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Automated Fetal Intracranial Volume Z-Scores and Multi-Vessel Doppler Velocimetry for the Assessment of Fetal Brain Growth in Severe Fetal Growth Restriction: A Retrospective Cross-Sectional Study

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Abstract

Objective. To evaluate automated three-dimensional fetal intracranial volume (ICV) measurement, alone and combined with multi-vessel Doppler indices, for assessing fetal brain growth in severe fetal growth restriction (FGR), and to quantify its repeatability.

Methods. This retrospective cross-sectional study included 111 examinations in 110 women with severe FGR and 235 controls undergoing automated ICV measurement (Smart ICV) and multi-vessel Doppler assessment. ICV, estimated fetal weight (EFW), and Doppler indices were expressed as gestational-age-adjusted Z-scores. Analyses included group comparisons, ROC analysis, bootstrap-validated logistic models, repeatability assessment, and external-reference validation.

Results. ICV Z-score was lower in severe FGR than in controls (−2.27 ± 1.55 vs −0.05 ± 1.08; $P < 0.0001$), as was EFW Z-score; the brain–body dissociation index (ICV Z minus EFW Z) was +2.06 vs −0.08 ($P < 0.0001$), consistent with adaptive head sparing. ICV Z-score discriminated severe FGR from controls with an AUC of 0.907 (95% CI 0.876–0.935; sensitivity 82.0%, specificity 85.4%). In the Doppler subset, the combined ICV + cerebroplacental ratio (CPR) model achieved an AUC of 0.923 with good calibration (optimism-corrected AUC 0.918), without significant improvement over ICV alone ($P = 0.118$). Repeatability was excellent (ICC 0.998, within-subject CV 1.98%). External-reference Z-scores correlated strongly with internal values ($r = 0.910$).

Conclusion. Automated ICV Z-scoring demonstrates high diagnostic performance for identifying reduced fetal brain growth in severe FGR and reveals head sparing; adding CPR yields a well-calibrated model without significant incremental discrimination. Automated ICV volumetry is a promising adjunct to Doppler surveillance; prospective outcome-linked validation is warranted.

Keywords: intracranial volume; fetal growth restriction; brain growth; Doppler; cerebroplacental ratio; Z-score; repeatability; automated measurement

Introduction

Fetal growth restriction (FGR) and other pregnancy complications that impair placental function are linked not only to reduced somatic growth but also to altered fetal brain growth[1]. Affected pregnancies show smaller brain volumes, disturbed cortical maturation, and adverse neurodevelopmental outcomes in childhood[2,3]. Current prenatal surveillance relies mainly on biometry, estimated fetal weight (EFW), and Doppler velocimetry of the umbilical artery (UA), middle cerebral artery (MCA), and ductus venosus (DV), as recommended by international guidelines. The cerebroplacental ratio (CPR) integrates placental resistance with the fetal cerebral vasodilatory response ("brain sparing") and has emerged as a marker of fetal adaptation to hypoxia[4,5]. However, Doppler indices reflect circulatory redistribution rather than brain growth itself. A direct, reproducible sonographic measure of fetal brain size remains lacking in routine practice.

Three-dimensional (3D) ultrasound enables volumetric assessment of the fetal intracranial cavity, but manual techniques such as VOCAL (Virtual Organ Computer-aided Analysis) are time-consuming and operator-dependent[6]. Fully automated measurement of fetal intracranial volume (ICV) from 3D neurosonography volumes has recently become commercially available (Smart ICV, Mindray)[7]. Validation studies show high agreement with manual volumetry and good reproducibility across the mid-trimester[8]. Automated ICV thus offers a practical way to bring fetal brain volumetry into the assessment of severe-FGR pregnancies[9]. MRI studies have demonstrated reduced total brain volume in growth-restricted fetuses, and ultrasound studies of midline structures suggest regionally selective vulnerability[10]. Whether automated ICV—a global but rapidly obtained measure—captures clinically meaningful signal in severe fetal growth restriction is unknown.

We hypothesized that fetuses of severe-FGR pregnancies have lower ICV than gestational-age-matched controls, and that ICV Z-scores provide diagnostic information complementary to multi-vessel Doppler indices. In a retrospective series of 346 fetal examinations (345 women) who underwent automated ICV measurement and comprehensive Doppler assessment, we (i) derived gestational-age-adjusted Z-scores for ICV, EFW, and Doppler indices; (ii) compared these Z-scores between severe-FGR and control pregnancies; (iii) examined correlations between volumetric and vascular indices; (iv) built and internally validated a combined prediction model, including calibration, decision-curve, and sensitivity analyses; and (v) quantified the repeatability of the automated ICV measurement.

Methods

Study design and population

This retrospective cross-sectional diagnostic accuracy study included consecutive pregnant women who underwent 3D neurosonography with automated ICV measurement and multi-vessel Doppler assessment at our center between February 2023 and September 2026. The severe-FGR group comprised

fetuses with severe fetal growth restriction, defined as an estimated fetal weight (EFW) or abdominal circumference below the 3rd percentile for gestational age; fetuses with EFW between the 3rd and 10th percentiles were not included. Coexisting conditions — hypertensive disorders of pregnancy, abnormal fetal Doppler findings at referral, fetal structural anomalies, gestational diabetes mellitus, and other maternal high-risk conditions (e.g., thyroid disease, thrombophilia, autoimmune disease, anaemia) — were documented as coexisting features of this severe-FGR group rather than as separate parallel diagnostic categories. Coexisting conditions were documented non-exclusively, so a single fetus could contribute to more than one category. For the subgroup display in Figure 5D, each fetus was assigned to a single category according to a pre-specified priority order: referral primarily for abnormal fetal Doppler findings first, followed by hypertensive disorders of pregnancy, major fetal structural anomalies, gestational diabetes mellitus, and other maternal high-risk conditions; fetuses with no documented coexisting condition constituted the isolated severe-FGR subgroup. The control group comprised women with uncomplicated singleton pregnancies and normal ultrasound findings; when a control woman had been scanned more than once, only one record was retained. To strengthen between-group Doppler comparisons, comprehensive control-group Doppler assessment (UA, MCA, DV, and UtA) was expanded during 2026. Exclusion criteria were multiple pregnancy, aneuploidy, major cerebral structural malformation precluding automated volumetry, and poor 3D volume quality. The study was conducted in accordance with the Declaration of Helsinki. The protocol was approved by the Medical Ethics Committee of Henan Provincial People's Hospital (approval No. (2023) Ethics Review No. 15), and the requirement for individual informed consent was waived for this retrospective analysis of anonymized data.

Ultrasound examination and automated ICV measurement

All examinations were performed on one of two Mindray ultrasound systems (Resona R or Nuewa R9; Mindray Medical International, Shenzhen, China) equipped with volumetric transabdominal convex probes (SD8-1U, 1–8 MHz, or SDM9-2U, 2–9 MHz); both systems incorporate the fully automated Smart ICV measurement software. A 3D volume of the fetal head was acquired from an axial transthalamic plane using Smart Planes CNS, and ICV was obtained automatically by the Smart ICV software, which segments the intracranial cavity and computes its volume without manual contouring (Figure 1). Each automated segmentation was visually inspected, and the acquisition was repeated if the calvarial contour was incomplete. To assess the repeatability of the automated measurement, the Smart ICV measurement was repeated three times at the same examination in a subset of 93 control examinations. EFW was calculated from standard biometry (biparietal diameter, head circumference, abdominal circumference, femur length) using the Hadlock formula7,11.

Doppler assessment

Pulsed-wave Doppler indices were measured according to ISUOG guidelines: UA pulsatility index (PI) from a free cord loop; MCA-PI from the proximal MCA in an axial plane with an insonation angle close to 0°; DV-PI with the sample volume at the inlet of the ductus venosus; and left and right UtA-PI

at the apparent crossover with the external iliac artery, averaged to mean UtA-PI. CPR was calculated as MCA-PI divided by UA-PI[11,12].

Z-score transformation

Because absolute ICV and EFW increase steeply and non-linearly with gestational age (GA), raw values were converted to Z-scores. Reference equations were derived internally from the 235 controls: $\log_{10}$-transformed values were regressed on GA with a quadratic polynomial, and Z-scores computed as ($\log_{10}$(observed) − predicted mean) / residual standard deviation (SD), following the practical approach of DeVore. Records with $|Z| > 3$ were excluded and the equations refitted. The final equations were: $\log_{10}(\text{ICV, cm}^3) = -0.8689 + 0.17327 \times \text{GA} - 0.002182 \times \text{GA}^2$ (residual SD 0.0391; n = 230); $\log_{10}(\text{EFW, g}) = 0.3858 + 0.13466 \times \text{GA} - 0.001393 \times \text{GA}^2$ (residual SD 0.0312; n = 228). Doppler indices (UA-PI, MCA-PI, and the cerebroplacental ratio [CPR] = MCA-PI/UA-PI) were converted to GA-adjusted Z-scores with the same internal-reference approach (quadratic regression of log-transformed values on GA; residual SDs 0.0703, 0.0832, and 0.0905, respectively), keeping all Z-scores on a common internally consistent scale and avoiding population- or equipment-related shifts associated with external Doppler references. A brain–body dissociation index was defined as ICV Z-score minus EFW Z-score. As a robustness check, ICV Z-scores were additionally computed against the externally published Smart ICV reference of Zhou et al.: the tabulated 5th, 50th, and 95th centiles at 16–34 weeks were interpolated linearly, the SD was derived as (95th − 5th centile) / (2 × 1.645), and Z-scores were computed on the raw scale; this analysis was restricted to examinations within the validated 16–34-week range. Finally, because the Hadlock EFW formula incorporates head biometry (biparietal diameter and head circumference), ICV and EFW share head-growth information, and their correlation and dissociation may partly reflect this common component; abdominal circumference, which contains no head biometry, was therefore additionally expressed as a GA-adjusted Z-score with the same internal-reference approach, and a head-independent dissociation index was defined as ICV Z-score minus AC Z-score.

