

Metabolic trajectories in twin pregnancies: longitudinal lipid and glucose profiling improves prediction of preterm birth

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Abstract

Background

Preterm birth (PTB) complicates nearly half of all twin pregnancies, yet current risk-stratification tools rely heavily on static anatomical markers such as cervical length. We hypothesised that longitudinal metabolic profiling across gestation could refine early identification of women at highest risk.

Methods

We conducted a retrospective cohort study including 601 dichorionic and monochorionic twin pregnancies delivered at Fujian Provincial Maternity and Children's Hospital (January 2023–December 2024). Fasting glucose and six lipid parameters were measured in early (< 14 weeks), middle (14–27⁺⁶ weeks), and late ($\geq$ 28 weeks) gestation. Group-based trajectory modelling identified latent metabolic phenotypes. Using partitioning around medoids clustering, we integrated glucose/triglyceride trajectories, mid-trimester cervical length, chorionicity, and neutrophil-to-lymphocyte ratio into four risk phenotypes. Multivariable logistic regression evaluated associations with PTB < 37 weeks. A Least Absolute Shrinkage and Selection Operator(LASSO)-penalised model incorporating continuous metabolic measures and trajectory classes was constructed and internally validated using five-fold cross-validation and bootstrap resampling. Model performance was compared against a baseline clinical model and a phenotype-only model.

Results

The overall PTB rate was 49.1%. Seven metabolic indices yielded stable trajectories. A sustained hypercholesterolaemic trajectory (TC1) carried the highest PTB risk (96.2%), whereas a physiologically rising High-Density Lipoprotein Cholesterol(HDL-C) trajectory (HDL2) was associated with the lowest (21.7%). Four distinct phenotypes emerged: P1 (low risk, PTB 25.9%), P2 (intermediate, 38.6%), P3 (high risk, 76.5%), and P4 (very high risk, 79.8%). Compared with P1, adjusted odds ratios for PTB were 1.97 (95% CI 1.13–3.44), 6.90 (2.81–16.94), and 12.65 (6.67–23.98) for P2–P4, respectively. The LASSO-enhanced model (M2) achieved a cross-validated Area Under the Receiver Operating Characteristic Curve(AUC) of 0.902 (Brier score 0.126), outperforming both the clinical model (AUC 0.565) and the phenotype model (AUC 0.730). Key predictors included mid-trimester fasting glucose, TC, HDL-C, Low-Density Lipoprotein Cholesterol(LDL-C), apolipoprotein B(ApoB), and TC trajectory class. Sensitivity analyses, including multiple imputation and exclusion of iatrogenic PTB, confirmed model robustness.

Conclusions

Longitudinal metabolic trajectories delineate dynamic metabolic maladaptation and serve as a valuable complement to conventional clinical variables for PTB risk assessment. While our findings support the potential utility of this framework, it remains an exploratory tool that requires prospective validation before it can be considered a standard component of personalised antenatal surveillance.

Introduction

Preterm delivery remains the leading cause of neonatal morbidity and mortality in twin gestations, with rates approaching 50% in contemporary cohorts [1]. Although short cervical length is widely used for risk assessment, its predictive performance in twins is modest at best, and it fails to reflect the evolving metabolic milieu that underpins parturition [2, 3].

Twin pregnancy imposes a uniquely exaggerated metabolic demand. Compared with singletons, women carrying twins exhibit more pronounced insulin resistance and lipid accumulation, driven by increased placental mass and hormonal output [4]. The Chinese Society of Perinatal Medicine has highlighted the need for improved metabolic monitoring in twin gestations [5]. Emerging evidence links dyslipidaemia—particularly hypertriglyceridaemia and low HDL cholesterol—to placental dysfunction, chronic inflammation, and spontaneous PTB [6, 7, 8]. The triglyceride-glucose (TyG) index in early pregnancy has been specifically identified as a predictor of gestational diabetes and adverse outcomes in twin pregnancies [9]. However, most studies report single time-point measurements, which cannot capture the temporal heterogeneity of metabolic adaptation or decompensation[10].

Latent class trajectory modelling offers a robust framework to delineate heterogeneous longitudinal patterns within a population [11]. By identifying subgroups following distinct metabolic trajectories, we can move beyond average trends to recognise phenotypes at greatest risk of adverse outcomes. In this study, we characterised longitudinal glucose and lipid trajectories across three trimesters in a large twin cohort, integrated these trajectories with clinical and sonographic parameters, and developed a parsimonious prediction model for PTB. Our aim was to provide clinicians with a practical, metabolically informed tool to guide surveillance intensity and therapeutic decision-making.

Methods

Study design and participants

We reviewed electronic medical records of all twin pregnancies delivered at Fujian Provincial Maternity and Children's Hospital between January 2023 and December 2024. Inclusion required documented gestational age at delivery and at least one set of fasting glucose and lipid profiles during each trimester. We excluded pregnancies complicated by pre-existing diabetes, thyroid disease, polycystic ovary syndrome, chronic renal or hepatic disease, severe pre-eclampsia, hemolysis, elevated liver enzymes, and low platelet count(HELLP) syndrome, or iatrogenic preterm delivery at initial analysis. After exclusions, 601 pregnancies constituted the primary analytic cohort.

This study has been approved by the Ethics Committee of Fujian Maternity and Child Health Hospital. IRB NO.(2024KY214).The requirement for informed consent was waived by the IRB because the study involved retrospective analysis of de-identified, routinely collected clinical data, which does not impact patient care and poses minimal risk to participants. This waiver is consistent with Article 39 of the **Measures for Ethical Review of Biomedical Research Involving Humans** issued by the National Health Commission of the People's Republic of China, which permits waiver of informed consent for retrospective studies using anonymized data.

