

Predicting Adverse Pregnancy Outcomes based on Maternal Serum Markers in Quad Test

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ABSTRACT

OBJECTIVE To compare adverse pregnancy outcomes (APOs) between low-risk and high-risk serum quadruple test for aneuploidy screening.

METHODS This cohort design study screened pregnant women who had undergone quad test serum screening in Ratchaburi province, Thailand. The sample of 400 women was divided into two groups, low-risk quad test (n=200) and high-risk quad test (n=200) using random allocation software. Participants were followed up for final outcomes and compared for APOs. The data were analyzed using binary logistic regression analysis and risk ratios.

RESULTS Of a total of 1,891 pregnant women, 206 (10.8%) had APOs. Of the women with APOs, 92 (46%) had high-risk quad test results and 32 (16%) were in the low-risk quad test group. The incidence of preeclampsia, intrauterine growth restriction (IUGR) and chromosome abnormality in the high-risk quad test group were all statistically significantly higher in the high-risk quad test group than in the low-risk quad test group ($p = 0.013, 0.001, 0.043$ respectively). The high-risk quad test group also had a higher incidence of preterm birth, abortion, gestational diabetic mellitus in high-risk quad test group, but the differences were non-statistically significant.

CONCLUSIONS High-risk serum quad test results can help predict the risk of APOs such as preeclampsia, IUGR and chromosome abnormality.

KEYWORDS quad test, maternal serum marker, adverse pregnancy outcome

INTRODUCTION

The quad screen test administered in the second trimester has been widely used as an effective serum pregnancy screening test for Down's syndrome and neural tube defects (1–2). This test, which is done before 20 weeks of gestation, comprises four components: maternal serum alpha-fetoprotein (AFP), human chorionic gonadotropin (β -hCG), unconjugated oestriol (uE3), and inhibin-A (IHA) (3). Recent evidence indicates the existence of a common underlying

pathophysiological mechanism involving abnormal placentation in early pregnancy for which is related to these pregnancy complications. It has been suggested that failure of trophoblast invasion into the maternal spiral arteries during the 1st and early 2nd trimesters can lead to reduced uteroplacental blood perfusion and placental insufficiency with subsequent intrauterine hypoxia and perinatal asphyxia (4,5).

Abnormal maternal serum quad test results have been reported to be associated with adverse

pregnancy outcomes (APOs) including preeclampsia, intrauterine growth restriction (IUGR), preterm birth, abortion, gestational diabetic mellitus (GDM) and chromosome abnormalities (6–10).

The second trimester serum biomarker or quad test can predict the risk of trisomy 21, trisomy 18 and trisomy 13. The present study compared APOs between low-risk and high-risk quad test results as a means of providing more organized additional information for use in counseling pregnant women in high-risk groups for predicted regarding the risk of APOs.

MATERIALS AND METHODS

The present study was approved by Ratchaburi Ethics Committee (RBHEC No. 033/64) and written consent for publication was received from all participants. The study design was a prospective cohort study. Study inclusion criteria were singleton gravids who had undergone a serum biomarker quad test at a gestational age of 15–17 weeks and for whom obstetric outcomes were available. Exclusion criteria were chronic maternal disease, e.g., autoimmune disease, chronic hypertension, a history of prior adverse pregnancy preterm labor, preeclampsia and intrauterine growth retardation (IUGR), fetal anomaly or aneuploidy, and multifetal gestation.

$$n = \frac{N * Z\alpha^2 * p * q}{d^2 * (N - 1) + Z\alpha^2 * p * q}$$

The minimum sample size needed, calculated using the cohort formula, was 156 cases. The study divided participants in two groups, a low-risk quad test group (n=200) and a high-risk quad test group (n=200) using a randomizing computer program. Participants were followed-up for final outcomes which were compared with APOs.

