Quad test for fetal aneuploidy screening as a predictor of fetal growth restriction: A population-based study

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Research article

Keywords: Quad test, fetal aneuploidy screening, fetal growth restriction

DOI: https://doi.org/10.21203/rs.3.rs-51253/v1

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Abstract

**Background:** To identify the relationship between quadruple test for aneuploidy screening (alpha-fetoprotein: AFP; free beta-human chorionic gonadotropin: b-hCG; unconjugated estriol: uE3 and inhibin-A: IHA) and fetal growth restriction and to construct predictive models for fetal growth restriction (FGR).

**Methods:** Women who underwent quadruple test for aneuploidy were followed-up for final outcomes. The multiple of median (MoMs) of the four biochemical markers for the FGR group and those of normal fetuses were compared. The models for predicting FGR by the individual biomarkers and their combination were constructed using binary logistic regression analysis, and their diagnostic performances in predicting FGR were determined.

**Results:** Of 10,155 eligible pregnant women, 578 (5.7%) and 9577 (94.3%) had FGR and normal growth, respectively. High levels of AFP, b-hCG and IHA but low levels of uE3 significantly increased the risk of FGR. The constructed predictive equations had predictive performance for FGR, with areas under the receiver-operated characteristic curve of 0.724, 0.655, 0.597, 0.664 and 0.754 for AFP, b-hCG, uE3, IHA, and the combination, respectively.

**Conclusion:** The quad test for aneuploidy screening could also be used as a predictor of FGR, without extra-effort and extra-cost.

**Background**

Intrauterine fetal growth restriction (FGR), usually defined as fetuses with birth weight of less than the 10th percentile, is one of the common conditions of high-risk pregnancy, leading to poor pregnancy outcomes, such as perinatal morbidity and mortality as well as abnormal neurodevelopment. Also, it can increase poor maternal outcomes, such as higher rate of cesarean section, maternal depression, higher cost of antenatal and postnatal care, etc. The incidence of FGR in developing countries varies from 6 to 30% of live births \(^1\), depending on definitions and criteria for diagnosis. Recently, many techniques have been developed to achieve early detection of FGR in order to render the care needed by a high-risk pregnancy and provide effective antenatal care, thereby ensuring the prevention of unexpected adverse outcomes for both mothers and infants. To date, there is no well accepted method to predict FGR among low-risk pregnant women; therefore, new effective methods must be sought. Recently, the implementation of serum screening for fetal aneuploidy commenced worldwide, and many studies have shown that both first and second trimester serum marker screenings can also predict some other pregnancy outcomes, such as fetal growth restriction, preeclampsia and preterm delivery \(^2\–8\). Nevertheless, to date, there is no consensus concerning how to apply this knowledge to actual practice. Several studies demonstrated an association between individual marker levels and rate of FGR, but most studies have only a limited number of women, and it is difficult to implement these findings in actual use. Moreover, it is well established that racial factors strongly impact on serum marker levels \(^9\–13\), and the normative data of serum biomarkers derived from Caucasian women cannot accurately be interpreted when used in other
parts of the world. Though several studies have linked abnormal serum marker levels to higher rate of FGR, no study provides objective methods or models derived from individual serum markers that can be clinically used to determine the probability of FGR. In many developing countries, serum marker screening for Down syndrome has been implemented free of charge as a national policy. FGR is one of leading causes of perinatal deaths, many of which could be prevented if higher-risk pregnancies are identified in early pregnancy. Serum biochemical markers are informative for not only the fetal risk of aneuploidy but also the risk of poor pregnancy outcomes (2, 4, 6–8, 14–17). The earlier the detection of such risks, the more effective the management would be. Therefore, we can take advantage of the daily serum biomarker screening for aneuploidy to detect the risk of FGR in the same tests without any additional work or expense. Accordingly, we carried out this study as a secondary analysis of a prospective database and as a population-based study. The study aims to identify the performance of the second trimester serum marker screening (quad test) in predicting FGR and to develop a predictive model for FGR, like the predictive model for fetal Down syndrome. With the newly created model, we hope that for each blood sample analysis, the serum biomarker machine could report the risk of trisomy 21, trisomy 18, and trisomy 13 and the risk of FGR in the same setting. The main objectives are as follows: 1) To identify the relationship between second trimester serum markers or quadruple (quad) test, consisting of alpha fetoprotein (AFP), free beta-human chorionic gonadotrophin (b-hCG), unconjugated estriol (uE3), and inhibin-A (IHA), and the rate of FGR. 2) In case of significant relationship, the model predicting the risk of FGR is constructed.

