A Propose of Effective Model For Prediction of Spontaneous Preterm Delivery With Quadruple Serum Biomarkers of Aneuploidy Screening.

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Abstract

Background:

Spontaneous preterm delivery (sPTD) is one of the most common global problems causing perinatal morbidity and mortality. However, there is no effective universal screening method for predicting sPTD. Therefore, we want to evaluate the extra benefit of quadruple maternal serum biomarkers for Down syndrome (DS) screening to predict sPTD. Moreover, to propose an effective model to predict sPTD.

Results:

From total of 2,822 pregnancies who underwent DS screening, 2604 (92.3%) were included in the study. There were 183 (7.02%) pregnant women had randomly measure cervical length. sPTD occurred in 221 (8.5%) of participants, 32 (14.5%) had early sPTD (<34 weeks gestation) and 189 (85.5%) had late sPTD (delivery between 34-36+6 weeks). The median MoM of AFP was significantly higher in women with early sPTD (1.2 VS 1.0, p =0.04), but uE3 had tendency to be lower than the women with term delivery. The most effective model to predict sPTD was the combination of serum AFP level > 1.2 MoM, uE3 level < 0.9 MoM, cervical length <35 mm. and had history of previous preterm delivery which has an AUC of 0.86.

Conclusions:

An abnormal increase of AFP or decrease of uE3 in quadruple Down syndrome screening showed a predictive ability to predict sPTD with no extra cost. The most effective model to predict sPTD is adding serum quadruple biomarkers with maternal characteristics and cervical length measurement gives a high predictive ability for sPTD.

Background

Preterm delivery is one of the most common global problems causing perinatal morbidity and mortality worldwide [1, 2] and has a significant impact on both short and long term neonatal health [3]. The cost of treatment can be very high for extremely preterm deliveries [4, 5]. The impact of such preterm delivery costs can create serious financial burdens, especially in developing countries [6, 7]. There is a method available to prevent preterm births in at-risk pregnant women, such as progesterone administration but indicated only in women who had history of spontaneous preterm delivery (sPTD) [8-12]. Currently there is no effective universal screening method for predicting preterm delivery [13, 14] . One common method of assessing the risk of preterm birth is cervical length measurement. If this length is shorter than 2.5 cm., the patient will be offered cervical cerclage or progesterone administration to prevent preterm delivery [9, 14-18]. However, screening for preterm delivery using cervical length measurement is still limited in most developing countries [19].

The serum quadruple test is a method for second trimester Down syndrome screening using a combination of four substances in a pregnant woman’s serum: alpha-fetoprotein (AFP), β-human

chorionic gonadotropin (β-hCG), unconjugated estriol (uE3) and inhibin A. The serum quadruple test is widely used in second trimester screening for Down syndrome in many countries [20-27]. In Thailand, the quadruple test has been adopted as a national screening program for Down syndrome and is free of charge. Maternal serum levels of AFP, β-hCG, inhibin A and uE3 are representative of the serum levels in fetal and placental circulation [28]. Fetal or placental abnormalities can cause abnormal levels of these serum biomarkers [28]. In addition to using the quadruple test for screening for Down syndrome, many studies have demonstrated the usefulness of abnormal serum quadruple markers in either individual or combined tests to predict other adverse pregnancy outcomes such as preterm birth, preeclampsia and fetal growth restriction [20, 21, 24, 25, 29-36]. Many studies have showed associations between abnormal serum biomarkers and adverse pregnancy outcomes, especially preterm outcomes in euploid fetuses [21, 23, 32, 36, 37]. High levels of AFP, β-hCG, and inhibin A with a low level of UE3 have been shown to be associated with adverse pregnancy outcomes, especially in preterm births [20, 21, 24, 25, 29, 31, 32, 36-38]. Many studies have attempted to elaborate the relationship between serum biomarkers and adverse pregnancy outcomes, particularly sPTD. However, there have been some conflicting findings regarding the protocol or cutoff levels of these serum biomarkers among these studies [20, 21, 24, 25, 38]. Our study aimed to examine the associations between the biomarkers assessed in the serum quadruple test and the prediction of sPTD as a further screening model as an adjunctive benefit of Down syndrome screening.

