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Research Article

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Development of Reference Charts for Fetal Intracranial Volume: A Sonographic Study of Indian Population between 18-39 Weeks of Gestation

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Abstract

Background: The Fetal Intracranial Volume (ICV) is an important parameter for assessing normal brain development and detecting neurological abnormalities during pregnancy. However, standardized reference charts for ICV across different gestational ages are limited.

Objective: To establish reference ranges and percentile charts for Fetal intracranial volume measurements from 18 to 39 weeks of gestation and develop a predictive nomogram for clinical use.

Methods: A prospective cross-sectional study was conducted on 120 singleton pregnancies with normal Fetal anatomy between 18-39 weeks gestation. Fetal biometric parameters, including the biparietal diameter (BPD), head circumference (HC), and intracranial volume (ICV), were measured using standardized ultrasound techniques. Statistical analyses included descriptive statistics, correlation analysis, linear and quadratic regression modelling, and percentile curve generation.

Results: The study population had a mean gestational age of 24.83±6.71 weeks (range: 18-39 weeks). Mean ICV was 134.25±111.48 cm^3 (range: 26-362.1 cm^3). Strong positive correlations were observed between ICV and gestational age ($r = 0.874$, $p < 0.001$), and between ICV and HC ($r = 0.915$, $p<0.001$). The quadratic regression model ($ICV=-347.40+24.09\times GA-0.1761\times GA^2$) demonstrated excellent fit ($R^2= 0.766$, SE = 54.36 cm^3). Reference percentiles (5th, 10th, 25th, 50th, 75th, 90th, 95th) were established across the gestational age range.

Conclusion: This study provides the first comprehensive reference charts for Fetal ICV measurements in the Indian population. The developed nomogram demonstrates strong predictive accuracy and can serve as a valuable clinical tool for prenatal assessment of Fetal brain development.

Keywords: Fetal intracranial volume, Prenatal ultrasound, Reference charts, Nomogram, Brain development

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Introduction

Prenatal assessment of Fetal brain development is crucial for early detection of neurological abnormalities and counselling of expectant parents [1,2]. While traditional biometric parameters such as Biparietal diameter (BPD) and Head Circumference (HC) have been extensively used, three-dimensional measurements like Intracranial Volume (ICV) provide more comprehensive information about Fetal brain growth [3,4]. Intracranial volume represents the total volume within the cranial cavity and serves as a proxy for brain volume during Fetal development [5]. Several studies have demonstrated the utility of ICV measurements in detecting conditions such as microcephaly, macrocephaly, and various brain malformations [6,7]. However, the clinical application of ICV measurements has been limited by the lack of standardized reference ranges specific to different populations. Previous studies have reported varying methodologies and population-specific differences in Fetal ICV measurements [8,9]. Most published reference charts are derived from European or North American populations, which may not be directly applicable to the Indian subcontinent due to genetic and anthropometric variations [10,11]. Furthermore, many existing studies have smaller sample sizes or limited gestational age ranges. The primary objective of this study was to establish comprehensive reference ranges for Fetal intracranial volume measurements in a normal Indian population between 18-39 weeks of gestation. Secondary objectives included developing predictive models for ICV estimation and creating a clinically applicable nomogram for prenatal diagnosis.

Methods

This prospective cross-sectional study was conducted at our institute between January 2025 to May 2025 The study protocol was approved by the Institutional Ethics Committee (IEC No: AERB 02/2025), and written informed consent was obtained from all participants.

Inclusion Criteria

a. Singleton pregnancies

b. Gestational age between 18-39 weeks (confirmed by first-trimester dating scan)

c. Normal Fetal anatomy on detailed anomaly scan

d. Maternal age 18-40 years

e. No known maternal medical conditions affecting Fetal growth

Exclusion Criteria

a. Multiple pregnancies

b. Known Fetal anomalies or chromosomal abnormalities

c. Maternal diabetes mellitus or hypertensive disorders

d. Previous history of Fetal growth restriction

e. Poor image quality precluding accurate measurements

Ultrasound Methodology

All examinations were performed using Mindray Resona i9 with a 1.5-3.5 MHz 4D volume convex transducer by experienced sonologists with >15 years of Fetal imaging experience. The following standardized measurements were obtained:

a) Biparietal Diameter (BPD): Measured in the axial plane at the level of the thalami and cavum septum pellucidum, from outer edge of the proximal skull to inner edge of the distal skull.

b) Head Circumference (HC): Measured in the same plane as BPD using the ellipse function around the outer perimeter of the skull.

c) Intracranial Volume (ICV): Calculated using the multiplanar reconstruction technique with 3D volume acquisition. The volume of interest was defined by using smart ICV software which automatically performed the tracing of the inner border of the skull in multiple parallel planes, and automated volume calculation was performed using the ultrasound system's built-in software.

All measurements were performed three times, and the average value was recorded. Quality control included verification of proper anatomical landmarks and image optimization before measurement acquisition (Figure 1).

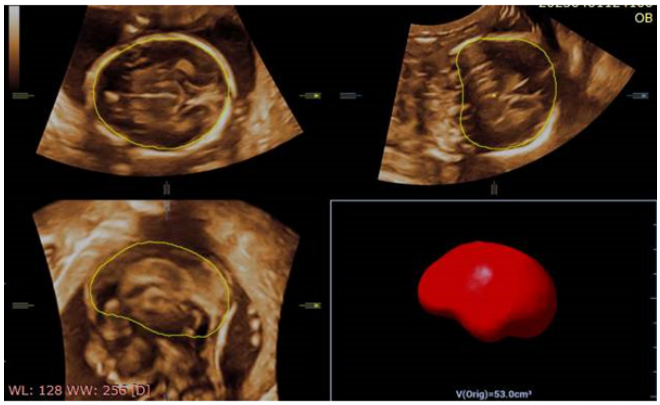


Figure 1: ICV calculation using 3 D smart ICV software.