Statistical analysis

Continuous variables are presented as mean ± SD and were compared between groups using Welch's t-test when both groups passed the Shapiro–Wilk normality test ($P > 0.01$) and the Mann–Whitney U test otherwise; effect sizes are reported as Cohen's d. GA-adjusted group differences in DV-PI and mean UtA-PI were estimated by analysis of covariance. Associations between ICV Z-score and Doppler or EFW Z-scores were examined with Pearson and Spearman correlation. Discrimination for severe FGR versus control pregnancy was quantified by the area under the receiver-operating-characteristic curve (AUC) with 95% confidence intervals (CI) obtained by the fast DeLong algorithm; optimal cut-offs were selected by the Youden index. Logistic regression models combining ICV Z-score with CPR Z-score (and, alternatively, MCA-PI and UA-PI Z-scores) were fitted in the subset with complete Doppler data; pairwise AUC comparisons used the DeLong test. Internal validation of the combined model used 1,000 bootstrap resamples to estimate optimism and the optimism-corrected AUC. Calibration was

assessed with the Hosmer–Lemeshow test and the calibration intercept and slope, and clinical utility with decision-curve analysis across threshold probabilities of 0.1–0.9. Repeatability of the automated ICV measurement was assessed in the 93 examinations with three consecutive automated measurements using the intraclass correlation coefficient (two-way random-effects, absolute agreement, single measurement; ICC(2,1)), the within-subject standard deviation (Sw), the within-subject coefficient of variation (CV), and the repeatability coefficient ($1.96 \times \sqrt{2} \times Sw$); 95% CIs for the ICC were obtained by bootstrap (2,000 resamples). Two pre-specified sensitivity analyses were performed: exclusion of cases referred primarily for abnormal Doppler findings (to address incorporation bias), and restriction of the case group to isolated severe FGR without any documented coexisting condition. Two-sided $P < 0.05$ was considered statistically significant.

Analyses were further stratified by gestational age at examination (<32 versus ≥32 weeks), corresponding to the conventional early- and late-onset definitions. The incremental value of the combined model over ICV Z-score alone was quantified by the integrated discrimination improvement (IDI) and the category-free net reclassification improvement (NRI), with 1,000-bootstrap 95% confidence intervals. As an exploratory analysis of adjusted associations, abnormal Doppler status (UA-PI Z-score > 1.645, i.e., above the 95th centile; or CPR Z-score < −1.645, below the 5th centile) was treated as the exposure and ICV Z-score as the outcome: average treatment effects (ATE) were estimated with double/debiased machine learning (cross-fitted residualisation) and cross-checked by augmented inverse-probability weighting (AIPW), in the whole Doppler subset and within severe-FGR pregnancies only, adjusting for maternal age, pre-pregnancy body mass index, height, and gestational age at examination; given the cross-sectional design, these estimates are reported as adjusted associations only. Reporting of the prediction-model components follows the TRIPOD+AI statement. Analyses were performed in Python 3.12 (pandas, numpy, scipy, statsmodels, scikit-learn); the complete analysis code accompanies this article.

Results

Study population

The analysis set comprised 346 fetal examinations (345 women): 111 examinations in 110 women with severe-FGR pregnancies and 235 controls (Figure 2). All severe-FGR pregnancies met the entry criteria (EFW or AC below the 3rd centile). Coexisting conditions were documented in most fetuses: hypertensive disorders of pregnancy (n = 28), gestational diabetes mellitus (n = 14), major fetal structural anomalies (n = 12), and other maternal high-risk conditions (n = 43, including thyroid disease, thrombophilia, autoimmune disease, and anaemia); 31 referrals were primarily prompted by abnormal fetal Doppler findings (Figure 5D). Categories were non-exclusive — a fetus could contribute to more than one — and 25 fetuses had isolated severe FGR without any documented coexisting condition. Comprehensive control-group Doppler data (MCA-PI and UA-PI) were available in 113–114 controls. Maternal age and GA at examination did not differ significantly between groups (Table 1); maternal

height was slightly lower and pre-pregnancy body mass index (BMI) modestly higher in the severe-FGR group (160.5 ± 4.5 vs 161.6 ± 5.5 cm, P = 0.024; 23.8 ± 4.4 vs 22.7 ± 3.6 kg/m², P = 0.023).

Intracranial volume and Z-scores

Absolute ICV was lower in severe-FGR pregnancies than in controls (162.7 ± 78.7 vs 187.2 ± 88.3 cm³, P = 0.015; d = −0.29), as was EFW (953.5 ± 512.1 vs 1240.5 ± 676.6 g, P < 0.001; d = −0.46). After Z-score transformation, the contrast was markedly amplified: ICV Z-score was −2.27 ± 1.55 in the severe-FGR group versus −0.05 ± 1.08 in controls (P < 0.0001; d = −1.77), and EFW Z-score was −4.33 ± 1.85 versus 0.04 ± 1.18 (P < 0.0001; d = −3.05) (Table 2, Figures 3 and 4). The brain–body dissociation index was positive in severe-FGR pregnancies and near zero in controls (2.06 ± 1.70 vs −0.08 ± 1.21, P < 0.0001; d = 1.54), indicating that head growth was relatively preserved compared with somatic growth. ICV Z-score was reduced in every coexisting-condition subgroup (means −1.83 to −2.65), with the lowest values in FGR with abnormal Doppler referrals (-2.65 ± 0.60) and FGR with other maternal high-risk conditions (-2.55) (Figure 5D). In the head-independent comparison, the AC Z-score was −4.61 ± 1.92 versus −0.07 ± 1.06 (P < 0.0001), and the head-independent dissociation index (ICV Z-score minus AC Z-score) was 2.34 ± 1.60 versus 0.02 ± 0.97 (P < 0.0001; d = 1.92) (Table 2).

Doppler indices

Multi-vessel Doppler indices were available in 95–114 controls and 95–99 severe-FGR fetuses (complete MCA-PI and UA-PI in 95 severe-FGR fetuses and 113 controls). UA-PI Z-score (+1.06 ± 1.72 vs 0.02 ± 1.21; P < 0.0001; d = 0.71) and CPR Z-score (−1.31 ± 1.84 vs −0.03 ± 1.25; P < 0.0001; d = −0.83) differed markedly between groups, and MCA-PI Z-score was modestly lower in severe-FGR pregnancies (−0.49 ± 1.14 vs −0.00 ± 0.99; P = 0.012) (Table 2). In raw units, UA-PI was higher (1.13 ± 0.37 vs 0.95 ± 0.24, P < 0.0001), CPR lower (1.53 ± 0.58 vs 1.90 ± 0.50, P < 0.0001), and mean UtA-PI higher (1.06 ± 0.46 vs 0.68 ± 0.22, P < 0.0001) in severe-FGR pregnancies. GA-adjusted mean UtA-PI remained substantially higher in the severe-FGR group (d = +0.40, P < 0.0001); the GA-adjusted difference in DV-PI was small (d = +0.08, P = 0.006).

Correlations

Across the full sample with Doppler data, ICV Z-score correlated inversely with UA-PI Z-score (r = −0.289, P < 0.0001, n = 213) and positively with CPR Z-score (r = 0.320, P < 0.0001, n = 208), with a weaker direct association with MCA-PI Z-score (r = 0.178, P = 0.010) (Figure 5). ICV Z-score correlated strongly with EFW Z-score (r = 0.733, P < 0.0001, n = 342). Within the severe-FGR group alone, correlations between ICV Z-score and Doppler Z-scores were attenuated and non-significant (MCA-PI Z r = 0.084; UA-PI Z r = −0.153; CPR Z r = 0.154; all P ≥ 0.13), whereas the ICV–EFW correlation persisted (r = 0.510, P < 0.0001); ICV Z-score was inversely correlated with DV-PI (r = −0.335, P < 0.001) and mean UtA-PI (r = −0.216, P = 0.033) (Table 3). ICV Z-score was also correlated with AC Z-score (r = 0.59, P < 0.0001, n = 342).

Repeatability of the automated ICV measurement

In the 93 control examinations with three consecutive automated ICV measurements (gestational age 20.3–34.0 weeks), repeatability of the automated measurement was excellent: the intraclass correlation coefficient was 0.998 (ICC(2,1); 95% CI 0.997–0.998), the within-subject standard deviation was 3.61 cm^3 (within-subject coefficient of variation 1.98%), and the repeatability coefficient was 10.0 cm^3 (Table 8, Figure S3).

Diagnostic accuracy and combined model

In the full sample, ICV Z-score discriminated severe-FGR from control pregnancies with an AUC of 0.907 (95% CI, 0.876–0.935); at the optimal cut-off (Z = -1.04), sensitivity was 82.0% and specificity 85.4% (Table 4, Figure 6A). The brain–body dissociation index yielded an AUC of 0.876 (95% CI, 0.829–0.919), lower than ICV Z-score alone (Figure 6A).

In the Doppler subset (95 severe-FGR, 113 controls), ICV Z-score achieved an AUC of 0.907 (95% CI, 0.867–0.942), compared with 0.601 (0.525–0.677) for MCA-PI Z-score, 0.724 (0.647–0.791) for UA-PI Z-score, and 0.733 (0.658–0.802) for CPR Z-score (ICV vs UA-PI, $P < 0.0001$; ICV vs CPR, $P < 0.0001$). The logistic model combining ICV and CPR Z-scores achieved an AUC of 0.923 (95% CI, 0.885–0.955), significantly higher than CPR Z-score alone (DeLong $P < 0.0001$) but not significantly different from ICV Z-score alone ($P = 0.118$); in this model the ICV term dominated ($\beta = -1.79$) over the CPR term ($\beta = -0.45$). The alternative combination of ICV, MCA-PI, and UA-PI Z-scores yielded an AUC of 0.924 (0.883–0.956).

Bootstrap internal validation of the combined ICV + CPR model gave an apparent AUC of 0.923, optimism of 0.004, and an optimism-corrected AUC of 0.918. Calibration was excellent (Hosmer–Lemeshow $\chi^2 = 5.77$, df = 8, $P = 0.673$; calibration intercept −0.00, slope 1.00; Figure 6C). Decision-curve analysis showed that both the ICV-only and combined models provided greater net benefit than treat-all or treat-none strategies across threshold probabilities from approximately 0.1 to 0.9, with the combined model marginally superior over most of the range (Figure 6D). A nomogram for the combined model is provided in Figure S1.