Data collection

Demographic characteristics, obstetric history, chorionicity (determined by first-trimester ultrasound), mode of conception, and mid-trimester cervical length were extracted. Laboratory data included fasting plasma glucose (FPG), triglycerides (TG), TC, HDL-C, LDL-C, apolipoprotein A (ApoA), and ApoB. Neutrophil-to-lymphocyte (NLR) and platelet-to-lymphocyte (PLR) ratios were calculated for each trimester. The primary outcome was spontaneous PTB < 37 weeks. Secondary outcomes included PTB < 34 and < 32 weeks.

Statistical analysis

Continuous variables were expressed as mean $\pm$ Standard Deviation(SD) or median Interquartile Range(IQR) depending on distribution; categorical variables as frequencies (percentages). Group comparisons used Student's t-test or Mann–Whitney U test, and χ^2 test as appropriate.

Trajectory modelling. Group-based trajectory modelling (GBTM) was applied separately to each metabolic indicator using a censored normal distribution. Models specifying 1–4 trajectory classes were compared using Bayesian Information Criterion (BIC), with a minimum class size threshold of 5%.

Risk phenotyping. Among 496 women with complete data, we performed partitioning around medoids (PAM) clustering based on Gower distance, integrating FPG and TG trajectory classes, mid-trimester cervical length, chorionicity, and NLR. The optimal number of clusters was selected based on silhouette coefficients. Phenotypes were labelled P1–P4 according to ascending PTB rates.

Predictive modelling. Three logistic regression models were developed in a shared cohort of 452 women: M1 (baseline): maternal age, chorionicity, mode of conception; M2 (LASSO-enhanced): M1 plus NLR, PLR, FPG, six lipid indices, cervical length, and FPG/TG trajectory classes; M3 (phenotype): M1 plus cluster phenotype. Models were evaluated using five-fold stratified cross-validation. Performance metrics included area under the AUC, Brier score, sensitivity, and specificity. Internal validation was strengthened by bootstrapping and multiple imputation (20 datasets, Rubin's rules). All analyses were performed in R (v4.5.3). Two-sided $P < 0.05$ denoted statistical significance.

Results

Cohort characteristics

Of 601 women, 295 (49.1%) delivered before 37 weeks, including 80 (13.3%) before 34 weeks and 30 (5.0%) before 32 weeks. Mid-trimester cervical length was significantly shorter in the PTB group (31.8 ± 8.5 mm vs 38.1 ± 6.7 mm, $P < 0.001$). Women delivering preterm had higher serial NLR, PLR, FPG, TG, TC, LDL-C, and ApoB, alongside lower HDL-C and ApoA across all trimesters (all $P < 0.05$). Monochorionic placentation was more prevalent among PTB cases (33.9% vs 19.3%, $P < 0.001$)(Table 1).

Table 1
Baseline characteristics and comparison of metabolic profiles

Variable	Overall (n = 601)	PTB < 37 weeks (n = 295)	Term (n = 306)	P value
Maternal age (years)	30.99 ± 3.94	31.00 ± 4.14	30.97 ± 3.73	0.927
Paternal age (years)	32.68 ± 4.55	32.89 ± 4.92	32.48 ± 4.16	0.309
Early-pregnancy BMI	21.69 ± 3.11	21.80 ± 3.13	21.59 ± 3.09	0.431
Mode of conception: AI	57 (9.5%)	30 (10.2%)	27 (8.8%)	0.456
IVF-ET	280 (46.6%)	129 (43.7%)	151 (49.3%)	
Natural conception	258 (42.9%)	131 (44.4%)	127 (41.5%)	
Chorionicity: Monochorionic	159 (26.5%)	100 (33.9%)	59 (19.3%)	< 0.001
Dichorionic	397 (66.1%)	180 (61.0%)	217 (70.9%)	
Mid-trimester cervical length (mm)	34.84 ± 8.31	31.84 ± 8.51	38.11 ± 6.72	< 0.001
First-trimester NLR	3.92 ± 1.53	4.07 ± 1.62	3.78 ± 1.43	0.024
Second-trimester NLR	4.60 ± 2.04	4.95 ± 2.23	4.21 ± 1.73	< 0.001
Third-trimester NLR	4.27 ± 1.67	4.74 ± 1.81	3.75 ± 1.33	< 0.001
First-trimester PLR	142.82 ± 45.76	146.99 ± 50.42	138.89 ± 40.58	0.036
Second-trimester PLR	136.26 ± 46.93	143.99 ± 47.53	127.81 ± 44.87	< 0.001
Third-trimester PLR	127.73 ± 43.85	139.14 ± 45.26	115.27 ± 38.66	< 0.001
First-trimester FPG (mmol/L)	4.75 ± 0.52	4.87 ± 0.42	4.63 ± 0.57	< 0.001
Second-trimester FPG (mmol/L)	4.72 ± 0.49	4.95 ± 0.47	4.46 ± 0.35	< 0.001
Third-trimester FPG (mmol/L)	5.17 ± 1.16	5.52 ± 1.15	4.80 ± 1.05	< 0.001
First-trimester TG (mmol/L)	1.65 ± 0.61	1.71 ± 0.58	1.60 ± 0.62	0.047
Second-trimester TG (mmol/L)	2.84 ± 1.07	3.11 ± 1.15	2.54 ± 0.88	< 0.001
Third-trimester TG (mmol/L)	4.13 ± 1.70	4.53 ± 1.86	3.71 ± 1.40	< 0.001
First-trimester TC (mmol/L)	4.79 ± 0.87	5.01 ± 0.87	4.58 ± 0.81	< 0.001

Footnote: Data are presented as mean ± SD or n (%) unless otherwise indicated. P-values were derived from Student's t-test or Chi-square test as appropriate.

