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Prediction of Cesarean Delivery in the Term Nulliparous Woman: Results from the Prospective Multi-center Genesis Study

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Short title: Prediction of Cesarean Delivery in Nulliparas

Condensation:

Maternal age, BMI, height, fetal AC and fetal HC can be used to accurately predict the risk of Cesarean Delivery in the term nulliparous woman.

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Abstract

Background

In contemporary practice many nulliparous women require intervention during childbirth such as operative vaginal delivery or Cesarean delivery (CD). Despite the knowledge that the rising CD rate is associated with increasing maternal age, obesity and larger infant birthweight, we lack a reliable method to predict the requirement for such potentially hazardous obstetric procedures during labor and delivery. This issue is important as there are higher rates of morbidity and mortality associated with unplanned CD performed in labor compared to scheduled Cesarean deliveries. A prediction algorithm to identify women at risk of an unplanned CD could help reduced labor associated morbidity.

Objective

In this primary analysis of the Genesis study, our objective was to prospectively assess the use of prenatally determined, maternal and fetal, anthropomorphic, clinical and ultrasound features to develop a predictive tool for unplanned CD in the term nulliparous woman, prior to the onset of labour.

Methods

The Genesis Study recruited 2,336 nulliparous women with a vertex presentation between 39+0 and 40+6 weeks' gestation in a prospective multi-center national study to examine predictors of CD. At recruitment a detailed clinical evaluation and ultrasound assessment were performed. To reduce bias from knowledge of this data potentially influencing mode of delivery, women, midwives and obstetricians were blinded to the ultrasound data. All hypothetical prenatal risk factors for unplanned CD were assessed as a composite. Multiple logistic regression analysis and mathematical modelling was used to develop a risk evaluation tool for CD in nulliparous women. Continuous predictors were standardized using z scores.

Results

From a total enrolled cohort of 2,336 nulliparous participants, 491 (21%) had an unplanned CD. Five parameters were determined to be the best combined predictors of

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CD. These were advancing maternal age (OR 1·21, 95% CI 1.09-1.34), shorter maternal height (OR 1·72, 95% CI 1.52-1.93), increasing BMI (OR 1·29, 95% CI 1.17-1.43), larger fetal abdominal circumference (AC) (OR 1·23, 95% CI 1.1-1.38) and larger fetal head circumference (HC) (OR 1·27, 95% CI 1.14-1.42). A nomogram was developed to provide an individualized risk assessment to predict CD in clinical practice, with excellent calibration and discriminative ability (KS, d-statistic 0.29 95% CI 0.28-0.30) with a misclassification rate of 0.21 (95% CI 0.19-0.25).

Conclusion

Five parameters (maternal age, BMI, height, fetal AC and fetal HC) can, in combination, be used to better determine the overall risk of CD in nulliparous women at term. A risk score can be used to inform women of their individualized probability of CD. This risk tool may be useful for reassuring most women regarding their likely success at achieving an uncomplicated vaginal delivery as well as selecting those patients with such a high risk for CD that they should avoid a trial of labor. Such a risk tool has the potential to greatly improve planning hospital service needs and minimizing patient risk.

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Introduction

Many nulliparous women undergo emergency obstetric procedures during labor, including operative vaginal delivery and cesarean delivery (CD) [1,2]. However, we lack a reliable strategy for predicting which women will experience the greatest difficulties during labor. This may be frustrating and disappointing for women and obstetricians alike. The issue is important because CD in advanced labor has a higher morbidity (and mortality) than an elective pre-labor CD[3,4] . Additionally, there has been increased attention on reducing the rates of CD by professional bodies and government agencies by introducing policies promoting vaginal delivery, often with little focus on the potential consequences of these recommendations[5]. If obstetricians and midwives could predict which women will need an operative delivery in their first labor, increased risk might be avoided by offering an elective procedure to those at highest risk, while those at low risk could be reassured and encouraged to pursue a vaginal delivery.

Although many risk factors for CD in nulliparous parturient have been identified, to date there has not been an established method for determining the effects of multiple risk factors for determining the probability of CD in an individual woman[6]. This may, in part, be attributable to the many indications for performing an emergency or unplanned CD, the complex nature of labor dystocia and the interactions of composite risk factors. The two principal indications for primary intrapartum CD in nulliparas are labor dystocia and abnormal fetal heart rate patterns, neither of which can be accurately diagnosed until there has been a trial of labor[7]. Indeed, both of these indications for primary CD may be present simultaneously in an individual patient. While many studies have tried to predict CD by prenatal diagnosis of cephalopelvic disproportion or fetal macrosomia, neither strategy has proved useful in the clinical setting [8-10]. Others have tried to predict CD using neural networks and intrapartum ultrasound but the methodology used is often too complex for everyday use [11,12].

In this primary analysis of the Genesis study, our objective was to prospectively assess the use of prenatally determined, maternal and fetal, anthropometric, clinical and ultrasound features to develop a predictive tool for unplanned CD in nulliparous women at term, before the onset of labor.

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Materials and Methods

This was a prospective, multicenter, blinded observational study conducted between October 2012 and June 2015. Nulliparous women were invited to participate at each of the seven Perinatal Ireland Research Consortium sites (Rotunda Hospital, Dublin; National Maternity Hospital, Dublin; Coombe Women and Infants University Hospital, Dublin; Galway University Hospital, Galway; University Maternity Hospital, Limerick; Cork University Maternity Hospital, Cork; Royal Jubilee Hospital, Belfast). There are approximately 70,000 deliveries per year in Ireland with a birth rate of 15 per 1,000 population across 19 hospitals delivering obstetric care [13]. The clinical activity of the seven participating sites represents almost 80% of deliveries on the island of Ireland and each site is affiliated with a university academic Department of Obstetrics and Gynecology. The national cesarean delivery rate in Ireland was 28·2% in 2013 [13].

The study was powered at 90% with a 5% level of significance (two-tailed) to assess the performance of a risk prediction model for CD in nulliparous women. An anticipated CD rate of 20% in the Robson group 1 and 2 participants (nulliparous patients with a singleton pregnancy in a cephalic presentation, who had spontaneous or induced labor respectively) was used. This rate was estimated from the clinical activity reports of the three largest hospitals included in the study. Since the number of potential predictors was not known a priori, the *powerlog* program for STATA was used to determine the sample size and statistical power for a multiple logistic regression model[14]. Assuming a minimum 20% increase in risk for CD (i.e. 24%) for a one standard deviation increase in any predictor, the estimated sample size was 2,268. This assumes a moderate correlation coefficient of 0.4 among the set of predictors. The study therefore had greater power (>90%) in situations with low correlations between the predictors or higher risks associated with a one standard deviation increase in a predictor. In the event of a lower CD rate at the mean value of a predictor, for example 15%, the study had 80% statistical power.

Inclusion criteria for this study were all nulliparous patients with a singleton, cephalic presentation from 39^{+0} to 40^{+6} weeks' gestation with an uncomplicated pregnancy at enrolment. All participants had a confirmed estimated date of delivery by either first

trimester ultrasound or a second trimester ultrasound which correlated with their menstrual dates. Those excluded from participation in the study were multiparas, multiple pregnancies, breech presentation, ruptured membranes (at time of study ultrasound) and pregnancy complications such as pre-eclampsia, hypertension (requiring anti-hypertensive medication), fetal growth restriction, obstetric cholestasis and gestational diabetes mellitus (GDM) requiring insulin or oral hypoglycemic agents at the time of recruitment. GDM treated with diet alone was not an exclusion criterion. Women who had a clinically indicated obstetric ultrasound performed after 34 weeks' gestation for fetal biometry were also excluded from the study to obviate the potential influence of late ultrasound-derived fetal size estimates on clinical decision-making regarding timing or mode of delivery. Pre-existing medical conditions such as cardiac disorders, pre-gestational diabetes mellitus, seizure disorder or bleeding disorders were also excluded.

