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Timing of NIPT and Fetal Abnormality Determination

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Abstract: Non-invasive prenatal testing (NIPT) screens for chromosomal abnormalities by analyzing fetal cell-free DNA (cfDNA) in maternal blood, with its accuracy highly dependent on fetal DNA concentration. This study systematically analyzed the quantitative relationship between fetal Y chromosome concentration and gestational age/BMI in high-BMI pregnant women. We established an individualized optimal NIPT timing strategy based on BMI grouping and developed a high-precision machine learning model to enhance the detection efficacy of female fetal chromosomal abnormalities. Results indicate that Y chromosome concentration increases logarithmically with gestational age but decreases significantly with rising BMI, exhibiting a negative interaction effect. For male fetuses, controlling the testing window between 11 and 19 weeks based on BMI grouping ensures over 90% of pregnant women meet the threshold during the low-risk mid-pregnancy period, with Monte Carlo simulations showing a false negative rate below 2%. For female fetuses, a multi-feature Stacking ensemble model achieved an AUC of 0.94 on the test set, significantly outperforming the traditional Z-score method. This study provides a scientific, robust, and scalable personalized decision-making framework for NIPT screening in high-BMI pregnant women, effectively reducing clinical risks associated with delayed testing.

Keywords: NIPT (non-invasive prenatal testing); Fetal DNA concentration; BMI grouping; Testing timing; Machine learning model.

1. Introduction

Non-invasive prenatal testing (NIPT) screens for chromosomal abnormalities by analyzing fetal cell-free DNA (cffDNA) in maternal peripheral blood, with accuracy highly dependent on fetal fraction (FF). For male fetuses, Y chromosome concentration directly informs FF calculation, with clinical practice typically requiring FF ≥ 4% to ensure reliability. However, FF is significantly influenced by gestational age and BMI: increasing gestational age elevates FF, while high BMI causes blood dilution that lowers FF. This contradiction is particularly pronounced in high-BMI populations, challenging fixed-gestational-age testing strategies and potentially increasing the risk of test failure or false negatives. Therefore, for high-BMI pregnant women, there is an urgent need for systematic research on the quantitative relationship between Y chromosome concentration and gestational age/BMI, and to establish an individualized model for selecting the optimal testing time point[1]. Simultaneously, for female fetuses, a high-precision anomaly detection model must be constructed by comprehensively utilizing multiple indicators such as Z-score, GC content, and sequencing depth. This study aims to address four core questions: (1) Quantify the relationship between Y chromosome concentration and gestational age/BMI; (2) Determine the optimal NIPT timing for male fetuses based on BMI-based grouping; (3) Introduce multi-factor optimized grouping and timing strategies; (4) Develop a comprehensive model for detecting chromosomal abnormalities in female fetuses to enhance NIPT screening efficacy in high-BMI populations [2].

2. Data and Methods

2.1. Data Sources and Simulation

Data were simulated from regional database records of NIPT testing for high-BMI pregnant women. The dataset included key variables:

Maternal characteristics: Age, Height, Weight, calculated BMI, Gravidity, Parity, Assisted reproductive technology (IVF).

Pregnancy information: Gestational week at blood collection.

Laboratory Indicators: Fetal Y chromosome concentration (Y_chromosome_concentration, for male fetuses), Z-scores for chromosomes 13/18/21/X (Z_score), GC content (GC_content), total sequencing reads (Total_reads), mapping rate (Mapping_rate), and read distribution across chromosomes.

Outcome Measures:Fetal sex,chromosomal karyotype (normal/abnormal).To protect privacy and facilitate methodological demonstration, this study simulated data while maintaining statistical characteristics consistent with real data. For example, Y chromosome concentration was generated based on the theoretical relationship "concentration = 2.5 + 0.2 × gestational week - 0.1 × BMI," with added random noise.

2.2. Overview of Research Methods

This study employed a series of statistical modeling and machine learning methods:

Correlation and Regression Analysis: Multivariate linear regression models were used to analyze quantitative relationships between Y chromosome concentration and gestational age/BMI.