Variable	Overall (n = 601)	PTB < 37 weeks (n = 295)	Term (n = 306)	P value
Second-trimester TC (mmol/L)	6.83 ± 1.33	7.32 ± 1.29	6.25 ± 1.14	< 0.001
Third-trimester TC (mmol/L)	7.24 ± 1.62	7.91 ± 1.67	6.53 ± 1.21	< 0.001
First-trimester HDL-C (mmol/L)	1.65 ± 0.31	1.61 ± 0.31	1.69 ± 0.32	0.002
Second-trimester HDL-C (mmol/L)	1.83 ± 0.36	1.74 ± 0.32	1.95 ± 0.37	< 0.001
Third-trimester HDL-C (mmol/L)	1.63 ± 0.35	1.50 ± 0.30	1.77 ± 0.34	< 0.001
First-trimester LDL-C (mmol/L)	2.46 ± 0.70	2.60 ± 0.71	2.33 ± 0.67	< 0.001
Second-trimester LDL-C (mmol/L)	3.80 ± 1.09	4.10 ± 1.05	3.46 ± 1.03	< 0.001
Third-trimester LDL-C (mmol/L)	4.04 ± 1.40	4.44 ± 1.43	3.62 ± 1.23	< 0.001
First-trimester ApoA (g/L)	1.52 ± 0.30	1.48 ± 0.28	1.56 ± 0.31	< 0.001
Second-trimester ApoA (g/L)	1.72 ± 0.30	1.65 ± 0.28	1.80 ± 0.30	< 0.001
Third-trimester ApoA (g/L)	1.65 ± 0.32	1.52 ± 0.25	1.79 ± 0.33	< 0.001
First-trimester ApoB (g/L)	0.77 ± 0.19	0.81 ± 0.19	0.73 ± 0.18	< 0.001
Second-trimester ApoB (g/L)	1.22 ± 0.29	1.33 ± 0.29	1.10 ± 0.25	< 0.001
Third-trimester ApoB (g/L)	1.39 ± 0.38	1.52 ± 0.38	1.25 ± 0.33	< 0.001
<i>Footnote: Data are presented as mean ± SD or n (%) unless otherwise indicated. P-values were derived from Student's t-test or Chi-square test as appropriate.</i>				

Metabolic trajectories

Seven metabolic indices yielded stable, clinically interpretable trajectories (Fig. 1). Notably: TG4 trajectory (persistently elevated TG with sharp late-pregnancy acceleration) carried a PTB rate of 80.4%; FPG G1 trajectory (sustained hyperglycaemia) 80.6%; TC1 trajectory (continuous hypercholesterolaemia) 96.2%; ApoB1 trajectory (persistently raised ApoB) 90.0%; HDL2 trajectory (progressive HDL-C rise) 21.7%; LDL1 trajectory (sustained LDL elevation) 76.5%; and ApoA2 trajectory (moderate stable ApoA) 20.9% (Table 2).

Table 2
Latent class trajectory models for FPG and lipid profiles Each row represents a distinct trajectory class for the specified biomarker.

Biomarker	Optimal classes	Class	N (%)	Within-class PTB rate	BIC
Triglycerides	4	TG1	299 (49.8%)	54.5%	-441.5
		TG2	199 (33.1%)	31.7%	
		TG3	52 (8.7%)	53.8%	
		TG4	51 (8.5%)	80.4%	
ApoB	3	ApoB1	50 (8.3%)	90.0%	-162.2
		ApoB2	216 (35.9%)	68.5%	
		ApoB3	335 (55.7%)	30.4%	
ApoA	3	ApoA1	446 (74.2%)	55.8%	367.2
		ApoA2	86 (14.3%)	20.9%	
		ApoA3	69 (11.5%)	40.6%	
HDL-C	2	HDL1	518 (86.2%)	53.5%	670.5
		HDL2	83 (13.8%)	21.7%	
FPG	4	G1	31 (5.2%)	80.6%	3546.9
		G2	316 (52.6%)	31.0%	
		G3	215 (35.8%)	68.8%	
		G4	39 (6.5%)	61.5%	
LDL-C	2	LDL1	179 (29.8%)	76.5%	4526.5
		LDL2	422 (70.2%)	37.4%	
Total cholesterol	3	TC1	53 (8.8%)	96.2%	5281.7
		TC2	353 (58.7%)	29.2%	
		TC3	195 (32.4%)	72.3%	

BIC values are presented for the optimal model selected; lower values indicate better model fit.

These patterns supported a pathophysiological schema wherein pro-atherogenic lipid accumulation coexists with attenuated protective lipoprotein responses in women destined for preterm delivery [12]. These patterns supported a pathophysiological schema wherein pro-atherogenic lipid accumulation

coexists with attenuated protective lipoprotein responses in women destined for preterm delivery, consistent with recent findings in twin cohorts [13].

Risk phenotypes

Four phenotypes emerged (Table 3): P1 (low risk, longest cervix, lowest metabolic aberrations, PTB 25.9%); P2 (intermediate, predominantly TG-high trajectory, PTB 38.6%); P3 (high risk, universal monochorionicity, shorter cervix, PTB 76.5%); P4 (very high risk, universal dichorionicity, combined metabolic excess and cervical shortening, PTB 79.8%). After adjustment for confounders, P2–P4 conferred progressively higher PTB risk relative to P1, with adjusted ORs of 1.97 (95% CI 1.13–3.44), 6.90 (2.81–16.94), and 12.65 (6.67–23.98), respectively (Table 4, Fig. 2).