Sensitivity analyses

After exclusion of the 31 cases referred primarily for abnormal Doppler findings, discrimination was essentially unchanged: ICV Z-score AUC 0.900 (95% CI, 0.867–0.931) and combined model AUC 0.909 (0.863–0.948) (Table 7). When the analysis was restricted to isolated severe FGR without any documented coexisting condition (n = 25), ICV Z-score retained an AUC of 0.893. Removing the single repeat examination (one woman scanned twice) also did not materially change discrimination (AUC 0.906; 95% CI, 0.875–0.934).

Onset-stratified, external-reference, and reclassification analyses

Discrimination was consistent across gestational-age strata (Figure 7, Table 5): the ICV Z-score AUC was 0.911 (95% CI, 0.877–0.943) among fetuses examined before 32 weeks (89 severe-FGR, 194 controls) and 0.893 (0.797–0.959) among those examined at or after 32 weeks (22 severe-FGR, 39

controls). ICV Z-scores were comparably reduced in severe-FGR pregnancies examined early and late (−2.37 ± 1.66 [n = 89] and −1.85 ± 0.92 [n = 22]; both P < 0.0001 versus controls), and in isolated severe FGR (−2.18 ± 1.47 [n = 25]; P < 0.0001 versus controls).

External-reference validation was performed in the 315 fetuses (100 severe-FGR, 215 controls) examined within the validated 16–34-week range. Z-scores computed from the internal equations and from the published Smart ICV reference of Zhou et al. correlated strongly (r = 0.910, P < 0.0001; Bland–Altman bias +0.37 SD, limits of agreement -0.93 to 1.66), and discrimination was preserved when the external reference was used (AUC 0.888 [95% CI, 0.851–0.922] versus 0.915 [0.882–0.944] with the internal reference; DeLong P = 0.922) (Figure 8A, B; Table 6).

Adding the CPR Z-score to the ICV Z-score produced a small but statistically significant improvement in integrated discrimination (IDI 0.048, 95% CI 0.021 to 0.073; bootstrap P = 0.0003) without significant category-free reclassification (NRI -0.082, -0.344 to 0.179; P = 0.537), indicating that the incremental value of CPR over ICV Z-scoring alone is limited (Figure 8C, Table 6).

Exploratory causal machine-learning analysis

In exploratory adjusted-association analyses, abnormal CPR (Z < −1.645; 45 exposed of 202 fetuses with complete data) was strongly associated with lower ICV Z-score at whole-sample level (DML ATE -1.216, 95% CI -1.294 to -1.138; AIPW ATE -2.953, 95% CI -3.716 to -2.191), an association largely reflecting the study design, because abnormal CPR is itself a feature of severe FGR. Within severe-FGR pregnancies only, the adjusted association was small and not robust across estimators — DML ATE -0.158 (95% CI -0.280 to -0.035), AIPW -0.430 (95% CI -1.524 to 0.664) — and abnormal UA-PI (Z > 1.645, 29 exposed) showed similarly small within-group associations (DML -0.148, 95% CI -0.267 to -0.029; AIPW -0.616, 95% CI -2.598 to 1.365) (Figure S2, Table S1). These same-day cross-sectional estimates should not be interpreted causally; they indicate that within affected pregnancies, Doppler status adds limited independent information about brain size beyond case status itself.

Discussion

Principal findings

In this retrospective series of 346 fetal examinations performed with automated 3D neurosonography, fetuses with severe FGR showed substantially reduced ICV once gestational age was accounted for, with a large standardized effect (d = −1.77) and an AUC of 0.907 for discriminating severe-FGR from control pregnancies. ICV was less severely reduced than EFW, yielding a positive brain–body dissociation index consistent with preferential preservation of head growth. Among Doppler indices, UA-PI and CPR Z-scores — reflecting placental resistance and its cerebral compensation — were associated with case status and with ICV Z-score, whereas MCA-PI Z-score showed only a modest difference[13,14]. The automated measurement itself proved highly repeatable (ICC 0.998), and the volumetric findings were robust to the choice of reference equation. A model combining ICV and CPR

Z-scores achieved excellent, well-calibrated discrimination (optimism-corrected AUC 0.918), although it did not significantly outperform ICV Z-score alone by the DeLong test.

Comparison with previous studies

Our volumetric findings align with MRI studies reporting reduced total brain volume in growth-restricted fetuses and with ultrasound work demonstrating altered midline and cortical development in late-onset FGR[10,15]. They extend these observations in two ways. First, we used a fully automated, commercially available ICV tool whose agreement with manual volumetry has been validated, making the measurement feasible in a routine workflow rather than a research MRI setting. Second, we expressed ICV as a Z-score against internally derived, gestational-age-specific reference equations, which removes the strong GA dependence of absolute volumes (14.7–38.3 weeks in this sample) and is, we believe, essential for clinical interpretation; reference-equation methodology for fetal ICV has recently been described in Chinese populations using VOCAL, and our internal equations serve the same purpose for the automated tool.

The Doppler findings deserve comment. UA-PI and CPR Z-scores discriminated groups and correlated with ICV Z-score, coherent with the pathophysiological model in which placental insufficiency drives both cerebral redistribution and impaired brain growth[16-18]. MCA-PI Z-score showed only a modest between-group difference — plausibly because brain-sparing vasodilatation, being an adaptive response that preserves cerebral perfusion, is variably expressed across severe-FGR pregnancies, and because our sample spans a wide gestational-age range. Importantly, the volumetric signal was preserved at later gestational ages: discrimination remained high at ≥32 weeks (AUC 0.893), and severe-FGR pregnancies examined at or after 32 weeks showed ICV Z-score reductions comparable to those examined earlier, supporting automated ICV as a complement to Doppler specifically where the Doppler signal is weakest. The attenuation of ICV–Doppler correlations within the severe-FGR group alone suggests that, once a complication is established, volumetric and vascular indices capture partially distinct information rather than lying on a single severity axis.

Clinical implications

Automated ICV Z-scoring may complement the current Doppler-centered surveillance paradigm by adding a direct, highly repeatable measure of fetal brain growth. Its standalone diagnostic performance was high, including in isolated severe FGR (AUC 0.893) and after exclusion of cases whose referral indication incorporated Doppler information (AUC 0.900), arguing against substantial incorporation bias[19]. The combined ICV + CPR model, presented as a nomogram, showed modest incremental value over ICV alone — statistically significant only against CPR alone and in integrated discrimination — so its main role may be in borderline cases or where volumetry is technically limited. Decision-curve analysis indicated potential net benefit across a wide range of threshold probabilities[20]. Prospective studies linking ICV Z-scores to perinatal and neurodevelopmental outcomes are required before these findings can inform risk assessment or management decisions.

Strengths and limitations

Strengths include the use of a validated automated volumetric tool with formally quantified repeatability; a comprehensive multi-vessel Doppler protocol now assessed in 113–114 controls; Z-score transformation using internally derived reference equations for both volumetric and Doppler indices, cross-checked against an external Smart ICV reference; and a rigorous statistical framework including DeLong comparisons, bootstrap internal validation, calibration assessment, decision-curve analysis, and pre-specified sensitivity analyses, with fully reproducible code. Two further features strengthen the credibility of the volumetric findings: discrimination was robust to the choice of reference equation — replacing our internal equations with the externally published Smart ICV reference changed the AUC only from 0.915 to 0.888 — and performance was stable across gestational-age strata, including the clinically difficult late-onset presentations. We report transparently that the combined model's incremental value over ICV alone was statistically confirmed for integrated discrimination (IDI) but not for category-free reclassification (NRI) or the DeLong AUC comparison, which argues for ICV Z-score as the primary marker. Exploratory adjusted-association analyses pointed in the biologically expected direction within severe-FGR pregnancies but were not robust across estimators; we present them as hypothesis-generating rather than causal evidence. Furthermore, because EFW is computed from biometry that includes head measurements, we additionally related ICV to AC, a somatic measure free of head biometry; the brain–body dissociation persisted when AC replaced EFW as the somatic comparator.

Several limitations must be acknowledged. First, the retrospective single-center design is subject to selection bias; although all study fetuses met severe-FGR criteria, the sample remains clinically heterogeneous, and some coexisting-condition subgroups were small (e.g., gestational diabetes, n = 14). Second, one severe-FGR record showed internally inconsistent biometry (measured EFW and AC discordant with the recorded referral diagnosis) and was retained in the analysis; a sensitivity analysis removing the single repeat examination gave virtually identical results. Third, ICV is a global measure that cannot resolve regional or microstructural brain abnormalities, and automated ICV has been formally validated mainly between 16 and 34 weeks, whereas our sample spanned 14.7–38.3 weeks; Z-scores at the extremes of this range rely on extrapolation of the quadratic reference equations. Fourth, the external Smart ICV reference covers only 16–34 weeks, so the external-validation analysis was necessarily restricted to this window. Fifth, we lacked neurodevelopmental follow-up, so the clinical significance of the observed volumetric reductions remains inferential and our findings establish diagnostic performance rather than outcome-based diagnostic performance; relatedly, the exploratory adjusted-association analyses derive from same-day exposure and outcome measurements and were underpowered for the rarer exposure (29 fetuses with abnormal UA-PI), so no causal interpretation should be drawn. Finally, our internal reference equations, derived from 235 controls at a single center, require external validation before general use, although the robustness check against an external Smart ICV reference mitigates this concern.

Conclusions

Automated measurement of fetal intracranial volume, expressed as a gestational-age-adjusted Z-score, identifies reduced fetal brain growth in severe fetal growth restriction with high diagnostic performance and reveals brain–body dissociation consistent with adaptive head sparing; the automated measurement is highly repeatable (ICC 0.998). Adding the cerebroplacental ratio yields a well-calibrated model with excellent discrimination that withstands bootstrap and sensitivity analyses, although it does not significantly outperform ICV Z-scoring alone. Automated ICV volumetry is a promising, workflow-compatible adjunct to Doppler surveillance of the compromised fetus; prospective outcome-linked validation is warranted.