Institutional Review Board approval was obtained at each of the seven hospitals involved in the study. Participant information leaflets were provided at each of the research sites in the prenatal clinics and ultrasound departments. Participants either self-presented for enrolment in the study or were recruited by a dedicated Perinatal Ireland research sonographer at each site from the prenatal clinics. Written informed consent was obtained from all women participating in the study. Once recruited a research ultrasound was carried out between 39 and 40^{+6} weeks' gestation. Baseline characteristics were obtained such as age, weight, height, BMI (all obtained at the first antenatal visit), gestational weight gain assessed at the study visit, whether or not they had been screened for GDM and the screening method, maternal head circumference, ethnicity, attendance at prenatal classes, model of prenatal care, presence of written birth plan, medical history, previous history of cervical surgery, family history of CD in a first degree relative, marital status, smoking status, alcohol and drug use, employment details and highest level of education achieved.

A study ultrasound examination was performed after 39 completed weeks and prior to 40 weeks and 6 days. Standard fetal biometry was measured including biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), and femur

length (FL), yielding a calculated estimated fetal weight (EFW) using the Hadlock-4 formula. The fetal head position and engagement were recorded at the time of the study ultrasound. Biometric data from this ultrasound examination were not revealed to study participants. Managing clinicians and midwives were also blinded to the results of fetal biometry, so as to avoid any potential for bias from suspicion of fetal macrosomia influencing decisions relating to timing and mode of delivery. A biophysical score was performed and documented in the participants medical records.

Findings of an abnormal biophysical profile (<6/8), a diagnosis of small for gestational age or an EFW >5,000 grams were revealed to the study participants and managing clinicians, with all such revealed cases being excluded from the study. Standard perinatal and obstetric data were collected contemporaneously and included gestational age at delivery, onset of labor, use of prostaglandin for pre-induction cervical priming, amniotomy, use of oxytocin, maternal fever, type of analgesia used, duration of labor, mode of delivery, indication for operative delivery, perineal trauma and blood loss.

Statistical Analysis

The primary objective of the statistical analysis was to predict individual absolute risk of CD with optimal calibration and discriminative ability. Simple and multiple logistic regression analyses were used to model the maternal demographics and ultrasound biometry risk factors for CD. Continuous predictors were standardized using z-scores (predictor value – mean / standard deviation) to show the relative effects of predictors. Pair-wise interaction terms and quadratic effects of variables were included in the set of potential predictors. In an analysis of a prediction model there are several areas of importance to be considered; the model performance in terms of the accuracy of predictions, the prediction error, the overall calibration and internal validation of the prediction model. Each of these assessments are outlined in detail here. The Akaike Information Criterion (AIC) was used to determine model fit. The AIC is the asymptotically equivalent to leave-one out cross-validation (LOOCV) for penalizing complexity [15]. Validation analyses were performed on the full data (“apparent” model fit) in addition to re-sampling methods: full boostrap sampling with replacement (1,000 repeats) and 10-fold cross-validation (100 repeats). The Brier score, scaled Brier score

and Pietra index were considered as overall measures of prediction error[16]. The Hosmer-Lemeshow test and Stukel tests were used to determine adequacy of calibration[17]. In addition, calibration intercept ("calibration-in-the-large") and calibration slope were assessed for potential model re-calibration and presented using smoothed loess curves[18]. Discriminative ability was assessed using the Komogorov-Smirnoff (KS) D-statistic, Gini coefficient, AUC c-statistic and the misclassification rate. Different link functions and their effect upon calibration were assessed, including the complementary log-log and generalized logistic function. Center effects were assessed using stratified logistic regression and random-coefficients logistic regression. SAS Version 9.2 was used for data management & data screening. SAS PROC LOGISTIC and PROC NLMIXED were used for statistical modelling. Stata version 13 and the nomolog package was used for the nomogram construction[19].

Results

The study population profile is described in Table 1. A total of 2,392 study participants were recruited. There were 56 (2·3%) participants excluded for the following reasons; lost to follow up (n=4), abnormal biophysical profile (n=33), EFW under 2.5kg or over 5kg (n= 5), EFW performed after enrolment (n=5) and pre-existing indication for CD such as breech presentation and placental abruption (n=9). Therefore, a total of 2,336 women were included in the final analysis, and they represented the cohort of nulliparas who underwent a blinded ultrasound evaluation of fetal weight after 39 weeks' gestational age and who were deemed suitable for trial of labor at the time of the final ultrasound assessment.

The average maternal age was 29 +/- 5·1 years and the average maternal BMI was 24·5 +/- 4·3 kg/m^2. Mean maternal gestational weight gain was 13·8 kg +/- 5·3 kg. The majority of those enrolled were of European ethnicity (n=2,221, 95·2%). Over half (1,215, 52%) attended for obstetrician-provided care with 1,120 (48%) attending midwifery-provided services. In relation to preparation for labor, 1,807 (77·4%) attended prenatal education classes with 940 (40·3%) preparing a formal written birth plan. The majority of the participants had never smoked (1,355, 58%), 774 (33·2%) were ex-smokers and 206 (8·8%) were current smokers. The highest level of education obtained

in this cohort was third level (college or university level) amongst 1,600 (68·6%) patients. In this cohort 1,010 (43·2%) were formally tested for GDM.

Labor and delivery outcomes are outlined in Table 2. The overall CD rate was 21% in this study but there was variation from 14·8% to 25·5% according to each site. The risk factors for CD identified in the study are listed in supplementary data 1.

In a multivariate analysis the combined effect of each potential individual risk factor for CD was considered and a model was developed which demonstrated that there were five parameters which were most important for predicting overall risk of CD. The odds ratios for continuous predictors are presented using z scores for standardization. These five parameters were advancing maternal age OR 1·21 (95% CI 1·09-1·34), p=0·0005, increasing maternal BMI OR 1·29 (95% CI 1·17-1·42) p<0·0001, shorter maternal height OR 1·72 (95% CI 1·54-1·92) p<0·0001, largerfetal HC OR 1·27 (95% CI 1·13-1·42) p=<0·0001 and larger fetal AC OR 1·23 (95% CI1·1- 1·37) p=0·0004. The best combined predictors are outlined in table 3 with the population means and standard deviations (SD). These parameters were used to develop a clinically useful nomogram (figure 1) to predict an individualized patient risk assessment for CD in nulliparous women at term. A worked example is presented in supplementary data 2 (autoslides) along with nomogram variable division scores which aid with using the nomogram.

With respect to internal validation of the prediction model, boostrap re-sampling and 10-fold cross-validation gave consistent estimates of model fit (supplementary data 3). Consequently, no correction of model fit for over-optimism nor shrinkage of parameter estimates were performed (original data model or “apparent fit” is presented in table 3 and figure 2). The Hosmer-Lemeshow and Stukel test’s for lack-of-fit were not statistically significant (p-value=0.218 and 0.562, respectively). The Brier score, or average quadratic-loss, was 0.14 and had low informative value due to skewness in the individual Brier distribution. The Pietra index, an absolute measure of loss, showed that the model achieved 37% gain of an error-free model. The AUC was 0.69 and the misclassification rate was 21%.

The calibration curve (figure 2) showed good calibration-in-the-large and approximate linearity. There is potential under-estimation and over-estimation of CD rates in the mid-

range of risk (prediction probabilities 0.30 to 0.40), the potential grey-area of decision-making. The under-estimation of CD rates in the high probability region (> 0.5) is very uncertain – just 3% of the study population lie within this region. The KS discrimination curve shows good separation between those with and without CD (KS p-value <0.001).

