to evaluate EPV as a tool that could potentially inform clinical decision making to prevent stillbirth. As it is cost effective and simple to use, EPV may be a key tool to use in stillbirth prevention dependent on if the ratio can be used to predict stillbirths. This study is a first step to inform the feasibility of using EPV during antenatal care for stillbirth prevention. In this paper, we use the ratio of the fetal to placental weight as a proxy for EPV, and we train and compare several machine learning algorithms to evaluate the feasibility of using this ratio to predict stillbirth.

Methods

We trained algorithms using summary data obtained from the Medical Birth Registry of Norway which contains information on all births in Norway as well as maternal and child health issues during pregnancy and at birth. [20]

For this study, we analyzed fetal and maternal data, from approximately 1 million women with singleton pregnancy of 24 weeks' gestation or later. We obtained average fetal birthweight to placental weight ratio and stillbirth. Stillbirth was defined as a baby with no sign of life while in utero or at delivery, any time from 24 weeks of pregnancy onward.

Covariates considered for entry in the machine learning algorithms included: maternal age, maternal weight pre-pregnancy (kg), maternal weight late pregnancy (kg), number of previous deliveries by mother, maternal body mass index (BMI) pre-pregnancy or early pregnancy, maternal body mass index (BMI) late pregnancy, gestational age in weeks and days, maternal height (cm), placental weight, birthweight of child (kg), eclampsia, preeclampsia, previous miscarriages before 12 weeks' gestation, previous miscarriages/stillbirth 12-22 weeks of gestation, diabetes (no diabetes, Type 1, Type 2, Gestational Diabetes Mellitus), smoking status (no, sometimes, daily), child's sex (male, female). These covariates were chosen because they could be identified prior to delivery and thus could be used by healthcare providers to identify pregnancies at higher risk for stillbirth.

Statistical Analysis

We used the statistical software R version 4.2.2 and the package Super Learner to conduct the analyses for stillbirth prediction. Super Learner follows a stacked method principle in which numerous algorithms are combined into a single "meta-algorithm" via cross-validation and weighted averaging of algorithms. [21] We used the dataset containing the fetal to placental weight ratio and stillbirth, along with the previously listed covariates, with Super Learner using 5-fold cross-validation.

Algorithms incorporated into the Super Learner included Bayesian GLMs (bayesglm), multivariate polynomial spline regression (polymars), the simple mean, extreme gradient boosting (xgboost), random forests (ranger), multivariate adaptive regression splines (earth) and standard GLMs. To determine predictive accuracy, we used AUC of ROC and concordance via a 70:30 train:test data split.

The training dataset was used to fit three different Super Learner algorithms which we labeled as Model 1, Model 2, and Model 3. Model 1, regressed the outcome stillbirth against all variables in our analytic dataset, excluding the fetal to placental ratio; Model 2, regressed stillbirth solely against fetal to placental ratio; Model 3, regressed stillbirth against all variables in our analytic dataset as well as the fetal to placental ratio. Model 3 represents the combination of Model 1 and Model 2 and enabled us to evaluate the additional role that fetal to placental ratio plays in predicting stillbirth, above and beyond the predictive contribution of base variables alone.

These models were trained in 70% of the original data, and performance metrics were obtained out-of-sample using the remaining 30% of the data. These metrics included the area under the Receiver Operating Characteristic (ROC) curves, which are obtained as a function of the sensitivity and specificity of each algorithm. We also used concordance as a metric of performance, which compares the proportion of stillbirth events for any two individuals in the data that had predictions in the same direction. For example, if pregnancy i ended in no stillbirth, and pregnancy j ended in a stillbirth, then concordance can be defined as $P\left(Y_j > Y_i \mid \hat{Y}_j > \hat{Y}_i\right)$.

Results

Currently, results are pending application of our programs to the Norway Medical Birth Registry data by our Norway colleagues. Below are potential figures and tables that may result from the outputs produced by our code. Overall, we anticipate being able to answer the following specific research questions with these analyses:

1) Can baseline demographic and clinical characteristics play an important role in predicting stillbirth?

2) Can fetal-placental weight ratio (a proxy for EPV) play an important role in predicting stillbirth?

3) Is the predictive performance of an algorithm that includes baseline demographic and clinical characteristics in addition to the fetal-placental weight ratio better than the predictive performance of one single set of variables alone?

Possible scenarios that can result from our analysis will include figures similar to Figures 1 and 2 presented below.