Statements

Ethics approval

The study protocol was approved by the Medical Ethics Committee of Henan Provincial People's Hospital (approval No. (2023) Ethics Review No. 15). The study was conducted in accordance with the Declaration of Helsinki and relevant Chinese regulations and guidelines. Individual informed consent was waived by the Ethics Committee for this retrospective analysis of de-identified data.

Data availability.

The de-identified analysis dataset and the complete analysis code are available from the corresponding author on reasonable request.

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Author contributions：

Zhaoling Zhu: Conceptualization, Methodology, Formal analysis, Data curation, Investigation, Visualization, Writing – original draft. Xiaolin Zhang: Investigation, Data curation. Yuan Gao: Investigation, Data curation. Ziyi Wang: Investigation, Data curation. Ruili Wang: Conceptualization, Methodology, Supervision, Project administration, Funding acquisition, Writing – review & editing. All authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

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Tables

Table 1. Baseline characteristics of the study population.

Characteristic	Severe FGR (n = 111)	Control (n = 235)	P value
Maternal age (years)	31.21 ± 4.47 (n = 111)	31.49 ± 4.09 (n = 234)	.978
Maternal height (cm)	160.45 ± 4.51 (n = 110)	161.55 ± 5.54 (n = 231)	.024
Pre-pregnancy weight (kg)	61.24 ± 11.44 (n = 107)	59.42 ± 10.10 (n = 223)	.115
Pre-pregnancy BMI (kg/m²)	23.81 ± 4.41 (n = 107)	22.73 ± 3.57 (n = 223)	.023
Gestational age at scan (weeks)	27.92 ± 4.79 (n = 111)	27.68 ± 4.55 (n = 235)	.481

Data are mean ± SD. BMI, body mass index.

Table 2. Ultrasound indices and Z-scores in severe-FGR versus control pregnancies.

Variable	Severe FGR	Control	P value	Cohen's d
EFW (g)	953.55 ± 512.12 (n = 111)	1240.54 ± 676.61 (n = 231)	< 0.001	-0.46
ICV (cm³)	162.71 ± 78.67 (n = 111)	187.15 ± 88.27 (n = 233)	.015	-0.29
ICV Z-score	-2.27 ± 1.55 (n = 111)	-0.05 ± 1.08 (n = 233)	< 0.0001	-1.77
EFW Z-score	-4.33 ± 1.85 (n = 111)	0.04 ± 1.18 (n = 231)	< 0.0001	-3.05
Brain–body dissociation index	2.06 ± 1.70 (n = 111)	-0.08 ± 1.21 (n = 231)	< 0.0001	+1.54
MCA-PI	1.58 ± 0.35 (n = 96)	1.74 ± 0.34 (n = 113)	.005	-0.44
UA-PI	1.13 ± 0.37 (n = 99)	0.95 ± 0.24 (n = 114)	< 0.0001	+0.57
CPR	1.53 ± 0.58 (n = 95)	1.90 ± 0.50 (n = 113)	< 0.0001	-0.68
DV-PI	0.56 ± 0.27 (n = 96)	0.49 ± 0.17 (n = 113)	.289	+0.29
Mean UtA-PI	1.06 ± 0.46 (n = 98)	0.68 ± 0.22 (n = 114)	< 0.0001	+1.07
MCA-PI Z-score	-0.49 ± 1.14 (n = 96)	-0.00 ± 0.99 (n = 113)	.012	-0.46
UA-PI Z-score	1.06 ± 1.72 (n = 99)	0.02 ± 1.21 (n = 114)	< 0.0001	+0.71
CPR Z-score	-1.31 ± 1.84 (n = 95)	-0.03 ± 1.25 (n = 113)	< 0.0001	-0.83

Data are mean ± SD. Doppler Z-scores computed against internally derived reference equations derived from the 235 controls; GA-adjusted differences in DV-PI and mean UtA-PI (analysis of covariance) are reported in the text. ICV, intracranial volume; EFW, estimated fetal weight; MCA, middle cerebral artery; UA, umbilical artery; CPR, cerebroplacental ratio; DV, ductus venosus; UtA, uterine artery; PI, pulsatility index.

Table 3. Correlations between ICV Z-score and vascular/somatic Z-scores.

Subset	Pair	n	Pearson r	P value
Full sample	ICV Z vs MCA-PI Z	209	.178	.010
Full sample	ICV Z vs UA-PI Z	213	−.289	< 0.0001
Full sample	ICV Z vs CPR Z	208	.320	< 0.0001
Full sample	ICV Z vs EFW Z	342	.733	< 0.0001
Severe FGR only	ICV Z vs MCA-PI Z	96	.084	.414
Severe FGR only	ICV Z vs UA-PI Z	99	−.153	.130
Severe FGR only	ICV Z vs CPR Z	95	.154	.135
Severe FGR only	ICV Z vs EFW Z	111	.510	< 0.0001
Severe FGR only	ICV Z vs DV-PI	96	−.335	< 0.001
Severe FGR only	ICV Z vs UtA-PI (mean)	98	−.216	.033

ICV, intracranial volume; MCA, middle cerebral artery; UA, umbilical artery; CPR, cerebroplacental ratio; EFW, estimated fetal weight.

Table 4. Diagnostic accuracy of ICV and Doppler Z-scores for severe FGR.

Marker	n (cases/controls)	AUC (95% CI)	Cut-off (Z)	Sensitivity (%)	Specificity (%)
ICV Z-score (full sample)	111/233	0.907 (0.876–0.935)	-1.04	82.0	85.4

Brain–body dissociation index (full sample)	111/231	0.876 (0.829–0.919)	1.10	77.5	86.6
ICV Z-score (Doppler subset)	95/113	0.907 (0.867–0.942)	-0.81	90.5	77.0
MCA-PI Z-score	95/113	0.601 (0.525–0.677)	-0.85	36.8	85.0
UA-PI Z-score	95/113	0.724 (0.647–0.791)	0.90	57.9	85.0
CPR Z-score	95/113	0.733 (0.658–0.802)	-0.75	64.2	79.6
Combined ICV + CPR Z	95/113	0.923 (0.885–0.955)	—	89.5	85.0
Combined ICV + MCA + UA Z	95/113	0.924 (0.883–0.956)	—	91.6	84.1

AUC, area under the receiver-operating-characteristic curve; CI, confidence interval. Combined-model performance given at the Youden-optimal predicted-probability threshold. DeLong comparisons: combined vs ICV alone, P = 0.118; combined vs CPR alone, P < 0.0001; ICV vs UA-PI, P < 0.0001; ICV vs CPR, P < 0.0001.

Table 5. Onset-stratified analysis (cut-off 32 weeks of gestation).

Stratum	n (cases/controls)	ICV Z, severe FGR	ICV Z, control	P value	AUC (95% CI)	Sens./Spec. (%)
Early (< 32 wk)	89/194	-2.37 ± 1.66	-0.03 ± 1.11	< 0.0001	0.911 (0.877–0.943)	88.8/80.9
Late (≥ 32 wk)	22/39	-1.85 ± 0.92	-0.17 ± 0.96	< 0.0001	0.893 (0.797–0.959)	86.4/84.6
Isolated severe FGR (no coexisting condition)	25/235	-2.18 ± 1.47	-0.05 ± 1.08	< 0.0001	—	—

ICV, intracranial volume; FGR, fetal growth restriction; AUC, area under the receiver-operating-characteristic curve; CI, confidence interval; Sens., sensitivity; Spec., specificity.

Table 6. External-reference validation and reclassification metrics.

Analysis	Estimate	95% CI	P value
AUC, internal reference (n = 315, 16–34 weeks)	0.915	0.882–0.944	—
AUC, external reference (Zhou 2024, 16–34 weeks)	0.888	0.851–0.922	0.922 (DeLong vs internal)
Internal vs external Z-score correlation	r = 0.910	—	< 0.0001
Bland–Altman bias (internal − external)	+0.37 SD	LoA −0.93 to 1.66	—
IDI (combined vs ICV alone)	0.048	0.021 to 0.073	0.0003 (bootstrap)

Category-free NRI (combined vs ICV alone)	-0.082	-0.344 to 0.179	.537 (bootstrap)

LoA, limits of agreement; IDI, integrated discrimination improvement; NRI, net reclassification improvement; CI, confidence interval.

Table 7. Sensitivity analyses: diagnostic accuracy after exclusion of referrals primarily for abnormal Doppler findings, restriction to isolated severe FGR, and removal of the repeat examination.

Analysis	n (cases/controls)	AUC (95% CI)	Sensitivity (%)	Specificity (%)
ICV Z-score, excluding referrals primarily for abnormal Doppler findings	80/233	0.900 (0.867–0.931)	—	—
Combined ICV + CPR, excluding referrals primarily for abnormal Doppler findings	66/113	0.909 (0.863–0.948)	—	—
Isolated severe FGR only (no coexisting condition)	25/235	0.893	—	—
ICV Z-score, one examination per woman (removing repeat scan)	110/233	0.906 (0.875–0.934)	—	—

AUC, area under the receiver-operating-characteristic curve; CI, confidence interval; FGR, fetal growth restriction.

Table 8. Repeatability of the automated ICV measurement (three consecutive automated measurements per examination in 93 control examinations).

Characteristic	Value
Examinations assessed (n)	93 (GA 20.3–34.0 weeks)
ICC(2,1) (95% CI)	0.998 (0.997–0.998)
Within-subject SD (Sw)	3.61 cm^3
Within-subject CV	1.98%
Repeatability coefficient ($1.96 \times \sqrt{2} \times Sw$)	10.0 cm^3

ICC, intraclass correlation coefficient (two-way random-effects, absolute agreement, single measurement); CI, confidence interval; GA, gestational age; Sw, within-subject standard deviation; CV, coefficient of variation.

Supplementary Table S1. Exploratory adjusted-association (causal machine-learning) estimates of abnormal Doppler status on ICV Z-score.