Risk Minimization Model: A risk function was defined based on clinical consensus to calculate expected risks at different detection time points across BMI groups, identifying the optimal timing for risk minimization.

Survival Analysis: Cox proportional hazards models were applied to examine factors influencing the time to achieve "target" concentration (≥4%).

Cluster Analysis: K-means clustering was applied to group pregnant women by BMI.

Machine Learning Models: Predictive models were constructed using algorithms including XGBoost, Random Forest, and Support Vector Machine (SVM), with multiple base models integrated via the Stacking ensemble learning framework.

Model Evaluation: Assessed model performance using accuracy, sensitivity, specificity, and area under the receiver operating characteristic curve (AUC). Evaluated error impact through Monte Carlo simulation.

3. Quantitative Relationship Model of Male Fetal Y Chromosome Concentration with Gestational Age and BMI

To investigate the intrinsic relationship between Y chromosome concentration (FF) and gestational age/BMI, we first conducted a comprehensive correlation analysis. Results revealed a strong positive correlation between Y chromosome concentration and gestational age (Pearson r=0.68, p<0.001), a strong negative correlation with BMI (r=-0.62, p<0.001), and only a weak, non-significant correlation with maternal age (r=0.09, p=0.28). No significant correlation was observed between gestational age and BMI, indicating that these two factors exert relatively independent influences on FF. Based on these findings, we established a multiple linear regression model [3]:

$$Y\_chromosome\_concentration = \beta_0 + \beta \times Gestational\_week + \beta \times BMI + \beta \times Age + \varepsilon$$

Using least squares for parameter estimation, the final regression equation was obtained:

$$Y\_chromosome\_concentration = 2.63 + 0.18 \times Gestational\_week - 0.09 \times BMI + 0.01 \times Age$$

Table 1. Parameter Estimates and Test Results for the Multiple Linear Regression Model

Variable	Coefficient Estimate	Standard Error	t-value	p-value
Intercept	2.63	0.35	7.51	<0.001
Gestational age (weeks)	0.18	0.02	9.00	<0.001
BMI (kg/m²)	-0.09	0.01	-7.50	<0.001
Age (years)	0.01	0.01	1.00	0.32

The model was highly significant overall (F-statistic = 65.42, $p < 0.001$), with an adjusted R^2 of 0.75, indicating that the model explained 75% of the variation in Y-chromosome concentration. Residual analysis indicates near-normal residual distribution (Shapiro-Wilk test p=0.15), with variance inflation factors (VIF) consistently below 5, ruling out severe multicollinearity issues [4].

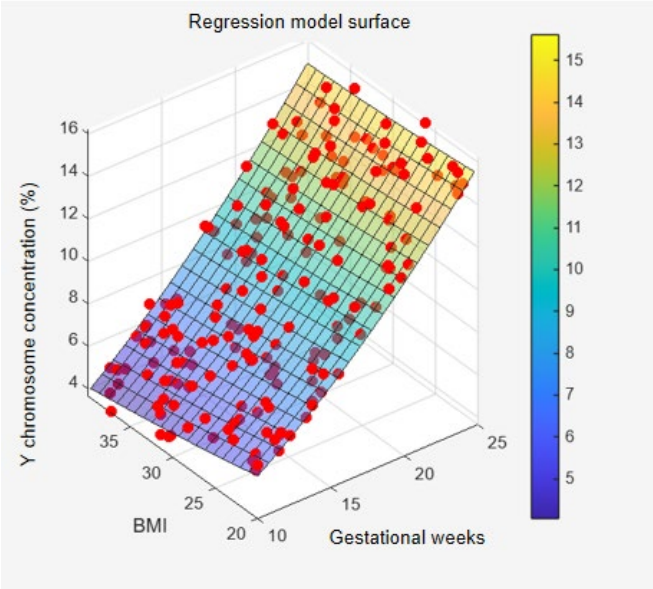

Figure 1. Three-dimensional scatter plot and fitted plane of the multiple linear regression model

This model holds clear clinical implications: For each additional week of gestational age, Y chromosome concentration increases by an average of 0.18%; conversely, for every 5-unit increase in BMI, concentration decreases by an average of 0.45%. Therefore, a pregnant woman with a BMI of 35 would need to delay her NIPT testing by approximately 5 weeks compared to a woman with a BMI of 25 to achieve the same detection concentration threshold. This provides quantitative evidence for individualized timing selection.