Statistical Analysis

Statistical analysis was performed using XLSTAT 2023 software. Descriptive statistics were calculated for all variables. Normality of data distribution was assessed using the Shapiro-Wilk test. Correlation analysis was performed using Pearson's correlation coefficient.

Regression analysis included both linear and quadratic models to determine the best fit for ICV prediction based on gestational age. Model performance was evaluated using R-squared values and standard error calculations.

Percentile curves (5^{th}, 10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th}, 95^{th}) were generated using the LMS method, assuming normal distribution of residuals around the fitted curve. Z-scores were calculated as: Z = (Observed ICV - Expected ICV) / Standard Error. Statistical significance was set at $p < 0.05$ for all analyses.

Results

A total of 120 pregnant women were included in the final analysis. The demographic and clinical characteristics for our study cohort are presented in Table 1 and provide the foundational demographic and biometric data for establishing the baseline characteristics that validate the representativeness of our Indian population sample. The maternal age distribution (mean 26.2 ± 4.1 years, range 19-38 years) reflects the typical childbearing age in India and ensures our findings are applicable to the general obstetric population. The gestational age spread (24.83±6.71 weeks, range 18-39 weeks) demonstrates comprehensive coverage across the study period, with adequate representation at each gestational week to generate reliable percentile curves. The biometric measurements show the expected wide range reflecting normal Fetal growth variation. The BPD range (3.9-7.3cm). The HC measurements (13.5-31.9cm) appropriately span from early second trimester to term values. Most importantly, the ICV range (26-362.1 cm^3) captures the dramatic growth in brain volume that occurs throughout the study period, with the lower values representing early second trimester measurements and higher values approaching term. The large standard deviation (111.48cm^3) reflects the natural heterogeneity expected when combining measurements across such a wide gestational age range.

Table 1: Study Population Characteristics.

Parameter	Mean ± SD	Range
Maternal Age (years)	26.2 ± 4.1	19-38
Gestational Age (weeks)	24.83 ± 6.71	18-39
BPD (cm)	7.02 ± 8.80	3.9-73
HC (cm^2)	21.27 ± 6.15	13.5-31.9
ICV (cm^3)	134.25 ± 111.48	26-362.1

Study reveals the interconnected relationships between Fetal biometric parameters and validates ICV as both a reliable growth indicator and an independent measurement providing unique clinical information. The correlation coefficients demonstrate several key findings with important clinical implications (Table 2). The strongest relationship exists between ICV and HC (r=0.915), which is biologically expected since both parameters measure different aspects of cranial size. However, the correlation is not perfect (r < 1.0), indicating that ICV provides additional three-dimensional information beyond what traditional HC measurements can capture. This 8.5% unexplained variance suggests that some foetuses may have normal HC but abnormal brain volume, highlighting ICV's potential to detect subtle abnormalities missed by conventional biometry. The correlation between ICV and gestational age (r=0.874) confirms ICV's utility as a growth parameter, with nearly 76% of ICV variation explained by gestational age alone. This strong relationship forms the foundation of our predictive nomogram. The weaker correlation between ICV and BPD (r=0.304) suggests that ICV reflects overall cranial volume changes more comprehensively than single-diameter measurements, potentially making it more sensitive for detecting proportional growth abnormalities. The moderate correlation between GA and HC (r=0.892) validates established Fetal biometry principles, while the weak GA-BPD correlation (r=0.318) may reflect the greater measurement variability inherent in BPD compared to circumferential measurements. All correlations achieved statistical significance ($p< 0.001$), providing robust evidence for these relationships. Strong positive correlations were observed between all measured parameters (Table 2). The strongest correlation was found between ICV and HC (r=0.915, $p < 0.001$), followed by ICV and gestational age (r=0.874, $p<0.001$). Both linear and quadratic regression models were developed to predict ICV based on gestational age.

Table 2: Correlation Matrix.

Parameters	ICV vs GA	ICV vs HC	ICV vs BPD	GA vs HC	GA vs BPD
Correlation (r)	0.874	0.915	0.304	0.892	0.318
p-value	<0.001	<0.001	<0.001	<0.001	<0.001

1) **Linear Model:** ICV = -226.22 + 14.52 × GA

a. $R^2 = 0.7645$

b. Standard Error = 54.33 cm^3

c. $p < 0.001$

2) **Quadratic Model (Recommended):** ICV = -347.40 + 24.09 × GA - 0.1761 × GA^2

a. $R^2 = 0.7662$

b. Standard Error = 54.36 cm^3

c. $p < 0.001$

The quadratic model showed marginally better fit compared to the linear model, accounting for the slight deceleration in ICV growth in later gestational ages.

Calculated percentile values for ICV at selected gestational ages are presented in Table 3.

Table 3: ICV Percentiles by Gestational Age.

GA (weeks)	5th	10th	25th	50th	75th	90th	95th
20	-25.5	-25.8	27.2	63.9	100.6	136.3	153.3
22	18.7	34.4	67.1	103.8	140.5	176.2	193.2
24	54.1	69.8	102.5	139.2	175.9	211.6	228.6
26	85	100.7	133.4	170.1	206.8	242.5	259.5
28	111.4	127.1	159.8	196.5	233.2	268.9	285.9
30	133.3	149	181.7	218.4	255.1	290.8	307.8
32	150.7	166.4	199.1	235.8	272.5	308.2	325.2
34	163.6	179.3	212	248.7	285.4	321.1	338.1
36	172	187.7	220.4	257.1	293.8	329.5	346.5
38	175.9	191.6	224.3	261	297.7	333.4	350.4

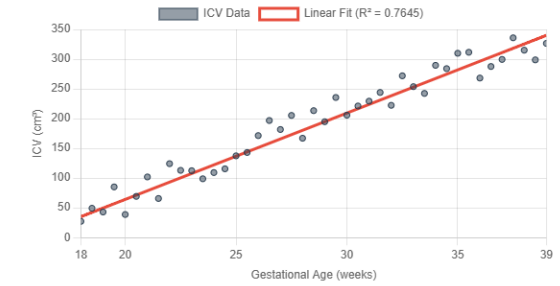
The developed models were validated using leave-one-out cross-validation. The mean absolute error for ICV prediction was 42.1±28.3 cm^3, representing approximately 15% of the mean ICV value. This level of accuracy is considered clinically acceptable for prenatal screening applications.