Methods

This retrospective study was conducted at Songklanagarind Hospital, a tertiary center in the south of Thailand. We offer the prenatal screening for Down syndrome between gestational age of 14 and 20 weeks during the period of 2012 to 2019. Ethical approval was granted by the institutional ethical committee. The study was a prospective design mainly for evaluating the efficacy of Down syndrome screening with quadruple test. We then recruited the pregnant women between year of 2012 to 2014, we were given a grant by the Faculty of Medicine, Prince of Songkla University Research Fund. Then, after 2016, we recruited patients who had undergone the quadruple screening offered by Thai National Policy which was free of charge. All participants had delivery in our hospital. The demographic data; maternal age, parity, race, medical disease, body mass index, history of preterm, gestational age and cervical length measurements were recorded. The serum markers of the quadruple test: alpha-fetaprotein (AFP), beta-hCG, unconjugated estriol (uE3) and inhibin A were measured using KRYPTOR compact PLUS (Thermo Fisher Scientific, Hennigsdorf, Germany), and inhibin A was measured using TRACE technology (time-resolved amplified cryptate emission Ansh Labs, Webster, TX, USA) and Immunomat (Institut Virion\Serion, Würzburg, Germany). The outcomes of pregnancy were followed during the study: gestational age of delivery, birth weight and complications of newborns after delivery such as NICU admission, ventilator use, and hospital stay. All newborn babies were evaluated by pediatricians. If the newborn was suspected of Down syndrome, the karyotype was checked.

Statistical analysis

The statistical analysis was performed using Stata version 14.1. The demographic data of the pregnant women and the outcomes of delivery were summarized. Women with chromosomal abnormality were dropped from the dataset. Using all women remaining in the dataset, the median value of the natural logarithm of each marker was estimated using quantile regression as a function of gestational age and body weight, incorporating quadratic terms as appropriate to obtain the best fit. Using the actual measured level of marker and body weight together with the corresponding estimated median value, the multiple of median (MoM) of each serum marker was calculated for each woman. The ability of the ln(MoM) of each marker as well as that of a combination of markers to predict the outcome of sPTD was explored using logistic regression models using each single marker and all markers, respectively, and the corresponding ROC curves constructed. Subsequently, the increase in ability to predict sPTD by adding selected results of the quadruple test to various known maternal clinical predictors was evaluated using logistic models and by comparing the resultant AUC of the ROC curves. The overall best-fitting model was identified.

Results

During the study period, 2822 pregnant women met the enrollment criteria. Prior to analysis 218 (7.73%) women were excluded from the study, mostly due to lost-to-follow up. Another 26 (0.9%) women were excluded due to indicated preterm. Finally, 2,604 (92.3%) women were eligible for analysis in Fig. 1. In our study, there were 221 (8.5%) sPTD. There were 32 (14.5%) cases of early preterm with gestational age less than 34 weeks, and 189 (85.5%) cases of late preterm delivery equal to or more than 34 weeks. The demographic data between term and preterm deliveries were not different between the two groups in Table 1. The median gestational age at delivery of the term group was 39 weeks and the preterm group was 36 weeks. A history of previous preterm delivery was significantly higher in the preterm group than term group. A subgroup of 187 (7.03%) participants in the study underwent cervical length measurement because they were enrolled in another study involving cervical length measurements to predict preterm delivery. A history previous preterm delivery was significantly associated with preterm delivery. The cervical length of the preterm group was significantly shorter than in the term delivery group, at 33.9 and 36 mm, respectively ($p< 0.05$). The median birthweight of the term infants was 3150 g and of the preterm infants was 2551.2 g, a difference which was statistically significant. Most of the other neonatal outcomes such as NICU admission, ventilator use and length of hospital stay were also statistically significantly different between the term and preterm groups in Table 2.

Table 1 The demographic data of study pregnant women who had term and preterm deliveries

Maternal characteristic	Term	Preterm	P value
Maternal age, years	31 (28, 33)	31 (28, 33)	0.424
Maternal BMI, kg/m2	22.5 (20.4, 25.3)	23 (20.3, 26)	0.226
Gestational age, wk	39 (38, 39)	36 (35, 36)	< 0.001
Parity			0.044
• Nulliparous, N (%)	1,349 (56.6)	109 (49.3)	
• Multiparous, N (%)	1,034 (43.4)	112 (50.7)	
History of preterm, N (%)	24 (1)	14 (6.3)	< 0.001
History of PIH, N (%)	15 (0.6)	4 (1.8)	0.119
Cervical length, mm, mean (SD) (N=183,7.02%)	36.9 (6.4)	33 (6.8)	0.004
PIH	70 (2.9)	13 (5.9)	0.029
GDM	192 (8.1)	28 (12.7)	0.026

When comparing the median MoM of the serum quadruple test in term and sPTD, there was no significant difference between the two groups in Table 3. However, in the subgroup analysis between early and late sPTD, there was a significantly higher MoM AFP in the early preterm group. The median MoMs of uE3 and inhibin A were lower in the early preterm group, but the difference was not statistically significant. When the performance of each serum biomarker was evaluated, only AFP had an increased prediction value with AUC of 0.55 in Fig. 2. When the quadruple serum markers were combined, the prediction for sPTD showed an AUC of 0.56 in Fig. 3.