Examination of alternative link functions did not improve the fit of the model in terms of calibration or discriminative ability. The fit of a generalized logistic link function gave lower and upper asymptotes of 7% and 70%, the potential extremes of risk prediction. The addition of quadratic and interaction terms did not improve the AIC or prediction value of the model. There was significant variation in CD rates across centers (15% - 25%, chi-square p-value=0.006). However, the addition of center as a factor in the multiple logistic regression was just borderline statistically significant (p-value=0.03) while a stratified analysis gave similar parameter estimates and discriminative ability to the unstratified analysis. The difference in CD rates was primarily due to different underlying risk populations, with differences in maternal demographics and fetal biometry observed.

Related to the Hosmer-Lemeshow test and the calibration curve, actual CD rates for prediction probability categories are presented in table 4. In the group with the highest predicted risk of CD (predicted >50% probability of CD), which represented 2.2% (n=52) of the cohort, 56% (n=29) actually underwent a CD. Only 13% (n=7) of women had an uncomplicated vaginal delivery in this high risk cohort. In this cohort 28% (n=15) required an operative vaginal delivery, 9% (n=5) had an obstetric anal sphincter injury and there was one case of a serious shoulder dystocia with a fractured clavicle. Using 50% as a high risk cut-off for CD the positive likelihood ratio (LR) was 4.92 and the negative LR was 0.95.

Comment

Principle Findings

Five parameters were identified as clinically informative in the estimation of overall risk of CD in the term nulliparous woman; namely: advancing maternal age, increasing maternal BMI, shorter maternal height, larger fetal head circumference and larger fetal

abdominal circumference, the latter blinded ultrasound-derived data obtained after 39 completed weeks' gestation. All such parameters are either routinely available or easily obtainable. These findings are consistent with previous studies on factors contributing to rising CD rates, but prior studies have not shown how these can be used in combination as a practical test to quantify individual CD risk in the nulliparous woman[20-24].

The association of higher birthweights and CD has been well described in the nulliparous population [25]. However, prediction of fetal macrosomia by EFW is fraught with difficulty due to inaccuracy, especially in the term fetus [26,27]. In this study while a composite estimation of fetal weight (above the 90th centiles for gestational age) was associated with an increased risk of CD, it did not perform as well as individual measurements of fetal HC and fetal AC in determining overall CD risk when other maternal and obstetric factors were also taken into consideration. It may be that simple single measurements perform better at predicting labor outcomes rather than more complex mathematical weight equations in the term fetus.

The blinding of fetal biometry from the participants, the obstetricians and midwives is a major strength of this study and contributed to the objectivity of the findings observed in this study. Blinding of the fetal biometry controlled for the potential bias of suspected fetal macrosomia affecting the decisions about timing and mode of delivery. There is some evidence that knowledge of an ultrasound obtained estimated fetal weight at term is a modifiable independent risk factor for CD and the same authors suggested that limiting the use of EFW acquisition at term may reduce the CD rate[28]. The results from our study, in which the obstetricians were blinded from ultrasound-derived estimates of fetal size, suggest that while composite fetal biometry alone should not be used to predict the risk of CD, the findings would in fact refute the observation that fetal biometry alone is a modifiable risk factor. [22]

Nomograms have been used previously in obstetric populations to assess the risk of CD. These nomograms focused on predicting the success of trial of vaginal delivery after CD. Grobman *et al* highlighted that there were six factors that were important in determining success of VBAC; maternal age, BMI, ethnicity, previous vaginal delivery, vaginal delivery since CD and recurrent indication for CD. This assessment was

performed at the initial prenatal visit and did not consider the fetal size as part of the risk evaluation [29]. Others have used nomograms to determine the risk of CD in the presence of fetal macrosomia. Mazouni *et al* retrospectively assessed the risk factors for CD in a small cohort (n=246) of women who delivered infants over 4,000grams. They discovered four parameters (age, parity, maternal height and previous CD) which were important in predicting a CD in the presence of macrosomia [30]. It is interesting that both of these studies identified age, BMI and height as predictors of CD, similar to what we found in our study. However, neither study examined the nulliparous population or the relationship between fetal biometry and risk of CD. Our study shows that a nomogram based on easily identifiable demographic and biometric data at term may be a clinically useful and simple method for predicting primary CD in nulliparous women. The accuracy of the prediction model is good, reflected in the calibration and discrimination curves and this model has been extensively internally validated.

Strengths and Weaknesses

Our study has other strengths including its prospective multi-center design, the blinding of clinicians to ultrasound-derived fetal biometry, large sample size, multiple risk factors assessed and multiple time points from initial antenatal assessment (maternal age, BMI and height) and late third trimester assessment to include fetal biometry. Another feature of the study is that the prediction model identified a small proportion with a very high risk (>50% or 1 in 2 chance) of CD, 2.2% (n=52). Even when these women avoided a Cesarean there was still a very high probability of other adverse outcomes associated with the high risk results. However, this study was not powered to detect differences in perineal trauma, post-partum hemorrhage or poor neonatal outcomes.

The average rate of induction for nulliparous patients in Ireland was 30% in 2009 but ranged from 18 to 47% nationally [31]. The rate of induction of labor was high at 40.5% in this cohort. At first analysis this may appear as a weakness of this study, as some readers may believe that their own induction rate is lower than this, thereby calling into question the generalizability of our findings. However, it must be noted that our study focuses on women who were enrolled only beyond 39 weeks' gestation thus excluding

those who spontaneously labored prior to 39 weeks' gestation. In our cohort the majority of women delivered after 40 weeks' gestation (n=2,027) and this is an additional explanation for the relatively high induction rate. Therefore, ours is a reasonable and acceptable induction rate, as our study focuses on those nulliparous patients who have remained undelivered after 40 weeks' gestation. Lower quoted induction rates in nulliparous patients in other studies tend to include nulliparous patients across all gestational ages.

Another possible weakness of our study is the fact that only 43% of the study population underwent a diagnostic test for gestational diabetes. A risk factor-based screening approach for GDM is in use at each of the seven centers in Ireland. It is, therefore, possible that there may have been some cases of undiagnosed GDM in the study population which may have contributed to the overall CD rate. With an overall CD rate of 21% we expect this effect to be small and better reflects current obstetric practice.

Clinical Implications

The information garnered from this study should be considered useful for the provision of contemporary antenatal care. It can provide an individualized assessment of the risk of primary CD which can better inform women in preparation for childbirth and may be useful in managing women's expectations. The identification of women at high risk of CD (>50% risk) would also provide the opportunity for informed decision making about the potential risks involved in pursuing a vaginal delivery versus an elective CD. As maternal request for CD without specific maternal or fetal indication becomes more common, this risk assessment tool may prove useful in perinatal counselling to encourage those with a low risk of CD to pursue a vaginal delivery.

Research Implications

A recent review of prognostic models in obstetrics highlighted the increasing number of prediction models which have been developed but not externally validated[32]. Kleinrouweler *et al* addressed the need to assess the performance and impact of prediction models in clinical practice and expressed concern over the lack of clear reporting in the development of prediction models. The information provided in this

manuscript contains all of the necessary information for the model to be externally validated by other researchers in different populations. Further studies are necessary to assess the potential impact of this prediction model. Potential clinical impact studies should focus on using this risk assessment tool for CD, to aid in decision making about timing and mode of delivery and whether morbidity associated with prolonged labor or obstetric interventions can be reduced.

Conclusion

This nomogram, using five parameters, (maternal age, BMI, height, fetal head circumference and fetal abdominal circumference), has the potential to assist with individualized consultation, and thereby optimal selection of women for a successful vaginal delivery. It may also serve as an audit tool for improved monitoring of primary CD rates in nulliparous women at a hospital or population level. We believe that this risk tool will be useful for reassuring most women regarding their likely success at having an uncomplicated vaginal delivery as well as selecting those patients with such a high risk for CD that they should avoid a trial of labor and the associated morbidity. Such a risk tool has the potential to greatly improve planning hospital service needs and minimizing patient risk.