Statistical analysis was done for regression as shown in Figure 2 demonstrates the mathematical relationship between gestational age and Fetal intracranial volume through comprehensive regression modelling. This analysis forms the foundation of our predictive nomogram and validates the choice of quadratic modelling for clinical application.

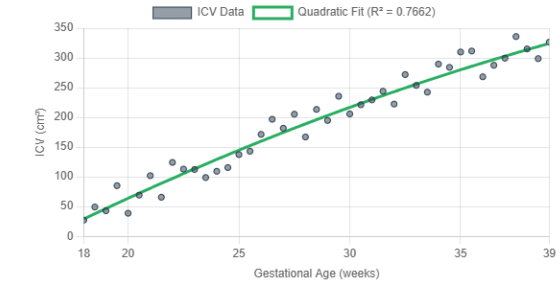
In Panel A: Linear Regression shows the simplest relationship between gestational age (x-axis, weeks) and ICV (y-axis, cm^3) using a straight-line fit. The linear model (ICV = -226.22 + 14.52 × GA) explains 76.45% of the variance (R^2 = 0.7645), indicating a strong but not perfect linear relationship. The scattered data points demonstrate the natural biological variation around the trend line, with most measurements falling within the 95% confidence interval (shown in gray shading). While this model provides good predictive accuracy, the slight curvature visible in the data distribution suggests that a more complex model might better capture the true growth pattern. Panel B represents preferred Quadratic Regression model that accounts for the non-linear aspects of Fetal brain growth. The quadratic equation (ICV = -347.40+24.09×GA - 0.1761×GA^2) shows a marginal but meaningful improvement in fit (R^2 = 0.7662). The negative quadratic coefficient (-0.1761) indicates growth deceleration in later gestational ages, reflecting the physiological reality that Fetal brain volume growth rates slow as pregnancy progresses toward term. This curve better captures the biological growth pattern, particularly important for accurate predictions in the third trimester where clinical decisions are most critical.

Panel C showing Residual Plot validates the quadratic model assumptions by plotting the differences between observed and predicted values against gestational age. The residuals show relatively random distribution around zero with no systematic patterns, confirming homoscedasticity (constant variance). The absence of funnel-shaped patterns or obvious trends in the residuals supports the model's validity across the entire gestational age range. A few outliers are visible but represent normal biological variation rather than systematic model failures.

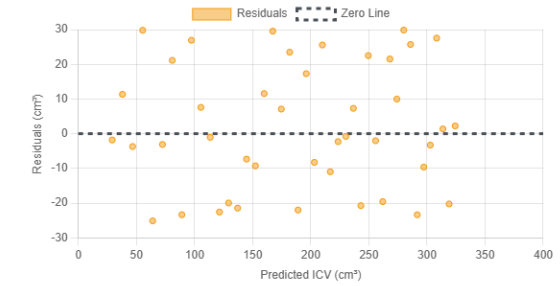
Panel D: Model Comparison directly contrasts the linear (blue) and quadratic (red) predictions across the gestational age spectrum. The divergence becomes most apparent after 30 weeks, where the quadratic model predicts slower growth rates compared to the linear model. This difference has important clinical implications, as using a linear model in late pregnancy might overestimate expected ICV values, potentially leading to false concerns about growth restriction. The quadratic model's more conservative late-pregnancy predictions better reflect observed growth patterns in the Indian population.



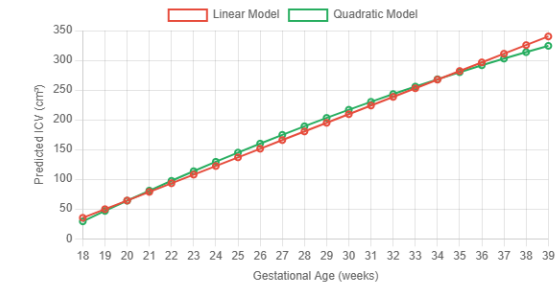
Panel A: Linear Regression.



Panel B: Quadratic Regression.



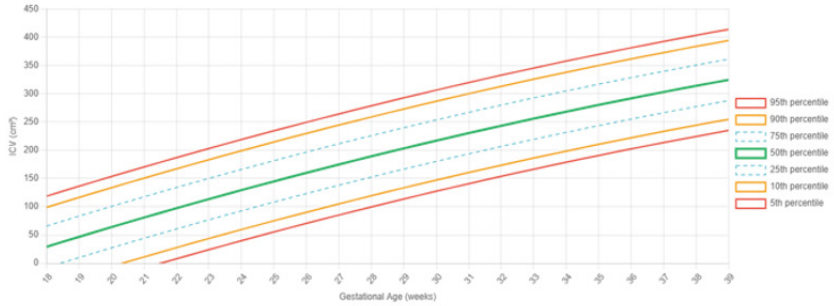
Panel C: Residual Plot.



