# Journal Pre-proof

Accurate prediction of growth-restricted neonates at term using machine learning

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# TITLE PAGE

# Accurate prediction of growth-restricted neonates at term using machine learning

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The findings from this study were presented orally at the International Society of Ultrasound in Obstetrics and Gynecology 34th Annual World Congress on September 25-27, 2024, Budapest, Hungary.

**Keywords:** small-for-gestational-age, adverse perinatal, outcomes, uterine artery, cerebroplacental ratio, Doppler; growth restriction, fetal biometry, third-trimester ultrasound scan; estimated fetal weight; artificial intelligence; machine learning

**Tweetable statement**: Machine learning algorithms can accurately predict the development of growth-restricted neonates at term using routine data from a late third-trimester ultrasound scan.

## Objective

Growth-restricted neonates are at risk of short and long-term adverse outcomes.[1] Accurate prenatal identification of at-risk fetuses is critical to improving these outcomes. False positives can lead to unnecessary interventions and increased healthcare costs, while missed cases increase the risk of perinatal morbidity and mortality. Machine learning can enhance the predictive accuracy of various health-related outcomes. This study uses late-third trimester scan data to evaluate a novel machine-learning algorithm to improve predictive accuracy at term.

## Study Design

This cohort study retrospectively analyzed data from singleton pregnancies that underwent routine third-trimester ultrasound scans between $35^{+0}$ and $37^{+6}$ weeks of gestation. Pregnancies with significant structural or genetic abnormalities or incomplete outcome data were excluded. Maternal demographic characteristics, extracted from hospital electronic records, included maternal age, ethnicity, nulliparity, previous stillbirth, body mass index, smoking or alcohol consumption, mode of conception, and the development of gestational diabetes or hypertensive disorders of pregnancy. The routine ultrasound scans measured the fetal head circumference, abdominal circumference (AC), femur length, the pulsatility index (PI) of the umbilical artery, middle cerebral artery, uterine artery Doppler and cerebroplacental ratio (CPR). Fetal biometry was evaluated following the ISUOG guidelines[2], and the estimated fetal weight (EFW) was calculated. AC, EFW, Doppler parameters, and neonatal birthweight were adjusted for gestational age by converting them into centiles.[3-6] Logistic regression and Random Forest machine learning models were developed to predict the study outcome: a growth-restricted neonate, defined as either a birthweight <3rd centile or a birthweight between the 3rd and 10th centiles with adverse outcomes, including intrauterine death, neonatal death, or neonatal intensive care unit admission for at least 48 hours. Model performance was assessed using the Area Under the Receiver Operating Characteristic Curve (AUROC), sensitivity, positive predictive value (PPV), negative predictive value (NPV), likelihood ratios (LR), and feature importance.

## Results

The study included 14,917 pregnancies, with a median gestational age of $36^{+0}$ weeks at an ultrasound scan. There were 182 (1.2%) growth-restricted neonates. The demographic and clinical characteristics of patients with and without a growth-restricted neonate as well as the variables included in the prediction models are presented in Supplementary Table 1. For the prediction of a growth-restricted neonate, at a false-positive rate of 10%, the machine-learning model had an AUROC of 0.94, sensitivity 81%, PPV 89% and NPV 82% compared to 0.95, 83%, 89%, 84%, respectively for the traditional logistic regression model (Table 1). Feature importance analysis revealed that the EFW centile was the most influential variable in the model. After removing the EFW centile from the model, the CPR centile emerged as the most important sonographic feature.

## Conclusion

Machine learning algorithms can predict the development of a growth-restricted neonate at term using routine data from a late third-trimester ultrasound scan with a high degree of accuracy, similar to that of traditional logistic regression models. The variables contributing most significantly to the machine learning models were the EFW centile, followed by the CPR and, to a lesser extent, other Doppler parameters. Future studies should aim to externally validate and practically implement these models in clinical settings to maximize their potential benefits.