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Table 1. Study Profile

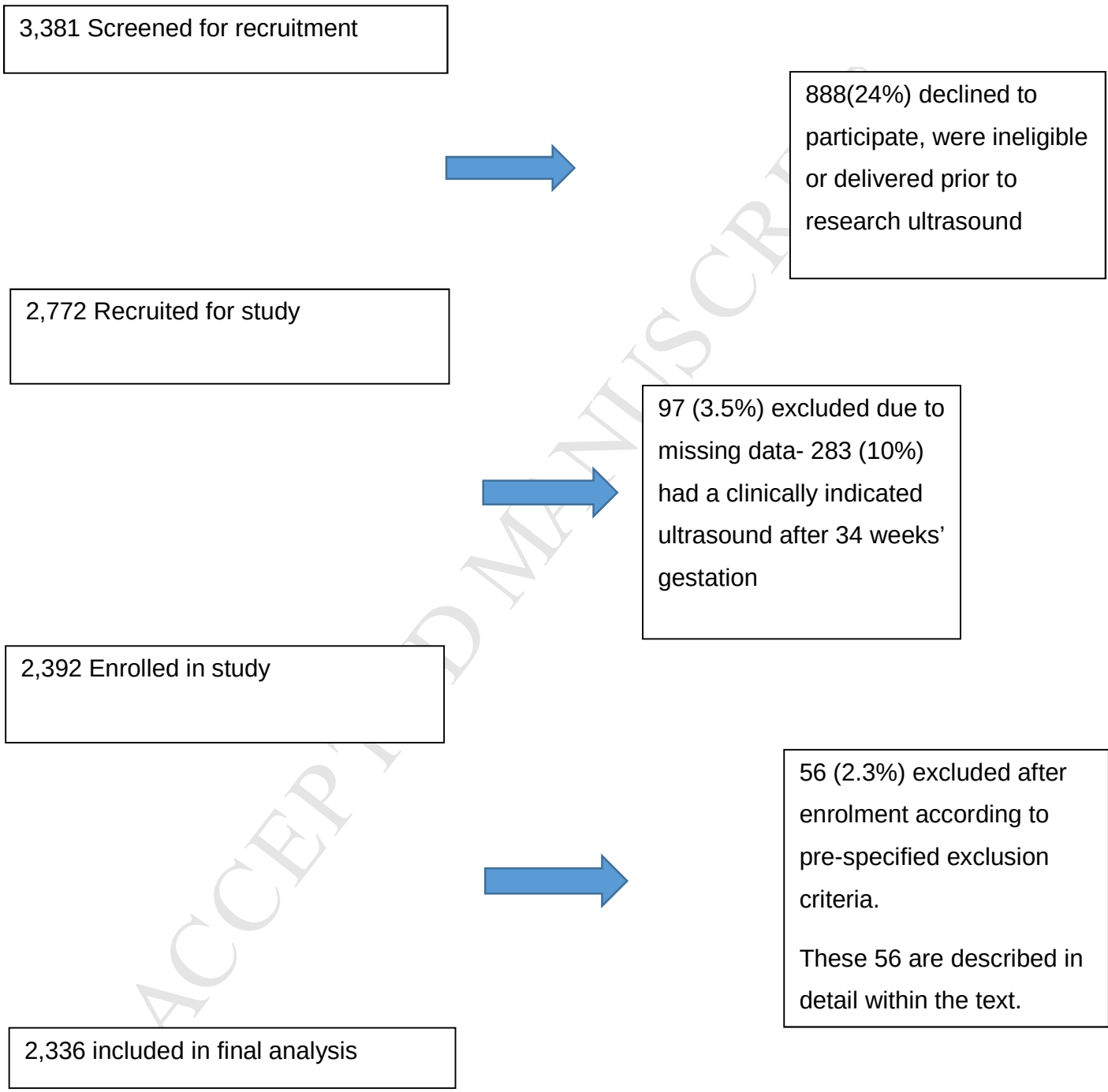

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Table 2. Labor and Delivery Outcomes in the Genesis Population

Outcome		Total	Percentage
Spontaneous labor		1,389	59·5%
Induced labor		947	40·5%
Method of induction	Cervical priming with prostaglandin	670	70·7%
	No cervical priming required	277	29·3%
Oxytocin use		1,178	49·6%
Meconium staining		540	23·1%
Mode of delivery	Spontaneous vaginal delivery	981	41·9%
	Vacuum assisted vaginal delivery	511	21·9%
	Unplanned Cesarean Delivery	491	21·0%
	Forceps assisted vaginal delivery	248	10·6%
	Vacuum followed by Forceps	105	4·5%
Indication for induction of labor N=947	Post-dates (>41 weeks gestation)	522	55·1%
	Prolonged Rupture of Membranes (>18 hours- 48 hours)	157	16·6%
	Suspected Maternal compromise**	154	16·3%
	Suspected Fetal compromise***	54	5·7%
	Other	35	3·7%
	Not recorded	25	2·6%
Indication for delivery* N=1,355 i.e. all operative deliveries	Failure to progress	504	37·2%
	CTG abnormalities	778	57·4%
	Abnormal fetal blood sample	85	6·3%

	Suspected infection or sepsis	88	6·5%
	Malposition	41	3·0%
	Other	53	3·9%
Post-partum hemorrhage (estimated and measured blood loss over 500mls)		279	11·9%
Anal sphincter injury		76	3·2%
Shoulder Dystocia		29	1·2%
NICU admission		177	7·6%

*Indication for delivery: more than one indication for delivery may have been recorded

** Suspected maternal compromise included; hypertension, vaginal bleeding, abdominal pain, exhaustion, discomfort.

***Suspected fetal compromise included; suspicious CTG pattern, reduced fetal movements, abnormal biophysical score

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Table 3. Best Combined Predictors of Cesarean Delivery

Demographic/ Ultrasound Information	Mean	SD	Odds Ratio Unit	At Initial Prenatal Visit OR (95% CI)	At 39+0 to 40+6 weeks OR (95% CI)
Age (years)	29.9	5.07	+ 1 SD	1.22 (1.10,1.35)	1.21 (1.09,1.34)
Height (cm)	165.5	6.55	- 1 SD	1.59 (1.43,1.78)	1.72 (1.52,1.93)
BMI (kg/m^2)	24.5	4.27	+ 1 SD	1.32 (1.20,1.46)	1.29 (1.17,1.43)
Fetal HC (mm)	337	12.9	+ 1 SD	Not applicable	1.27 (1.14,1.42)
Fetal AC (mm)	351	16	+ 1 SD	Not applicable	1.23 (1.10,1.38)

Results from a multiple logistic regression of z-scores are displayed. Odds-ratios (OR) correspond to a +/-1 SD increase/reduction in a predictor. This table can be used to calculate Z scores.

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Table 4. Predicted versus actual Cesarean Delivery Rates

Predicted Cesarean Delivery Rate		**Actual Cesarean Delivery Rate**	
Range (%)	**Mean (%) within Range**	**n**	**%**
< 10%	8%	36/348	10%
10-20%	15%	124/935	13%
20-30%	24%	160/614	26%
30-40%	33%	75/258	29%
40-50%	44%	66/127	51%
> 50%	56%	29/52	56%

Figure Captions:

Figure 1. Cesarean Delivery Risk Assessment Tool

Figure 2. Model Calibration and Discrimination Curves

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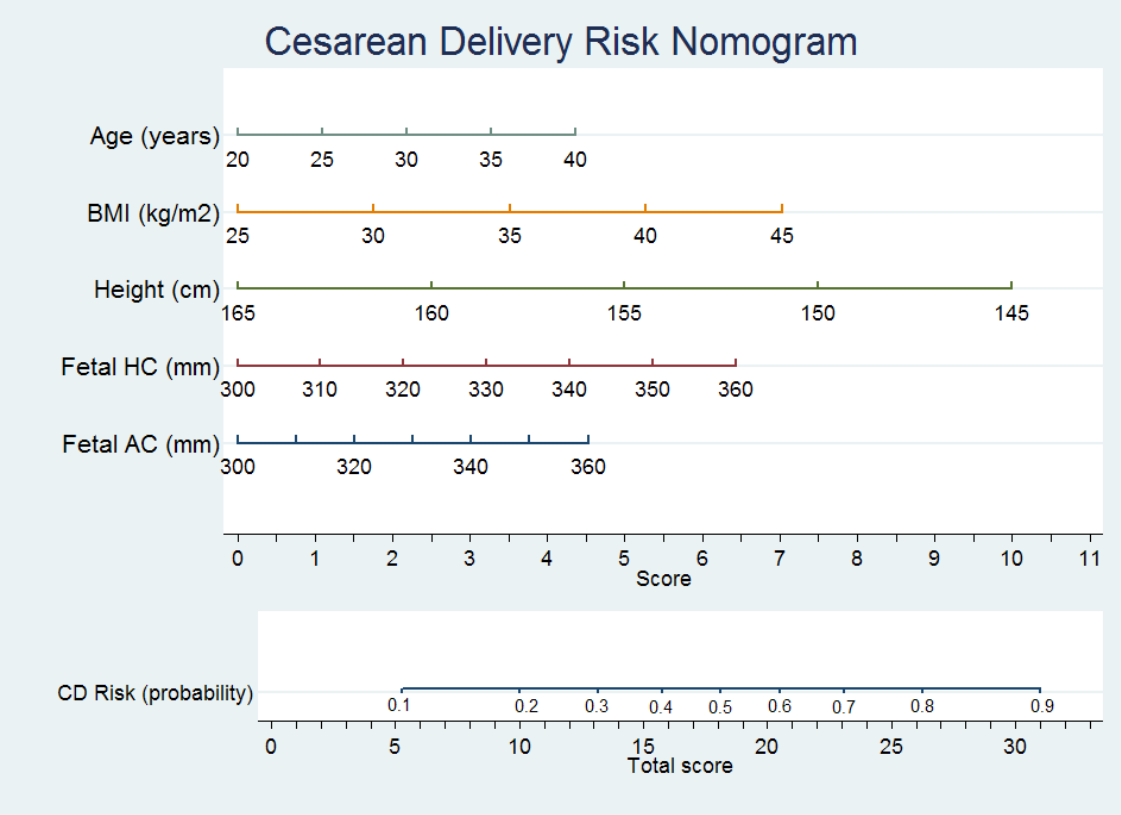
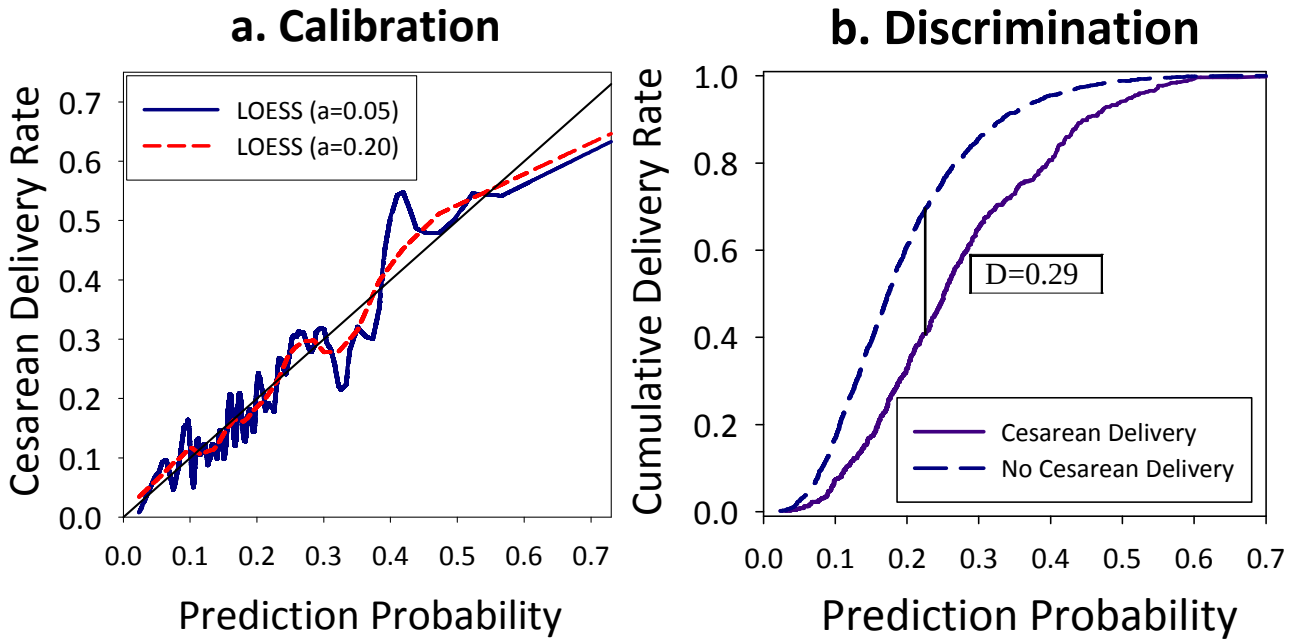
Figure 1. Cesarean Delivery Risk Assessment Tool



Example: For a patient aged 35 (score=3.3) with a BMI of 35 (score=3.5), height of 160cm (score=2.5), fetal HC of 350 (score=5.4), fetal AC of 350 (score=3.8), the total score is 18.5 corresponding to a 51% risk of CD.

Figure 2. Model Calibration and Discrimination



D= Discrimination
LOESS= Locally weighted scatterplot smoothing
a= LOESS smoothing parameter

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Glossary of Terms

Akaike Information Criterion is a method for selecting a statistical model by estimating the relative quality of models for a given dataset

Brier score assess overall performace of a prediction model

C statistic is a measure of the area under the curve (AUC) in a receiver operating curve (ROC) and tells how well a prediction model will work on average

Gini co-efficeint is a measure of statistical heterogenicity

Hosmer Lemeshow (goodness-of-fit) test is a statistical method for assessing the calibration of a prediction model

Link functions relate the mean of the response to linear predictors in the model

Misclassification rate is a measurement error of a prediction model

Pietra Index is a measure of statistical heterogenicity

Re-sampling is the statistical process of validating prediction models by using subsets of the data. When is the data is selected randomly this is termed bootstrapping.

Stukel test is another method to assess the goodness of fit or calibration of a prediction model

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Supplementary data 1. Univariate Analysis to Identify Antenatal Factors Associated with Cesarean Delivery

Characteristic	Category	CD Rate (%)	Odds ratio	95% CI	p value
Maternal age (years)	<25	16.4	control		
	25-35	20.8	1.3	(1.0-1.8)	0.89
	>35	26.6	1.9	(1.3-2.6)	<0.001
Maternal height (cm)	>160cm	18.1	control		
	<160cm	35.8	2.5	(2.0-3.2)	<0.001
Maternal BMI (kg/m^2)	<25	17.7	control		
	25-30	25.1	1.6	(1.2-1.9)	0.75
	>30	32.5	2.2	(1.7-3.0)	<0.001
Maternal head circumference (cm)	<58.2cm	20.0	control		
	>58.2cm	29.4	1.7	(1.2-2.2)	<0.001
Ethnicity	White European	20.1	control		
	Other	28.1	1.5	(1.0-2.3)	0.06
History of miscarriage	No	21.1	control		
	Yes	20.1	1.1	(0.7-1.6)	0.77
Family history of Cesarean Delivery	No	19.5	control		
	Yes	25.3	0.72	(0.6-0.9)	0.003
Birth plan	No	19.4	control		
	Yes	23.4	1.3	(1.0-1.5)	0.022
Education level (max level achieved)	Second level	21.0	control		
	Third level	21.0	1	(0.8-1.2)	0.95
Alcohol use (any) in pregnancy	No	20.7	control		
	Yes	24.7	0.8	(0.6-1.1)	0.20
Smoking Status	Never	22.0	control		
	Ex	18.6	0.8	(0.7-1.0)	0.04
	Current	24.0	1.1	(0.8-1.6)	0.22
Type of care	Obstetric provided	21.7	control		
	Midwife provided	20.3	0.9	(0.8-1.1)	0.38
Fetal Head Circumference	<90th centile	20.0	control		
	>90th centile	30.0	1.7	(1.3-2.3)	<0.001
Fetal Abdominal Circumference	<90th centile	20.1	control		
	>90th centile	28.8	1.6	(1.2-2.2)	0.002
Estimated Fetal Weight	<90th centile	19.9	control		