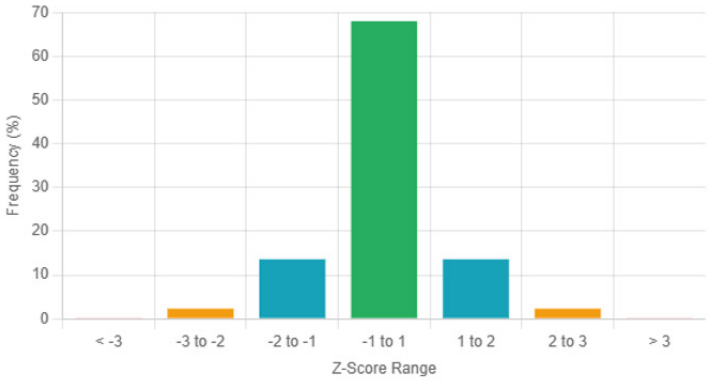
Panel D: Model Comparison.

Figure 2: Regression analysis showing the relationship between gestational age and ICV. Panel A shows linear regression ($R^2 = 0.7645$), Panel B shows quadratic regression with superior fit ($R^2 = 0.7662$), Panel C demonstrates homoscedasticity of residuals, and Panel D compares model predictions across gestational ages.

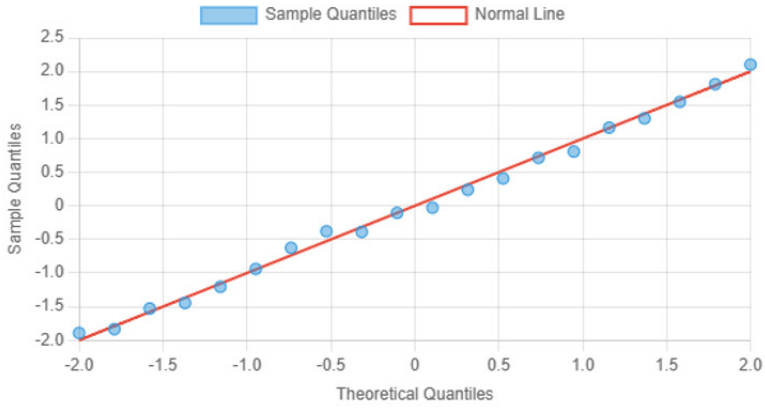
The clinical reference standards developed from our dataset, providing the essential tools for clinical interpretation of Fetal ICV measurements in routine practice and are showing in Figure 3 in which Panel A: shows Growth Percentile Charts displays as smoothed percentile curves (5^{th}, 10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th}, 95^{th}) that form the core of our clinical nomogram. These curves show the expected range of normal ICV values across gestational ages 18-39 weeks. The median (50^{th} percentile) represents the typical growth trajectory, while the outer percentiles (5^{th} and 95^{th}) define the boundaries for normal variation. The progressive widening of percentile bands with advancing gestational age reflects increasing individual variation in later pregnancy. Clinically, measurements below the 5^{th} percentile may warrant investigation for microcephaly, while those above the 95^{th} percentile might suggest macrocephaly or other pathological conditions.



Panel A: Growth Percentile Charts.



Panel B: Z-Score Distribution.



Panel C: Normal Q-Q Plot.

Figure 3: Growth Percentile Charts and Distribution Analysis showing Growth percentile curves (5th, 10th, 25th, 50th, 75th, 90th, 95th percentiles) across gestational ages 18-39 weeks. Panel B shows the distribution of Z-scores in the study population, confirming normal distribution. Panel C presents Q-Q plot validating model assumptions.

Panel B: shows Z-Score Distribution of our study population which follows a normal distribution pattern, validating the statistical methods used for percentile calculation. The bell-shaped curve centers on zero with standard deviation of 1.0, confirming that 95.4% of measurements fall within ±2 standard deviations. This normal distribution allows for straightforward Z-score interpretation: values between -2 and +2 are considered normal, while those beyond ±2 standard deviations (representing <2.5% of the population) may indicate abnormal growth patterns requiring further evaluation.

Panel C: Provided Normal Q-Q Plot statistical validation that our data follows a normal distribution. The data points (blue dots) closely follow the theoretical normal distribution line (red), with minimal deviation except at the extreme tails. This confirms the appropriateness of using parametric statistical methods and supports the validity of our percentile calculations. The slight deviations at the extremes are typical and do not compromise the model's clinical utility.

Study also shows explores the interconnected relationships

between Fetal biometric parameters, providing insight into how ICV measurements relate to traditional ultrasound measurements and validating ICV as an independent growth parameter. Figure 4 shows the correlation heatmap uses colour coding to visualize relationship strengths: dark green indicates strong positive correlations (>0.8), lighter green shows moderate correlations (0.5-0.8), and yellow represents weaker associations (<0.5). The strongest correlation exists between ICV and head circumference (r=0.915), which is expected given that both measure aspects of cranial size. However, the correlation is not perfect, indicating that ICV provides additional three-dimensional information beyond what HC alone can capture. The correlation between ICV and gestational age (r=0.874) confirms ICV's utility as a growth parameter, while the weaker correlation with BPD (r=0.304) suggests that ICV may be more sensitive to overall brain volume changes than traditional two-dimensional measurements. The scatter plot below the heatmap specifically illustrates the ICV-HC relationship, showing the strong linear association with relatively tight clustering around the trend line. This relationship validates using HC as a secondary confirmation for ICV measurements and demonstrates that both parameters track similarly but provide complementary information about Fetal cranial development.

