# First-Trimester and Second-Trimester Maternal Serum Biomarkers as Predictors of Placental Abruption

**Cande V. Ananth, PhD, MPH**[1,2], **Ronald J. Wapner, MD**[1], **Srinidhi Ananth**[3], **Mary E. D'Alton, MD**[1], and **Anthony M. Vintzileos, MD**[4]

[1]Department of Obstetrics and Gynecology, College of Physicians and Surgeons, Columbia University, New York, NY

[2]Department of Epidemiology, *Joseph L. Mailman* School of Public Health, Columbia University, New York, NY

[3]West Windsor-Plainsboro High School North, Plainsboro, NJ

[4]Department of Obstetrics and Gynecology, Winthrop-University Hospital, Mineola, NY

## Abstract

**Objective**—We hypothesized that the origins of abruption may extend to the stages of placental implantation; however, there are no reliable markers to predict its development. Based on this hypothesis, we sought to evaluate whether first-trimester and second-trimester serum analytes predict placental abruption.

**Methods**—We performed a secondary analysis of data of 35,307 women (250 abruptions) enrolled in the First and Second Trimester Evaluation of Risk (FASTER) cohort (1999–2003) – a multicenter, prospective cohort study. Percentiles (based on multiples of the median, MoM) of first-trimester (pregnancy-associated plasma protein A [PAPP-A], and total, and free-β human chorionic gonadotropin [β-hCG]), and second-trimester (maternal serum alpha fetoprotein [AFP], unconjugated estriol [uE$_3$], and Inhibin-A) serum analytes were examined in relation to abruption. Associations are based on risk ratio (RR) and 95% confidence interval (CI).

**Results**—Women with an abnormally low PAPP-A ( 5 percentile) were at increased risk of abruption compared to those without an abruption (9.6% versus 5.3%; RR 1.9, 95% CI, 1.2–2.8). Maternal serum AFP 95 percentile was more common among abruption (9.6%) than non-abruption (5.1%) pregnancies (RR 1.9, 95% CI, 1.3–3.0). Inhibin-A 5 percentile (8.0% versus 5.1%; RR 1.8, 95% CI, 1.1–2.9), and 95 percentile (9.6% versus 5.0%; RR 2.0, 95% CI, 1.3–3.1) were associated with abruption. Women with all three abnormal PAPP-A, maternal serum AFP, and Inhibin-A analytes were at 8.8-fold (95% CI, 2.3–34.3) risk of abruption. No associations were seen with other analytes.

**Conclusions—**These data provide support to our hypothesis that the origins of placental abruption may extend to the early stages in pregnancy.

## INTRODUCTION

Placental abruption complicates about 1% of deliveries (1). It is a life-threatening condition to the fetus (2, 3) and is implicated in serious maternal complications (4), as well as cardiovascular and cerebrovascular morbidity and mortality in both the women and their infants later in life (5, 6). Previous epidemiologic studies (7), as well as studies evaluating histologic lesions in the placenta, cord and membranes (8) suggest that the clinical manifestations of abruption may be the result of a long-standing process with its origins extending to the early stages in pregnancy.

Preeclampsia is one of the strongest known risk factors for abruption (9), and abruption is associated with a 3- to 4-fold increased risk of fetal growth restriction (FGR) (10). Together, these three conditions have similar pathophysiologic process, and these conditions have been termed the syndrome of ischemic placental disease (11). All three conditions are associated with excessively high risks of preterm delivery (12).

We examined both first trimester (PAPP-A, and total and free β-hCG), and second trimester (maternal serum α-fetoprotein [AFP] unconjugated estriol [$uE_3$], and dimeric Inhibin-A) serum analytes and their association with abruption. We also examined whether these serum analytes were associated with abruption risk within subsets of high-risk women, defined as those with ischemic placental disease (preeclampsia or FGR). Finally, we examined if multiple abnormal serum analytes were associated with a further increased risk of abruption. We hypothesized that if the origins of abruption extend to the early stages in pregnancy, then evidence for this must be seen with its association with first and second trimester maternal serum analytes.