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	>90th centile	30.6	1.8	(1.3-2.4)	<0.001
Fetal head engagement on clinical palpation (at time of study ultrasound)	Engaged	20.2	control		
	Not engaged	21.4	1.1	(0.9-1.3)	0.30
	Uncertain	28.2	1.6	(1.0-2.4)	0.07
Occiput posterior (at time of study ultrasound)	No	21.5	control		
	Yes	19.7	1.1	(0.9-1.4)	0.37

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Prediction of Cesarean Delivery in the Term Nulliparous Woman: Results for the Multi-center Genesis Study

Naomi Burke, Gerry Burke, Michael Turner, Fionnuala Breathnach, Fionnuala McAuliffe, John J Morrison, Samina Dornan, John Higgins , Amanda Cotter, Michael Geary, Peter McParland, Sean Daly, Fiona Cody, Pat Dicker, Elizabeth Tully, Fergal Malone
Perinatal Ireland Research Consortium

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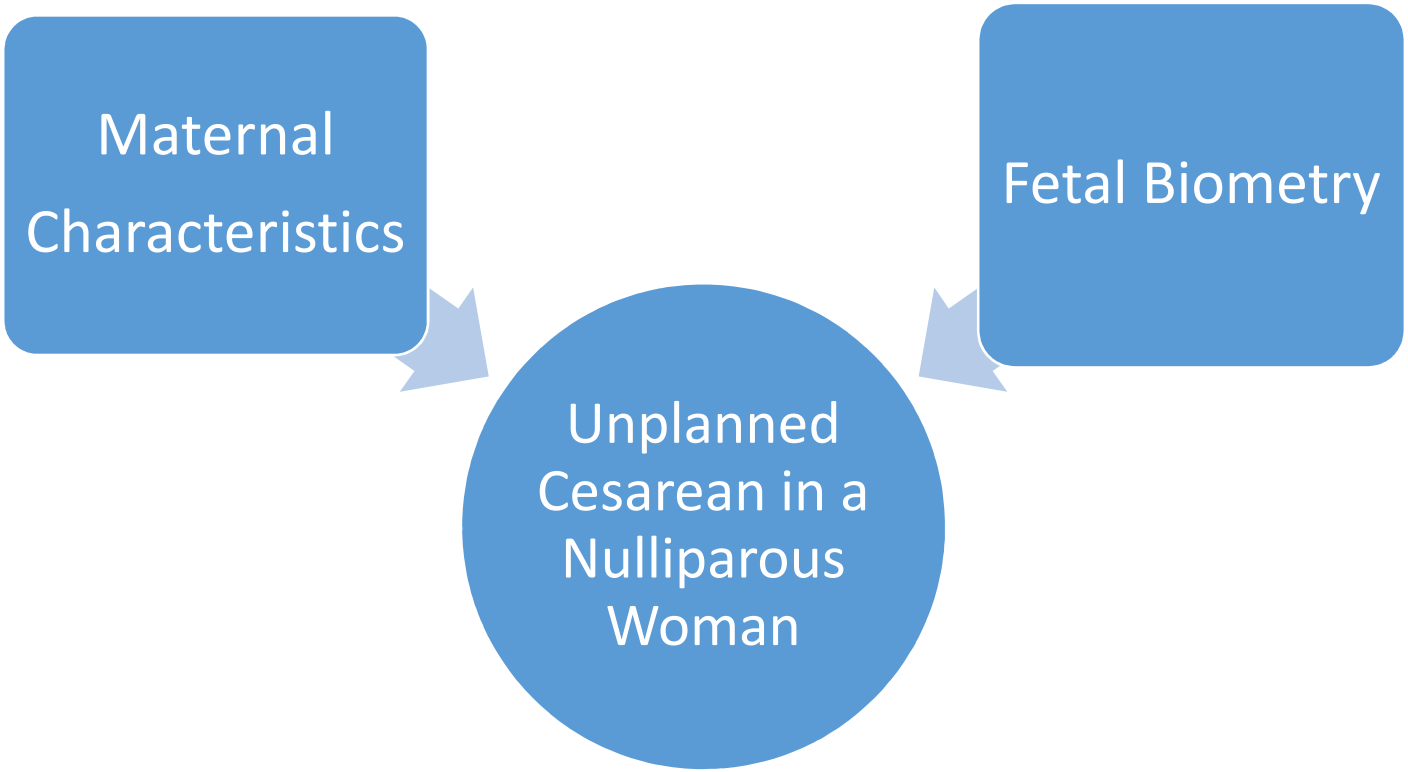
Primary Analysis to Develop a Mathematical Prediction Model for Cesarean Delivery



Naomi Burke, Gerry Burke, Michael Turner, Fionnuala Breathnach, Fionnuala McAuliffe, John J Morrison, Samina Dornan, John Higgins , Amanda Cotter, Michael Geary, Peter McParland, Sean Daly, Fiona Cody, Pat Dicker, Elizabeth Tully, Fergal Malone from the Perinatal Ireland Research Consortium Prediction of Cesarean Section AJOG 2017

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Study Design

- Prospective Observational Blinded Study of 2336 women
- Seven Perinatal Ireland research sites
- Nullipara
- 39^{+0} to 40^{+6}
- Standard fetal biometry
- Blinded to the fetal biometry
- Standard perinatal and obstetric data
- Multivariate analysis to identify best combined predictors for Cesarean Delivery
- Development of prediction model and risk assessment tool for clinical use

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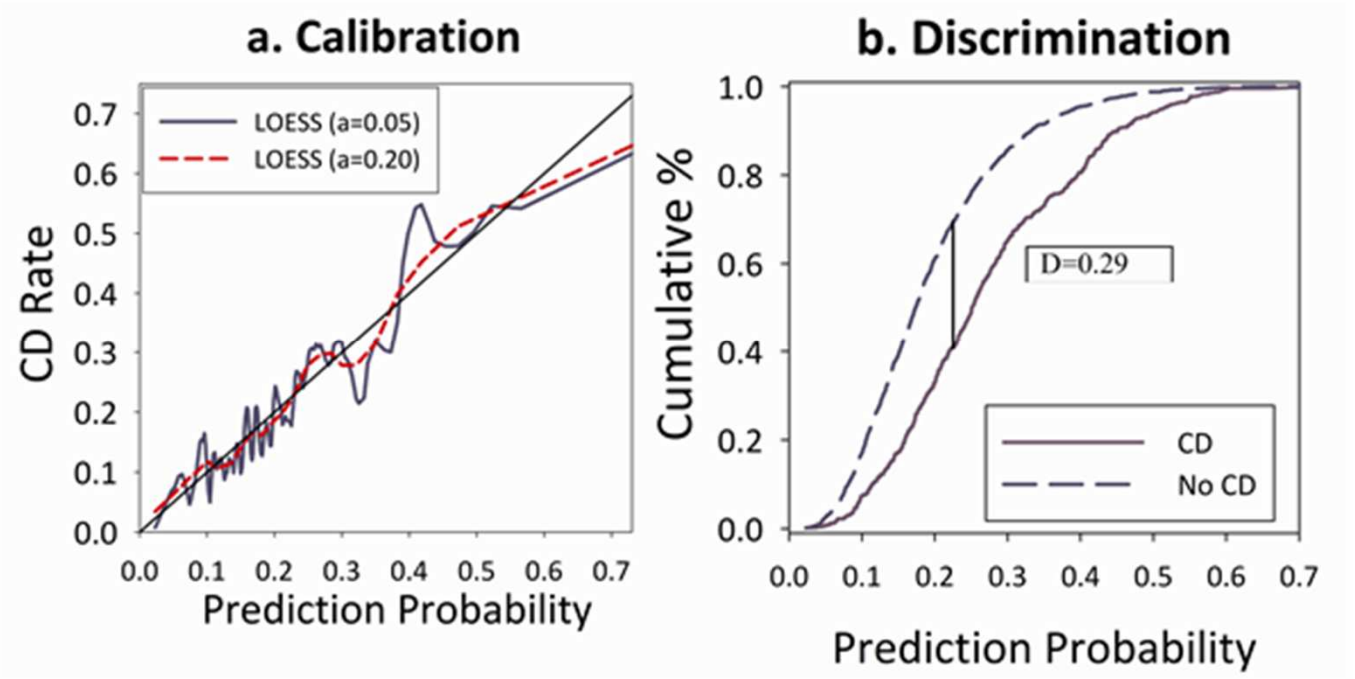
Prediction Model

