Prediction of cesarean delivery in class III obese nulliparous women: an externally validated model using machine learning

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Competing interests

The authors have no competing interests to declare.

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Author roles

Philippe Deruelle and Benoît Gallix conceived the study. Benoît Gallix designed the study. Massimo Lodi and Camille Brien performed the bibliographic selection and acquired relevant data. Audrey Poterie and Georgios Exarchakis developed the model. Massimo Lodi, Audrey Poterie and Georgios Exarchakis wrote the initial draft. Pierre Lafaye De Micheaux, Philippe Deruelle and Benoit Gallix contributed to critical discussion and manuscript finalization.

Data Availability Statement

The model will be openly available online at url: xxx.xxx (to be updated). Patient data is not available.

Condensation page

Condensation:

We developed a machine learning-based predictive model of cesarean delivery in class III obese women

Short Title:

Cesarean delivery prediction in nulliparous obese women

AJOG at a Glance:

- Delivery planning in obese women is an every-day clinical challenge, and cesarean section during labor is at higher risk compared to planned cesarean section and vaginal delivery. To date, there is no tool able to stratify individual risk of cesarean section in this population.
- We developed a probability forest model, based on machine learning, able to predict cesarean section risk during labor in nulliparous class III obese pregnant women with singleton pregnancy, based on only two pre-labor parameters: labor induction and initial weight.
- This model is effective for predicting unplanned cesarean section risk, easy to use and can participate to the choice of trial of labor versus planned cesarean section, enhance quality of patient information and provide personalized risk calculation.

Abstract page

Abstract

Background: class III obese women, defined as a body mass index $\geq$ 40 kg/m^2, are at higher risk of cesarean section during labor and cesarean section is responsible of increased maternal and neonatal morbidity in this population. Despite the fact that planned cesarean section is at higher risk compared to vaginal delivery, it is safer compared to unplanned cesarean section during labor. However, there is no available method to quantify the unplanned cesarean section during labor among class III obese women. *Objective*: the objective was to develop a method able to quantify cesarean section risk among a population of class III obese pregnant women before labor. *Study Design*: this is a multicentric retrospective cohort study conducted on 410 nulliparous class III obese pregnant women with attempt of vaginal delivery in 2 French University hospitals. Exclusion criteria were multiple pregnancy, medical interruption of pregnancy and stillbirth, and delivery $<$ 22 weeks of gestation. The primary endpoint was the risk of unplanned cesarean section. We developed two predictive algorithms: a logistic regression model (classical approach) and a probability forest model (based on machine learning). We then assessed model performances and compared them. *Results*: The logistic regression model found that only the initial weight and labor induction were significant in the prediction of unplanned cesarean section. In the probability forest model the most important predictor was the labor induction followed by the initial weight. The probability forest was able to predict a cesarean section probability with only 2 pre-labor characteristics: initial weight and labor induction. Its performances were calculated for a cut-point of 49.5% (prediction of cesarean section if the risk was higher than the cut-point) and were (with 95% confidence intervals) : area under the curve 0.70 (0.62,0.78), accuracy 0.66 (0.58, 0.73), specificity 0.87 (0.77, 0.93) and sensitivity 0.44 (0.32, 0.55). Probability forest performances were better compared to the logistic model ones. *Conclusions*: this is an innovative and effective approach for predicting unplanned CS risk in nulliparous class III obese women undergoing trial of labor, and could improve maternal and neonatal outcomes due to unplanned cesarean section-related morbidity in this population. This model could participate to the choice of trial of labor versus planned cesarean section. Further studies are needed within a prospective clinical trial.

Keywords: obesity, cesarean delivery, personalized medicine, random forests, machine learning, predictive model, predictor selection.

1 Introduction

Obesity, defined as a body mass index (BMI) $\geq$ 30 kg/m^2, is a major public health hazard. [1] It is the most common medical condition in women of childbearing age (with a prevalence of 39.7% in the United States [2]) and can have consequences both on the mother and the child during pregnancy [3]. Moreover, prevalence of obesity among pregnant women is increasing worldwide [4, 5]. In 2009, obesity rates for pregnant women were estimated between 6.2% and 9.9% in France [6] and 16.1% in Canada [7]. In the United States, 34.9% of women are obese, and it was estimated that in 2014 there were 1.1 million obese pregnant women [4]. Thus, obesity in pregnancy will become more challenging with time.

It has been well established that, during pregnancy, obesity is associated with increased maternal and fetal morbidity such as gestational hypertension, gestational diabetes, and large-for-gestational-age fetuses [8, 9, 10, 11, 5]. Moreover, obesity has an impact on delivery as it is an independent risk factor of cesarean section (CS). [12, 13, 14, 11, 15] Indeed, obese women are at higher risk of CS delivery compared to non-obese women [11, 16]. In addition of higher CS rates, scientific literature shows that CS in obese women is more likely to cause maternal and neonatal morbidity. Indeed, obese women undergoing CS are at greater risk of postoperative infection and thrombosis [17, 18, 11] compared to non-obese women. Infants of obese women need more often intensive care and have higher rates of fetal compromise and meconium-stained liquid [11].

Moreover, obesity is defined in 3 classes according to the World Health Organization: class I as a BMI between 30.0 and 34.9 kg/m^2; class II between 35.0 and 39.9 kg/m^2; and class III as a BMI $\geq$ 40 kg/m^2 [19]. Studies suggest that obesity-related risks during pregnancy increase with BMI, and complications are higher among class III obese women. Indeed, it has been shown [15] that CS risk increases proportionally to BMI (between 2 and 5% for each 1 kg/m^2 of BMI) and rates are >50% in laboring women with BMI $\geq$ 40 kg/m^2, and CS odds increases 3.5 fold for an increase of 10 kg/m^2 BMI [20].