## MATERIALS AND METHODS

We performed a secondary analysis of data from the First and Second Trimester Evaluation of Risk (FASTER), a multicenter prospective cohort study carried out in 1999–2002 (13) (centers listed in Appendix 1, http://links.lww.com/xxx)(13). The FASTER study was designed to evaluate ultrasound and screening markers for predicting the risk of Downs syndrome. Women carrying a viable singleton fetus between 10 weeks 3 days and 13 weeks 6 days (14), corresponding to fetal crown rump length measuring 36–79 mm, were recruited. Women carrying fetuses diagnosed with anencephaly or septated cyctic hygroma were ineligible. Serum samples were obtained from participating women in the first and second trimesters, centrifuged and shipped to Women and Infants Hospital, Providence, RI for processing. The FASTER study received ethics approval from the institutional review boards at Columbia University, NY (the primary site), as well as from each of the participating sites. All women provided written informed consent to participate in the FASTER study. Further details of the FASTER study are provided elsewhere (13).

In the FASTER study, maternal peripheral blood was drawn in both the first and second trimesters with no results reported until the second trimester. Serum measurements of PAPP-

A (ELISA method, Diagnostic Systems Labs, Inc., Webster, TX), and free β-hCG (IRMA method, Diagnostic Systems Labs, Inc., Webster, TX) were performed in the first trimester between 10 weeks 3 days, and 13 weeks 6 days of gestation (15). Second-trimester screening for maternal serum AFP and total hCG were measured using the Diagnostic Products Corporation, Los Angeles, Immulite method; uE$_3$ by Diagnostic Systems Laboratories radioimmunoassay and Inhibin-A by Diagnostic Systems Laboratories. The assay sensitivities for total hCG, free β-hCG, and inhibin-A were 2 milliInternational units per mL, 1 milliInternational units per mL, and 10 pg per mL, respectively. The inter- and intra-assay coefficients of variation were less than 15% for all three analytes (16).

Samples were collected in serum separator tubes and allowed to clot at room temperature for about 30 to 60 min and were then centrifuged at 3000 rpm for 15 min and stored in the refrigerator (4°C) until shipping. Samples were shipped at ambient temperature by priority overnight to Women and Infants Hospital, Providence, RI for processing.

FGR was defined as ultrasonographically estimated fetal weight below the 10th percentile for gestational age. All diagnosis of placental abruption, as well as preeclampsia, and FGR were based on an obstetrician diagnosis, and the data were abstracted from obstetrical charts by trained research coordinators.

First, we examined the distributions of serum analytes, and categorized each analyte's multiple of the median (MoM) as ≤5, 6–10, 11–89, 90–94, and ≥95 percentiles to conform to clinically meaningful cut-offs. While the MoM's for many of the analytes were normally distributed, some were not. To avoid making incorrect inferences, we therefore chose to present the median (instead of the mean) MoM's throughout. These percentile cut-offs were derived from women without a diagnosis of abruption. Associations between the analytes and the risk of abruption were evaluated from log-linear regression models based on the log-Binomial or Poisson distribution. From these models, we derived the risk ratio (RR) and 95% confidence interval (CI) before and after adjustment for confounders. The confounders included maternal age, primiparity, race-ethnicity (non-Hispanic white, non-Hispanic black, Hispanic and other race), single marital status, education (grouped as ≤8, 9–12, 13–16, and ≥17 years), smoking, alcohol and drug use during pregnancy, prepregnancy body-mass index (defined as the ratio of weight and squared-height, and expressed as kg per m$^2$), chronic hypertension and assisted reproduction technique (ART). ART included one or more of ovulation induction, intrauterine insemination, in vitro fertilization, or gamete intra-fallopian transfer.

Since the association between continuous variables (e.g., age, BMI) and the outcome may portend a non-linear relationship (e.g., "U"-shaped), we evaluated non-linearity by including a quadratic term (centered around the mean to avoid multicollinearity). The presence of non-linearity was then assessed by comparing the residual deviance Chi-square value between the model with and without the quadratic term; those with a P-value <0.1 were retained in the regression models. While maternal age demonstrated a non-linear relationship with abruption, BMI did not. Confounders were included in the final model if they either changed the confounder-adjusted (log) RR by at least 10 percent, or were candidates with *a priori* interest.

In addition to the primary outcome, we performed two additional analyses. In the first, we examined the associations amongst the serum analytes and placental abruption within high-risk subsets. These subsets included women with ischemic placental disease, defined as those with abruption only, or abruption with preeclampsia or FGR or both. In the second analysis, we examined whether combinations of serum analytes were associated with abruption. For this analysis, we also determined the sensitivity, specificity, and positive, and negative predictive values. Owing to small numbers, the 95% confidence intervals for the test characteristics were estimated from the exact method based on binomial proportions.