Exposure	Estimator	ATE (95% CI)	P value

Abnormal CPR — whole Doppler subset (n = 202; 45 exposed)	Double/debiased ML	-1.216 (-1.294 to -1.138)	< 0.0001
Abnormal CPR — whole Doppler subset (n = 202; 45 exposed)	AIPW	-2.953 (-3.716 to -2.191)	< 0.0001
Abnormal UA-PI — whole Doppler subset (n = 202; 29 exposed)	Double/debiased ML	-0.844 (-0.921 to -0.768)	< 0.0001
Abnormal UA-PI — whole Doppler subset (n = 202; 29 exposed)	AIPW	-2.085 (-3.518 to -0.651)	.004
Abnormal CPR — severe-FGR pregnancies only (n = 92; 39 exposed)	Double/debiased ML	-0.158 (-0.280 to -0.035)	.012
Abnormal CPR — severe-FGR pregnancies only (n = 92; 39 exposed)	AIPW	-0.430 (-1.524 to 0.664)	.441
Abnormal UA-PI — severe-FGR pregnancies only (n = 92; 25 exposed)	Double/debiased ML	-0.148 (-0.267 to -0.029)	.015
Abnormal UA-PI — severe-FGR pregnancies only (n = 92; 25 exposed)	AIPW	-0.616 (-2.598 to 1.365)	.542

ATE, average treatment effect; CI, confidence interval; CPR, cerebroplacental ratio; UA, umbilical artery; AIPW, augmented inverse-probability weighting; DML, double/debiased machine learning. All estimates are adjusted for maternal age, pre-pregnancy body mass index, height, and gestational age at examination, and are interpreted as adjusted associations only; whole-sample-level estimates largely reflect the study design, because abnormal Doppler status is itself a feature of severe FGR.

Figure legends

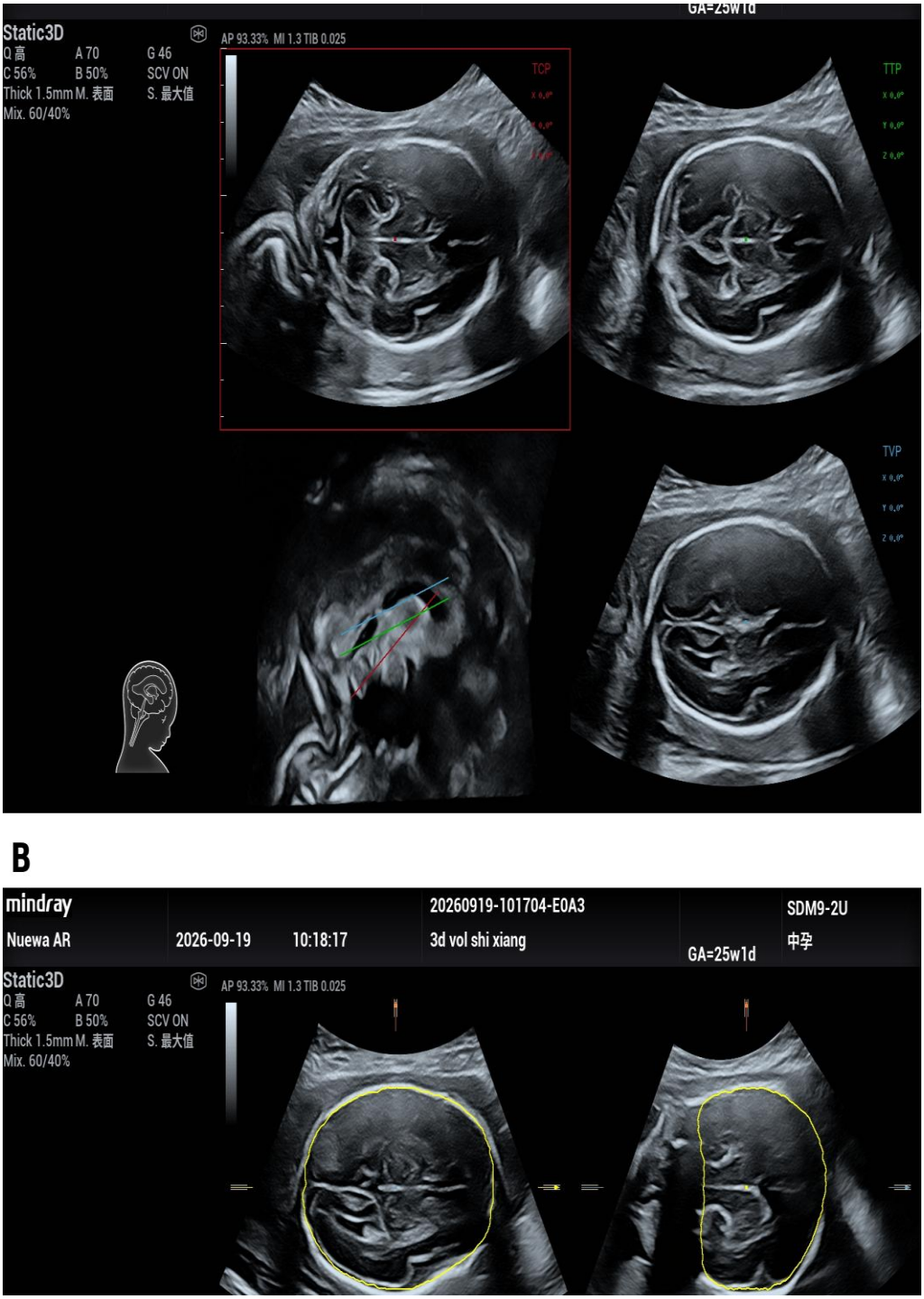


Figure 1. Automated measurement of fetal intracranial volume with the Smart ICV software in an enrolled fetus at 25 weeks 1 day of gestation. (A) After acquisition of a 3D volume from the axial transthalamic plane, the software automatically generates and displays the three axial cranial planes (transventricular, transthalamic, and transcerebellar) and the reconstructed mid-sagittal plane. (B) The software segments the intracranial cavity automatically (yellow contours), computes the ICV without manual contouring (V = 118.7 cm³ in this example), and renders the segmented intracranial cavity in three dimensions. Each automated segmentation is visually inspected plane by plane, and minor contour adjustments can be made in the Edit mode (Figure S5).

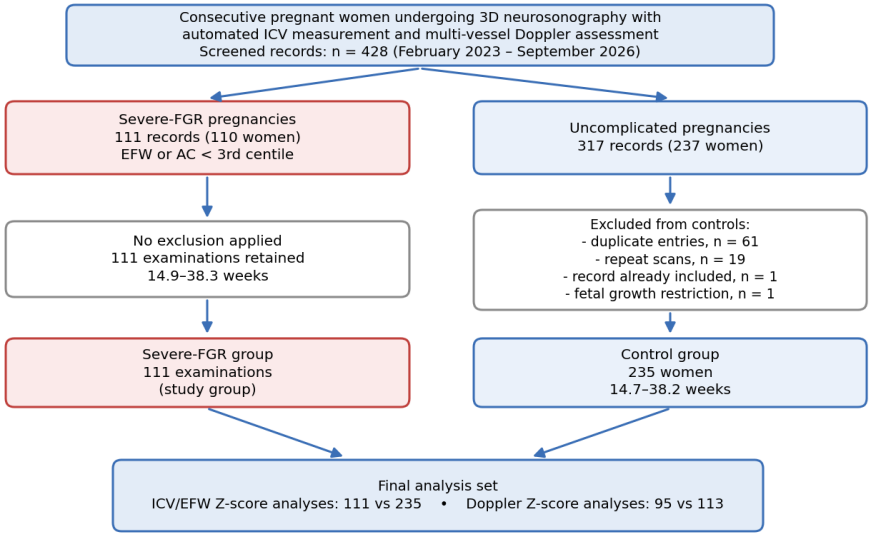


Figure 2. Flowchart of the study population. ICV, intracranial volume; EFW, estimated fetal weight; AC, abdominal circumference; FGR, fetal growth restriction. Consecutive pregnant women undergoing 3D neurosonography with automated ICV measurement and multi-vessel Doppler assessment were screened; after applying the exclusion criteria, 346 fetal examinations (111 severe-FGR pregnancies in 110 women, and 235 controls) constituted the final analysis set.