Table 2 Neonatal outcomes of the term and preterm newborns

Outcome	Term	Preterm	P value
Birthweight, gm, mean (SD)	3150 (394.2)	2551.2 (538)	< 0.001
Apgar score, 1 min, median (IQR)	8 (8,9)	9 (8,9)	< 0.001
Apgar score, 5 min, median (IQR)	9 (9,9)	9 (9,9)	0.026
NICU admission, N (%)	92 (3.9)	57 (25.8)	< 0.001
Ventilator used, N (%)	32 (1.3)	23 (10.4)	< 0.001
Hospital stay, day	3.6 (2.7)	8.4 (12.3)	< 0.001

Models to predict sPTD from selected factors involved with preterm delivery were created. Using only the serum quadruple test, the sensitivity to predict sPTD was low in Fig. 3. When cervical length was combined with the serum markers, the AUC increased to 0.67. When a maternal history of preterm delivery was added, the AUC further increased to 0.71, and finally combining maternal serum AFP > 1.2 MoM, uE3 < 0.9, a previous history of preterm delivery and cervical length measurement < 35 mm gave the highest AUC of 0.86 . The model to predict sPTD using maternal histories and serum biomarkers related to preterm delivery were constructed by regression equation. To calculate the odds ratio for the risk of sPTD, and then the probability of sPTD could be calculated from the equation as follows:

In (*odds*) = [0.687x Cervical length + 1.714x history of preterm delivery + 1.083 + 0.463 x MoM uE3≤ 0.9 - 2.772]

$$odds = exp\ exp\ (ln\ ln\ (odds))$$

$$\text{Probability of sPTD} = \frac{odds}{1+odds}$$

Table 3 The median MoM of the serum biomarkers between the term and preterm pregnancies

Serum biomarkers Median (IQR)	Term (2,383)	Early Preterm (32)	Late Preterm (189)	P value
AFP MoMs	1(0.8,1.2)	1.2(0.8,1.4)	1(0.8,1.3)	0.04
uE3 MoMs	1(0.7,1.4)	0.9(0.5,1.3)	1(0.7,1.4)	0.153
β-hCG MoMs	0.9(0.6,1.4)	1(0.6,1.5)	0.9(0.6,1.4)	0.893
Inhibin A MoMs	1(0.7,1.3)	0.9(0.6,1.3)	1(0.7,1.3)	0.472

Discussion

Preterm delivery especially before 34 weeks gestation is a major cause of morbidity and mortality of newborns worldwide, particularly in developing countries [2, 4, 6, 7, 39, 40]. The recently reported incidence of preterm in Thailand was about 10-13% [41]. In our study, we had sPTD incidence of 8.5%, while other studies reported incidences between 7.8-10.6 % [42, 43]. There are numerous risk factors involved with preterm delivery such as a previous history of preterm birth, some medical diseases or hypertension associated with pregnancy[40, 42, 44, 45]. However, a considerable number of preterm deliveries have no clear risk factors, especially in the sPTD group [43, 46, 47]. Concerning the prediction of sPTD, many strategies have been proposed for use with basic clinical history [43, 46]. Cervical length measurement has been supported from many prior studies [46, 48-50]. However, it is still limited in some centers due to lack of specialists and being inconvenient to use as routine screening. Many laboratory investigations including maternal serum biomarkers, urine, and cervical mucus have been used to screening for sPTD [51-55]. However, to date no biomarker has been identified which can reliably predict

sPTD as a general screening tool [52, 53, 56]. In Thailand, the quadruple test, offered by the National Health Policy free of charge, has been used for many years as a universal screening method for Down syndrome. Many studies have reported the extra benefit of the serum quadruple test as a predictor of adverse pregnancy outcomes, including preterm delivery [20, 21, 24, 25, 29, 36, 38]. However, the results of the serum quadruple test vary for the cutoff of each serum biomarker and it has to date shown limited use in predicting sPTD [20, 21, 24, 25, 29, 36]. Moreover, all of the prior studies assessing the use of serum biomarkers for prediction of preterm delivery included indicated preterm deliveries [20, 21, 24, 29, 36]. In our study, we wanted to clarify the association of quadruple biomarkers with sPTD, which has never been done in other studies.