Adverse pregnancy outcomes (APOs) were defined as the presence of at least one of the following: (1) preeclampsia (based on blood pressure of 140/90 mmHg or higher with proteinuria more than 300 mg for 24 hours), (2) gestational diabetic mellitus (GDM), (3) intrauterine growth restriction (IUGR) (fetal birth weights lower than the 10th percentile, as

confirmed for the infant's gestational age, (3) abortion (fetal loss at less than 24 weeks), (4) preterm (delivery before 34 weeks gestation), (5) chromosome abnormalities and (6) neural tube defect.

Data on AFP, uE3, inhibin A, and β -hCG from the quad screen test were collected as the multiple of the median (MoM). The study size was calculated following A Foundation of Analysis in the Health Sciences, 6th ed. (John Wiley & Sons). Binary logistic regression analysis was used for analysis of the predictive values of APO-associated serum markers in the quad test. The 95% confidence intervals (CIs) of odds ratio were used to compare the predicted risks. The predictive power of this new nomogram for APOs was determined using area under receiver operator characteristic (ROC) curve analysis. All statistical analyses were done using SPSS version 23. Results were considered statistically significant when $p < 0.05$.

RESULTS

The present study recruited 1,891 pregnant women who had undergone the quad test. Of those, two hundred and six cases (10.8%) had high-risk quad test results. The population was divided in two groups (low-risk quad test N=200 and high-risk quad test N=200) using a computer randomization program. The baseline characteristics of the two groups are shown in [Table 1](#). There were no significant differences between the two groups in terms of maternal weight, BMI or gestational sampling. Statistically significant differences were found in maternal age (maternal age in the high-risk group was higher than in the low-risk group), gestational age at delivery (gestational age in the high-risk group was lower than in the low-risk group), birth weight (birth weight in the high-risk group was lower than in the low-risk group), and MoMs of AFP, uE3, inhibin A, and β -hCG.

This study found 92 (46%) of the high-risk quad test group and 32 (16%) of the low-risk quad test group had APOs. The incidence of preeclampsia, IUGR and chromosome abnormality in the high-risk quad test group were statistically significantly higher than in the low-risk quad test group. The high-risk quad

Table 1. Baseline characteristics of the pregnant women in the high-risk and low-risk Quad groups (N=400)

	High-risk Quad test (mean±SD) N=200	Low-risk Quad test (mean±SD) N=200	p-value
Age (years)	31±7.4	29±5	< 0.001
Weight (kg)	63±17	63±14	0.383
BMI	24±6.1	23±4.2	0.115
Gestational at Sampling (weeks)	16±1	16±0.9	0.432
Gestational at Delivery (weeks)	37±3.9	38±1	0.041
Birth weight (gm)	2800±408	3166±427	< 0.001
AFP (MoMs)	1.57±1.40	1.19±0.38	< 0.001
uE3 (MoMs)	1±2.02	1.94±1.60	< 0.001
Inhibin A (MoMs)	2.17±1.24	1.17±0.54	< 0.001
β-hCG (MoMs)	2.64±1.97	1.25±0.73	< 0.001

BMI, body mass index; AFP, alpha-fetoprotein; MoMs, multiple of the median; uE3, unconjugated oestriol, β-hCG: human chorionic gonadotropin. **p* < 0.05 indicates statistically significant

Table 2. Comparison of adverse pregnancy outcomes between high-risk and low-risk Quad test groups

	High-risk Quad test n (%)	Low-risk Quad test n (%)	Odds ratio (95% CI)	p-value
Preeclampsia	14 (7.37)	3 (1.55)	4.94 (1.40–17.48)	0.013
GDM	14 (7.37)	9 (4.64)	1.60 (0.68–3.78)	0.391
IUGR	24 (12.63)	3 (1.55)	8.96 (2.65–30.27)	0.001
Abortion	10 (5.0)	6 (3.0)	1.70 (0.61–4.78)	0.445
Preterm	18 (9.47)	9 (4.64)	2.01 (0.92–4.79)	0.111
Chromosome abnormality	8 (4.21)	1 (0.52)	8.28 (1.03–66.94)	0.043
NTD	4 (2.11)	1 (0.52)	4.06 (0.45–36.66)	0.369
Total	92 (46.0)	32 (16.0)		

GDM, gestational diabetic mellitus; IUGR, intrauterine growth restriction; NTD, neural tube defect; CI, confidence interval. **p* < 0.05 indicates statistically significant

test group also had a higher risk of GDM, abortion and preterm birth, but the differences were not statistically significant (Table 2).