Table 1. Characteristics of Norway Birth Registry Women ≥ 24 weeks gestation (to be updated)

Characteristic	**n =1052178**	
	%	Mean (SD)
Maternal age (years)		29.73 (5.11)
Gestational age (weeks)		39.42 (1.80)
Maternal BMI		
Pre pregnancy		24.32 (4.78)
Late pregnancy		29.64 (5.21)
Maternal height (cm)		166.70 (6.48)
Placenta weight (g)		670.14 (149.05)
Weight of child (g)		3550.38 (557.28)
Fetal birthweight to placenta ratio		5.48 (1.95)
Preeclampsia		
Yes	3.20	
No	96.80	
Eclampsia (Yes)		
Yes	0.04	
No	99.96	
Smoking status (early pregnancy)		
Non-Smoker	74.70	
Smoker sometimes	1.40	
Daily smoker	9.70	
Diabetes		
No Diabetes	97.10	
Type 1 Diabetes	0.40	
Type 2 Diabetes	0.30	
Gestational Diabetes	2.20	
Previous Miscarriage (12-22 weeks)		
None	87.80	
One	2.20	
Two	0.30	
Three	0.10	
Four or more	0.00	

Previous Deliveries	
Nulliparous	41.50
One	36.30
Two or more	22.20

In Figure 1, the three models, represented by colored curves all present a similar AUC of 0.90.

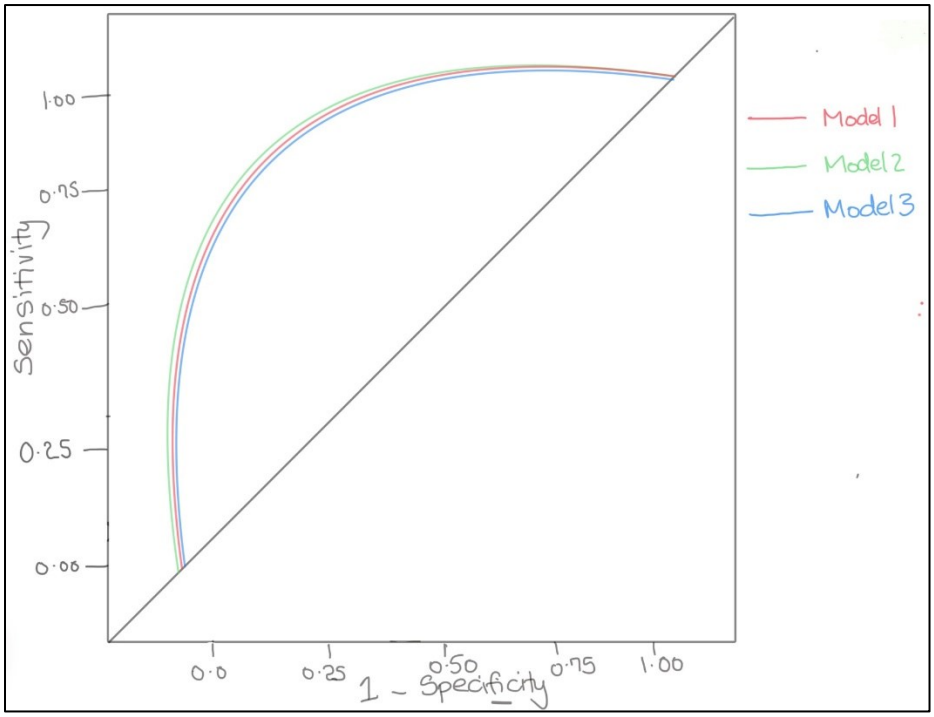

Figure 1. Potential receiver operating characteristic (ROC) curves displaying the estimated predictive accuracy of Super Learner on the outcome of stillbirth for the three models. The red line represents the regression of the outcome stillbirth against all variables in our analytic dataset, excluding the fetal to placental weight ratio (Model 1). The green line represents regression of stillbirth solely against fetal to placental weight ratio (Model 2). The blue line represents regression of stillbirth against all variables in our analytic dataset as well as the fetal to placental weight ratio (Model 3).

Table 2. Average concordance values from the algorithms for Model 1, Model 2 and Model 3 used to evaluate predictive accuracy of fetal to placental weight ratio in the outcome of stillbirth.

Model	Average Concordance Value
Model 1	0.85
Model 2	0.82

Model 3	0.88

In Figure 2, the models represented by colored curves present different AUCs, with Model 2 having the highest, close to 0.90, Model 2 with an AUC of 0.75 and Model 3 with an AUC of 0.60.