When all serum quadruple biomarkers were combined to predict sPTD, predictive ability was low with an AUC of 0.56%, sensitivity of 55.6 % and false positive rate of 5% in total preterm deliveries. For early preterm deliveries, the sensitivity was 63.5 % with a false positive rate of 5%. However, a similar low percentage was found in the study in Thailand with triple serum biomarkers to predict preterm delivery as well [29]. But the data of previous study included indicated preterm delivery [29]. Our study found a relationship between high levels of AFP and relatively low levels of uE3 in early sPTD before 34 weeks, similar to the studies of Nunthapiwat et al [29] and preterm deliveries before 37 weeks in previous studies [20, 24, 25, 36]. In our study, the median serum level of AFP in the early sPTD group was 1.2 MoM, which was lower than in other studies which have reported levels between 1.34 and 2.0 MoM [20, 21, 25, 29, 36]. However, maternal serum AFP is mainly produced in the fetal yolk sac and liver, and high levels of this chemical have been associated with many fetal structural abnormalities and placental abnormalities [28] which were reported in the other studies [57-59]. The serum uE3 level was slightly lower in early sPTD pregnancies in our study, which has also been reported in other studies, varying between 0.5 and 0.9 MoM [20, 21, 24, 25, 29, 36]. The average serum level of uE3 in the early preterm group of our study was close to the study in a Thai ethnic group of Nanthapiwat et al. [29]. Abnormally low levels of uE3 have also been reported as associated with fetal structural and placental abnormalities [28]. These factors could be associated with indicated preterm and sPTD deliveries; however, we excluded pregnancies with fetal anomalies that can cause preterm delivery in our study.

When earlier models to predict sPTD using serum biomarkers were evaluated, they generally indicated that the association of maternal characteristics with serum biomarkers increased the ability to predict preterm delivery [21, 36]. Previous preterm delivery had a strong association with preterm delivery in many previous studies, which also recommended the administration of progesterone to reduce the risk of preterm delivery [10, 60-63]. Thus, combining a history of previous preterm with serum biomarkers can increase the rate of prediction of sPTD, as found in our study. We also found an association between sPTD and a short cervical length less than 35 mm. One recent study reported an association between preterm delivery and cervical length less than 25 mm before 24 weeks gestation [64]. Our study proposes that the optimal model to predict sPTD combines serum AFP > 1.2 MoM and uE3 < 0.9 MoM with cervical length measurement less than 35 mm. and history of previous preterm delivery, which gave the highest ability to predict sPTD with an AUC of 0.86, sensitivity of 85% and a false positive rate of 10%. Our study suggests the quadruple test can also be uses as a national screening test for sPTD. When pregnant

women are found to have an abnormally high level of AFP and a low level of uE3 whether or not a history of previous preterm delivery is found, these pregnant women should also have a cervical length measurement. Then, if the cervical length is less than 35 mm, progesterone should be administered to reduce the risk of sPTD. To select only women in the sPTD high risk group can reduce number of pregnant women who need to do a cervical length measurement, which is especially important for hospitals that lack a trained gynecologist who can measure cervical length as a universal screening tool for preterm delivery or in developing countries, where such women need to be referred to a larger center that has a specialist. After that, these high-risk pregnancy women should be monitored as a high risk for early sPTD in a tertiary center. The use of this proposed model will decrease the cost for measuring cervical length as a routine antenatal screening test without neglecting pregnancies at high risk of early sPTD, for which it is difficult to find an effective screening method. These are the extra benefits of serum biomarkers for Down syndrome screening which have never been reported before.