Table 3

Phenotypic clustering of twin pregnancies based on metabolic trajectories, cervical length, chorionicity, and inflammation Phenotypes (P1–P4) were derived using PAM clustering.

Phenotype	N (%)	PTB rate	Cervical length (mm)	Mid-trimester NLR	Monochorionic proportion	High-risk FPG class	High-risk TG class
P1	147 (29.6%)	25.9%	37.6	4.13	13.6%	4.1%	4.1%
P2	127 (25.6%)	38.6%	37.0	4.49	16.5%	8.7%	6.3%
P3	98 (19.8%)	76.5%	32.3	4.73	100.0%	6.1%	19.4%
P4	124 (25.0%)	79.8%	31.1	5.03	0.0%	7.3%	7.3%

High-risk FPG class refers to G1; high-risk TG class refers to TG4. This table is a descriptive summary of the four phenotypic clusters.

Table 4

Association between risk phenotypes and PTB (< 37 weeks) Odds ratios (ORs) and 95% confidence intervals (CIs) were derived from logistic regression.

Model	Phenotype	Events/Sample	OR (95% CI)	P value	Overall P value
Adjusted	P1	32/124	1.00 (reference)		< 0.001
Adjusted	P2	47/119	1.97 (1.13, 3.44)	0.017	
Adjusted	P3	72/94	6.90 (2.81, 16.94)	< 0.001	
Adjusted	P4	90/113	12.65 (6.67, 23.98)	< 0.001	
Unadjusted	P1	38/147	1.00 (reference)		< 0.001
Unadjusted	P2	49/127	1.80 (1.08, 3.01)	0.025	
Unadjusted	P3	75/98	9.35 (5.16, 16.97)	< 0.001	
Unadjusted	P4	99/124	11.36 (6.40, 20.15)	< 0.001	

The base model was adjusted for maternal age, pre-pregnancy BMI, parity, and mode of conception. P1 served as the reference category.

Prediction model performance

Cross-validated discrimination differed markedly across models (Table 5). The LASSO-enhanced model (M2) achieved an AUC of 0.902 (Brier 0.126), significantly exceeding M1 (AUC 0.565, Brier 0.244) and M3 (AUC 0.730, Brier 0.198)(Fig. 3). M2 retained mid-trimester FPG, TC, HDL-C, LDL-C, ApoB, and TC trajectory class (Table 6). Multiple imputation yielded consistent results (average AUC 0.919), confirming stability.

Table 5

Five-fold cross-validation performance of three logistic regression models for predicting PTB M1: baseline clinical model; M2: LASSO-enhanced model incorporating metabolic trajectories and lipid indices; M3: phenotype-based model.

Model	Description	N	Events	Apparent AUC	5-fold CV AUC	5-fold CV Brier	5-fold CV Sensitivity	5-fold CV Specificity
M1	Baseline model	452	239	0.593	0.565	0.244	0.368	0.803
M2	LASSO-enhanced model	452	239	0.925	0.902	0.126	0.774	0.892
M3	Phenotype model	452	239	0.765	0.730	0.198	0.669	0.803

The primary discriminative metric is the 5-fold CV AUC (higher is better). The Brier score reflects overall prediction error (lower is better). The apparent AUC reflects in-sample fit only.

Table 6
Multivariable logistic regression coefficients of the final LASSO-penalised prediction model (M2) Variables were selected via LASSO regression. Only non-intercept terms are shown.

Variable	OR (95% CI)	P value
Mid-trimester HDL-C	0.00 (0.00, 0.01)	< 0.001
Mid-trimester FPG	14.66 (6.05, 35.53)	< 0.001
Mid-trimester TC	44.25 (15.85, 123.56)	< 0.001
Mid-trimester LDL-C	0.16 (0.07, 0.37)	< 0.001
Mid-trimester ApoB	0.00 (0.00, 0.01)	< 0.001
TC trajectory: Class 2 vs Class 1	0.19 (0.09, 0.42)	< 0.001

TC trajectory Class 1 served as the reference group.

In subgroup analyses, M2 discriminated well in both monochorionic (AUC 0.938) and dichorionic (AUC 0.893) twins, and across spontaneous (AUC 0.774) and suspected iatrogenic (AUC 0.839) PTB. Time-dependent ROC analysis demonstrated strong dynamic prediction (AUC 0.859 at 32 weeks). Risk stratification by predicted probability quartiles showed observed PTB rates of 6.2%, 34.5%, 76.1%, and 94.7% from lowest to highest quartile, indicating excellent calibration.

Sensitivity analyses excluding potential iatrogenic cases or applying alternative PTB definitions preserved the graded risk associations across phenotypes (Table 7). Restricted cubic splines suggested a linear relationship between cervical length and PTB risk without a clear threshold effect. The inflection points for the preterm and term groups were 25.1 weeks and 24.6 weeks, respectively. These findings suggest that the rate of cervical shortening accelerates at approximately 24–25 weeks of gestation in both groups, although the clinical implications of this time window require validation using external datasets. Exploratory spline fitting is illustrated in Fig. 4.

Table 7

Sensitivity analysis: association between risk phenotypes and PTB under alternative definitions Base model adjusted for maternal age, pre-pregnancy BMI, parity, and mode of conception.