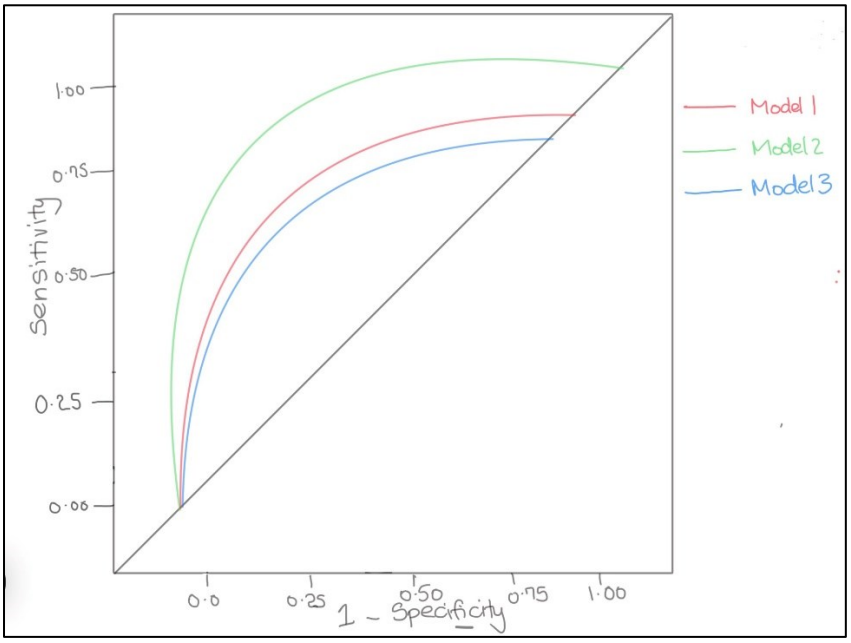

Figure 2. Potential receiver operating characteristic (ROC) curves displaying the estimated predictive accuracy of Super Learner on the outcome of stillbirth for the three models. The red line represents the regression of the outcome stillbirth against all variables in our analytic dataset, excluding the fetal to placental weight ratio (Model 1). The green line represents regression of stillbirth solely against fetal to placental weight ratio (Model 2). The blue line represents regression of stillbirth against all variables in our analytic dataset as well as the fetal to placental weight ratio (Model 3).

Table 3. Average concordance values from the algorithms for Model 1, Model 2, and Model 3, used to evaluate predictive accuracy of fetal to placental weight ratio in the outcome of stillbirth.

Model	Average Concordance Value
Model 1	0.77
Model 2	0.90
Model 3	0.65

Discussion

Previous studies have not been conducted to use EPV as a tool for predicting stillbirth. However, Super Learner continues to be a useful tool in establishing predictive accuracy. It is with this understanding that we performed analysis on the data obtained from the Medical Birth Registry data on pregnancies across Norway to evaluate predictive performance of the fetal to placental weight ratio for stillbirth.

These results can be used to evaluate the performance of the models using the AUC and concordance values. This is examined through two dimensions: the absolute performance and the relative performance. The absolute performance describes whether the algorithms sufficiently predicts the risk of stillbirth in the Norway data. The relative performance evaluates whether the fetal to placental weight ratio contributes sufficient predictive accuracy to warrant use in clinical settings, relative to other possible variable sets.

To obtain algorithm performance measures, we applied the “firewall principle” to avoid overfitting our models. The “firewall principal” requires that data used to train the algorithms (i.e., the training dataset we used for fitting the models) will at no point be used to evaluate the

performance of the data (i.e., the test dataset we used for evaluating the predictive performance). Hence, a separation between the two datasets allows for more impartial predictions.

For concordance and AUC, the closer the values are to 1, the more accurate the predictions and the better the performance. Hence, if either value is 0.5 (50%) the performance will be deemed very poor. While if the value is higher (e.g.) 0.9 (90%), this suggests that the algorithms performed very well.

In Figure 1, the three models had high AUC values of 0.9. Overall, this would indicate that the algorithms performed well. Additionally, the average concordance was also close to 1, it was approximately 0.8 for all three models as shown in Table 2. The consistent higher values implied the performance metric worked for the prediction of stillbirth.

In Figure 2, the three models had varied AUC values. Model 2, which was regression of stillbirth solely against fetal to placental ratio, had the highest AUC of 0.90, while Models 1 and 3 had AUC values of 0.75 and 0.60 respectively. Additionally, the average concordance for Model 1 was 0.77 , Model 2 was 0.90 and Model 3 was 0.65. In evaluating these numbers, we would determine that the predictive accuracy of the fetal to placental wight ratio and stillbirth model, (Model 2), was high and suggested a good performance. However, Model 1 had a mid-performance and Model 3 had a poorer performance outcomes as it related to predictive accuracy of stillbirth. These two models both had covariates as part of the models.