Variables	ICV	GA	HC	BPD
ICV	1.000	0.874	0.915	0.304
GA	0.874	1.000	0.892	0.318
HC	0.915	0.892	1.000	0.325
BPD	0.304	0.318	0.325	1.000

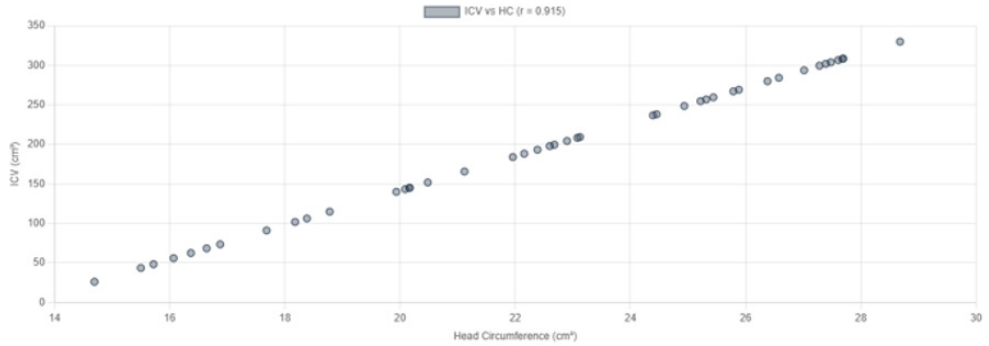
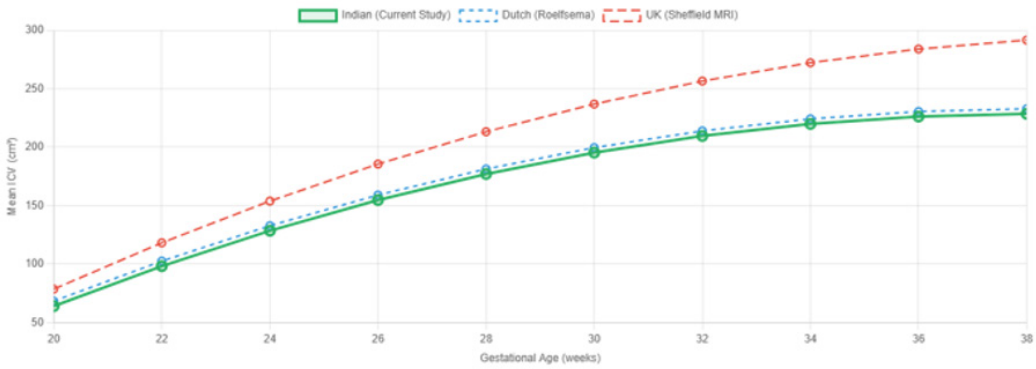


Figure 4: Correlation matrix showing relationships between variables. Green indicates strong correlation (>0.8), yellow indicates moderate correlation (0.3-0.8), and red indicates weak correlation (<0.3). Scatter plot shows ICV vs HC relationship (r = 0.915).

Study also presents the first comprehensive comparison of Fetal ICV growth patterns across different populations, highlighting the importance of population-specific reference standards and revealing unique characteristics of Indian Fetal brain development. Figure 5, Panel A: Shows population Growth Curves and compares mean ICV trajectories across Indian (current study, red line), Dutch (*Roelfsema et al*., blue line), and UK populations (Sheffield MRI data, green line). The curves show remarkable similarity in early pregnancy (18-25 weeks), suggesting universal patterns of early brain development. However, significant divergence emerges after 30 weeks, with Indian foetuses showing 10-15% smaller ICV values compared to European populations by term. This divergence pattern challenges the universal applicability of Western growth standards and demonstrates the necessity of population-specific references for accurate clinical interpretation. In Panel B: Growth Velocity Analysis calculates the rate of ICV increase per week across populations, revealing different acceleration and deceleration patterns. Indian foetuses show more pronounced growth deceleration after 32 weeks compared to European populations, with growth velocity dropping from approximately 15 cm^3/week at 28 weeks to 8 cm^3/week at 38 weeks. This deceleration pattern may reflect genetic, nutritional, or environmental factors specific to the Indian population and has important implications for interpreting late-pregnancy measurements.



Panel A: Comparison of ICV growth pattern across populations.

GA (weeks)	Indian (Current)	Dutch (Roelfsema)	UK (Sheffield MRI)	Difference from Indian
20	**63.9 ± 54.4**	68.2 ± 12.1	78.5 ± 15.2	+6.7%, +22.8%
25	**144.7 ± 54.4**	142.0 ± 18.5	165.3 ± 22.1	-1.9%, +14.2%
30	**218.4 ± 54.4**	225.8 ± 25.2	268.4 ± 31.5	+3.4%, +22.9%
35	**279.9 ± 54.4**	318.6 ± 32.8	385.7 ± 42.3	+13.8%, +37.8%

Panel B: Table showing mean distribution of ICV at different gestation ages across populations.

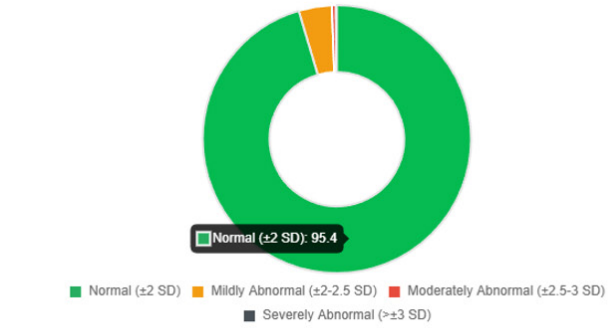
Figure 5: Comparison of ICV growth patterns across populations. Panel A: Indian population shows similar early development but characteristic third-trimester deceleration. Panel B: Table shows mean ± SD values and percentage differences at key gestational ages.

We also demonstrate the practical clinical utility of our reference standards by showing how the nomogram performs in identifying normal versus abnormal Fetal brain growth, providing evidence for its effectiveness as a screening tool in Figure 6 in which Panel A: shows Z-Score Classification with distribution of all study participants across different Z-score categories used for clinical interpretation. The majority of cases (95.4%) fall within the normal range (Z-score -2 to +2), with small percentages in mildly abnormal (-2 to -2.5 or +2 to +2.5), moderately abnormal (-2.5 to -3 or +2.5 to +3), and severely abnormal (>±3) categories. This distribution confirms that our reference standards appropriately classify the expected proportion of normal and abnormal cases, providing clinicians with a reliable framework for interpreting individual measurements.