Sensitivity scenario	Phenotype	Events/Sample	OR (95% CI)	P value	Overall P value
Alternative outcome: diagnostic code PTB	P1	30/124	1.00 (reference)		< 0.001
	P2	43/119	1.84 (1.04, 3.24)	0.036	
	P3	71/94	6.26 (2.56, 15.31)	< 0.001	
	P4	85/113	10.77 (5.78, 20.10)	< 0.001	
Excluding suspected iatrogenic PTB	P1	28/120	1.00 (reference)		< 0.001
	P2	39/111	1.80 (1.00, 3.23)	0.051	
	P3	54/76	4.79 (1.93, 11.89)	< 0.001	
	P4	68/91	11.31 (5.81, 22.00)	< 0.001	

The primary analysis did not pre-exclude suspected iatrogenic PTBs; these analyses test the robustness of phenotypic risk gradients under alternative outcome definitions.

The horizontal axis represents mid-trimester cervical length (mm), and the vertical axis represents the cross-validated predicted probability derived from the M2 model. This probability reflects the integrated output of all six variables comprising the M2 model, rather than being determined solely by cervical length. The solid line indicates the fitted trend, and the dashed lines denote the 95% confidence intervals.

Notably, the adverse effects of aberrant metabolic trajectories were more pronounced for earlier PTB. Subgroup analyses revealed that the incidence of PTB < 34 weeks in the TC1 and TG4 subgroups reached 65.3% and 58.9%, respectively, significantly higher than those in the reference groups ($P < 0.05$). Similarly, the risk of PTB < 32 weeks was markedly elevated among mothers exhibiting sustained hyperlipidaemia, underscoring that severe lipid metabolic maladaptation is strongly associated with very and extreme prematurity in twin gestations.

Discussion

Our findings reinforce that PTB in twins is not merely a mechanical consequence of overdistension but a process closely associated with metabolic dysregulation. By mapping longitudinal FPG and lipid trajectories, we identified distinct phenotypic patterns that convey markedly different risks. Most strikingly, a small subset of women (~ 9%) exhibited relentless total cholesterol elevation throughout

gestation (TC1), with attendant PTB rates exceeding 95%. Such extreme phenotypes likely represent failed metabolic adaptation, wherein chronic lipid overload fosters endothelial dysfunction, oxidative stress, and placental hypoperfusion [14, 15]. This is consistent with broader epidemiological evidence linking early-pregnancy metabolic syndrome to a nearly threefold increase in PTB risk [16].

The biological plausibility of these observations aligns with accumulating evidence linking atherogenic dyslipidaemia to uteroplacental insufficiency. Sustained elevations in ApoB-rich lipoproteins (TC1, ApoB1, LDL1) may promote foam cell formation within decidual vessels, impairing spiral artery remodelling and triggering a cascade culminating in preterm parturition [14, 17]. Conversely, the apparently protective HDL2 trajectory underscores the importance of efficient reverse cholesterol transport and anti-inflammatory actions in maintaining placental homeostasis, although this benefit appears attenuated when coexisting with severe pro-atherogenic shifts [7, 15].

A notable strength of our approach lies in capturing trajectory slope rather than absolute values. The TG4 phenotype—characterised by late third-trimester surges—exemplifies how metabolic decompensation may precipitate iatrogenic or spontaneous preterm delivery. This complements prior work highlighting mid-trimester TG elevations as harbingers of adverse outcomes [12, 13]. and extends to the observation that lipid trajectory shape—not merely baseline levels—determines long-term metabolic risk [18]. Integrating such dynamic information may offer a potential approach to mitigating a key limitation of static biomarkers.

From a predictive analytics perspective, the LASSO-enhanced model (M2) represents a notable step forward and an incremental improvement over existing models. Its AUC of 0.902 surpasses most published algorithms for twin PTB prediction, which typically rely on static anatomical markers such as cervical length or uterine artery Doppler and yield AUCs below 0.80 [19, 20]. For instance, Lv et al. recently developed a nomogram specifically targeting spontaneous extremely PTB (< 28 weeks) in twins using cervical length, dilation, and CRP, achieving a C-index of 0.88–0.89 in development and external validation cohorts [21]. While their model addressed the critical yet narrower endpoint of extreme prematurity, our study captures the full spectrum of PTB (< 37 weeks) and incorporates longitudinal metabolic trajectories—rather than single time-point anatomic or inflammatory indices—which may explain the incremental gain in discriminative performance (AUC 0.902) observed in this cohort. Importantly, M2 retained metabolic trajectory class alongside conventional lipids, reinforcing that how these indices evolve across gestation matters as much as their absolute concentrations. The incremental value over the phenotype-only model (M3) suggests that continuous metabolic variables convey prognostic information beyond categorical clustering alone. Tan et al. recently demonstrated that machine learning models incorporating metabolic and inflammatory features can achieve high discriminative performance (AUC 0.952) for PPRM prediction, further supporting the value of multi-dimensional metabolic integration [22].

Interestingly, systemic inflammatory markers (NLR, PLR) lost significance in multivariable models once metabolic trajectories were accounted for. This supports the hypothesis that dyslipidaemia may be an

upstream driver of chronic inflammation in pregnancy, rather than a mere epiphenomenon [6, 23, 24]. While NLR and PLR have demonstrated modest predictive value for spontaneous PTB in selected populations (AUC 0.67–0.69) [25], their incremental contribution appears attenuated when comprehensive metabolic profiling is available. Recent studies have similarly shown that early pregnancy inflammatory indices lose independent predictive value after adjusting for metabolic parameters. Future mechanistic studies should explore whether targeted lipid modulation attenuates inflammatory activation and delays preterm delivery.