The remarkable strength of our study was that we included only sPTD patients while earlier studies included indicated preterm deliveries. In the indicated preterm delivery group, most of the causes can be identified from medical history or obstetrics complications. These conditions are associated with the indications for preterm delivery and can be predicted beforehand, and early management can be provided for prevention of sPTD. On the other hand, sPTD may involve many factors but a definite cause is difficult to clearly identify. Moreover, our study had only a small number of lost to-follow-up cases compared with most other studies. In addition, our study was conducted in the same setting as the laboratory tests were done, reducing the potential problem of serum measurement errors caused by offsite analysis. The current study originated from a prospective cohort that had retrospective analysis, thus the results were naturally blinded. Finally, our study was done in a homogeneous Thai population unlike other studies which have had mixed ethnicities. The cut off level of serum biomarkers we determined is appropriate for use as a universal screening for sPTD in Thailand without the need to adjust the serum levels according to various ethnicities. The notable limitation of our study was then small number of spontaneous early preterm deliveries, thus determining clear cut off levels for the serum biomarkers in this group needs further evaluation.

Conclusions

The combined maternal serum quadruple biomarkers have a low predictive ability for sPTD. An abnormal increase of AFP or decrease of uE3 in the screening for sPTD can increase the accurate prediction of spontaneous early preterm delivery with no extra cost. The most effective model to predict sPTD is serum quadruple biomarkers with maternal characteristics and cervical length measurement gives a high predictive ability for sPTD.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Boards; The Office of Human Research Ethics Committee (HREC), Faculty of Medicine, Prince of Songkla University.

Study code: No. 62465124

All participants were recruited with written informed consent.

I confirm that the experiment protocol for involving humans was in accordance to guidelines of national/international/institutional or Declaration of Helsinki in the manuscript.

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

The authors declare that they have no competing interests.

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Authors' contributions

SP: Conceptualization, study design, proposal writing, acquisition of data, data analysis, manuscript writing. KW: Database development, data analysis, manuscript editing. OK: Conceptualization and database development, network administration. TS: Contributed to the acquisition of data. CS: Contributed to the acquisition of data. NP: Contributed to the acquisition of data. CP: Contributed to the acquisition of data. MS: Contributed to the acquisition of data. NC: Contributed to the acquisition of data. RS: Contributed to the acquisition of data. All authors contributed to approved the final version.