Demographic	Mean	SD	OR Unit	At Initial Booking Visit	At 39+0 to 40+6 weeks
Ultrasound Information				OR (95% CI)	OR (95% CI)
Age (years)	29.9	5.07	+ 1 SD	1.22 (1.10,1.35)	1.21 (1.09,1.34)
Height (cm)	165.5	6.55	- 1 SD	1.59 (1.43,1.78)	1.72 (1.52,1.93)
BMI (kg/m^2)	24.5	4.27	+ 1 SD	1.32 (1.20,1.46)	1.29 (1.17,1.43)
Fetal HC (mm)	337	12.9	+ 1 SD	Not applicable	1.27 (1.14,1.42)
Fetal AC (mm)	351	16	+ 1 SD	Not applicable	1.23 (1.10,1.38)

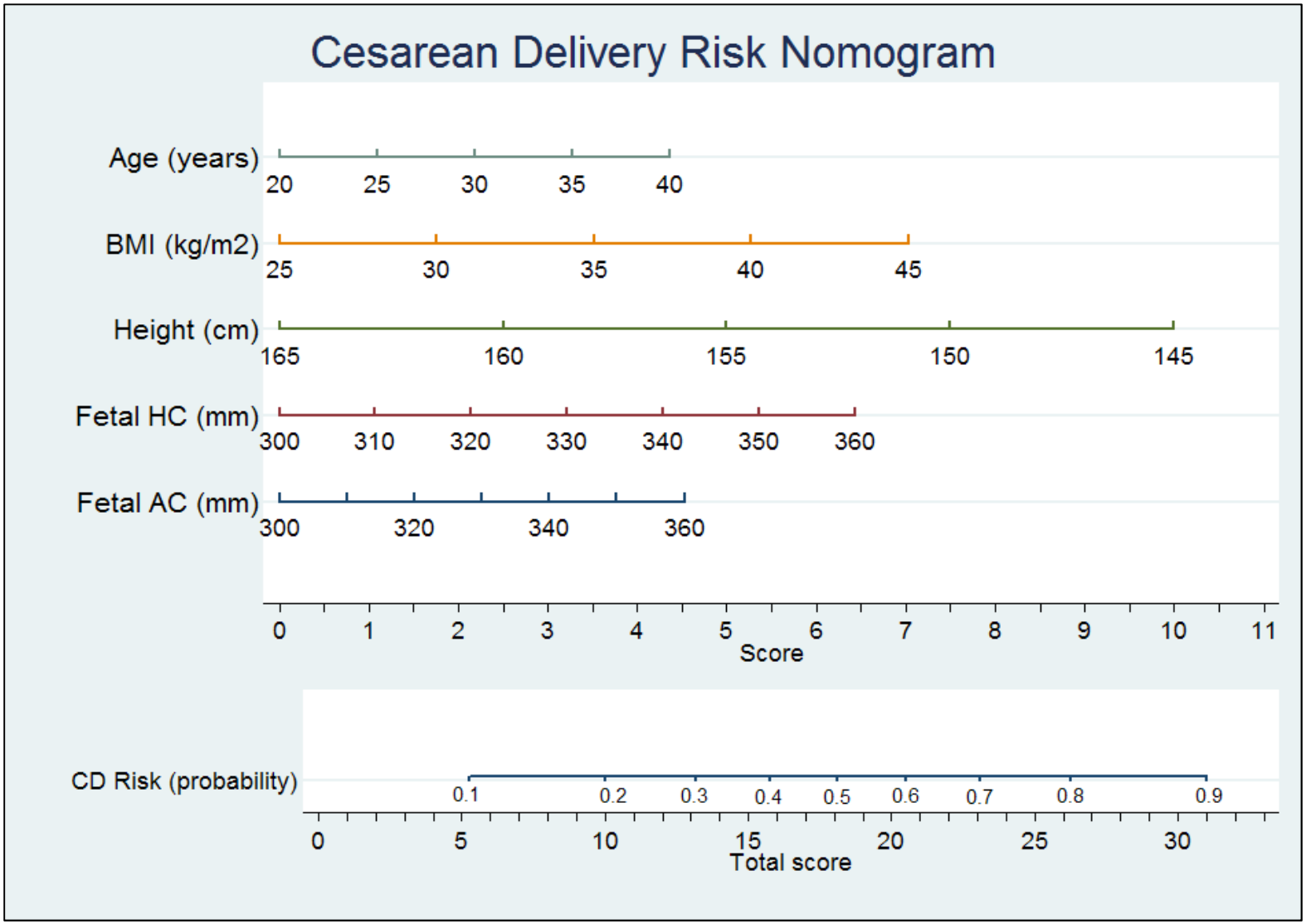
Results from a multiple logistic regression of z-scores are displayed. Odds-ratios (OR) correspond to a +/-1 SD increase in a predictor.

Prediction Model



CD= Cesarean Delivery
D= Discrimination
LOESS= Locally weighted scatterplot smoothing
a=0.05 Large LOESS
a= 0.20 Approximate LOESS

Naomi Burke, Gerry Burke, Michael Turner, Fionnuala Breathnach, Fionnuala McAuliffe, John J Morrison, Samina Dornan, John Higgins , Amanda Cotter, Michael Geary, Peter McParland, Sean Daly, Fiona Cody, Pat Dicker, Elizabeth Tully, Fergal Malone from the Perinatal Ireland Research Consortium Prediction of Cesarean Section AJOG 2017