Limitations

Several limitations warrant mention. First, as a single-centre retrospective study, selection bias and unmeasured confounders (e.g., dietary habits, physical activity, socioeconomic status, and detailed maternal comorbidities) cannot be excluded. Although we adjusted for key clinical covariates and conducted extensive sensitivity analyses, residual confounding may persist. Second, while our model achieved high internal discrimination, definitive causal inference and generalizability require prospective multicentre external validation in geographically and ethnically diverse populations. Third, differentiating spontaneous from iatrogenic PTB remains challenging in retrospectively curated datasets; nonetheless, our model performed reasonably across both subtypes, and sensitivity analyses excluding suspected iatrogenic cases preserved the risk gradients. Fourth, our lipid profiling relied on standard clinical assays rather than advanced lipoprotein subfraction analysis or metabolomics profiling; future work incorporating these finer molecular phenotypes may uncover additional gradations of risk and refine predictive accuracy further. Finally, the exploratory spline analysis of cervical length (Fig. 4) identified inflection points at approximately 24–25 weeks, but the clinical implications of this window require validation using external datasets before any practice recommendations can be made [26, 27].

Clinical implications

Our data support potential refinement in twin antenatal care—from reliance solely on static snapshots towards the incorporation of longitudinal metabolic monitoring. Identifying a “malignant trajectory” (e.g., TC1, TG4) by late second trimester could prompt intensified surveillance, nutritional counselling, or consideration of prophylactic interventions such as progesterone or cervical cerclage in select cases. Conversely, reassuring trajectories (HDL2, ApoA2) might allow safe reduction in visit frequency, optimising resource allocation. Notably, such metabolic phenotyping may help identify women at risk for perpetuating intergenerational metabolic risk, warranting extended follow-up, given that maternal overweight and GDM jointly exacerbate offspring adiposity trajectories into adolescence [28]. However, the clinical utility of these findings requires confirmation through prospective, multicentre validation before widespread implementation. The clustering approach demonstrated that combining metabolic phenotypes with cervical length and chorionicity yields superior risk stratification compared with single parameter alone [4].

Conclusion

In conclusion, longitudinal glucose and lipid trajectories delineate biologically coherent phenotypes that effectively stratify the risk of PTB in twin pregnancies. A parsimonious model integrating these trajectories with routine clinical variables achieved robust predictive accuracy in this cohort. If validated externally in future multicenter studies, incorporating metabolic trajectory assessment into routine antenatal care may offer a pragmatic pathway for PTB prevention in this high-risk population.

Abbreviations

AUC

Area Under the Receiver Operating Characteristic Curve

ApoA

Apolipoprotein A

ApoB

Apolipoprotein B

BIC

Bayesian Information Criterion

CI

Confidence Interval

CL

Cervical Length

GBTM

Group-Based Trajectory Modelling

GDM

Gestational Diabetes Mellitus

HDL-C

High-Density Lipoprotein Cholesterol

HELLP

Hemolysis, Elevated Liver Enzymes, and Low Platelet count

IQR

Interquartile Range

LASSO

Least Absolute Shrinkage and Selection Operator

LDL-C

Low-Density Lipoprotein Cholesterol

M1

Baseline Clinical Prediction Model

M2

LASSO-Enhanced Metabolic Prediction Model

M3

Phenotype-Based Prediction Model

NLR

Neutrophil-to-Lymphocyte Ratio

PLR

Platelet-to-Lymphocyte Ratio

PTB

Preterm Birth

ROC

Receiver Operating Characteristic

SD

Standard Deviation

TC

Total Cholesterol

TG

Triglycerides

TyG

Triglyceride-Glucose Index

Declarations

Ethics approval and consent to participate

This study has been approved by the Ethics Committee of Fujian Maternity and Child Health Hospital. IRB NO.(2024KY214). The requirement for informed consent was waived by this IRB. The waiver was granted because the study used exclusively retrospective, de-identified, routinely collected clinical data, posed no more than minimal risk to participants, and did not influence patient care. This waiver is consistent with Article 39 of the Measures for Ethical Review of Biomedical Research Involving Humans, issued by the National Health Commission of the People's Republic of China, which permits waiver of informed consent for retrospective studies using anonymized data. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Consent for publication

The requirement for individual patient consent was waived by the IRB of Fujian Maternity and Child Health Hospital (No. 2024KY214), as the study involved retrospective analysis of fully anonymized data extracted from an administrative database and did not influence patient care or clinical decision-making.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

KH conceived and designed the study, drafted and revised the manuscript. YG collected data and performed statistical analyses. TY collected data, ZL and JY supervised the research and critically revised the manuscript. All authors read and approved the final version.

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Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Figures