Finally, CS-related complications seem to be higher in case of an emergency or unplanned CS rather than elective or planned CS [21, 22]. These data indicates that unplanned CS-related complications rates could be lowered if a planned CS is performed. Some studies investigated risk factors of unplanned CS among class III obese pregnant women besides BMI, and that some characteristics are independent risk factors of CS such as maternal age, parity, and cervical dilation [20]. Despite the fact that risk factors are well-known, there is insufficient evidence in the scientific literature to allow clinicians to stratify the unplanned CS-risk for obese women during labor, and consequently to individualize those at high risk which could be counseled for a planned CS before labor. Our objective was therefore to develop a method able to quantify CS risk among a population of class III obese pregnant women before labor.

2 Methods

2.1 Study Design

This is a multicentric retrospective cohort study conducted on 410 women in 2 French University hospitals (Strasbourg and Lille). It has been conducted following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [23] and the Developmental and Exploratory Clinical Investigations of DEcision support systems driven by Artificial Intelligence (DECIDE-AI) [24].

2.1.1 Eligibility Criteria

Eligibility criteria were as follows: 1) nulliparous women with a body mass index $\geq$ 40 kg/m^2 at the beginning of the pregnancy; 2) singleton pregnancies; 3) delivery in Strasbourg or Lille University Hospitals after 22 weeks of gestation; and 4) with attempt of vaginal delivery. Non eligibility criteria were 1) stillbirth and medically interruption of pregnancy: and 2) planned cesarean sections and unplanned cesarean sections before labor

2.1.2 Data collection

In this retrospective study, data from two cohorts were used to evaluate the cesarean risk on obese nulliparous women. The first cohort includes $n_S = 247$ women who delivered at Strasbourg University Hospitals between the 1st January 2009 and the 31st December 2019. The second data set contains $n_L = 163$ women who gave birth at Lille University Hospitals between the 1st January 1997 and the 31st December 2014 (published in a previous study [16]). For each patient, maternal characteristics (age, height, initial and final weight, gestational weight gain, smoking, diabetes mellitus/gestational, high blood pressure) and delivery characteristics (labor onset, gestational age at delivery, epidural analgesia, mode of delivery) were recorded. Epidural analgesia and height were subsequently excluded from analysis because they were not pertinent for the purpose of the model or redundant with other information (BMI).

2.1.3 Study endpoints

The primary endpoint was the quantification of unplanned CS risk. The secondary endpoints were the performances of the developed predictive algorithm: sensitivity, specificity, positive and negative predictive values.

2.1.4 Ethics

This work was conducted according to the ethical standards of the French Government Agency "Commission Nationale de l'Informatique et des Libertés

(CNIL)" and registered at the Strasbourg University Hospitals ethics committee (21-025). It was also authorized for Lille University Hospitals by the National Society of Obstetrics and Gynecology "Collège National des Gynécologues Obstétriciens Français (CNGOF)" Research Ethics Committee (CEROG OBS 2014-04-04).

2.2 Statistical analysis and model development

The Strasbourg cohort was used as the training set to elaborate the predictive models while the Lille cohort was used to assess the performance of the predictive models. Two predictive models were built. The first model was constructed by using classical logistic regression and the second one was built by using the probability forest algorithm [25]. All the statistical analyses were performed in `R` statistical software (version 4.1.3). All the steps of the statistical analysis are described below.

2.2.1 Step 1 - data pre-processing and descriptive analysis of the data

A descriptive statistical analysis was conducted on both cohorts. Observations with missing values were removed from both cohorts for the next steps of the statistical analysis.

2.2.2 Step 2 - Development of a classical logistic regression model

Logistic regression is one of the classical methods used to estimate risk probabilities in clinical research. The logistic model was built on the train set (i.e. the complete cases in the Strasbourg cohort) by using the $p = 10$ recorded variables (age, initial and final weight, gestational weight gain, smoking, diabetes mellitus/gestational, high blood pressure, labor onset, gestational age at delivery, mode of delivery). A stepwise variable selection procedure based on the Akaike Information Criterion was used to determine the best subset of predictors for the logistic regression model.

2.2.3 Step 3 - Development of a predictive model based on the probability forest algorithm

As a parametric regression method, the logistic regression is known to perform well only conditionally upon several assumptions [26] that can be difficult to satisfy in practice. Machine learning such as random forest algorithms are non-parametric methods that do not need the assumptions required with model-based approaches. That is why, since the last decade, machine learning have been increasingly used instead of more classical model-based approaches such as logistic regression. Here, we decided to use machine learning to build another predictive model. This predictive model is based on a Random Forest (RF) algorithm. These algorithms originally introduced by Breiman [27] have been successfully applied in many fields including medicine [28] and bio-informatics