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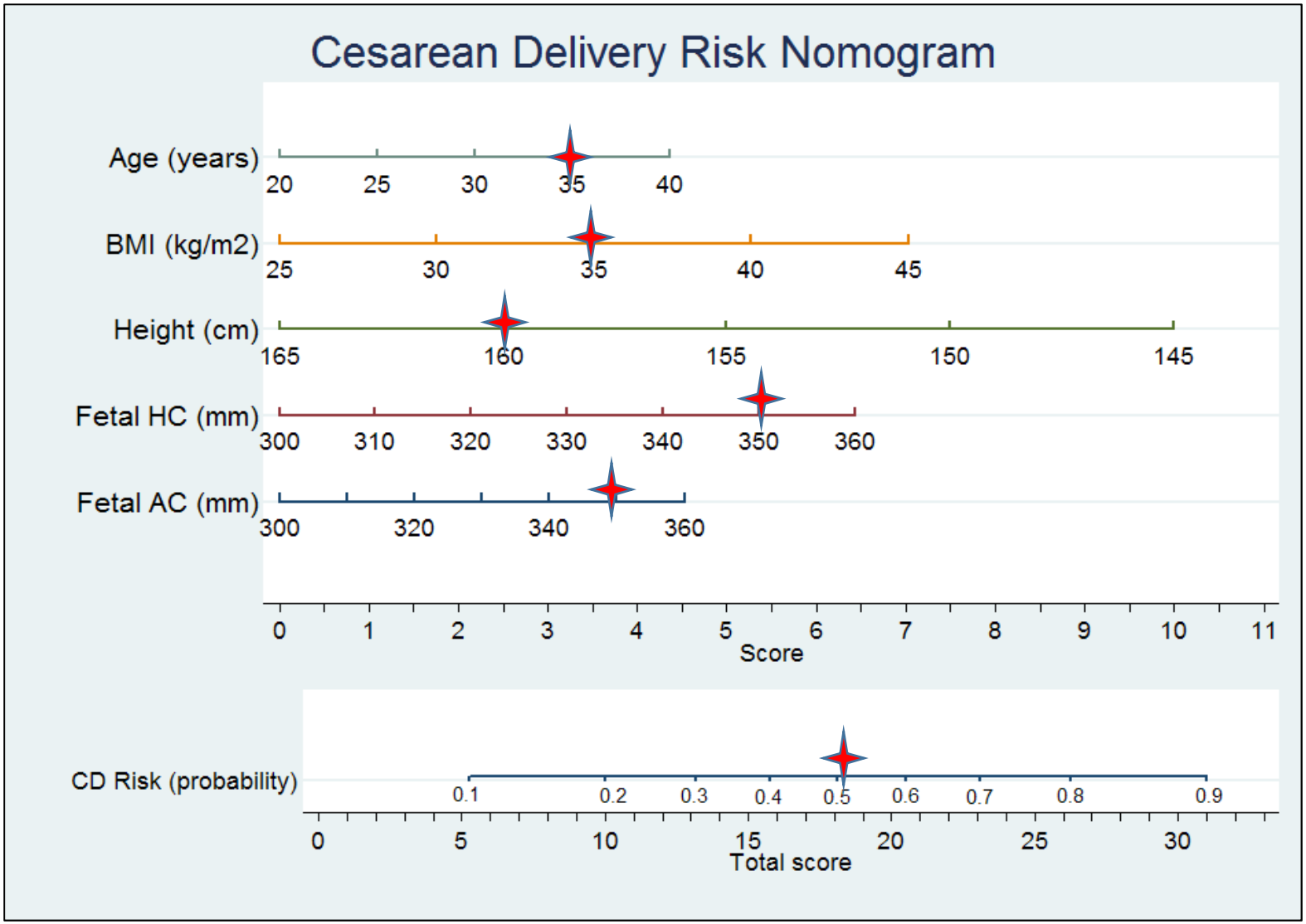
Example

- 35 year old, nulliparous, with a height of 160cm and BMI 35. The fetal HC is 350mm and the fetal AC is 350mm

- Risk scores from the nomogram 35 years (3.3), BMI 35 (3.5), height 160cm (2.5), fetal HC 350mm (5.4), fetal AC 350 (3.8). Total score is 18.5 which corresponds to a 51% risk of cesarean delivery.



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Nomogram Variable Division Scores

Age (years)		BMI (kg/m^2)		Height (cm)		Fetal HC (mm)		Fetal AC (mm)	
Value	Score	Value	Score	Value	Score	Value	Score	Value	Score
20	0.0	25	0.0	165	0.0	300	0.0	300	0.0
25	1.1	30	1.8	160	2.5	310	1.1	310	0.8
30	2.2	35	3.5	155	5.0	320	2.1	320	1.5
35	3.3	40	5.3	150	7.5	330	3.2	330	2.3
40	4.4	45	7.0	145	10.0	340	4.3	340	3.0
						350	5.4	350	3.8
						360	6.4	360	4.5

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Supplementary Data 3. Cross-validation & Boostrap Results
Means and 95% confidence intervals[1]

Model Fit Statistic	**Apparent Fit**	**10-fold Cross-validation (Repeats=100)**		**Bootstrap Resampling (Repeats=1000)**	
		Training Sample ($9/10^{th}$)	Validation Sample ($1/10^{th}$)	Training (Bootstrap) Sample	Validation (Original) Sample
Cesarean Delivery Rate	0.21	0.21 (0.21, 0.22)	0.21 (0.16, 0.26)	0.21 (0.19, 0.23)	0.21
Predictor correlation[2]	0.17	0.17 (0.16, 0.18)	0.19 (0.11, 0.28)	0.17 (0.14, 0.20)	0.17
Parameter Estimates					
Intercept	-1.46	-1.46 (-1.50, -1.42)	N/A	-1.47 (-1.58, -1.35)	N/A
Maternal age (z-score)	0.19	0.19 (0.15, 0.22)	N/A	0.19 (0.08, 0.29)	N/A
Maternal BMI (z-score)	0.26	0.26 (0.22, 0.29)	N/A	0.26 (0.16, 0.36)	N/A
Maternal height (z-score)	0.54	0.54 (0.50, 0.58)	N/A	0.54 (0.42, 0.66)	N/A
AC (z-score)	0.20	0.20 (0.17, 0.24)	N/A	0.21 (0.09, 0.32)	N/A
HC (z-score)	0.24	0.24 (0.20, 0.27)	N/A	0.23 (0.13, 0.35)	N/A
Goodness-of-fit					
AIC	2235	2004 (1962, 2045)	225 (182, 266)	2222 (2117, 2330)	2231 (2228, 2239)
Hosmer-Lemeshow χ^2 (8 df)	10.7	8.77 (4.40, 14.65)	8.33 (2.40, 17.20)	17.75 (5.35, 35.75)	9.98 (4.80, 17.40)
Stukel χ^2 (2 df)	1.2	1.34 (0.10, 3.55)	1.58 (0.10, 6.60)	3.36 (0.10, 13.00)	1.56 (0.10, 4.35)
Overall Performance					
Brier Score	0.14	0.15 (0.15, 0.16)	0.15 (0.13, 0.18)	0.15 (0.14, 0.16)	0.15 (0.15, 0.15)
Scaled Brier Score	0.15	0.08 (0.07, 0.09)	0.07 (-0.00, 0.14)	0.08 (0.06, 0.11)	0.08 (0.07, 0.08)
Pietra Score	0.37	0.27 (0.26, 0.28)	0.28 (0.24, 0.34)	0.27 (0.23, 0.31)	0.27 (0.23, 0.31)
Calibration					
Intercept	N/A	N/A	-0.01 (-0.38, 0.32)	N/A	0.00 (-0.10, 0.11)
Slope	N/A	N/A	1.00 (0.51, 1.59)	N/A	0.98 (0.84, 1.15)
Discrimination					
D-statistic (KS)	0.34	0.29 (0.27, 0.31)	0.33 (0.20, 0.45)	0.30 (0.25, 0.35)	0.29 (0.28, 0.30)
Gini coefficient	0.37	0.37 (0.36, 0.39)	0.37 (0.21, 0.53)	0.38 (0.32, 0.43)	0.37 (0.36, 0.37)
c-statistic (AUC)	0.69	0.69 (0.68, 0.70)	0.68 (0.60, 0.76)	0.69 (0.66, 0.72)	0.68 (0.68, 0.69)
Misclassification rate	0.21	0.21 (0.20, 0.21)	0.21 (0.16, 0.25)	0.21 (0.19, 0.22)	0.21 (0.21, 0.21)

Notes.
[1]95% confidence intervals are the 2.5^{th} and 97.5^{th} percentiles of the sampling distribution. To illustrate the range of cross-validation findings, the sampling distribution includes both folds and replications from each cross-validation (10 x 100= 1000 samples).
[2] The "predictor correlation" is the maximum multiple correlation among predictors for each sample.