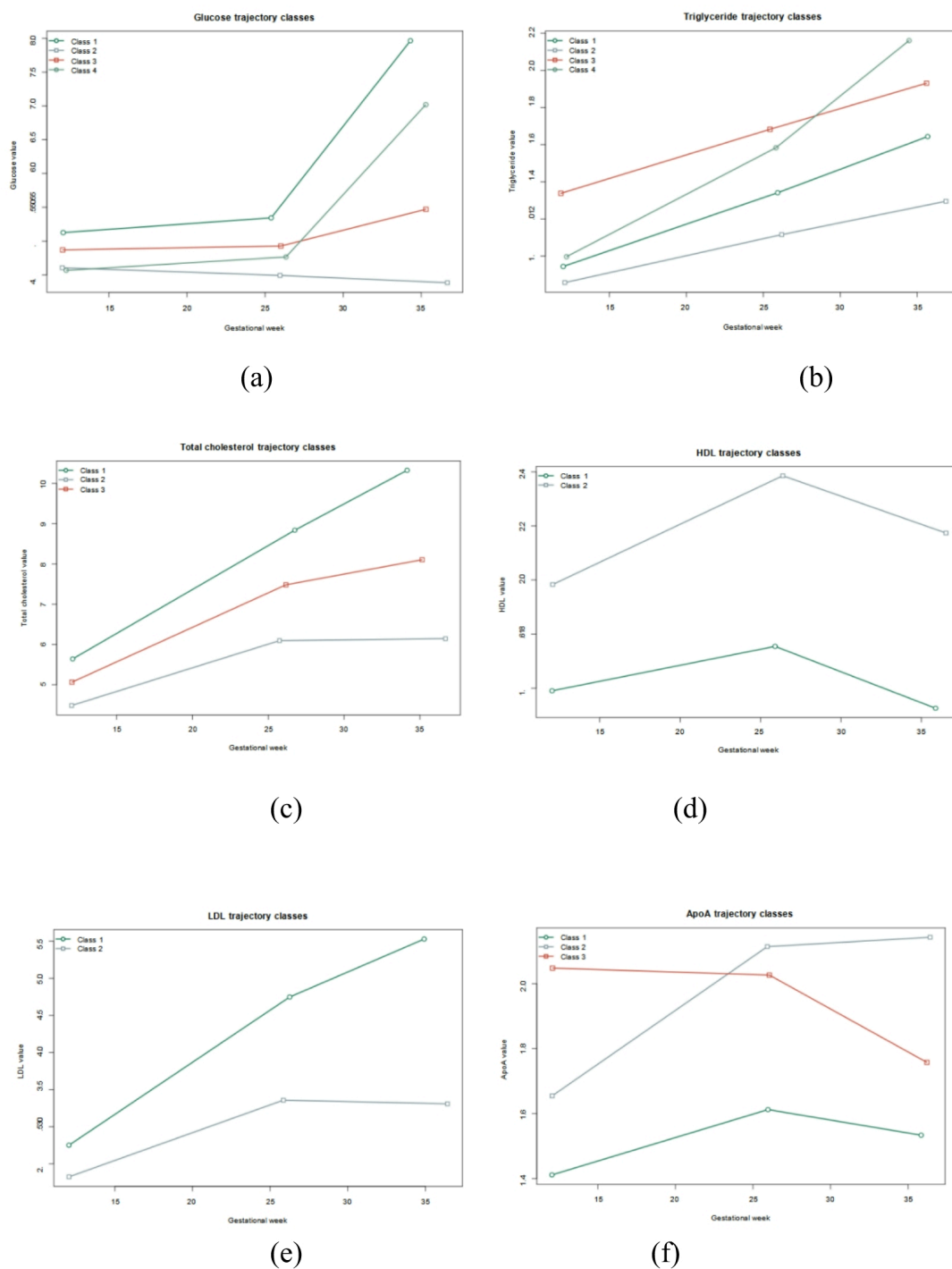


Figure 1

Longitudinal trajectories of FPG and lipid profiles during twin pregnancy. Longitudinal trajectories of FPG and lipid profiles. Each curve represents the mean trajectory of each latent class across the first, second, and third trimesters. . (a) FPG trajectory; (b) Triglyceride (TG) trajectory; (c) Total cholesterol (TC) trajectory; (d) High-density lipoprotein cholesterol (HDL-C) trajectory; (e) Low-density lipoprotein cholesterol (LDL-C) trajectory; (f) Apolipoprotein A (ApoA) trajectory; (g) Apolipoprotein B (ApoB) trajectory.