[29]. RF are still nowadays part of the most successful machine learning methods [30]. A random forest algorithm consists in building a large number n_{tree} of independent decision trees. The forest construction involves two random processes. At first, each tree is built using a bootstrap sample that is obtained by randomly drawing (with or without replacement) $m \leq n_S$ patients from the training set. The second random process occurs during the tree construction. A tree is built by means of a recursive and binary partitioning of the data into the bootstrap sample. For each tree node, a subset of $q \leq p$ features are randomly selected among the p features and the split using only this subset and an impurity criterion. After construction, the random forest provides a prediction that is the average of the predictions over all the single trees. Random forest methods have been described elsewhere [27, 31]. In our study, as we are interested in predicting the cesarean risk, we used the RF algorithm introduced by [25] that elaborates probability forests. A probability forest is a RF model for which predictions are probabilities. In our case, these probabilities correspond to estimates of the cesarean risk. Before building our probability forest, we first applied the RF-based algorithm VSURF [32] to keep only the most discriminant subset of features in our forest and thus obtain more stable individual probability estimates. Moreover, to correct for class imbalance in the training set (34% women with cesarean section vs. 66% with no cesarean section), upsampling with probabilities 65% for cesarean women and 35% for non-cesarean women was used when generating the bootstrap samples. Next, to construct the probability forest, we applied the standard bootstrap strategy that consists in drawing with replacement $m = n_S$ patients from the training set. The number of trees n_{tree} was selected by building 50 random forests made of 200,000 trees and looking at the out-of-the-bag error rate (a method of measuring prediction error for models utilizing bootstrap, which is the mean prediction error of a subsample with replacement from the training cohort). Then, we selected a number of trees $n^{\star}_{\text{tree}}$ for which the out-of-the-bag error was stabilized. Next, to tune the two other important hyper-parameters of the probability forest, namely the minimum size of a node $\min_{\text{node}}$ and the size q of the subset of features used to split, we used 3-fold cross validation repeated 100 times on the train set (the Strasbourg data). We then chose the couple $(\min^{\star}_{\text{node}}, q^{\star})$ that maximizes 1) the specificity and 2) the sensitivity based on the 1-SE rule. After that, we checked another time that the adjusted number of trees $n^{\star}_{\text{tree}}$ is still sufficiently large to get the out-of-the-bag error stable when we used the adjusted couples $(\min^{\star}_{\text{node}}, q^{\star})$.

Finally, the final probability forest was built using the most discriminant subset of features and the tuned values $(n^{\star}_{\text{tree}}, \min^{\star}_{\text{node}}, q^{\star})$ of the hyper-parameters. The final forest provides individual estimates of the cesarean risk with their associated standard errors. To interpret the probability forest and so to explain the cesarean risk according the predictors, we computed feature permutation importance indices [27]. The permutation importance indices are numerical scores that enable to order predictors according to their discriminatory power.

2.2.4 Step 4 - Model assessment and comparison

For each model, a risk threshold also called the cut-point c was determined. Clinically, this cut-point c represents the CS risk value from which a CS risk value is considered as high and so CS delivery should be planned. Here, the optimal cut-point is determined on the train set and it refers to as the value which maximizes the sensitivity with at least 80% of specificity. Performances of both the probability forest and the logistic model were assessed and compared by using the following 4 criteria computed on the test set: the area under the curve, the sensitivity, the specificity and the accuracy. Exact binomial confidence limits were calculated for sensitivity, specificity and accuracy (see [33] for details). Confidence interval for AUC was computed according to the non-parametric approach proposed by DeLong *et al.* [34].

3 Results

3.1 Cohort description

In total, 410 obese women were included in both centers. The study population is described in Table 1. Among all women, 164 had unplanned CS (40%) while 246 had vaginal delivery (60%). Mean BMI was 43.6 kg/m^2 (range 40.0 – 59.6 kg/m^2). In univariate analysis, higher maternal height (p-value = 0.001) and labor induction (p-value $<$ 0.001) were associated with unplanned CS delivery.

Table 1: Total cohort description according to the delivery mode

Variable	**Cesarean section** (N=164)	**Vaginal delivery** (N=246)	**Total** (N=410)	**P-Value**
Age (years)				
Mean (SD)	28.8 (5.1)	27.8 (5.1)	28.2 (5.1)	0.063
Range	18 – 42	18 – 43	18 – 43	
Height (cm)				
Mean (SD)	163.6 (5.9)	165.7 (7.0)	164.9 (6.6)	0.001
Range	148 – 186	148 – 183	148 – 186	
Initial Weight (kg)				
Mean (SD)	118.0 (13.9)	119.1 (12.9)	118.7 (13.3)	0.432
Range	89 – 160	90 – 162	89 – 162	
Body Mass Index (kg/m2)				
Mean (SD)	44.1 (4.2)	43.3 (3.4)	43.6 (3.8)	0.0501
Range	40.0 – 59.6	40.0 – 56.3	40.0 – 59.6	
Gestational Weight Gain (kg)				
Mean (SD)	6.4 (8.3)	5.6 (9.0)	5.9 (8.7)	
Range	-19 – 30	-36 – 29	-36 – 30	0.389
Unknown	5	11	16	
Smoking				
No	132 (80.5%)	198 (80.8%)	330 (80.7%)	
Yes	32 (19.5%)	47 (19.2%)	79 (19.3%)	0.934
Unknown	0	1	1	
Diabetes mellitus				
No	131 (79.9%)	196 (79.7%)	327 (79.8%)	0.960
Yes	33 (20.1%)	50 (20.3%)	83 (20.2%)	
High Blood Pressure				
No	137 (83.5%)	203 (82.5%)	340 (82.9%)	0.789
Yes	27 (16.5%)	43 (17.5%)	70 (17.1%)	
Labor induction				
No	48 (29.3%)	126 (51.2%)	174 (42.4%)	$<$0.001
Yes	116 (70.7%)	120 (48.8%)	236 (57.6%)	
Gestational age at delivery (weeks ^{days})				
Mean (SD)	39w ^{6d} (1w ^{5d})	39w ^{4d} (2w ^{4d})	39w 5d (2w ^{2d})	0.257
Range	31w ^{3d} – 42w ^{1d}	22w ^{0d} – 42w ^{2d}	22w 0d – 42w ^{2d}	

Before building the predictive models, we investigated whether there were differences between both centers (see Table 2) and found out that maternal age

and diabetes prevalence were greater in Strasbourg (respectively p-value = 0.004 and < 0.001). Conversely, initial weight, BMI, high blood pressure prevalence were greater in Lille (respectively p-value = 0.003, < 0.001 and 0.036). Delivery mode was also different: we observed a higher rate of unplanned CS in Lille compared to Strasbourg (49.1% versus 34.0%, p-value = 0.002).