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**Table 1.** Evaluating the predictive performance for growth-restricted neonates. A comparison of Random Forest and Logistic Regression models using maternal demographics, Estimated fetal weight, and Doppler parameters

| | **Logistic Regression** | **Random Forest** |
|---|---|---|
| **Area under the receiver operator curve (AUROC)** | 0.945 (0.941 - 0.950) | 0.940 (0.936 - 0.946) |
| **Sensitivity** | | |
| 10% FPR | 83% | 81% |
| 15% FPR | 88% | 90% |
| 20% FPR | 93% | 93% |
| **Positive predictive value** | | |
| 10% FPR | 89% | 89% |
| 15% FPR | 85% | 85% |
| 20% FPR | 82% | 82% |
| **Negative predictive value** | | |
| 10% FPR | 84% | 82% |
| 15% FPR | 88% | 89% |
| 20% FPR | 92% | 92% |
| **Likelihood ratio (-, +)** | | |
| 10% FPR | 0.188, 8.298 | 0.206, 8.135 |
| 15% FPR | 0.129, 5.197 | 0.117, 6.000 |
| 20% FPR | 0.084, 4.649 | 0.083, 4.640 |

FPR – False positive rate.
Estimated fetal weight centile, Doppler parameters, and demographic parameters were used in the model.
**Maternal demographic characteristics:** Nulliparity, Ethnicity, Body Mass Index, Smoking status, Hypertensive disorders of pregnancy (HDP), BMI
**Doppler characteristics:** **Doppler characteristics: Umbilical artery pulsatility index (PI) centile, Middle cerebral artery  PI centile, Cerebroplacental ratio centile, Uterine artery PI centile

**Supplementary Table 1.** Baseline demographic, clinical, and sonographic characteristics of the study cohort according to whether they resulted in a growth-restricted neonate or not

| | **FGR (n=182)** | **Controls (n=14735)** | ***P* value** |
|---|---|---|---|
| Maternal age in years, median (IQR) | 31.7 (27.2-36.6) | 33.3 (29.8-36.3) | ***<0.001*** |
| Nulliparity, n (%) | 125 (68.7) | 7485 (50.8) | ***<0.001*** |
| Maternal ethnicity, n (%) | | | |
| White (1) | 57 (31.3) | 7196 (48.8) | ***<0.001*** |
| Black (2) | 20 (11.0) | 1564 (10.6) | 0.870 |
| Asian (3) | 61 (33.5) | 2465 (16.7) | ***<0.001*** |
| Mixed (4) | 10 (5.5) | 570 (3.9) | 0.259 |
| Other (5) | 34 (18.7) | 2940 (20.0) | 0.670 |
| Fertility treatment, n (%) | 10 (7.9) | 743 (6.7) | 0.582 |
| Previous stillbirth, n (%) | 0 (0.0) | 33 (0.5) | 0.590 |
| Smoker, n (%) | 19 (10.4) | 447 (3.0) | ***<0.001*** |
| Alcohol, n (%) | 2 (1.1) | 108 (0.7) | 0.567 |
| Maternal BMI at booking in Kg/m2, median (IQR) | 24.0 (21.0-27.0) | 24.4 (22.0-28.0) | ***0.012*** |
| Gestational diabetes, n (%) | 17 (9.3) | 1756 (11.9) | 0.286 |
| Hypertensive disorders of pregnancy, n (%) | 15 (8.2) | 453 (3.1) | ***<0.001*** |
| Induction of labor, n (%) | 107 (58.8) | 5200 (35.3) | ***<0.001*** |
| Gestational age at ultrasound in weeks, median (IQR) | 36.0 (36.0-36.0) | 36.0 (36.0-36.0) | 0.451 |
| Estimated fetal weight centile, median (IQR) | 19.7 (8.8 – 33.0) | 61.3 (44.4 - 76.7) | ***<0.001*** |
| Abdominal circumference centile, median (IQR) | 15.6 (6.3-30.4) | 56.0 (38.7-72.4) | ***<0.001*** |
| Gestational age at birth in weeks, median (IQR) | 39.0 (37.0 - 40.0) | 39.0 (39.0 - 40.0) | ***<0.001*** |
| Scan to birth interval in weeks, median (IQR) | 3.0 (1.0 - 4.0) | 3.0 (3.0 - 4.0) | ***<0.001*** |
| Birthweight in grams, median (IQR) | 2350 (2160-2500) | 3400 (3100-3700) | ***<0.001*** |
| Birthweight centile, median (IQR) | 2.1 (1.2 - 2.5) | 59.5 (34.2 - 81.4) | ***<0.001*** |
| Umbilical artery PI centile, median (IQR) | 58.3 (36.1 -80.9) | 43.7 (21.1 – 65.7) | ***<0.001*** |
| Middle cerebral artery PI centile, median (IQR) | 39.6 (19.1 - 66.3) | 53.3 (30.8 – 75.3) | ***<0.001*** |
| Cerebroplacental ratio centile, median (IQR) | 37.7 (20.0 – 67.4) | 59.5 (38.4 – 79.1) | ***<0.001*** |
| Uterine artery PI centile, median (IQR) | 52.4 (20.2 – 90.0) | 36.7 (16.3 – 66.8) | ***<0.001*** |