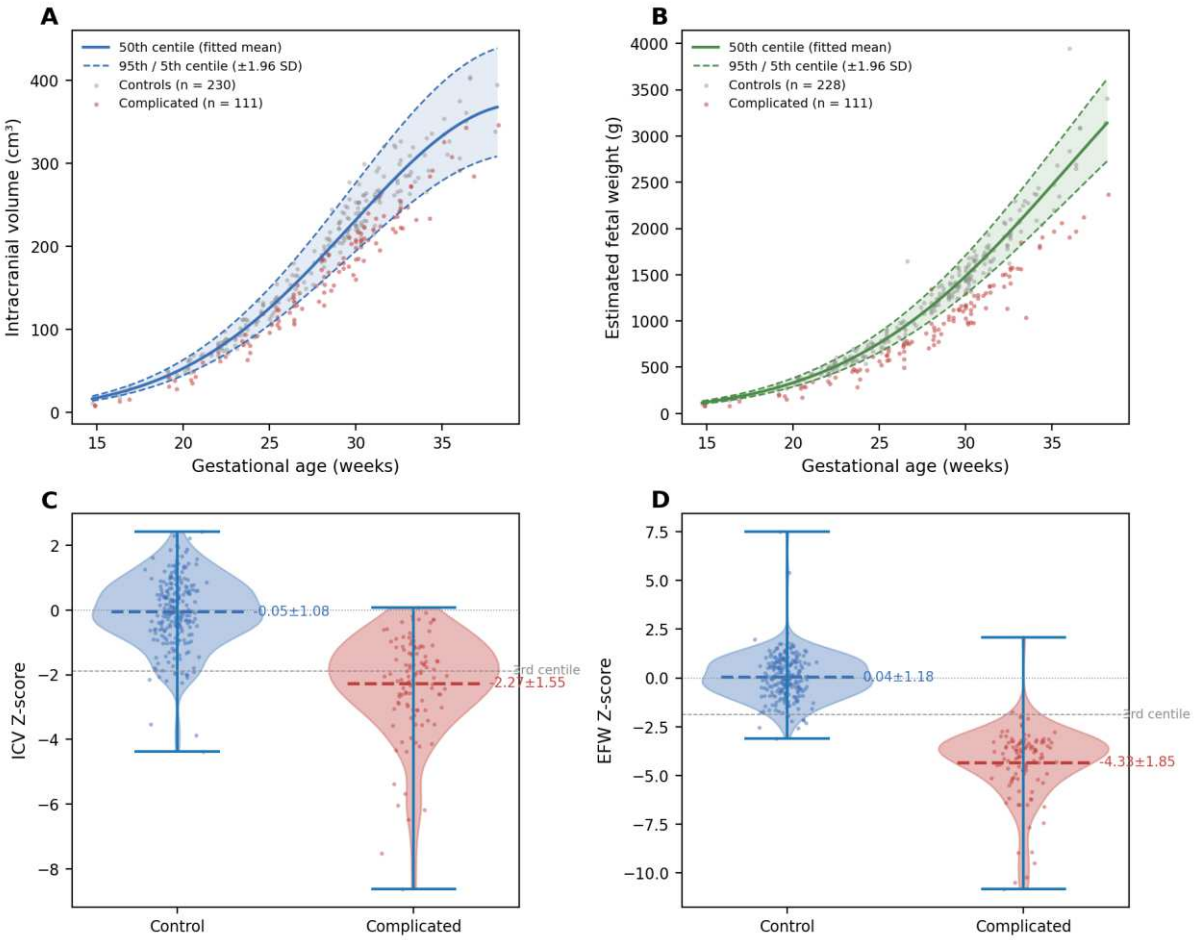


Figure 3. Internal reference ranges for fetal intracranial volume (ICV) and estimated fetal weight (EFW) derived from the 235 control pregnancies (230 and 228 used after exclusion of outliers, respectively). (A) ICV and (B) EFW versus gestational age with fitted quadratic mean and ± 2 SD limits; grey points, controls; red points, severe-FGR pregnancies. (C) ICV and (D) EFW Z-score distributions in controls (blue) and severe-FGR pregnancies (red); dashed lines, group means; dotted grey lines, 3rd centile (Z = −1.88).

Figure 4. Violin plots of Z-scores, brain–body dissociation, and Doppler indices in severe-FGR (red) versus control (blue) pregnancies. P values from Welch's t-test or Mann–Whitney U test according to normality. Dashed lines indicate group means; n shown beneath each group.

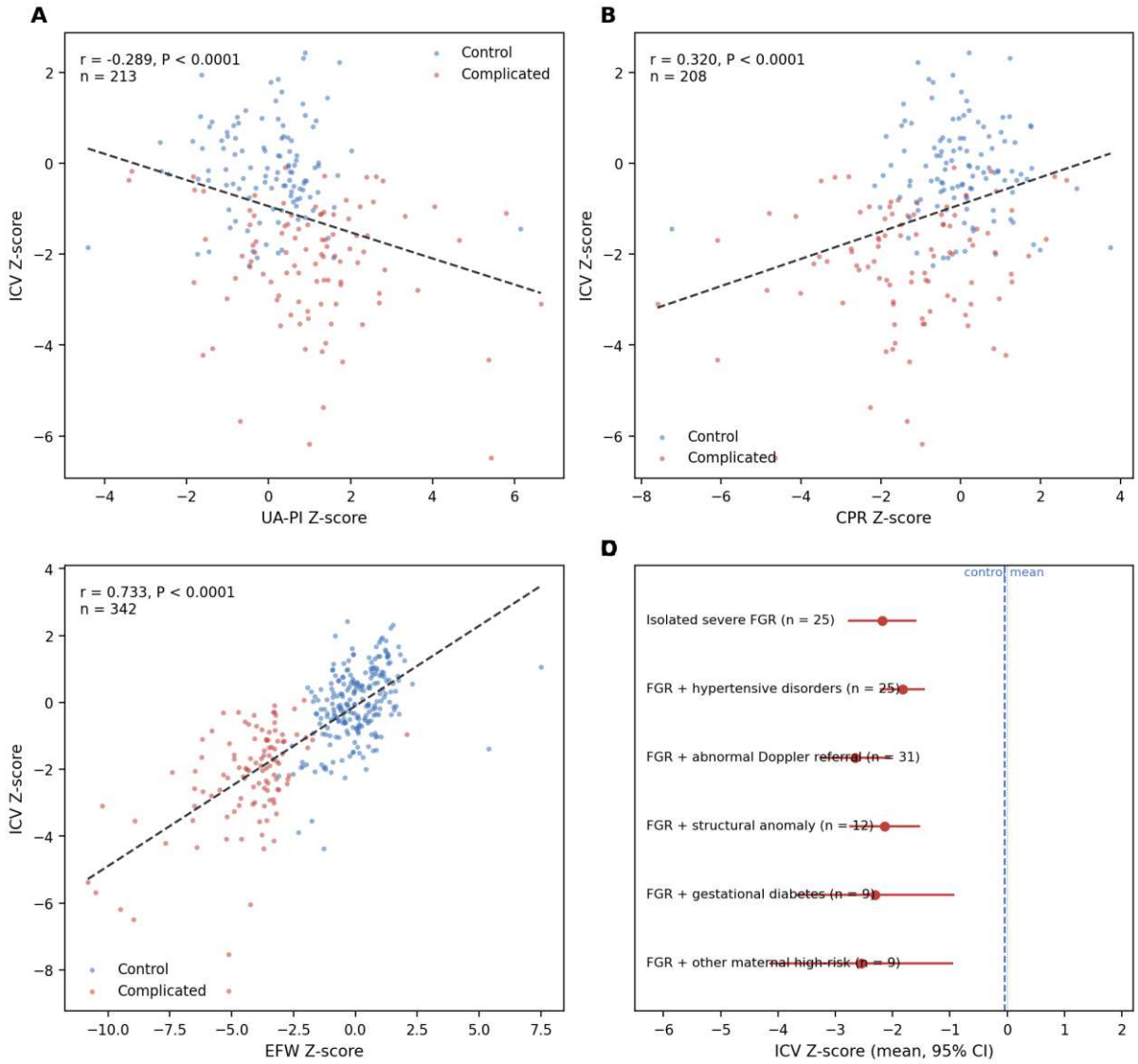


Figure 5. Correlations of ICV Z-score with UA-PI Z-score (A), CPR Z-score (B), and EFW Z-score (C) across the full sample (Pearson r shown). (D) ICV Z-score (mean, 95% CI) by coexisting-condition subgroup (hierarchical classification; see Methods). FGR, fetal growth restriction; HDP, hypertensive disorders of pregnancy; GDM, gestational diabetes mellitus.

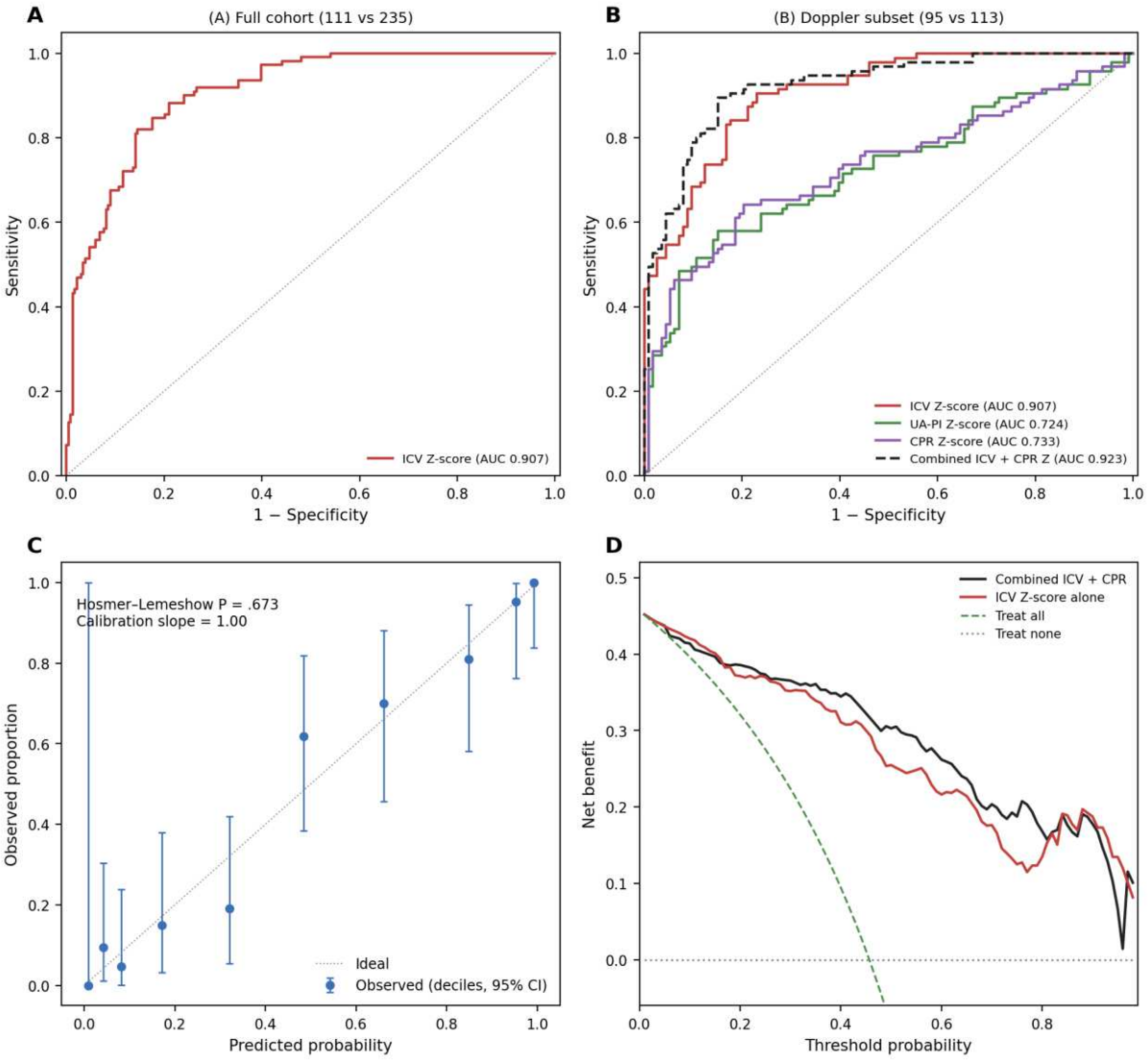


Figure 6. (A) Receiver-operating-characteristic (ROC) curve of the ICV Z-score in the full sample (111 severe-FGR vs 235 controls); AUC = 0.907 (95% CI 0.876–0.935). (B) ROC curves of the ICV Z-score, UA-PI Z-score, CPR Z-score, and the combined ICV + CPR model in the Doppler subset (95 vs 113); AUCs were 0.907 (95% CI 0.867–0.942), 0.724 (0.647–0.791), 0.733 (0.658–0.802), and 0.923 (0.885–0.955), respectively. (C) Calibration plot of the combined model: binned observed versus predicted frequencies with 95% confidence intervals; Hosmer–Lemeshow P = 0.673, calibration slope = 1.00. (D) Decision-curve analysis comparing the combined model, ICV Z-score alone, and treat-all/treat-none strategies.