Table 2: Total cohort description according to the center

Variable	**Lille** (N=163)	**Strasbourg** (N=247)	**Total** (N=410)	**P-value**
Age (years)				
Mean (SD)	27.3 (5.2)	28.8 (5.1)	28.2 (5.1)	0.004
Range	18 – 40	19 – 43	18 – 43	
Height (cm)				
Mean (SD)	165.1 (6.6)	164.8 (6.7)	164.9 (6.6)	0.659
Range	148 – 183	148 – 186	148 – 186	
Initial Weight (kg)				
Mean (SD)	121.0 (13.9)	117.1 (12.7)	118.7 (13.3)	0.003
Range	90 - 162	89 - 156	89 - 162	
BMI (kg/m^2)				
Mean (SD)	44.4 (4.4)	43.1 (3.2)	43.6 (3.8)	<0.001
Range	40.0 - 59.6	40.0 – 54.0	40.0 - 59.6	
Gestational Weight Gain (kg)				
N-Miss	3	13	16	
Mean (SD)	5.8 (8.7)	6.0 (8.7)	5.9 (8.7)	0.790
Range	-18 – 27	-36 – 30	-36 – 30	
Smoking				
No	125 (76.7%)	205 (83.3%)	330 (80.7%)	
Yes	38 (23.3%)	41 (16.7%)	79 (19.3%)	0.096
Unknown	0	1	1	
Diabetes				
No	108 (66.3%)	219 (88.7%)	327 (79.8%)	<0.001
Yes	55 (33.7%)	28 (11.3%)	83 (20.2%)	
High Blood Pressure				
No	143 (87.7%)	197 (79.8%)	340 (82.9%)	0.036
Yes	20 (12.3%)	50 (20.2%)	70 (17.1%)	
Delivery				
Cesarean	80 (49.1%)	84 (34.0%)	164 (40.0%)	0.002
Vaginal	83 (50.9%)	163 (66.0%)	246 (60.0%)	
Labor induction				
No	75 (46.0%)	99 (40.1%)	174 (42.4%)	0.234
Yes	88 (54.0%)	148 (59.9%)	236 (57.6%)	
Gestational age at delivery (weeks ^{days})				
Mean (SD)	39w ^{6d} (2w ^{0d})	39w 4d (2w ^{3d})	39w ^{5d} (2w ^{2d})	0.277
Range	22w ^{0d} – 42w ^{1d}	22w 5d – 42w ^{2d}	22w ^{0d} – 42w ^{2d}	

Predictive model training and testing was performed on $n = 393$ women as the following statistical analyses were conducted only on complete cases (incomplete cases were: 16 missing values of gestational weight gain and 1 for smoking status). Complete cases cohort is described in Tables S1 and S2 and there were no significant differences with the total cohort. The training phase was performed by using the complete cases in the Strasbourg cohort ($n = 233$) while the performance of the predictive model was assessed on the complete cases in the Lille cohort ($n = 160$). For convenience, in the following, the Strasbourg and Lille cohorts will always be used to refer to the complete cases in both cohorts, respectively.

3.2 Classical predictive model for Delivery Prediction

We first built a predictive model by following a classical approach based on a logistic regression with a stepwise variable selection procedure. The logistic model that we finally obtained consisted of four predictors including three maternal characteristics (initial weight, diabetes and age) and one delivery characteristic (labor induction). The fitted model is described in Table 3. Note that in the logistic model, only the initial weight and labor induction seem to statistically significantly influence the unplanned CS risk. According to this model, the unplanned CS risk decreased when the initial weight increased (OR[initial weight] = 0.97; 95%CI = 0.95 - 1.0; p-value = 0.031) whereas it increased greatly in case of labor induction (OR[labor induction]=3.06; 95%CI = 1.66 - 5.84; p-value = <0.001). Conversely, maternal age and diabetes did not seem to impact delivery.

Table 3: Final logistic model built on Strasbourg cohort

Variable	**Estimate (Std Error)**	**Odds ratio (95%CI)**	**P-value**
Initial weight	-0.03 (0.01)	0.97(0.95;1.00)	0.031
Labor induction	1.12 (0.32)	3.06(1.66;5.84)	<0.001
Age	4.84E-2 (0.03)	1.05(0.99;1.11)	0.095
Diabetes	-7.11E-1 (0.48)	0.49(0.18;1.22)	0.142

3.3 Probability Forest Model for Accurate Delivery Prediction

The probability forest obtained is based on only two predictors: one maternal characteristic, the initial weight, and one delivery characteristic, the labor induction. These two predictors represent the best subset of predictors selected by using VSURF [32] and that they are two significant predictors included in the logistic model. Our probability forest is built using the following tuned hyper-parameters: 100,000 trees, a minimum size of a node of 23 and a size of the subset of features used to split equals to 1. Note that the probability

forest error stays stable starting from 20,000 trees. Nonetheless, as we were not limited by the time because the construction of the probability forest model with the selected subset of predictors and the tuned hyper-parameters was not time-consuming (execution time:<5s), we chose to use more trees so that the convergence of the probability forest error was guarantee. In this model, the most important predictor is the labor induction followed by the initial weight. According to this model, for any given value of the initial weight, the risk of unplanned CS delivery seems greater in case of labor induction (see Figure 1). The predicted CS risk does not seem to be linearly correlated with the labor induction and the initial weight. For women with an initial weight inferior to 113kg or superior to 130kg, the predicted CS risk seems to increase when the initial weight increases and this augmentation seems more important if there is labor induction. On the contrary, for women with an initial weight between 113kg and 130kg, the CS risk seems to decrease when the initial weight increases, whatever the labor induction status. Note that the regression curve showing the predicted CS risk for women with no labor induction must be interpreted with many caution for women with an initial weight superior to 130kg because the estimated local polynomial regression curve depends only on a single observation.