For relative performance, if the performance metrics for Models 1, 2, and 3 indicate roughly the same values, then we cannot make a clear conclusion about the role of fetal to placental weight ratio in predicting stillbirth. However, if the model with stillbirth and only fetal to placental weight ratio (Model 2) has higher predictive accuracy values than Model 1, we can

determine that fetal to placental weight ratio is a better predictor than the set of covariates in Model 1.

In Figure 1, the models in the graph had a similar AUC of approximately 0.9. Hence, in regard to the relative performance it would be noted that as these values are very close to each other, suggesting that fetal to placental ratio is not needed above and beyond basic demographic and clinical covariates in predicting stillbirth. The results indicated that Model 2, which only had the fetal to placental weight ratio was performing at the same level as the model without it, Model 1. We would therefore be less likely to advise clinicians to use the EPV as a proxy for predicting stillbirth although the absolute performance of the Super Learner was high.

In Figure 2 the models in the graph did not have similar AUC value or concordance values. Model 2 presented the highest values, closest to 1, which indicated that the algorithms performed very well for predictive accuracy as explained in the absolute performance. We observed that when fetal to placental weight ratio was removed from the model (i.e Model 1), the predictive accuracy for stillbirth based on covariates decreased and the performance was mid at 0.75 for AUC. Additionally, the model with all the variables (Model 3), had the lowest performance among the three and was closer to the 0.50 mark, at 0.60, meaning predictive accuracy was quite poor. If our model returns these values, it could be suggested that fetal to placental weight ratio does play a role in stillbirth and this EPV tool may be useful for clinicians to assess whether a pregnancy is likely to end in stillbirth.

The dataset was ideal for evaluating the feasibility of using the fetal to placental weight ratio to predict stillbirth as the Medical Birth Registry of Norway includes decades' worth of data on all deliveries, thus yielding a large enough sample to study the rare outcome, stillbirth. Furthermore, we implemented cross-validation in Super Learner, which helped to reduce

overfitting and hence provided better predictive performance and less misleading results. Super Learner fits multiple algorithms and in this study, we were also able to produce 3 models for analysis, which provided greater predictive accuracy than if we had used a single algorithm. Additionally, the use of machine learning in this context allows for conservation of resources that would have been expended had we evaluated the use of EPV as a prediction tool in real-time.

In terms of performance, Super Learner is highly dependent on the algorithms that are used for the analyses. Hence, there could be different predictions based on which algorithms were used, for example, if the algorithms are weaker it may not improve predictive accuracy. The package is also quite technical and may not be as intuitive as to an individual dependent on one's preference. Additionally, Super Learner uses multiple algorithms, hence took a longer time to run compared to the runtime a single algorithm. However, each algorithm used in our Super Learner algorithm depends on its own unique set of assumptions. For example, GLM models require correct parametric modeling assumptions to obtain valid predictions. Similarly, random forests require appropriate selection of tuning parameters to obtain valid predictions. However, when combined into the super learner algorithm, the role that each set of assumptions plays in obtaining valid predictions is reduced relative to the overall number of algorithms in the Super Learner.

Conclusion

Overall, stillbirth remains a health issue that requires more advocacy and better prevention strategies. While this continues to be a challenge, research methods such as this can help health care providers navigate whether to use EPV as a tool for predicting stillbirth or whether there are other factors that can be used to predict stillbirth. Upon receipt of the model

performance, we will be able to determine whether fetal to placental weight ratio is indeed or is not a predictor of stillbirth. This determination will provide key insights into the utility of incorporating EPV into decision making for stillbirth prevention.