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Figures

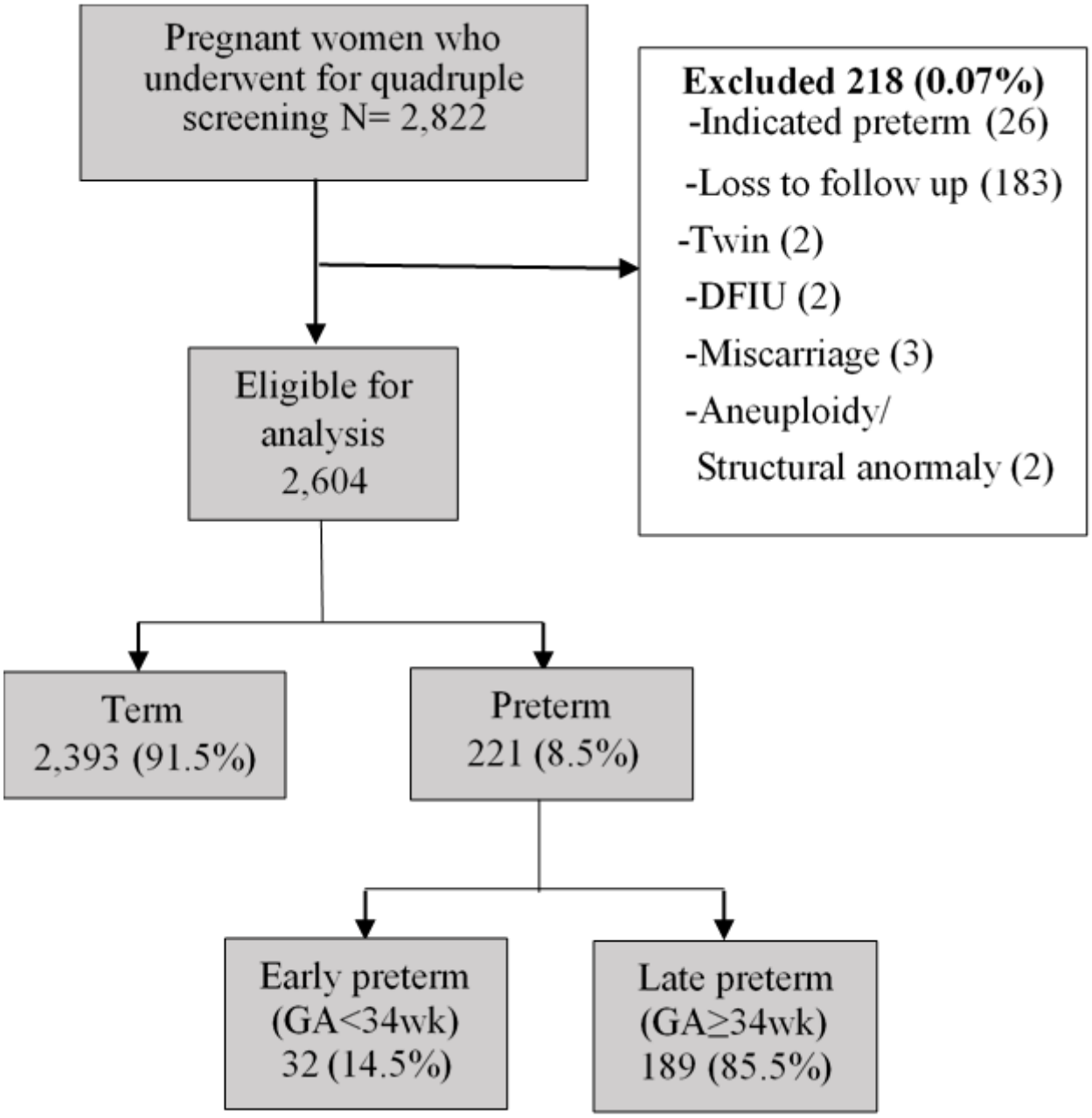

Figure 1

The study flow chart

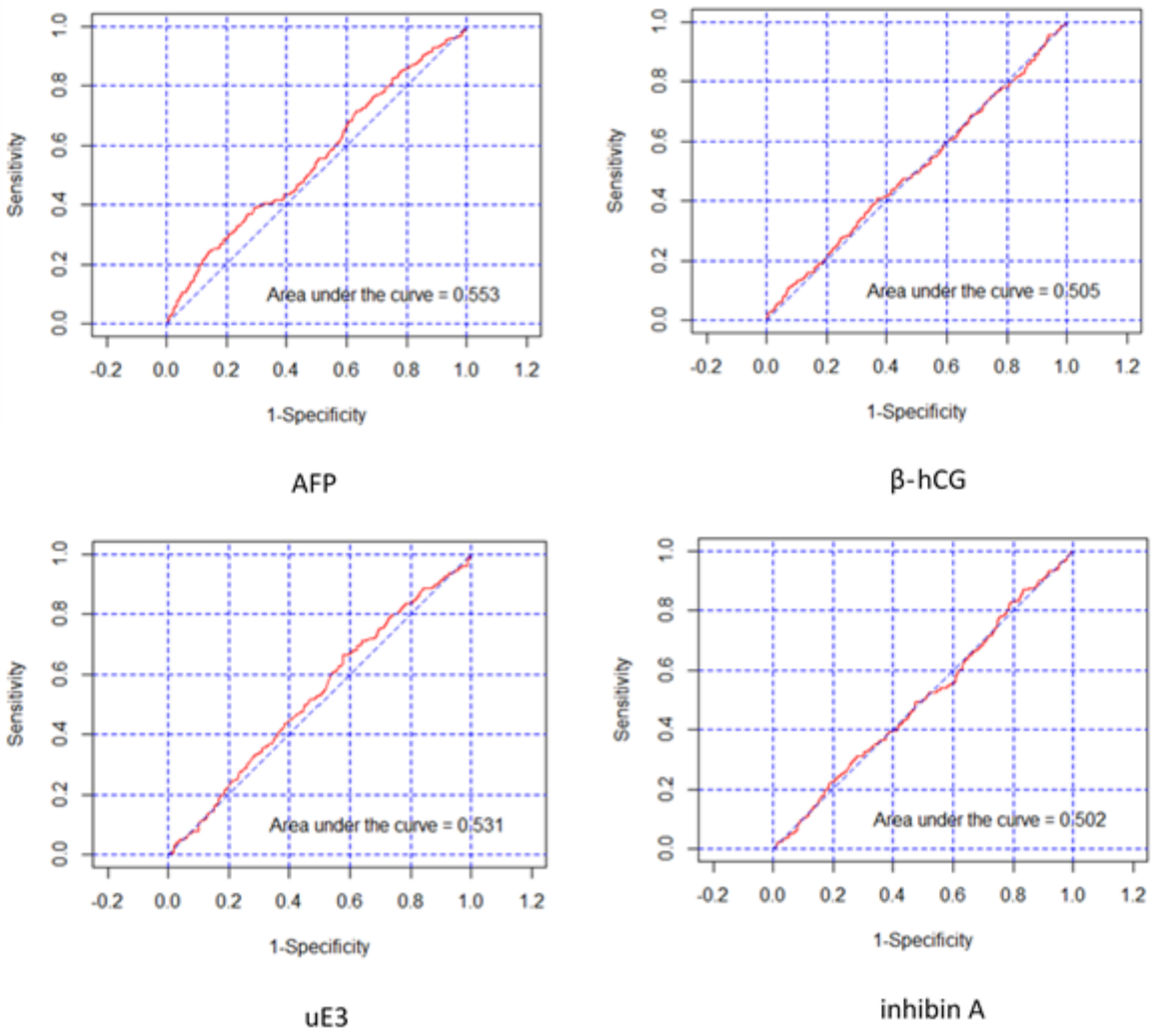

Figure 2