3.4 Predictive-model comparison

Table 4 and Figure 2 outline the performance of both the logistic model and the probability random forest model. The two predictive models were built to estimate and to stratify individual unplanned CS risk among class III-obese pregnant women in order to counsel them during a delivery planning consultation. Each model was developed to predict a probability of unplanned CS, ranging from 0 to 1. Then, the cut-point which represents the threshold risk from which the CS risk is considered as high (and so the model predicts a CS delivery) was determined using the Strasbourg cohort. The cut-point of each model was selected in order to maximize the sensitivity (*i.e.*, the probability of correctly predicting CS delivery among obese pregnant women who underwent CS delivery) with a specificity of at least 80% (*i.e.*, the probability of wrongly predicting CS delivery among women who had vaginal delivery is less than 20%). Thus, the optimal cut-point in the probability forest was calculated at 0.495. With this cut-point, in the probability forest, the specificity evaluated on the Lille cohort was 87% which means that false-positive rate was 13% (*i.e.*, the risk of wrongly predicting CS delivery for women who had vaginal delivery). Conversely, the sensitivity evaluated on the Lille cohort was 44%. The optimal cut-point in the logistic model was 0.452. Based on this cut-point, the specificity of the logistic model was quite similar to the one observed with the probabilistic forest model whereas the sensitivity evaluated on the Lille cohort was in comparison significantly lower (0.18). Overall, the probability forest outperformed the logistic model in terms of predictive performances (Accuracy = 0.66 *versus* 0,55 ; AUC = 0.70 *i.e.* 0.60). The roc curves drawn on the train set are in appendix (see Figure S1).

Legend: AUC = area under the curve; 95% confidence interval were written in

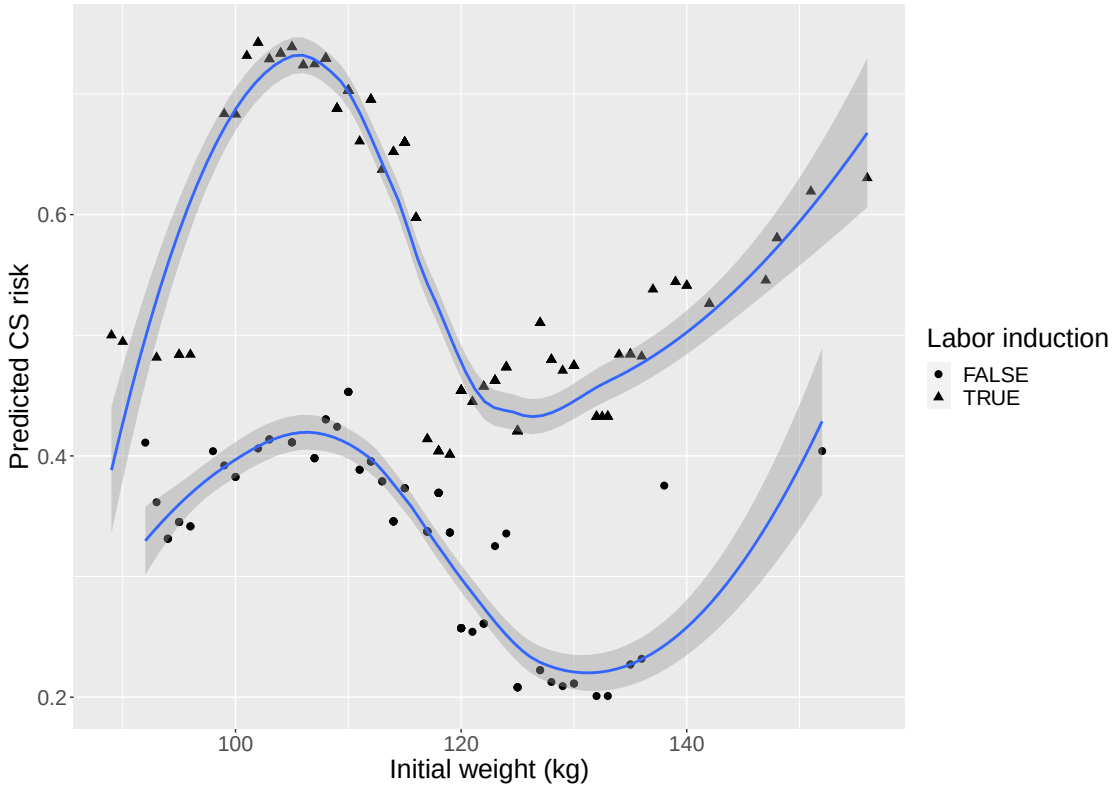

Figure 1: Predicted CS risk in the Strasbourg cohort for the probability forest model according to the labor induction status and the initial weight.*Note: the lines represents the estimated local polynomial regression curves with their 95% confidence interval.*

Table 4: Model performances evaluated on the test cohort.

Model	**Prob forest**	**Logistic model**
Cut-point	0.495	0.452
AUC	0.70 (0.62, 0.78)	0.66 (0.58, 0.75)
Specificity	0.87 (0.77, 0.93)	0.90 (0.82, 0.96)
Sensitivity	0.44 (0.32, 0.55)	0.18 (0.10, 0.28)
Accuracy	0.66 (0.58, 0.73)	0.55 (0.47, 0.63)

bracket for AUC, sensitivity, specificity and accuracy and results were rounded to the nearest hundredth.