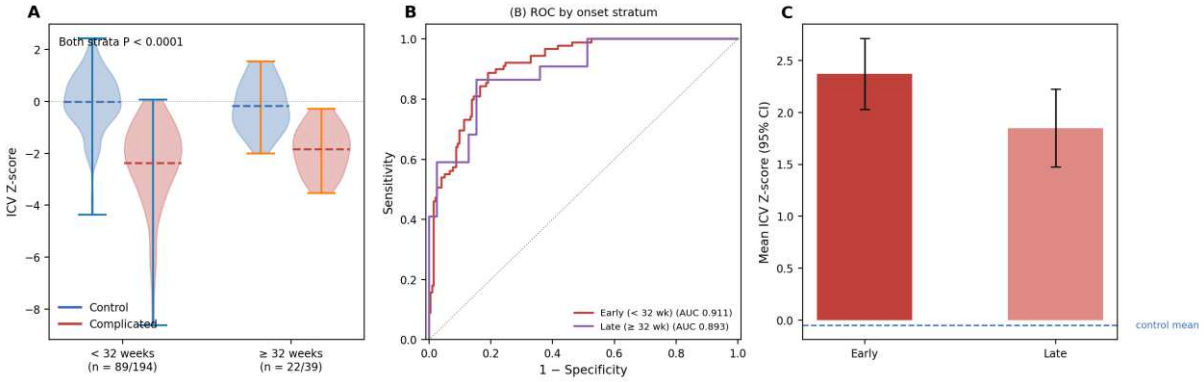


Figure 7. Onset-stratified analysis (cut-off 32 weeks). (A) ICV Z-score distributions in severe-FGR (red) versus control (blue) pregnancies by stratum. (B) ROC curves of the ICV Z-score by stratum. (C) Mean ICV Z-score (95% CI) in severe-FGR pregnancies examined before versus at or after 32 weeks; dashed line, control mean.

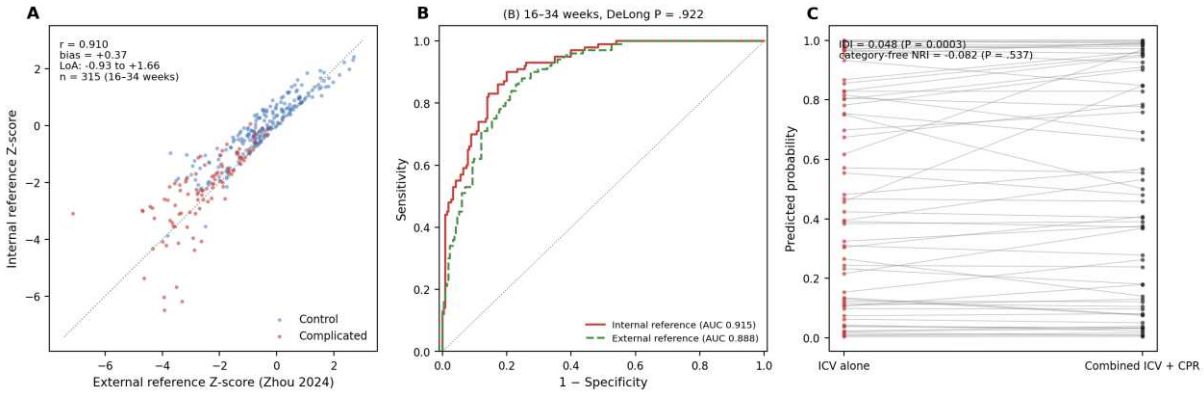


Figure 8. External-reference validation and reclassification. (A) Agreement between internal and external (Zhou 2024) ICV Z-scores (n = 315; 16–34 weeks; Pearson r = 0.910; Bland–Altman bias +0.37, limits of agreement −0.93 to 1.66). (B) ROC curves using internal versus external reference equations (AUC 0.915 vs 0.888; DeLong P = 0.922). (C) Slope graph of predicted probabilities for ICV alone versus the combined ICV + CPR model (IDI = 0.048, P = 0.0003; category-free NRI = −0.082, P = 0.537).

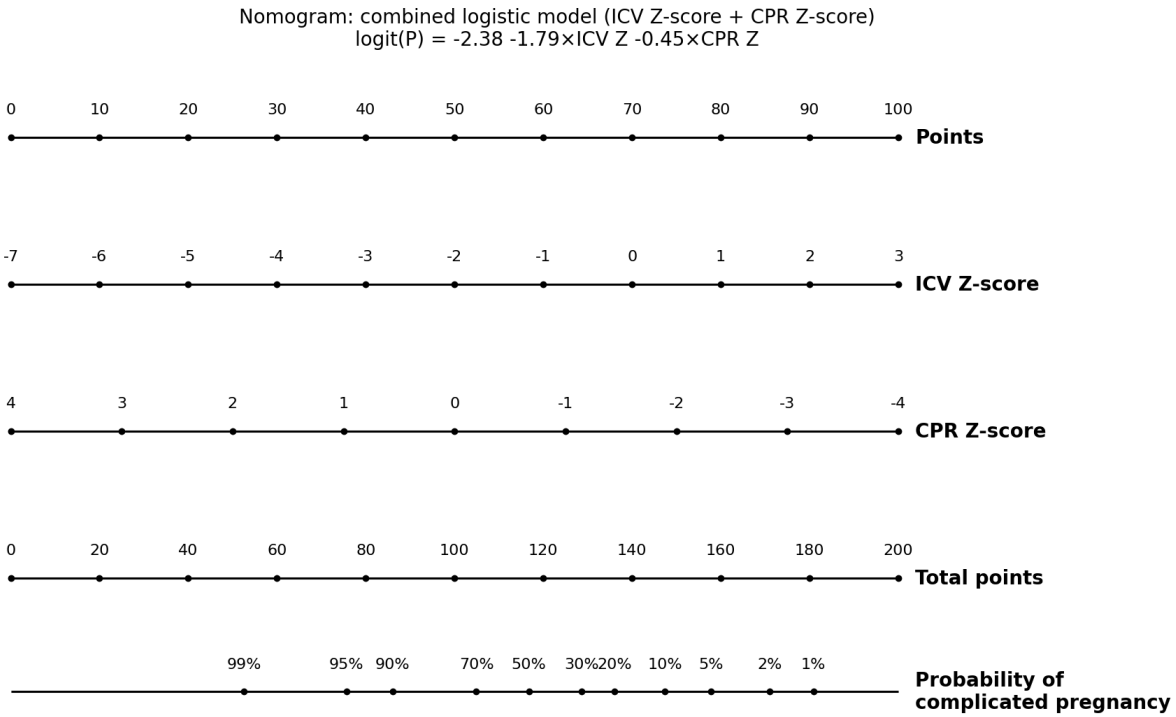


Figure S1. Nomogram of the combined logistic model (ICV Z-score + CPR Z-score) for estimating the probability of severe FGR; logit(P) = −2.38 − 1.79 × ICV Z-score − 0.45 × CPR Z-score.

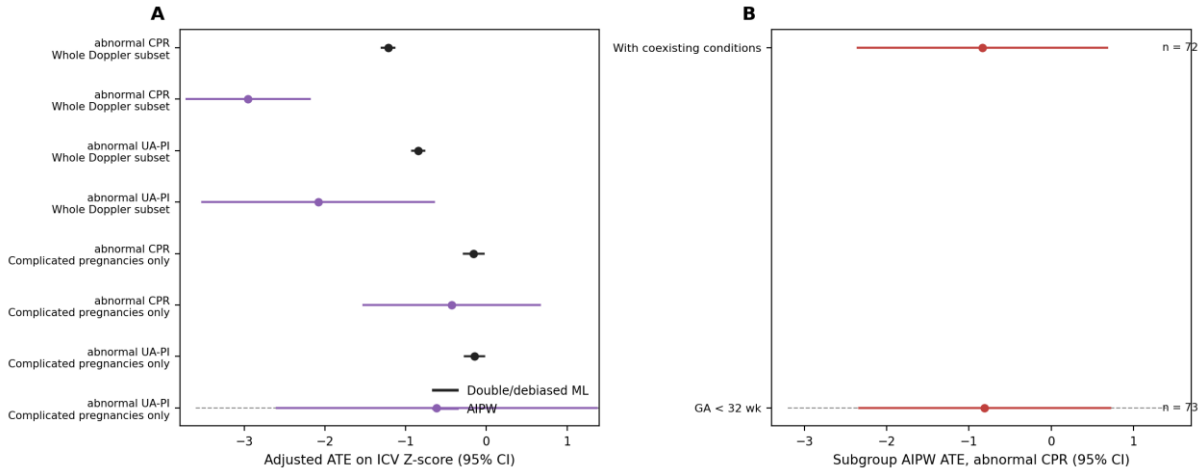


Figure S2. Exploratory adjusted-association (causal machine-learning) analysis. (A) Average treatment effect (ATE) estimates on ICV Z-score by estimator (double/debiased machine learning, DML; augmented inverse-probability weighting, AIPW) for the abnormal CPR and abnormal UA-PI exposures, in the whole Doppler subset and within severe-FGR pregnancies only. (B) Subgroup AIPW ATE estimates for the CPR exposure within severe-FGR pregnancies. All estimates are adjusted for maternal age, pre-pregnancy body mass index, height, and gestational age at examination, and are interpreted as adjusted associations rather than causal effects.