Methods

A cohort as well as diagnostic study was conducted as a secondary analysis of a prospective database of the maternal-fetal medicine (MFM) unit of Chiang Mai University, Thailand. The database was developed under the “Prenatal Control of Down Syndrome Project” of the National Health Security Office, Thailand. Under the project, all pregnant women that attended our antenatal care clinic and our network hospitals were offered quad test as a screening test for fetal Down syndrome in the second trimester free of charge. This study was conducted with ethical approval by the Institutional Review Board. (The Research Ethics Committee 4; Faculty of Medicine, Chiang Mai University; Study Code: OBG-2562-06069 / Research ID: 06069) All women who participated in the project provided written informed consent. The study population was pregnant women who attended antenatal care at Maharaj Nakorn Chiang Mai Hospital and the network hospitals in the northern part of Thailand and underwent second trimester quad test for fetal Down syndrome screening, with known pregnancy outcomes, between January 2016 and October 2019.

Database development

The primary project was undertaken to assessing the efficacy of the maternal quadruple (quad) test in our population in the detection of fetal Down syndrome. All pregnancies were prospectively followed up for the pregnancy outcomes and fetal status of aneuploidy. All participants were of Thai ethnicity and were living in the North of Thailand. They participated with the project with informed consent after
counseling by the project team. The baseline characteristics (age, parity, body weight, ethnicity, medical conditions, etc.) and laboratory analysis of the serum biomarkers were reviewed by the authors and prospectively obtained. The serum biomarker levels of all collected samples were determined at the same project laboratory (completely automated assay, DELFIA® Xpress system; Perkin Elmer, Waltham, MA, USA), with the standard immunoassay kits of AFP, b-hCG, uE3, and IHA. The quad screens were tested for free, financially covered by the National Health Security Office, Thailand. The participants were followed-up for obstetric outcomes such as birth weight, gestational weeks at birth, route of delivery, fetal anomalies, obstetric complications, etc. The newborns were assessed by pediatricians. Chromosome studies were performed only in women categorized as high risk by the quad test or the newborns with suspicion of abnormalities after assessment by the neonatologists. The chromosome abnormalities were confirmed either by amniocentesis or cytogenetic studies after birth, whereas diagnoses of normal chromosomes were confirmed by cytogenetic work-up or the conclusion by the neonatologists in cases that cytogenetic study was not done.

**Data Retrieval:** The project database, which was developed between 2016 and 2019, was accessed to obtain the records meeting the inclusion criteria as well as complete information of baseline characteristics and obstetric data such as maternal age and weight, underlying medical diseases, smoking history, gestational week of blood sampling for maternal serum biomarkers, gestational week at birth, baby weight and anomalies. The inclusion criteria for retrieval of the records are as follows: 1) single gestation, 2) undergoing serum biomarker test (quad test) at gestational age of 15–21 weeks, and 3) availability of final obstetric outcomes. The cases with the following criteria were excluded: 1) multifetal gestation, 2) fetal anomaly or aneuploidy, 3) unavailability of obstetric outcomes, 4) pregnancy termination before 20 weeks of pregnancy and 5) significant medical complications, for examples, uncorrected cyanotic heart disease, uncontrolled hyperthyroidism, renal impairment, etc.

**Data Processing:** The women who met the inclusion criteria were divided into two groups: pregnancies without FGR (control group) and pregnancies with FGR (study group). All records, including baseline characteristics, serum biomarker levels, obstetric and neonatal outcomes, were reviewed and validated. The definitions used in this study are as follows: 1) Gestational age: Gestational age was based on crown-rump length (CRL) in the first trimester or biparietal diameter (BPD) in the second trimester. 2) Second trimester serum screening: Screening test for fetal aneuploidy in the second trimester (quad screen) using four serum biomarkers, including maternal serum AFP, b-hCG, uE3, and IHA, collected at gestational age of 15–21 weeks. Abnormal levels of the biomarkers were defined as the levels of greater than 2 MoM for AFP, b-hCG and IHA and less than 0.5 MoM for uE3 (based on previous studies). 3) Fetal growth restriction: A fetus with birth weight lower than the 10th percentile of the gestational date (18).

**Sample size estimation**

Based on previous studies, the relative risk of FGR among pregnant women with abnormal quad screen (elevated AFP) is approximately 1.6-4.0 (7). To estimate the sample size, a cohort study with estimated
relative risk of 1.8 and prevalence of FGR in the control group of approximately 7% needs a sample size of at least 536 affected cases, at 95% confidence and 80% power of test.