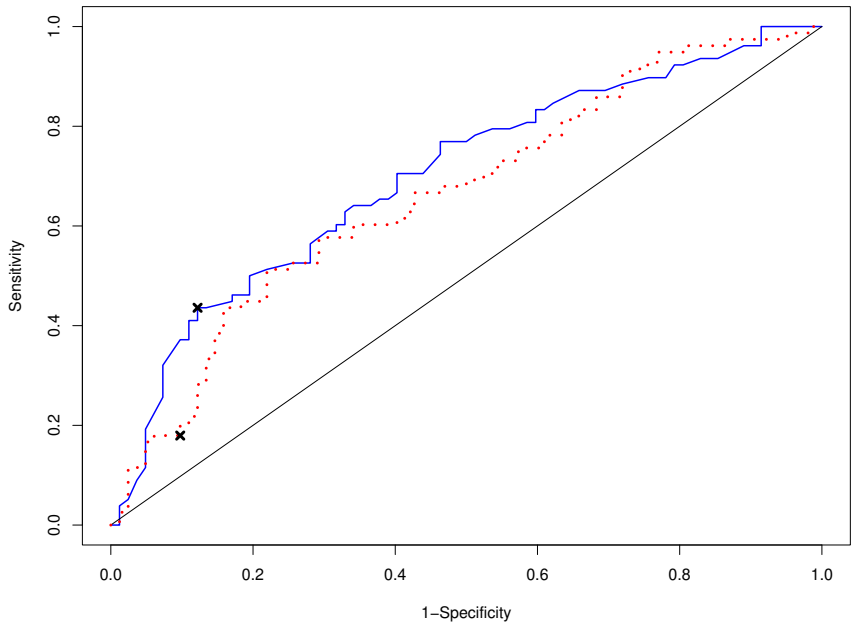

Figure 2: Receiver Operating Characteristic curve of the models on the test set

Legend: the ROC curve of the probability forest model (solid line) and of the logistic model (dotted line) drawn on the test set. The black cross on each curve indicates the selected cut-point and its coordinates are the values of 1-specificity and the sensitivity measured in the test set.

4 Discussion

In this study, we wanted to identify a population of obese women at high-risk of unplanned CS during labor, this risk being high enough to eventually suggest a planned CS instead of a trial of labor. Classical statistical analysis failed to identify specific maternal or pregnancy characteristics important enough to determine obstetrical management of these women and to accurately predict unplanned CS. Consequently, we developed a machine learning-based algorithm to stratify the risk of unplanned CS and tested it for both internal and external validation. This innovative methodology allowed us not only to stratify and predict individual unplanned CS risk for obese women during labor, but also to gain insights on understanding of this risk. This model is easy to use in clinical practice as it need only two parameters: initial weight and labor induction.

In this study, we found that labor induction significantly increased the risk of cesarean section in the nulliparous patient with a BMI $\geq$ 40 kg/m^2, which is consistent with previously reported data [35, 13, 36, 37]. Interestingly, the predictive models (both logistic and random forest) found that initial weight was inversely proportional to the CS risk, and this can be explained by the fact that we excluded women which had planned or unplanned CS before trial of labor. Furthermore, the predictive model also allowed us to individually quantify unplanned CS risk with only pre-labor data, which to our knowledge had never been published. Nonetheless, the parameter which could limit clinical applications of such model are false positive, i.e., women with predicted high-risk of unplanned CS which would have had a vaginal delivery. This parameter is represented by the specificity: high specificity means a low false positive rate. Indeed, false negative women would undergo labor trial as standard clinical care, but false positive women could undergo unnecessary planned CS which could be iatrogenic.

Based on actual scientific literature, class III obese women are at higher risk of CS [37]. In a large retrospective cohort of 64,272 infants born of obese pregnant women published in 2012, the authors showed that for nulliparous class III obese women primary scheduled CS accounted for 21.9% of deliveries, and emergency CS for 24.6% [38]. Moreover, planned and unplanned CS rates increased with BMI ($p < 0.0001$) [38]. In the perspective of reducing the rate of unplanned CS during labor without however increasing the overall CS rate in a significant way, we opted for a specificity threshold of 80%, which is proportional to the rate of planned CS in this population. Based on this parameter, we wanted to maximize sensitivity with the goal of screening as many women as possible who will have an unplanned CS during labor to reduce morbidity related to emergency CS.

It has been shown that CS has more morbidity than vaginal delivery in obese women [17, 18]. Conversely, without specification of maternal obesity, a recent meta-analysis showed that planned CS has significantly lower maternal and neonatal morbidity compared to unplanned CS, such as infection (relative risk [RR] = 0.44), postoperative fever (RR = 0.29), urinary tract infection (RR = 0.31), wound dehiscence (RR = 0.67), disseminated intravascular coagulation

(RR = 0.34), reoperation (RR = 0.44), and infant mortality (RR = 0.16) [22]. Another study found similar outcomes in terms of post-operative wound infection, post-partum hemorrhage and necessity of blood transfusion, urinary tract infection, fever and maternal intensive care unit admission. Neonatal outcomes such as birth asphyxia, meconium-stained liquid and need for neonatal intensive care unit admission were also significantly higher when an unplanned CS was performed compared to a planned CS [21]. From these data, we can extrapolate that similar maternal complications trends could be observed in obese women, and even worse infant outcomes as the decision-incision time could be increased because of more problematic transfer and the incision-birth time could also be lengthened because of surgical difficulties [39].

It must be noted that this model was developed on pre-labor characteristics as we wanted to discuss the unplanned CS risk before labor, and eventually suggest a planned CS. It was therefore not possible to obtain a very high accuracy for this predictive model because several parameters will only intervene at the time of labor and are not predictable: for example, an abnormality of the fetal heart rate or a mechanical dystocia. The use of pre-labor data makes model performance lower, but is more relevant in case of choice between a trial of labor and a planned CS.