FGR – Fetal growth restriction, IQR – Interquartile range, BMI – Body Mass Index, GA – Gestational age, PI – Pulsatility Index

**Supplementary Table 2.** Prediction models for growth-restricted neonates using Random Forest machine learning and traditional logistic regression with different variable combinations

| | **AUROC (95% CI)** | **Shrinkage (%)** | **Sensitivity (10% FPR)** |
|---|---|---|---|
| **Logistic regression** | | | |
| Umbilical artery PI centile only | 0.632 (0.620 - 0.644) | -0.005 | 27% |
| Middle cerebral artery PI centile only | 0.616 (0.604 - 0.628) | -0.005 | 23% |
| Cerebroplacental ratio centile only | 0.666 (0.654 - 0.678) | 0.007 | 28% |
| Uterine artery PI centile only | 0.592 (0.581 - 0.604) | -0.001 | 25% |
| Estimated fetal weight centile only | 0.908 (0.903 - 0.914) | 0.006 | 67% |
| Demographic characteristics* and Doppler parameters** | 0.812 (0.803 - 0.821) | -0.001 | 68% |
| EFW centile and Doppler parameters** | 0.925 (0.920 - 0.931) | 0.002 | 73% |
| EFW with demographic characteristics* and Doppler parameters** | 0.945 (0.941 - 0.950) | 0.002 | 83% |
| **Random Forest Machine learning** | | | |
| Umbilical artery PI centile only | 0.841 (0.833 - 0.849) | 0.011 | 54% |
| Middle cerebral artery PI centile only | 0.770 (0.760 - 0.780) | 0.020 | 42% |
| Cerebroplacental ratio centile only | 0.771 (0.761 - 0.781) | 0.031 | 40% |
| Uterine artery PI centile only | 0.740 (0.730 - 0.750) | 0.029 | 40% |
| Estimated fetal weight centile only | 0.930 (0.925 - 0.935) | 0.020 | 78% |
| Demographic characteristics* and Doppler parameters** | 0.840 (0.832 - 0.848) | 0.002 | 71% |
| EFW centile and Doppler parameters** | 0.968 (0.966 - 0.972) | 0.009 | 93% |
| EFW with demographic characteristics* and Doppler parameters** | 0.940 (0.936 - 0.946) | 0.005 | 81% |

AUROC: Area under the receiver operator curve, CI: confidence interval, FPR: False positive rate, EFW – Estimated fetal weight, PI – Pulsatility index.
*Demographic characteristics: Nulliparity, Ethnicity, Body Mass Index, Smoking, Hypertensive disorders of pregnancy **Doppler characteristics: Umbilical artery PI centile, Middle cerebral artery PI centile, Cerebroplacental ratio centile, Uterine artery PI centile

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