**Primary outcome**

Incidences of FGR among pregnant women with normal and abnormal concentrations of the four serum biochemical markers; AFP, b-hCG, uE3, and IHA.

**Statistical analysis:** The statistical procedures were undertaken using the SPSS software (IBM Corp. Released 2012; IBM SPSS Statistics for Windows, Version 21.0. Armonk, New York). The statistical techniques are the same as those used in determining the fetal risk of aneuploidy, summarized as the followings. The multiple of the medians (MoMs) of the four biochemical markers (AFP, b-hCG, uE3 and IHA) were obtained by the following steps: (1) performing regression analysis, using a stepwise technique, of the log10 levels of the four serum markers as a dependent variable against potential independent factors, for examples gestational week of blood sampling, maternal age and weight, history of smoking, etc.; (2) determining the expected log10 levels of the serum markers for individual woman by using the constructed regression model in the prior step; (3) transforming the log10 value to the expected level of the biomarker; (4) calculating the MoMs by dividing the actual measured levels of the serum markers of all women by their expected levels. Fetal growth restriction (FGR) predictive models were constructed using a binary logistic regression method, with serum markers as dependent variables and FGR as an independent variable. With using the adjusted MoM values, the log-Gaussian distributions of each serum marker for FGR were derived. The performances of the created models were validated by receiver-operated characteristics (ROC) curves, with sensitivities and false positive rates predicting fetal growth restriction. The diagnostic indices of each serum marker and their combination were compared, using the ROC area under the curve. A likelihood ratio was also determined by dividing the density of the distribution of fetal growth restriction group by that of the normal group. The final risk of FGR was obtained by multiplying the likelihood ratio by the background risk.

**Results**

During the study period of our project of prenatal screening for fetal Down syndrome, 13,406 women underwent quad test (AFP, b-hCG, uE3 and IHA). Among them, 3,251 cases were excluded because of various reasons, as presented in Fig. 1, and the remaining 10,155 pregnancies were available for analysis, including 9,577 (94.3%) pregnancies with non-FGR and 578 (5.7%) pregnancies with FGR. The baseline characteristics of the two groups are presented in Table 1. Based on multiple regression analyses of the serum biomarker levels (AFP, b-hCG, uE3 and IHA), the fitted models for expected levels of the four serum biomarkers were constructed, as shown in Table 2.
Table 1
Baseline characteristics of the pregnant women according to fetal growth status

| Characteristics                          | Non-FGR | FGR     | P-value* |
|-----------------------------------------|---------|---------|----------|
| Maternal age (yr) ± SD                  | 28.3 ± 11.2 | 28.8 ± 6.3 | 0.464    |
| Maternal weight (Kg) ± SD              | 57.5 ± 11.3 | 53.9 ± 11.2 | < 0.001  |
| Gestational week at sampling ± SD      | 15.5 ± 2.0 | 15.5 ± 2.9 | 0.824    |
| Gestational week at delivery ± SD      | 38.4 ± 1.7 | 37.4 ± 2.8 | < 0.001  |
| Birth weight (gm) ± SD                 | 3068 ± 444 | 2162 ± 418 | < 0.001  |
| Parity                                  |          |         | 0.129    |
| • Nulliparous                           | 48.7%    | 51.9%   |          |
| • Parous                                | 51.3%    | 48.1%   |          |

* Student T test for continuous data, Chi-square test for categorical data

Table 2
The models predicting serum biomarker levels

| Biomarkers | The models                                                                 |
|------------|-----------------------------------------------------------------------------|
| AFP levels | ln (AFP level) = 1.536 + 0.0161 (GA: week) − 0.0054 (Weight: Kg) − 0.0293 (DM); (r = 0.368; p-value < 0.001) |
| b-hCG levels | ln (b-hCG level) = 1.875 − 0.0164 (GA: week) − 0.0052 (Weight: Kg) + 0.0006 (Age, year) − 0.0487 (DM); (r = 0.392; p-value < 0.001) |
| uE3 levels | ln (uE3 level) = 0.2610 + 0.0236 (GA: week) − 0.0013 (Weight: Kg) − 0.0345 (DM) − 0.0005 (Age, year); (r = 0.274; p-value < 0.001) |
| IHA levels | ln (IHA level) = 2.6962 − 0.0068 (GA: week) − 0.0032 (Weight: Kg) + 0.0007 (Age, year) − 0.1383(DM); (r = 0.398; p-value < 0.001) |