Moreover, the model was established only for nulliparous patients with class III obesity (BMI $\geq$ 40 kg/m^2). Therefore, it cannot be used for patients with a BMI between 30 and 40 kg/m^2 nor for patients with a history of cesarean section although they are also among the patients most at risk of cesarean section during labor. It must also be noted that unlike Anglo-Saxon populations, the number of women with extreme BMIs ($>$ 50 kg/m^2) is lower in France. Finally, results of this model should be interpreted with caution for women with initial weight $>$ 130 kg and no labor induction, as the estimated regression curve depends only on a single observation.

Based on the algorithm's performance, the use of this model in routine practice could decrease the rate of unplanned CS at the cost of a modest increase in the overall CS rate. Yet, according to scientific evidence, it seems that in obese patients, benefits of avoiding one unplanned CS out of two outweigh the cost of performing one unnecessary planned CS out of five women, both on maternal and neonatal outcomes. Nonetheless, it should be taken into account when discussing obstetrical management in any individual situation. This model has two important advantages in clinical practice. First, it is simple to use as it needs only two parameters: initial weight and labor induction. Therefore, when discussing the route of delivery with a pregnant woman with class III obesity, an estimate of risk can be quickly obtained during the consultation. In addition, when there is an indication to perform a labor induction at a specific time, for example for overdue delivery, the risk can be estimated in each situation (in case of spontaneous labor before the planned induction date or in case of planned induction). This could allow better advice to be given to women at the end of their pregnancy by proposing personalized management according to the term and the mode of onset of labor. For instance, a pregnant woman with a high risk of cesarean section for induction of labor but a low risk of cesarean section for

spontaneous labor could be advised to perform a trial of labor if she goes into spontaneous labor, and if she arrives at the expected induction date without going into spontaneous labor, opt for a scheduled cesarean section instead.

Recently, different predictive models have been published in obstetrics, which allow delivery planning and enhance information quality for discussion during the consultation. Those models can predict delivery outcomes based on machine learning algorithms, and they also employed random forest algorithms but with different clinical objectives [40, 41, 42]. Performances of this kind of model are remarkable and some of them can already be used in clinical practice. Nonetheless, this innovative approach must also meet several quality criteria, some of them being applicable to all clinical studies, but others specific to artificial intelligence-based models. For these reasons, this retrospective, population-based, observational study was conducted according to a rigorous methodology following the STROBE checklist, but also to the CONSORT-AI guidelines [43] published in September 2020, which specify the quality criteria to be applied to machine learning models developed within the framework of randomized trials: in particular, the performance of a test on a different cohort, allowing the internal validation to be completed by an external validation. To date, no specific guidelines are available on machine learning models developed from retrospective cohort studies.

In order to meet important quality criteria, we included women from two different centers and found that both cohorts were different in some points, such as age, initial weight, BMI, diabetes and high blood pressure prevalence, but also on clinical practices as unplanned CS rates were different. These differences can be explained by a center effect with different populations: Lille's cohort had higher BMI and diabetes; while Strasbourg's cohort had more women with high blood pressure and higher maternal age. Moreover, the center effect can also explain differences in clinical practices, as unplanned CS indications may differ not only because of a different population but also because of different internal protocols and obstetrical practices. Finally, these differences can also be explained by a time effect due to the difference in years between the Strasbourg and Lille recruitment. Within the context of this study, heterogeneity between training and testing cohorts reinforces the value of the model in external validation, and makes it more applicable to other centers. On the contrary, the fact that the 2 cohorts came from 2 different centers and time-periods limited the model because the pre-labor characteristics of the women in the Lille cohort were not all available for the analysis, and we therefore had to restrict the training variables of the algorithm because we had only a small number of common variables between the two cohorts. Some criteria of the Strasbourg patients that could be involved in the risk of cesarean section could therefore not be tested, thus reducing the power of the model (for example, uterine height, Bishop score at admission, and ultrasound estimation of fetal weight).

4.1 Conclusion

Delivery planning in obese women is an every-day clinical challenge in obstetrics, and each choice has its specifics advantages and risks. With its innovative approach, this model is effective for predicting unplanned CS risk in nulliparous class III obese women undergoing trial of labor, and could improve maternal and neonatal outcomes due to unplanned CS-related morbidity in this population. Still, at the end of this study, it is not reliable enough to become the sole element of obstetrical decision, but it could be an additional argument for explaining unplanned CS risk and to participate to the choice of trial of labor versus planned CS. Further investigations are needed within a prospective clinical trial, as this model could meet a demand of patient information and risk calculation in a personalized care fashion.