The ROC curve of maternal serum biomarkers for prediction of spontaneous preterm deliveries

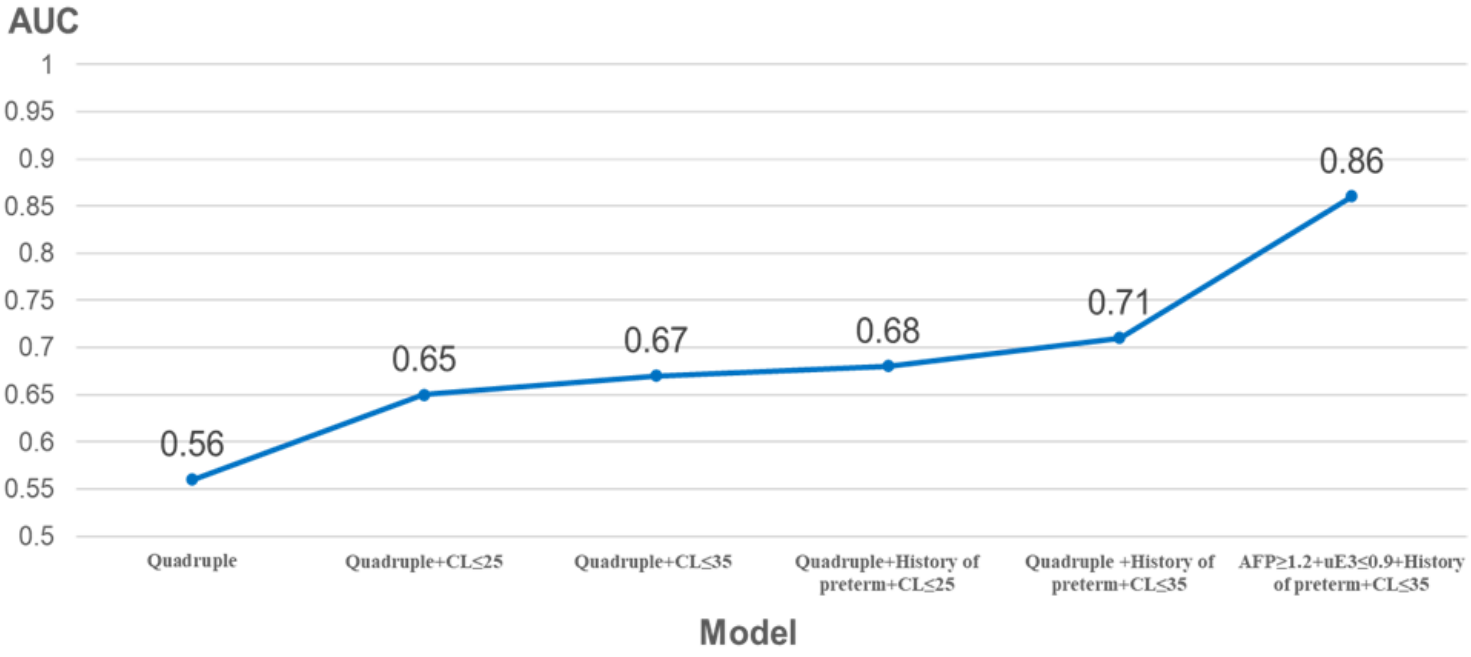

Figure 3

The models of serum markers combined with other factors to predict spontaneous preterm delivery