DM: diabetes mellitus

Notably, all four serum biomarkers are significantly associated with gestational age, maternal age, maternal weight, and DM status, except that maternal age is not significantly associated with AFP levels. The means and medians of the MoMs of AFP, b-hCG and IHA are significantly higher in the group of FGR than those in the non-FGR group, whereas the mean and median of the MoMs of uE3 are significantly lower in the FGR group, as shown in Table 3 and Fig. 2.
Table 3
Comparisons of mean and median MoMs of AFP, b-hCG, uE3 and IHA between non-FGR vs FGR group

| Group | Non-FGR | FGR | P-value |
|-------|---------|-----|---------|
| Group | MoMs    | MoMs|         |
| Means ± SD* |       |     |         |
| AFP MoMs | 1.077 ± 0.736 | 1.417 ± 0.706 | < 0.001 |
| b-hCG MoMs | 1.192 ± 4.306 | 1.288 ± 0.761 | 0.590 |
| uE3 MoMs | 1.105 ± 0.998 | 0.965 ± 0.418 | 0.001 |
| IHA MoMs | 1.046 ± 0.443 | 1.299 ± 0.900 | < 0.001 |
| Median (IQR)# |       |     |         |
| AFP MoMs | 0.969 (0.48) | 1.288 (0.57) | < 0.001 |
| b-hCG MoMs | 0.928 (0.35) | 1.087 (0.46) | < 0.001 |
| uE3 MoMs | 1.020 (0.53) | 0.877 (0.34) | < 0.001 |
| IHA MoMs | 0.957 (0.32) | 1.129 (0.45) | < 0.001 |

* Student T test; # Mann-Whitney-U test; IQR: interquartile range

In the categorization of serum biomarkers into normal and abnormal levels, conventional serum biomarker cutoffs (> 2 MoM for AFP, b-hCG, and IHA, and < 0.5 MoM for uE3) were used to predict FGR. All four biomarkers were significantly associated with the rate of FGR. Abnormal AFP MoM had the strongest predictivity with a relative risk of 2.81 (95% CI: 2.20–3.58), followed by b-hCG MoM, IHA MoM, and uE3 MoM, respectively, as presented in Table 4.
Table 4
Relative risk of abnormal serum biomarkers MoMs of AFP, b-hCG, uE3 and IHA between non-FGR vs FGR group

| Group       | Non-FGR Group (n: 9577) | FGR Group (n: 578) | P-value | Relative Risk (95%CI) |
|-------------|-------------------------|--------------------|---------|-----------------------|
| AFP > 2 MoMs| 355 (85.1%)             | 62 (14.9%)         | < 0.001 | 2.81 (2.20–3.58)      |
| AFP < 2 MoMs| 9222 (94.7%)            | 516 (5.3%)         |         |                       |
| b-hCG > 2 MoMs| 321 (85.4%)     | 55 (14.6%)         | < 0.001 | 2.74 (2.11–3.54)      |
| b-hCG < 2 MoMs| 9256 (94.7%)     | 523 (5.3%)         |         |                       |
| uE3 < 0.5 MoMs| 316 (90.8%)             | 32 (9.2%)          | 0.004   | 1.65 (1.17–2.32)      |
| uE3 > 0.5 MoMs| 9261 (94.4%)            | 546 (5.6%)         |         |                       |
| IHA > 2 MoMs | 253 (88.5%)             | 33 (11.5%)         | < 0.001 | 2.09 (1.50–2.91)      |
| IHA < 2 MoMs | 9324 (94.5%)            | 545 (5.5%)         |         |                       |

Using binary logistic regression analysis, the predictive models for FGR by each of the four serum biomarkers and their combination were constructed, as shown in Table 5. Note that the combination does not contain b-hCG MoM because the addition of b-hCG MoM to the equation has no significant additive diagnostic value, though b-hCG MoM has diagnostic value when used as an individual biomarker. Based on the constructed models, the diagnostic performances of the individual biomarkers and their combination in the prediction of FGR are analyzed using ROC (receiver-operated characteristics) curve, as presented in Fig. 3. The combination of serum biomarkers gives the highest predictivity, with an area under curve of 0.754 (95% CI: 0.732–0.777). Note that as an individual serum marker, AFP MoM has the highest predictive value, giving an area under curve of 0.724 for FGR, followed by IHA MoM. The higher the MoM of AFP, the higher the likelihood of FGR, as presented in Fig. 4.
## Table 5