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Supplementary material

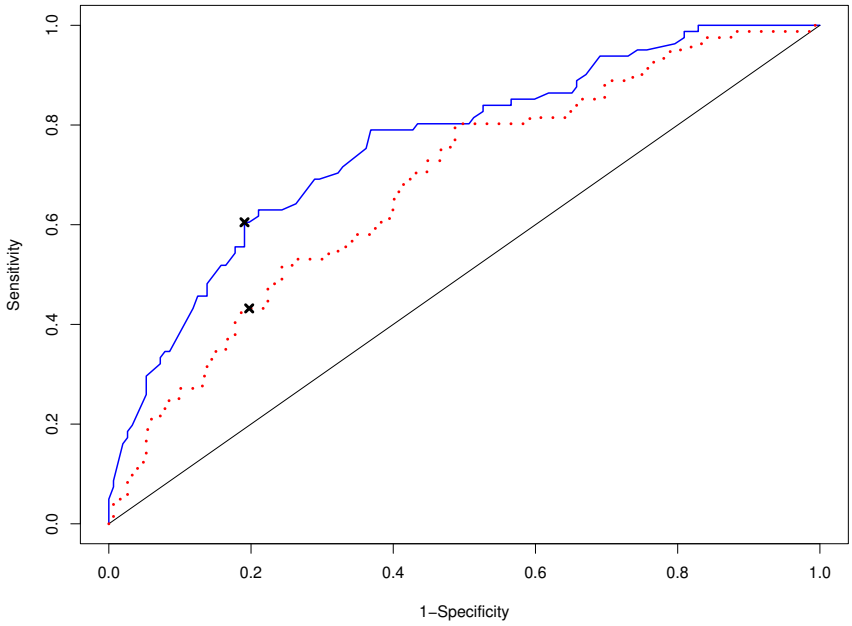

Figure S1: ROC curve of the probability forest model (solid line) and of the logistic model (dotted line) drawn on the train set. The black cross on each curve indicates the selected cut-point and its coordinates are the values of 1-specificity and the sensitivity measured in the train set.

Table S1: Complete case cohort description according to the delivery mode

Variable	**Cesarean section** (N=159)	**Vaginal delivery** (N=234)	**Total** (N=393)	**P-Value**
Age (years)				
Mean (SD)	28.7 (5.1)	27.7 (5.0)	28.1 (5.1)	0.060
Range	18 – 42	18 – 42	18 – 42	
Height (cm)				
Mean (SD)	163.5 (5.9)	165.9 (7.0)	164.9 (6.7)	< 0.001
Range	148 – 186	148 – 183	148 – 186	
Initial Weight (kg)				
Mean (SD)	117.7 (13.8)	119.4 (12.8)	118.7 (13.2)	0.229
Range	89 – 160	90 – 162	89 – 162	
Body Mass Index (kg/m2)				
Mean (SD)	44.0 (4.2)	43.3 (3.4)	43.6 (3.8)	0.078
Range	40.0 – 59.6	40.0 – 56.3	40.0 – 59.6	
Gestational Weight Gain (kg)				
Mean (SD)	6.4 (8.3)	5.6 (9.0)	5.9 (8.7)	0.423
Range	-19 – 30	-36 – 29	-36 – 30	
Smoking				
No	128 (80.5%)	189 (80.8%)	317 (80.7%)	0.948
Yes	31 (19.5%)	45 (19.2%)	76 (19.3%)	
Diabetes				
No	129 (81.1%)	185 (79.1%)	185 (79.1%)	0.615
Yes	30 (18.9%)	49 (20.9%)	79 (20.1%)	
High Blood Pressure				
No	135 (84.9%)	196 (83.8%)	331 (84.2%)	0.760
Yes	24 (15.1%)	38 (16.2%)	62 (15.8%)	
Labor induction				
No	46 (28.9%)	120 (51.3%)	166 (42.2%)	< 0.001
Yes	113 (71.1%)	114 (48.7%)	227 (57.8%)	
Gestational age (weeks ^{days})				
Mean (SD)	39w ^{6d} (1w ^{5d})	39w ^{5d} (2w ^{5d})	39w 4d (2w ^{1d})	0.393
Range	31w ^{3d} – 42w ^{1d}	22w ^{0d} – 42w ^{2d}	22w 0d – 42w ^{2d}	

Table S2: Complete case cohort description according to the center

Variable	**Lille** (N=160)	**Strasbourg** (N=233)	**Total** (N=393)	**P-value**
Age (years)				
Mean (SD)	27.2 (5.1)	28.7 (5.0)	28.1 (5.1)	0.004
Range	18 – 40	19 – 42	18 – 42	
Height (cm)				
Mean (SD)	165.0 (6.6)	164.9 (6.7)	164.9 (6.6)	0.861
Range	148 – 183	148 – 186	148 – 186	
Initial Weight (kg)				
Mean (SD)	121.0 (13.9)	117.1 (12.5)	118.7 (13.2)	0.004
Range	90 - 162	89 - 156	89 - 162	
BMI (kg/m^2)				
Mean (SD)	44.4 (4.5)	43.0 (3.1)	43.6 (3.8)	< 0.001
Range	40.0 - 59.6	40.0 – 54.0	40.0 - 59.6	
Gestational Weight Gain (kg)				
Mean (SD)	5.8 (8.7)	6.0 (8.7)	5.9 (8.7)	0.790
Range	-18 – 27	-36 – 30	-36 – 30	
Smoking				
No	122 (76.2%)	195 (83.7%)	317 (80.7%)	0.067
Yes	38 (23.8%)	38 (16.3%)	76 (19.3%)	
Diabetes				
No	107 (66.9%)	207 (88.8%)	314 (79.9%)	< 0.001
Yes	53 (33.1%)	26 (11.2%)	79 (20.1%)	
High Blood Pressure				
No	142 (88.8%)	189 (81.1%)	331 (84.2%)	0.041
Yes	18 (11.2%)	44 (18.9%)	62 (15.8%)	
Delivery				
Cesarean	78 (48.8%)	81 (34.8%)	159 (40.5%)	0.006
Vaginal	82 (51.2%)	152 (65.2%)	234 (59.5%)	
Labor induction				
No	74 (46.2%)	92 (39.5%)	166 (42.2%)	0.182
Yes	86 (53.8%)	141 (60.5%)	227 (57.8%)	
Gestational age (weeks ^{days})				
Mean (SD)	39w ^{6d} (2w ^{0d})	39w 5d (2w ^{1d})	39w ^{6d} (2w ^{1d})	0.516
Range	22w ^{0d} – 42w ^{1d}	22w 5d – 42w ^{2d}	22w ^{0d} – 42w ^{2d}	