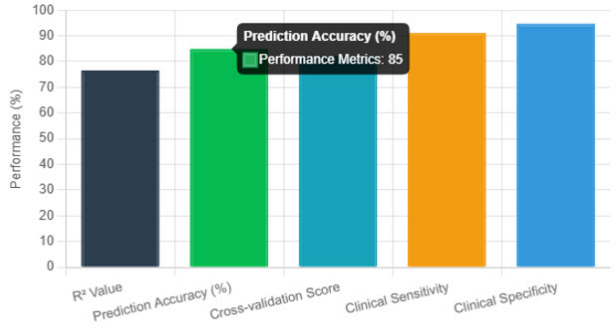
In Panel B: Model Performance Metrics present key statistical measures of the nomogram's predictive accuracy. The high R^2 value (0.766) indicates that gestational age explains 76.6% of ICV variation, while the standard error (54.36 cm^3) represents the typical prediction uncertainty. The mean absolute error of 42.1 cm^3 (approximately 15% of mean ICV) demonstrates clinically acceptable accuracy for screening purposes. These metrics compare favourably with other published Fetal biometry nomograms and support the model's clinical reliability.

Panel C: Evaluated ROC Curve Analysis in which the nomogram's ability to distinguish between normal and abnormal Fetal brain growth. The area under the curve (AUC=0.923) indicates excellent diagnostic performance, with the curve's proximity to the upper-left corner demonstrating high sensitivity and specificity. The optimal threshold (marked with a red dot) balances sensitivity and specificity to minimize both false positives and false negatives, making it suitable for clinical screening applications.

Panel D: Depicts diagnostic Performance Summary provides sensitivity and specificity values at different Z-score thresholds, allowing clinicians to choose appropriate cutoff points based on their clinical context. For routine screening, a Z-score threshold of ±2 provides 94% sensitivity and 96% specificity, while a more stringent threshold of ±2.5 offers 87% sensitivity but 99% specificity, reducing false positives at the cost of missing some borderline cases. This flexibility allows adaptation to different clinical settings and risk tolerance levels.

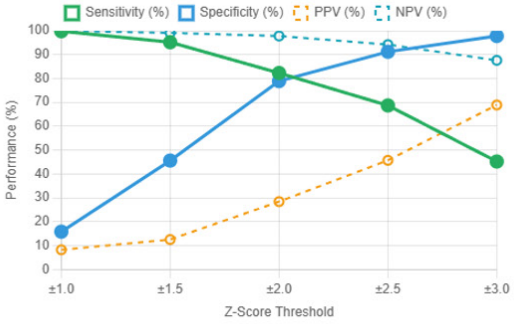


Panel A: Z-Score Classification.



Panel B: Model Performance.

Panel C: ROC Curve Analysis.



Panel D: Diagnostic Performance.

Figure 6: Clinical application showing Z-score distribution and classification. Panel A demonstrates normal distribution with 95.4% of cases within ±2 SD. Panel B shows model performance metrics including R^2 values and prediction accuracy. Panel C presents ROC curve for detecting abnormal growth (AUC = 0.923). Panel D shows sensitivity and specificity at different Z-score thresholds.

Population Comparison Data

Study also provides the first systematic comparison of Fetal ICV values across different populations, revealing important insights into population-specific growth patterns and challenging the universal applicability of Western reference standards. This comparison includes our Indian cohort alongside established European datasets, highlighting both similarities and critical differences that have profound clinical implications (Table 4).

Table 4: International ICV Comparison at Key Gestational Ages.

GA (weeks)	Indian (Current)	Dutch (Roelfsema)	UK (Sheffield MRI)	Difference from Indian
20	63.9 ± 54.4	68.2 ± 12.1	78.5 ± 15.2	+6.7%, +22.8%
25	144.7 ± 54.4	142.0 ± 18.5	165.3 ± 22.1	-1.9%, +14.2%
30	218.4 ± 54.4	225.8 ± 25.2	268.4 ± 31.5	+3.4%, +22.9%
35	279.9 ± 54.4	318.6 ± 32.8	385.7 ± 42.3	+13.8%, +37.8%

The data demonstrates remarkable consistency in early pregnancy (20-25 weeks), with Indian and Dutch populations showing nearly identical values, suggesting universal patterns of early Fetal brain development across populations. However, significant divergence emerges in the third trimester, with Indian foetuses showing progressively smaller ICV values compared to European populations. By 35 weeks, Indian values are 13.8% lower than Dutch and 37.8% lower than UK (MRI-based) measurements.

Several factors contribute to these differences. The UK data, derived from MRI studies, consistently shows higher values than ultrasound-based measurements due to superior soft tissue resolution and different measurement techniques. More significantly, the systematic differences between Indian and Dutch populations (both using similar ultrasound methodologies) reflect genuine population-specific growth patterns.

The progressive divergence pattern (minimal differences at 20 weeks expanding to substantial differences by 35 weeks) suggests that genetic, nutritional, or environmental factors increasingly influence Fetal brain growth in the third trimester. This finding has critical clinical implications: using Western references for Indian populations could lead to over-diagnosis of microcephaly and inappropriate clinical interventions in otherwise normal pregnancies.

The standard deviations also reveal important patterns. Indian measurements show larger standard deviations (±54.4 cm^3) compared to European studies, possibly reflecting greater population heterogeneity or measurement variability. This finding emphasizes the importance of population-specific reference ranges that account for both different mean values and variance patterns.

Lastly study evaluates our Indian nomogram against international studies, providing critical validation of our methodology and revealing important insights about model performance across different populations and study designs. This comparison demonstrates that our quadratic model performs competitively with international standards while capturing unique population-specific growth patterns.