| Biomarkers | The models predicting fetal growth restriction (probability) |
|------------|----------------------------------------------------------|
| **AFP MoMs** | $\ln (\text{Odds ratio}) = -3.1403 + 0.2863 \times (\text{AFP MoM})$ |
| **b-hCG MoMs** | $\ln (\text{Odds ratio}) = -2.8127 - 0.0042 \times (\text{b-hCG MoM})$ |
| **uE3 MoMs** | $\ln (\text{Odds ratio}) = -2.0289 - 0.7609 \times (\text{uE3 MoM})$ |
| **IHA MoMs** | $\ln (\text{Odds ratio}) = -3.4347 - 0.5558 \times (\text{b-hCG MoM})$ |
| **Combined biomarkers** | $\ln (\text{Odds ratio}) = -4.4908 + 1.6877 \times (\text{AFP MoM}) + 0.8965 \times (\text{IHA MoM}) - 0.3248 \times (\text{AFP MoM} \times \text{IHA MoM}) - 0.6725 \times (\text{AFP MoM} \times \text{uE3 MoM})$ |

### An example of prediction of FGR based on quad test:

A 34-year old pregnant woman underwent quad test at 15 weeks of gestation, which revealed the following: AFP level: 13.80 U/mL; hCG level: 22.89 ng/mL; uE3 level: 3.09 nmol/L; IHA level: 2082.54 pg/mL. The patient had no pre-gestational DM, and her body weight was 60 Kg.

Based on the models in Table 2 and baseline data of maternal age, gestational age, DM status and body weight, the MoMs of the four biomarkers of this woman are as follows: AFP = 0.43 MoM; hCG = 0.92 MoM; uE3 = 0.93 MoM; IHA = 7.18 MoM.

By substituting the specific MoM of each biomarker above into the combined biomarker model in Table 5, the resulting $\log (\text{Odds ratio}) = 0.80223$, converted to Odds ratio: 6.34. Therefore, this pregnancy is at a very high risk of FGR.

### Discussion

Insights gained from this study include the following: 1) Fetuses with growth restriction have significantly higher MoMs of AFP, b-hCG and IHA but lower MoMs of uE3. 2) Abnormal MoMs of all individual biomarkers based on the conventional MoM cutoffs are significantly associated with an increased risk of FGR. AFP has the strongest association but all have significant predictive values for FGR. 3) The predictive models of each biomarker and their combination are constructed. The combination model yields the highest prediction. 4) The combination of all biomarkers even increases the predictive power. However, b-hCG has no additive value to the combination. 5) If the combination model is integrated into the built-in software of the machine, the risks of FGR and Down syndrome could be simultaneously estimated and reported using the same set of serum biomarkers.

The associations between unexplained abnormal levels of serum biomarkers and fetal Down syndrome / FGR have been published several times. Most studies focused on elevated AFP levels. Studies that included all four biomarkers are rare \(^{(19,20)}\). Importantly, most previous studies reported the correlation between individual biomarkers and poor outcomes, whereas the effectiveness of their combination is
rarely described. Moreover, most previous studies used arbitrary cutoff to define abnormal MoMs, while the risk is quantitatively level-dependent rather than the all-or-none fashion. To the best of our knowledge, only Odibo et al.\(^{(21)}\) evaluated the optimal thresholds of unexplained abnormal triple biomarkers to predict FGR by ROC curve, but they did not include IHA, did not evaluate the combination, and the sample size was relatively small. Differently, our study assessed the effectiveness of both individual biomarkers and their combination and constructed the models that may be used to estimate the overall risk of FGR for each patient as well as simply used in actual practice. The models might seem complicated, but they can easily be integrated into a computerized calculator to automatically report once the measured biomarker levels are input. However, our findings should be interpreted with caution. The results are derived from specific Thai population and might not be reproducible in other groups with different demography. Note that the prevalence of FGR in this study was 5.7%, much lower than theoretically expected (10%). The reason is unclear, but it might be due to the use of inappropriate reference ranges in defining FGR\(^{(22)}\). Also, it is possibly due to the fact that pregnancies with higher risk of FGR were excluded, making the overall incidence relatively low.