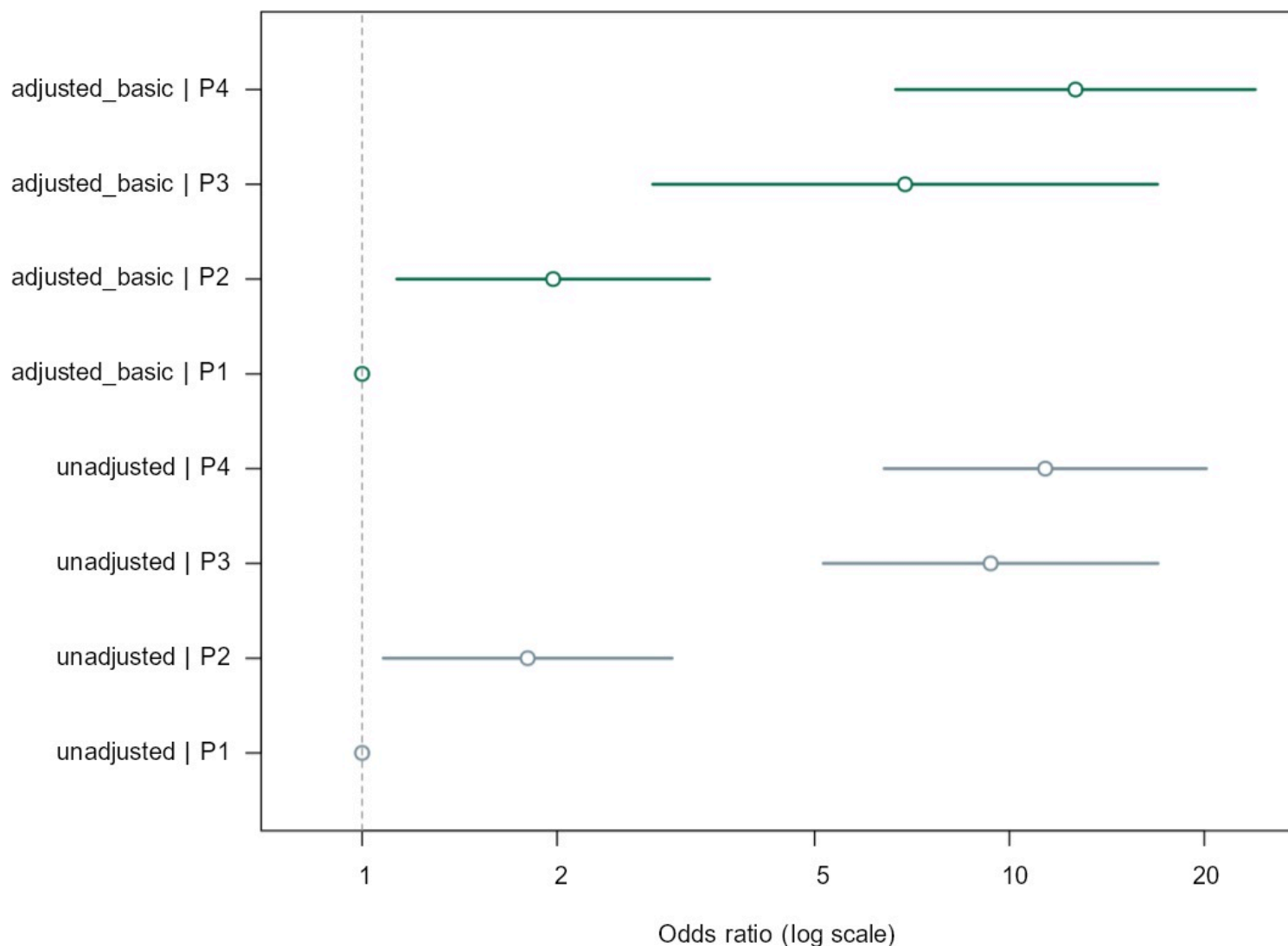


Figure 2

Forest plot illustrating the association between risk phenotypes and PTB(<37 weeks). Odds ratios (ORs) and 95% confidence intervals (CIs) were derived from multivariable logistic regression adjusting for maternal age, pre-pregnancy BMI, parity, and mode of conception. P1 serves as the reference category. Error bars represent 95% CIs; statistical significance ($P < 0.05$) is indicated by CIs not crossing the null value of 1.0.

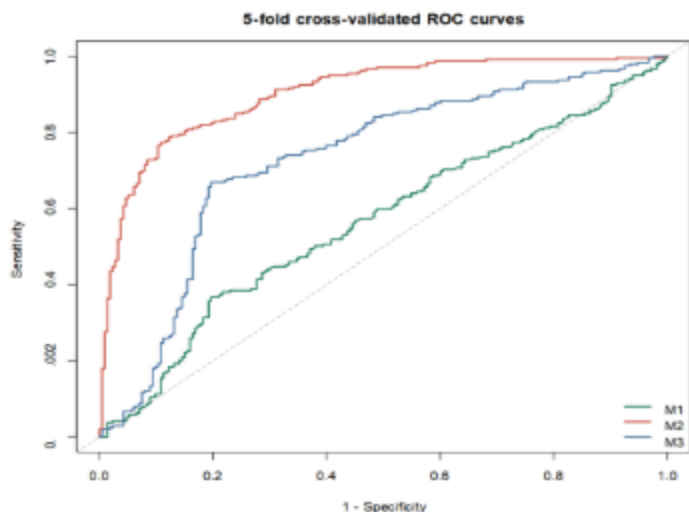


Figure 3

ROC curves for the three prediction models. M1 (blue dashed line) represents the baseline clinical model; M2 (red solid line) the LASSO-enhanced model incorporating metabolic trajectories and lipid indices; M3 (green dotted line) the phenotype-based model. AUC values were derived from five-fold cross-validation.

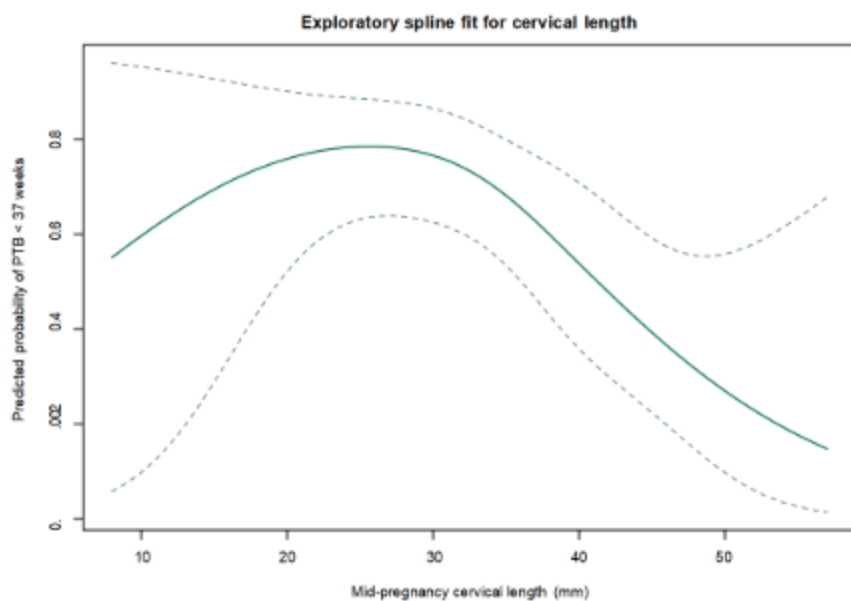


Figure 4

Restricted cubic spline analysis of mid-trimester cervical length and PTBrisk.

The horizontal axis represents mid-trimester cervical length (mm), and the vertical axis represents the cross-validated predicted probability derived from the M2 model. This probability reflects the integrated output of all six variables comprising the M2 model, rather than being determined solely by cervical length. The solid line indicates the fitted trend, and the dashed lines denote the 95% confidence intervals.