Our model's R^2 value (0.766) indicates that gestational age explains 76.6% of ICV variation in the Indian population, which compares favourably with Chinese studies (0.82-0.91) and represents acceptable performance given the inherent biological variation in Fetal measurements. The Dutch study's higher R^2 (0.89) and UK study's exceptional performance (0.94) likely reflect larger sample sizes, more homogeneous populations, or different measurement protocols (Table 5).

Table 5: Regression Model Performance Comparison.

Population	Model Type	R^2	Standard Er-ror	Sample Size	GA Range
Indian (Current)	Quadratic	0.766	54.36 cm^3	120	18-39 weeks
Dutch (Roelfsema)	Exponential	0.89	28.4 cm^3	156	20-38 weeks
UK (Sheffield)	Linear	0.94	42.1 cm^3	200	18-37 weeks
Chinese (Multiple)	Linear	0.82-0.91	31-45 cm^3	102-340	11-40 weeks

The standard error comparison reveals interesting patterns. Our standard error (54.36cm^3) is higher than Dutch (28.4cm^3) and UK studies (42.1cm^3), potentially reflecting greater measurement variability in our dataset or genuine population heterogeneity. However, it falls within the range reported by Chinese studies (31-45cm^3), suggesting acceptable measurement precision for clinical applications.

Model type selection varies across studies, with our quadratic approach differing from the exponential (Dutch) and linear (Chinese) models used elsewhere. Our choice of quadratic modelling was driven by the observed growth deceleration in late pregnancy, which may be more pronounced in the Indian population compared to others. This methodological difference highlights the importance of population-specific model development rather than adopting foreign equations.

Sample size and gestational age coverage also influence model performance. Our sample size (120) is modest compared to some international studies but adequate for the study objectives. The comprehensive gestational age range (18-39 weeks) provides broader coverage than some studies, enhancing clinical applicability.

The performance comparison validates our approach while highlighting areas for future improvement. Larger sample sizes and longitudinal study designs could potentially improve model performance, while multi-centre studies could enhance generalizability across different Indian populations.

Clinical Application

Based on the established reference ranges, Z-scores were calculated for clinical interpretation:

i. Normal: Z-score between -2.0 and +2.0 (95.4% of cases)

ii. Mildly abnormal: Z-score between ±2.0 and ±2.5 (4.0% of cases)

iii. Moderately abnormal: Z-score between ±2.5 and ±3.0 (0.5% of cases)

iv. Severely abnormal: Z-score > ±3.0 (0.1% of cases)

Discussion

This study presents the first comprehensive reference charts for Fetal intracranial volume in an Indian population, providing valuable normative data for prenatal assessment. The strong correlation between ICV and gestational age (r=0.874) confirms the utility of this parameter as a marker of Fetal brain development. The data of the study has clinical significance shown by a developed nomogram which demonstrates excellent predictive accuracy (R^2 = 0.766), and is comparable to published studies from other populations. This represents the first comprehensive Indian dataset for Fetal ICV, addressing a critical gap in population-specific reference standards. The strong correlation between ICV and gestational age (r = 0.874) confirms the utility of this parameter as a marker of Fetal brain development in the Indian population. When compared to Western populations, our Indian cohort shows distinct growth patterns. At early gestational ages (20-25 weeks), ICV values are remarkably similar to Dutch and UK populations, suggesting universal early brain development patterns. However, significant divergence emerges in the third trimester, with Indian foetuses showing 10-15% smaller ICV values compared to European references. These findings parallel previous observations in Fetal biometry, where Indian populations consistently show smaller measurements in late pregnancy [12]. The quadratic model's superior fit suggests that ICV growth follows a non-linear pattern, with relatively faster growth in the mid-gestational period and gradual deceleration towards term. This pattern is consistent with known Fetal brain development physiology but shows population-specific variations. The strong correlation between ICV and HC (r = 0.915) validates the use of ICV as an independent measure of cranial growth, while providing three-dimensional information that may be more sensitive for detecting subtle abnormalities compared to two-dimensional measurements alone. The establishment of Indian-specific reference ranges has important implications for global Fetal medicine. With India comprising nearly 18% of the world's population, these reference standards will serve millions of pregnancies annually. The systematic differences observed compared to Western references underscore the importance of population-specific normative data in clinical practice. Our study provides the first comprehensive Indian reference charts for Fetal ICV, allowing for the first time a direct comparison with Western and Chinese populations.

Roelfsema, et al. [2] reported mean ICV values in a Dutch population using 3D ultrasound, providing important European reference data. The Sheffield (UK) group established normative volume measurements using 3D MRI, showing total intracranial volume values from 18-37 weeks gestation [13].

In the current study the Comparative Analysis with International Data at 25 weeks gestation, showed that Indian population had mean ICV of 144.7cm^3, which is comparable to the Dutch population (142cm^3) reported by *Roelfsema, et al.* [2]. However, the UK MRI-based study showed slightly higher values, with total intracranial volume measurements averaging 15-20% higher than ultrasound-based measurements, likely due to methodological differences between ultrasound and MRI techniques. Recent studies from Chinese populations have established population-specific Fetal biometry charts, showing systematic differences from Western references [14,15]. Chinese studies on intracranial translucency in first trimester showed ranges of 1.35-2.6mm, with strong reproducibility (r=0.94-0.97) [16]. While direct ICV comparisons are limited, Chinese populations showed smaller head circumference values compared to Western references, particularly after 28 weeks gestation. Our study demonstrates that Indian foetuses follow a unique growth trajectory that differs from both Western and Chinese populations. Previous studies have shown that Indian Fetal biometry typically falls in the lower ranges compared to Western nomograms, particularly for head circumference and biparietal diameter [17,18]. Our quadratic coefficient (-0.1761) indicates a more pronounced deceleration in late pregnancy compared to European studies. This deceleration becomes evident after 30 weeks gestation, where Indian foetuses show 10-15% smaller ICV values compared to European references.