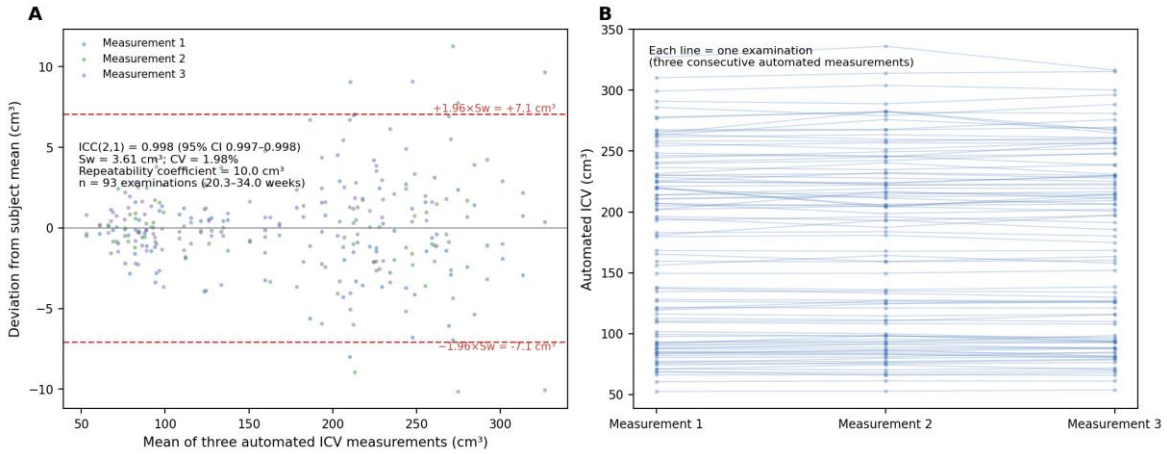


Figure S3. Repeatability of the automated ICV measurement (93 control examinations, 20.3–34.0 weeks; three consecutive automated measurements per examination). (A) Deviation of each measurement from the examination mean against the mean; dashed lines, ±1.96 × within-subject SD (Sw = 3.61 cm³); ICC(2,1) = 0.998 (95% CI 0.997–0.998); within-subject coefficient of variation = 1.98%; repeatability coefficient = 10.0 cm³. (B) The three consecutive automated measurements per examination, connected by lines.

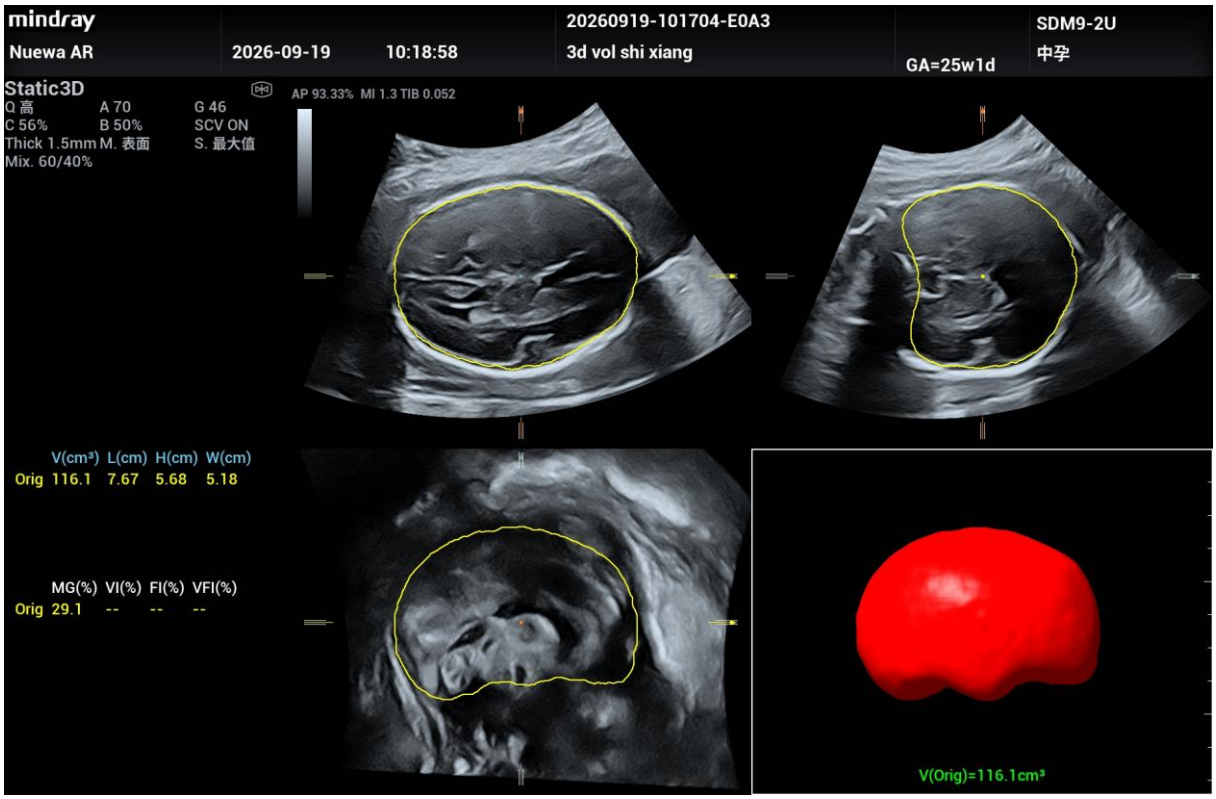


Figure S4. Within-examination repeatability of the automated ICV measurement (same fetus as in Figure 1, gestational age 25 weeks 1 day). The second automated Smart ICV measurement, performed 41 seconds after the first (Figure 1B), yielded an ICV of 116.1 cm³ versus 118.7 cm³ for the first measurement (relative difference 2.2%).

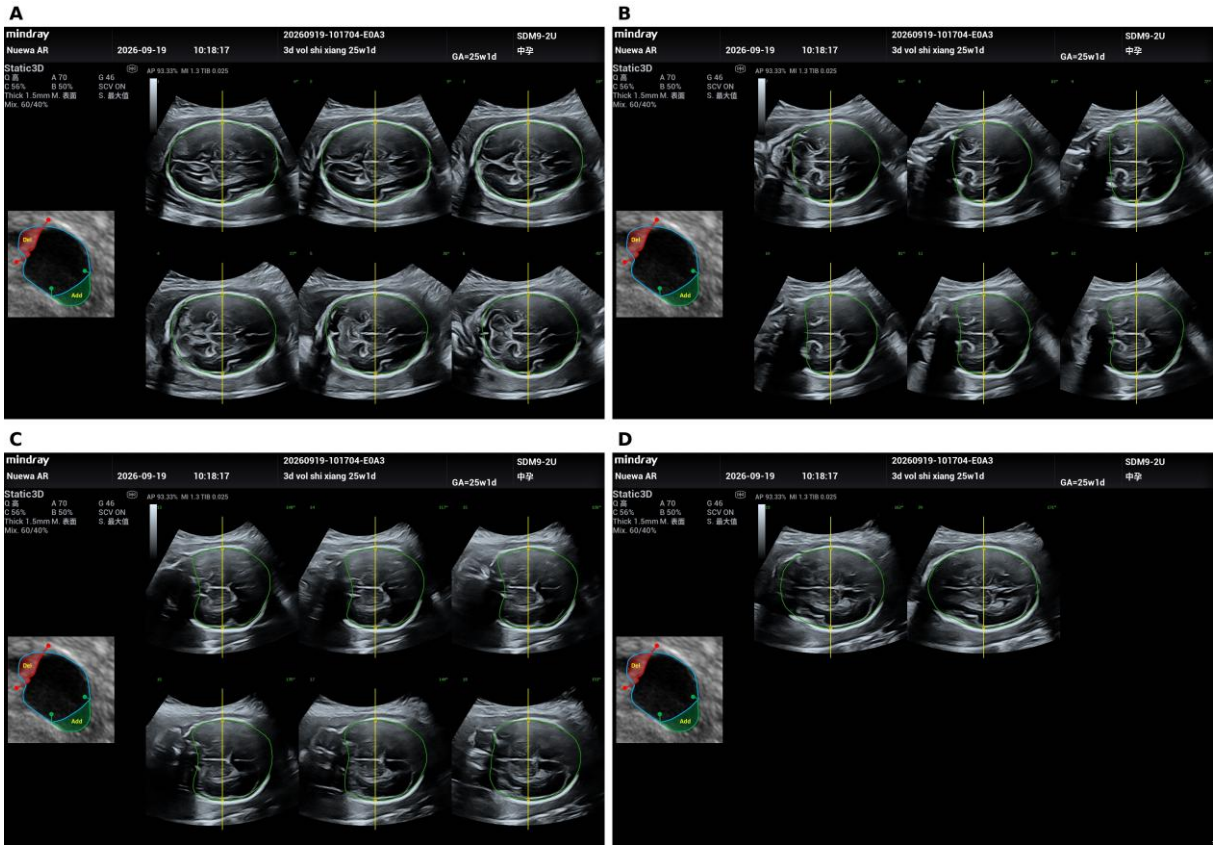


Figure S5. Operator quality control of the automated segmentation in the Edit mode (same fetus as in Figure 1). After the automated measurement, the operator can enter the Edit mode and review the radially sampled planes in sequence; individual contour segments can be removed (Del) or added (Add) on any plane, and the volume is recomputed automatically after editing. (A–D) Consecutive sets of radially sampled axial planes (plane number and rotation angle shown) with the automatically generated segmentation contours; insets show the defining plane with the Del (red) and Add (green) editing tools.

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