Analysis of the association between maternal serum quad test results and pregnancy complications found uE3 levels in APOs (preeclampsia, IUGR and chromosome abnormality) were lower than the 25th percentile maternal serum MoM values in normal pregnancies. High levels of Inhibin A MoMs and β-hCG-MoMs were associated with preeclampsia and IUGR. AFP MoMs lower than the 25th percentile was associated with chromosome abnormality (Figure 1).

Based on the constructed models, the diagnostic performance of the individual biomarkers in the prediction of APOs were analyzed using the ROC (receiver-operated characteris-

tics) curve. Results showed MoMs of AFP: 0.766 (95%CI: 0.648–0.884), MoMs of uE3: 0.653 (95%CI: 0.494–0.813), MoMs of IHA: 0.717 (95%CI: 0.516–0.918), and MoMs of β-hCG: 0.557 (95%CI: 0.365–0.749) had high predictive value for APOs (Figure 2).

DISCUSSION

The purpose of the quad test serum screening was to screen identify genetic diseases (chromosome abnormality and NTD). Importantly, most previous studies have reported a correlation between the serum biomarkers quad test and adverse pregnancy outcomes (10–19). Recent evidence has shown that abnormal quad test results indicating reduced uteroplacental blood perfusion are related to associated with preeclampsia and IUGR, results similar to earlier

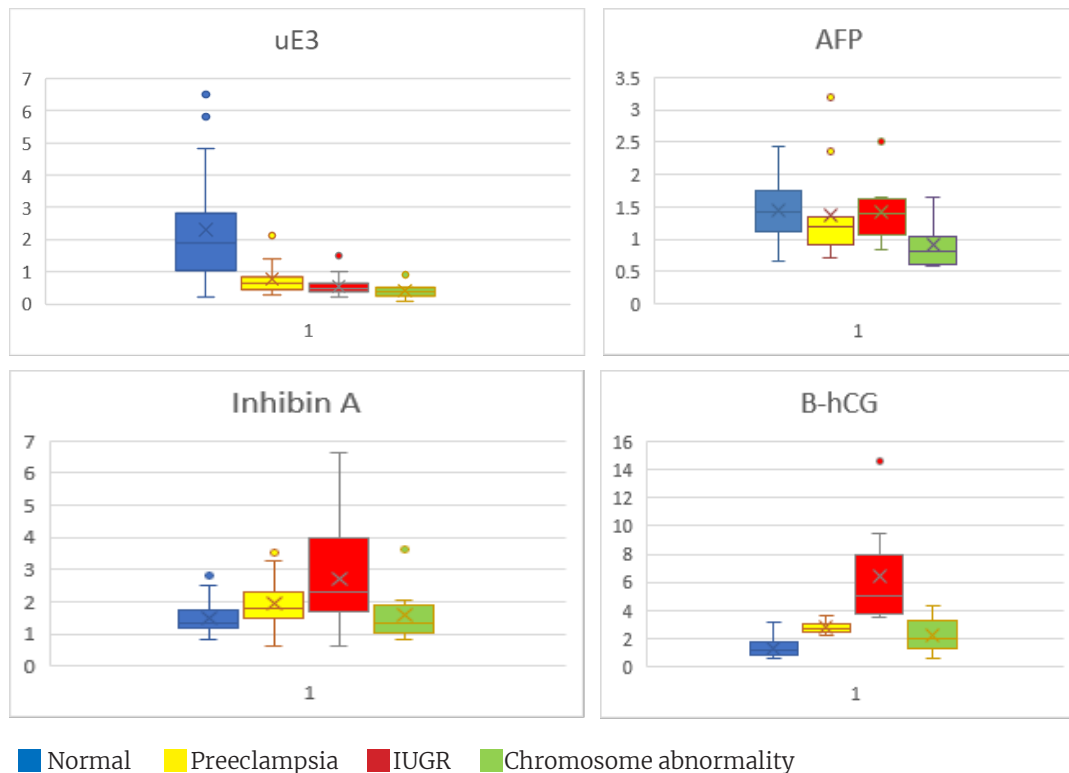


Figure 1. Box-and-whisker plot of serum quad test (uE3 MoMs, AFP MoMs, inhibin A MoMs and β -hCG MoMs levels) in normal pregnancies and pregnancies complicated by preeclampsia, IUGR and chromosome abnormality.