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Appendix A

Super Learner Algorithm Code

```
packages <- c("data.table","tidyverse","skimr","here","SuperLearner",
              "data.table","nnls","mvtnorm","ranger","xgboost",
              "splines","Matrix","ggplot2","xtable","pROC","dplyr",
              "polspline", "haven", "survival")

for (package in packages) {
  if (!require(package, character.only=T, quietly=T)) {
    install.packages(package, repos='http://lib.stat.cmu.edu/R/CRAN')
  }
}

for (package in packages) {
  library(package, character.only=T)
}

## Step 1: Set the working directory
setwd("")

## Step 2: import the data into R

## Step 3: Select Only Relevant Variables
norway_data <- norway_d %>%
select(MORS_ALDER, MORS_VEKT_FOER, MORS_VEKT_SLUTT, MORS_HOYDE,
KMI_FOER, KMI_SLUTT, ga, Gestation_at_birth, Plac_weight, Birthweight,
BW_plac_W_ratio, Preeclampsia, EKLAMPSI, Stillbirth, Diabetes_3_categories, Gender,
ROYK_BEG, PARITET, SPABORT_12_5, SPABORT_23_5, DODFODTE_5)
```

```
head(norway_data)
dim(norway_data)

## Step 4: Run the Super Learner

set.seed(123)
# Specify the number of folds for V-fold cross-validation
folds=5



#Fit using the SuperLearner Package
#----------------------------------------------------------------------------
# Specify the outcome-for-prediction (y), the predictors (x),
# family (for a binary outcome), measure of performance (1-AUC),
# the library (sl.lib), and number of folds
sl.lib <- c("SL.bayesglm","SL.polymars", "SL.mean", "SL.glm", "SL.xgboost",
            "SL.ranger", "SL.earth")

index <- sample(1:nrow(norway_data),ceiling(.3*nrow(norway_data)), replace = F)
index

test_dat <- norway_data[index,]
train_dat <- norway_data[-index,]

nrow(test_dat)
nrow(train_dat)
```

```
y <- train_dat$ Stillbirth #outcome for the norway_data

x1<- train_dat %>% select(-Stillbirth, -BW_plac_W_ratio) #excluding outcome and ratio variable for the Norway data

x2 <- train_dat$BW_plac_W_ratio # just the ratio (placental to fetal) variable

x3 <- train_dat[, - Stillbirth]# everything except outcome, so x1 + ratio variable


#regresses stillbirth against all except the ratio variable

fitY1 <-SuperLearner(Y=y,X=x1,family="binomial",

                     method="method.AUC",

                     SL.library=sl.lib,

                     cvControl=list(V=folds))

fitY1


saveRDS(fitY1, "fitY1.rds")


#regresses stillbirth against just the ratio variable

fitY2 <-
SuperLearner(Y=y,X=data.frame(intercept=1,BW_plac_W_ratio=x2),family="binomial",

                      method="method.AUC",

                      SL.library=sl.lib,

                      cvControl=list(V=folds))

fitY2

saveRDS(fitY2, "fitY2.rds")


#regresses stillbirth against everything

fitY3 <-SuperLearner(Y=y,X=x3,family="binomial",

                      method="method.AUC",

                      SL.library=sl.lib,

                      cvControl=list(V=folds))
```

```
fitY3
saveRDS(fitY3, "fitY3.rds")

y_pred1 <- predict(fitY1, newdata = data.frame(test_dat), onlySL=T)$pred

x2_test <- data.frame(intercept=1,
                      BW_plac_W_ratio=test_dat$BW_plac_W_ratio)

y_pred2 <- predict(fitY2, newdata = x2_test, onlySL=T)$pred
y_pred3 <- predict(fitY3, newdata = data.frame(test_dat), onlySL=T)$pred

p <- data.frame(y=test_dat$STILLBIRTH,
                y_pred1=y_pred1,
                y_pred2=y_pred2,
                y_pred3=y_pred3)
head(p)

# Use the roc() function to obtain measures of performance for binary classification
a <- roc(p$y, p$y_pred1, direction="auto")
b <- roc(p$y, p$y_pred2, direction="auto")
c <- roc(p$y, p$y_pred3, direction="auto")

saveRDS(a, "./misc/roc_output_model1.rds")
saveRDS(b, "./misc/roc_output_model2.rds")
saveRDS(c, "./misc/roc_output_model3.rds")

# To plot the ROC curve, we need the sensitivity and specificity
A <- data.frame(sens=a$sensitivities, spec=a$specificities, Model = "Base")
```

```
B <- data.frame(sens=b$sensitivities, spec=b$specificities, Model = "Ratio")
C <- data.frame(sens=c$sensitivities, spec=c$specificities, Model = "Base + Ratio")

head(C)
plot_dat <- rbind(A,B,C)

head(plot_dat)
tail(plot_dat)

ggplot() + geom_step(data=plot_dat,
                     aes(x = 1-spec, y = sens, color = Model),size=.25) +
  theme_light() + theme(panel.grid.major = element_blank(),
                        panel.grid.minor = element_blank()) +
  labs(x = "1 - Specificity",y = "Sensitivity") +
  geom_abline(intercept=0,slope=1,col="gray")

ggsave("roc_curves.png")

head(p)
dummy1 <- lm(y ~ y_pred1, data=p)
dummy2 <- lm(y ~ y_pred1, data=p)
dummy3 <- lm(y ~ y_pred1, data=p)
cfit <- concordance(dummy1, dummy2, dummy3)

saveRDS(cfit, "./misc/cfit_all_three.rds")
```