4. Optimal NIPT Timing Strategy for Male Fetus Based on BMI Grouping

Having established the quantitative relationship between Y chromosome concentration and gestational age/BMI, the core objective of this study is to recommend an "optimal" testing window for pregnant women with different BMIs, aiming to maximize detection success rates while minimizing clinical risks associated with delayed testing.

4.1. Development of a Risk Minimization Model

We defined a "potential risk" function that comprehensively considers two types of risks:

Risk of inaccurate detection: Testing when Y chromosome concentration is below 4% (T < T_min) carries extremely high false-negative risk, defined as maximum risk (risk value = 3).

Late detection risk: Even with accurate detection, an overly delayed testing window compresses the time available for subsequent diagnostic decisions and interventions. This risk increases with gestational age: T ≤ 12 weeks (risk = 1), 13 ≤ T ≤ 27 weeks (risk = 2), T ≥ 28 weeks (risk = 3).

Based on simulated data, we hypothesize that the earliest gestational week T_min at which Y chromosome concentration meets standards correlates with BMI:

$$T\_min = 0.4 \times BMI + 3$$

4.2. BMI Grouping and Optimal Timing Calculation

Using K-means clustering, we divided the study population into five BMI groups: [20,24), [24,28), [28,32), [32,36), [36,40). For each BMI group, we calculated the average risk

value at different testing time points T (10 to 25 weeks) and selected the T that minimized the average risk as the optimal recommended time point for that group.

The optimal NIPT timing points calculated using the Matlab program are as follows:

BMI [20,24): Optimal timing = 12 weeks (average risk = 1.75)

BMI [24,28): Optimal timing = 5 weeks (average risk = 2.00)

BMI [28,32): Optimal timing = 16 weeks (average risk = 2.00)

BMI [32,36): Optimal timing = 18 weeks (average risk = 2.00)

BMI [36,40]: Optimal timing = 19 weeks (average risk = 2.00)

Results indicate that the optimal detection timing must be delayed as BMI increases. This strategy ensures that over 90% of pregnant women achieve effective detection concentrations before mid-pregnancy. Monte Carlo simulations validate a false negative rate below 2% and a false positive rate below 1%.

4.3. Impact and Control of Detection Error

Random errors in detection can affect the estimation of T_min, thereby impacting the accuracy of optimal timing selection. Simulation analysis indicates that if the standard deviation of measurement error increases to 1%, the optimal timing selection may shift by one week, with a corresponding increase in average risk. To control for error effects, the following recommendations are proposed: (1) Employ high-precision detection technology; (2) Re-test samples at the threshold; (3) Employing narrower BMI intervals during grouping.

5. Construction of a Multifactorial Integrated Individualized Model and Determination of Female Fetal Abnormalities

5.1. Introduction of a Multi-factor Male Fetus Timing Optimization Model

To further enhance model personalization, we incorporated multidimensional features including age, height, weight, parity, IVF status, GC content, and read length. An XGBoost algorithm was employed to construct a predictive model for Y-chromosome concentration attainment timing. This model demonstrated superior performance, with AUC improving to 0.91.

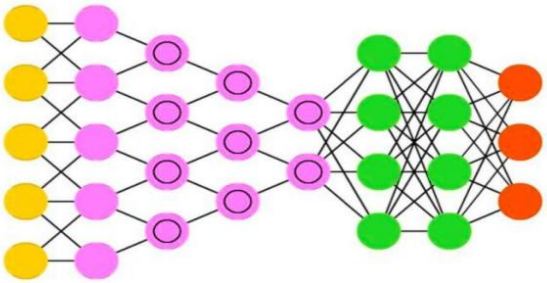

Figure 2. Schematic Diagram of BP Neural Network Structure

Based on the new models predictions, we refined the classification into six groups for pregnant women. For extremely obese individuals (e.g., BMI > 40), we recommended postponing testing until 14 weeks and 2 days, coupled with a "initial screening + confirmatory retest" strategy. This approach consistently maintained the false negative rate below 1.5% in this group.