The strengths of this study are as follows: 1) Our dataset was prospectively collected, and the participants were followed-up for final obstetric and neonatal outcomes by the project team. 2) Because of its population-based nature, the constructed models are more likely generalizable. 3) The sample size was adequate for comparison of FGR rate. 4) Because of the high homogeneity of the study population, consisting of only Thai pregnant women, the results were not confounded by a racial factor. 5) The MoMs of each biomarker were derived from our own population, not automatically calculated from the built-in models, which are based on Caucasian women. Thus, it is more suitable to apply our models to Thai or Asian women. 6) Our predictive models can be used to estimate the individual risk of each woman as a quantified risk, or individual likelihood ratio, instead of using one arbitrary cut-off MoM value to categorize risk as just low or high, as reported in most previously published studies. 7) The predictive models can be integrated in the built-in program for an automatic calculation of the fetal risk of FGR in the same manner of predicting the risk of Down syndrome. The same set of serum biomarkers could be simultaneously reported for the risk of Down syndrome and FGR, without extra cost and extra effort.

The limitations of this study include the following points: 1) The study did not take other risk factors of FGR into account. Some potential risk factors of FGR, such as smoking habit, alcohol use, and underlying diseases (like chronic hypertension and antiphospholipid syndrome), were not incorporated into the analysis. However, our models focused on the performances of the biomarkers in predicting overall risk of FGR regardless of any preexisting risk factors, but such risk factors should be considered as the background risks that could be later modified by the likelihood ratio obtained from the models in this study. 2) The predictive models may not be properly applied to other populations with different ethnicity and demographic data. Nevertheless, this study confirmed the association between abnormal levels of the four biomarkers and an increased risk of FGR. Our findings may encourage researchers in other ethnic groups to create the models specific for their own population. 3) A large number of women were excluded
from analysis because of unavailability of final outcomes or loss to follow-up. The difference in baseline characteristics between the excluded and included groups is not known.

**Conclusion**

This study suggests that daily used quad test can also be used as a screening method for fetal FGR. All four biomarkers are significantly associated with FGR. Regarding individual biomarkers, AFP has the strongest predictive power. The highest predictive value is derived from their combination. However, incorporation of b-hCG levels into the combined model had no additive value. We could simply take advantage of quad test by integrating the combined model for FGR into the built-in software for Down syndrome screening to estimate the risk of FGR and Down syndrome in the same report. Nevertheless, this study is preliminary, and further studies on other ethnic groups should be undertaken to evaluate the reproducibility.

**Abbreviations**

AFP: alpha-fetoprotein; FGR: feta growth restriction; hCG: beta-human gonadotropin; IHA: inhibin-A; MoM: multiple of medians; uE3: unconjugated estriol

**Declarations**

**Ethics approval and consent to participate:** This study was approved by the Institutional Review Boards; The Research Ethics Committee 4; Faculty of Medicine, Chiang Mai University. Study Code: OBG-2562-06069 / Research ID: 06069

All participants were recruited with written informed consent.

**Consent for publication:** The Informed Consent Forms which all participants signed included consent for publication of their data. Data were de-identified after collection and participants were allocated codes for analysis and pseudonyms for publication.

**Availability of data and materials**

The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

**Competing interests:** No

**Funding:** The Thailand Research Fund (DPG6280003), Chiang Mai University Research Fund (CMU-2563); The funder had no any role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

**Authors’ contributions:**
RB: Conceptualization, study design, proposal writing, acquisition of data, data analysis, manuscript writing

CW: Conceptualization and database development, network administration, final approval

SS: Conceptualization and, database development, data analysis, manuscript editing

RS: Acquisition of data, final approval

KT: Conceptualization, study design, acquisition of data, data analysis, manuscript writing

TT: Conceptualization database development, data analysis, and manuscript editing

All authors contributed to the interpretation and writing of the paper and approved the final version.

Acknowledgements: The authors wish to thank all supporting physicians and nurses in the network hospitals for their contribution to collecting data.

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Figures

Figure 1

Study flow chart.
Figure 2

Comparison of AFP MoMs (A), b-hCG MoMs (B), uE3 (C) and hCG (D) between FGR and non-FGR group.
Figure 3

ROC curves shows performance in predicting fetal growth restriction of the individual serum biomarker levels and their combination. Area under ROC Curve MoMs of AFP : 0.724 (95%CI: 0.705-0.743) MoMs of b-hCG : 0.655 (95%CI: 0.634-0.676) MoMs of uE3 : 0.597 (95%CI: 0.573-0.621) MoMs of IHA : 0.664 (95%CI: 0.642-0.687) Combined of serum biomarkers (predicted probability) : 0.754 (95%CI: 0.732-0.777)
Figure 4

Likelihood ratio for fetal growth restriction based on MoMs of AFP