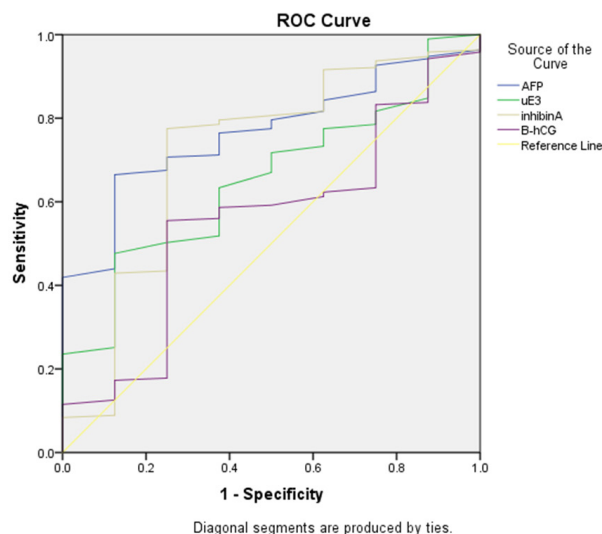


Figure 2. ROC curve showing the sensitivity and specificities of individual serum biomarker levels 2nd trimester quad test AFP, uE3, inhibin A and β -hCG for prediction of APOs

studies (5,12-14). For example, In a study of 344 pregnant women, Towner found a statistically significant relationship between the risk of preterm birth and abortion in patients with a high-risk quad test (18-20). This study also found increased risk but non- statistically significant. A study by Huang et al. which included 141,698 gravids, found AFP and β -hCG levels to be significantly higher in cases of preeclampsia,

IUGR and abortion (17). Boonpiam et al. found lower levels of uE3 (less than 0.5 MoM) to be associated with an increased incidence of preeclampsia but not IUGR, but that elevated β -hCG levels (over 3.0 MoMs) were associated with IUGR (20). Sayin et al. found low uE3 levels were not associated with preeclampsia (15). In this study, uE3 levels lower than the 25th percentile MoM were associated with all

types of APOs, including IUGR, preeclampsia and chromosome abnormality, while high levels of β -hCG and inhibin A were associated with preeclampsia and IUGR. The multicenter FASTER (First and Second Trimester Evaluation of Risk) study which included 34,271 pregnant women found a statistically significant correlation between low PAPP-A levels and preeclampsia, abortion IUGR, and preterm birth (7). Unfortunately, results of the first trimester PAPP-A blood test were not available in this study. Although many studies have shown a clear association between abnormal maternal analyte levels and APOs, currently used serum markers have sensitivities varying from 5% to 43% (11,13).

Strengths of this study include the use of a prospective cohort, enrolling a larger sample size for comparison of APOs and the MoMs of each biomarker. The study also consisted exclusively of pregnant Thai women, thus avoiding a potentially confounding racial factor.

Limitations of this study include that some potential risk factors of APOs such as smoking, alcohol use, and other underlying disease were not included in analysis. Additionally, a large number of women who had undergone the quad test were excluded because of unavailability of information on the final outcome of their pregnancies. Differences in baseline characteristics between the excluded and included subjects is not known and results of the first trimester screening (PAPP-A) test of included subjects were not available.

CONCLUSIONS

The abnormal maternal serum quad test used for screening of fetal aneuploidy during the 2nd trimester may be helpful in the detection of possible adverse pregnancy outcomes and also may also strongly predict the risk of preeclampsia, IUGR and chromosome abnormality.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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