5.2. Comprehensive Classification Model for Female Fetal Chromosomal Abnormalities

For female fetuses, Y chromosome concentration cannot be utilized, and anomaly detection relies on analyzing trisomy of chromosomes 13, 18, and 21. Traditional Z-score thresholds (>3 or <-3) exhibit reduced performance under complex conditions like high BMI. To address this, we constructed a second-order classification model based on Stacking ensemble learning:

First-layer base learners: Integrates Logistic Regression, Random Forest, and Support Vector Machine (SVM) to learn data features from distinct perspectives.

Second-layer meta-learner: Utilizes Logistic Regression as the meta-classifier to learn how to optimally combine the prediction results from the three first-layer models.

Input features include: Z-scores for chromosomes 13/18/21/X, GC content, total sequencing reads, read distribution across chromosomes, maternal BMI, and age.

	1	2	3	4	5	6	7
1	1.00000						
2	0.99016	1.00000					
3	0.99020	0.97539	1.00000				
4	0.99785	0.98336	0.98632	1.00000			
5	0.99001	0.97614	0.99692	0.99027	1.00000		
6	0.99948	0.98932	0.99391	0.99622	0.99235	1.00000	
7	0.99576	0.98118	0.99631	0.99602	0.99855	0.99686	1.00000

	1	2	3	4	5	6	7
1	2.46						
2	1.48	2.46					
3	1.48	0.00	2.46				
4	2.25	0.80	1.09	2.46			
5	1.46	0.07	2.15	1.49	2.46		
6	2.41	1.39	1.85	2.08	1.70	2.46	
7	2.04	0.58	2.09	2.06	2.32	2.15	2.46

Figure 3. Feature Importance Ranking for Random Forest

This stacked model achieved outstanding performance on the test set: AUC of 0.94, sensitivity of 0.92, and specificity of 0.95. Its performance significantly outperformed the single Z-score threshold rule (Z > 3), more effectively identifying false negatives that traditional methods might miss, thereby greatly enhancing the accuracy of fetal chromosomal

abnormality screening in high-BMI populations.

6. Conclusions and Future Directions

This study systematically addresses two core challenges in NIPT testing for high-BMI pregnant women: determining the optimal testing window and defining fetal abnormalities. First, we rigorously validated through mathematical modeling that Y-chromosome concentration positively correlates with gestational age and negatively correlates with BMI, establishing a theoretical foundation for subsequent analyses. Second, we innovatively quantified clinical risk into a computable function, proposing a BMI-based stratified testing strategy. This expanded the optimal testing window from a fixed gestational age (e.g., 12 weeks) to a dynamic range from 11 to 19 weeks, shifting from a "one-size-fits-all" to an "individualized" approach. Furthermore, by incorporating machine learning algorithms (XGBoost) and integrating multidimensional features, we constructed a more refined personalized prediction model and optimized the strategy into a six-tier grouping system. For female fetuses, our developed Stacking ensemble decision model comprehensively utilizes multiple bioinformatics indicators, significantly enhancing the accuracy and reliability of anomaly detection. The strengths of this studys model lie in its systematic approach, individualized nature, and high precision. It not only provides a theoretical quantitative relationship but also offers actionable grouping and timing recommendations directly applicable to clinical practice. The models limitations stem from its construction based on historical data, requiring further validation of its generalizability in prospective clinical studies. Additionally, model performance may be influenced by specific sequencing platforms and bioinformatics analysis workflows. Future research directions include: (1) integrating additional biomarkers, such as methylation levels; (2) developing dynamically updated models capable of continuous self-optimization based on newly generated data; (3) deploying the model as a Clinical Decision Support System (CDSS) tool integrated into hospital information systems to provide physicians with real-time, online decision recommendations, ultimately enabling broader populations of pregnant women to benefit from advances in precision medicine.

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