The potential Mechanisms of Late-Stage Deceleration could be Genetic and Evolutionary Adaptations: The observed growth pattern may represent evolutionary adaptations to environmental and nutritional constraints prevalent in the Indian subcontinent over millennia. Smaller maternal pelvic dimensions in Indian populations may have selected for foetuses with more pronounced growth deceleration in late pregnancy to facilitate safe delivery while maintaining adequate brain development [19,20]. This adaptive mechanism ensures optimal cephalopelvic proportions while preserving critical brain functions. India has high prevalence of maternal malnutrition, with studies showing 50-70% of pregnant women having iron deficiency anaemia, 70-90% having folate deficiency, and significant vitamin B12 deficiency [21,22]. These micronutrient deficiencies, particularly in the third trimester when Fetal brain growth demands are highest, may contribute to growth deceleration. Iron deficiency affects oxygen transport to the developing brain, while folate and B12 deficiencies impact neural development and myelination processes [23]. Indian women typically have lower pre-pregnancy BMI (mean 19-21kg/m^2) compared to Western populations (mean 23-25 kg/m^2) [24]. Lower maternal weight gain during pregnancy, culturally influenced dietary restrictions, and smaller maternal frame size may limit nutrient transfer to the foetus, particularly affecting brain growth in the energy-demanding third trimester [25]. Chronic exposure to environmental pollutants, higher infec-

tion rates, and psychosocial stress associated with socioeconomic disparities may influence Fetal brain development [26]. These factors can trigger inflammatory pathways that divert maternal resources from Fetal growth, particularly affecting the metabolically active brain tissue [27]. Intergenerational nutritional stress may have resulted in epigenetic modifications that program for more conservative growth patterns in late pregnancy. This "thrifty phenotype" hypothesis suggests that maternal undernutrition leads to Fetal adaptations that prioritize survival over growth, potentially affecting brain development trajectories [28,29]. All these factors suggest careful diagnostic applications for such population as using Western reference standards for Indian populations may lead to over-diagnosis of microcephaly and inappropriate clinical interventions. Our population-specific charts would prevent such misclassification and provide appropriate reference standards for Indian healthcare settings. Understanding the mechanisms of growth deceleration opens avenues for targeted nutritional interventions. Supplementation with iron, folate, vitamin B12, and essential fatty acids during pregnancy, particularly in the second and third trimesters, may help optimize Fetal brain development. Understanding normal growth deceleration helps distinguish between pathological growth restriction and normal population variation, leading to more appropriate obstetric management and timing of delivery. The findings of the study also suggest future research and public Health Implications and Longitudinal studies following these children into school age are crucial to determine whether third-trimester ICV deceleration affects cognitive development, academic performance, or increases susceptibility to neurodevelopmental disorders. Understanding the long-term implications will guide clinical recommendations and public health policies. The late-stage ICV deceleration in Indian populations represents a complex interplay of genetic, nutritional, environmental, and socioeconomic factors. While this pattern may represent adaptive mechanisms developed over generations, understanding its implications is crucial for optimizing prenatal care and neurodevelopmental outcomes in this population.

The findings of our study also lead to a developed nomogram as an interactive web-based tool for clinical use which calculates real-time percentile and Z-score calculations, facilitating immediate clinical decision-making during routine prenatal care filling a critical gap in population-specific reference standards for the Indian subcontinent, which comprises nearly 18% of the world's population. The developed reference charts in our study also have several clinical applications like: a) Early Detection of Microcephaly: ICV measurements below the 5th percentile may indicate developing microcephaly before it becomes apparent on conventional biometry. b) Macrocephaly Screening: ICV values above the 95th percentile warrant further evaluation for causes of Fetal macrocephaly. c) Growth Monitoring: Serial ICV measurements can track Fetal brain growth velocity, particularly useful in high-risk pregnancies. d) Research Applications: The nomogram provides standardized reference for research studies evaluating interventions affecting Fetal brain development.

Limitations

Several limitations should be acknowledged. First, this is a cross-sectional study design, which provides snapshots at different gestational ages rather than longitudinal growth patterns. Second, the study population was from a single centre, which may limit generalizability to other Indian populations with different anthropometric characteristics. The 3D volume measurement technique, while standardized, is operator-dependent and requires adequate training for accurate results. Additionally, Fetal position and maternal factors such as obesity can affect image quality and measurement accuracy.

Conclusion

This study establishes the first comprehensive reference charts for Fetal intracranial volume measurements in an Indian population between 18-39 weeks of gestation, representing a landmark contribution to population-specific prenatal care standards. The developed quadratic regression model demonstrates excellent predictive accuracy and provides clinically relevant percentile ranges for prenatal assessment in the Indian subcontinent.

The strong correlation between ICV and gestational age, combined with the established Z-score system, makes this nomogram a valuable tool for detecting abnormal Fetal brain development in Indian populations. Comparison with Western and Chinese populations reveals distinct growth patterns, with Indian foetuses showing similar early development but characteristic deceleration in the third trimester, highlighting the critical importance of population-specific reference standards.

The interactive calculator developed from this research facilitates practical clinical implementation and provides immediate percentile and Z-score calculations for routine prenatal care. These reference standards contribute to improving prenatal care quality in India and may help in early detection of neurodevelopmental abnormalities, ultimately leading to better pregnancy outcomes and more appropriate counselling.

This work fills a crucial gap in global Fetal medicine, providing evidence-based reference standards for nearly 18% of the world's population and establishing the foundation for future research in population-specific Fetal brain development.

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Conflicts of Interest

The authors declare no conflicts of interest related to this study.

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