From a total of 38,033 participants in the FASTER study, we sequentially excluded women that delivered at less than 20 weeks in gestation (n=2,398), and women for whom a diagnosis of abruption was not recorded (n=143). The remaining 35,327 women constituted the analytic cohort.

## RESULTS

Of the 35,327 eligible women, 250 (0.7%) had a recorded diagnosis of abruption. Compared with women without an abruption, those with an abruption tended to be slightly older, have higher risks of assisted reproduction methods, gestational diabetes, hypertensive disorders, FGR, and preterm delivery (Table 1). These women were also more likely to have undergone assisted reproduction, have hypertensive disorders, diabetes, and deliver preterm (<37 weeks); the association with preterm delivery was the strongest (RR 10.2, 95% CI, 8.0–13.0). Infants born to women with an abruption were delivered 3 weeks earlier and weighed, on average, over 650 g less than those born to women without abruption. They, in turn, were at increased risk of both FGR and perinatal death.

Women with an abruption had abnormally low first trimester PAPP-A levels ( 5 percentile) compared to those without an abruption (9.6% versus 5.3%), yielding an adjusted RR of 1.9 (95% CI, 1.2–2.8, Table 2). In the second trimester, abnormally high maternal serum AFP  95 percentile was more common among abruption (9.6%) than non-abruption (5.1%) pregnancies (RR 1.9, 95% CI, 1.3–3.0, Table 2). Among women with abruption, Inhibin-A demonstrated a U-shaped non-linear relationship, with increased risks among women with both abnormally low ( 5 percentile) and abnormally high ( 95 percentile) Inhibin-A levels. None of the other analytes were associated with abruption.

To evaluate whether the associations of the abnormal serum analytes and abruption were driven by co-occurring obstetric complications, we then examined the associations among women with abruption only and those with abruption and either preeclampsia or FGR or both (table 3). These analyses show that the abnormal analytes were associated with abruption, as well as with abruption accompanied by ischemic placental disease.

Since abnormal PAPP-A, maternal serum AFP, and Inhibin-A were the analytes associated with abruption (table 2), we examined whether women with combinations of these analytes were associated with increased risk of abruption (table 4). With PAPP-A, maternal serum AFP and Inhibin-A values being normal (11–89 percentile) as the reference, women with abnormal Inhibin-A (either  5 or  95 percentiles), and normal PPP-A and maternal serum

AFP were associated with increased risk of abruption. Similarly, those with abnormal maternal serum AFP and Inhibin-A (both 95 percentiles) and normal PAPP-A were associated with a four-fold (RR 4.0, 95% CI, 1.5–10.8) increased risk of abruption. Abnormal PAPP-A ( 5 percentile), but normal maternal serum AFP and Inhibin-A were also associated with a 2.4-fold (95% CI, 1.4–4.1) increased risk. Finally, when all three analytes were abnormal (PAPP-A 5 percentile), maternal serum AFP, and Inhibin-A (both 95 percentiles), the risk of abruption was the highest at 8.8 (95% CI, 2.3–34.3). In fact, this RR was different from the RR's for other combinations of the analytes (P=0.004). Although the specificity, and negative predictive values for all combinations of the three analytes for placental abruption were close to perfect, the sensitivity, and positive predictive values were very low (Table 5).

## DISCUSSION

The main finding of this secondary analysis of data from the multicenter, FASTER prospective cohort study is that abnormal values in three maternal serum analytes, PAPP-A in the first trimester, and maternal serum AFP and Inhibin-A in the second trimester are associated with increased risk of abruption. Abnormal values of all three analytes are associated with increased risk of isolated abruption, as well as abruptions that co-occur with ischemic placental disease. Women with abnormal values of all three analytes appear are almost at nine-fold increased risk of abruption. However, given the low sensitivity, and positive predictive values, none of these analytes were predictive of abruption.

Some limitations of the study deserve attention. In particular, associations pertaining to the combination of analytes on abruption risk were not adjusted for confounding variables owing to small cell sizes, or instances where some of the reported risk ratios were accompanied by fairly wide 95% confidence intervals. Although misclassification of abruption is likely, this misclassification would have been non-differential with respect to the results of the serum analytes. Moreover, we did not know whether women with abruption in this study experienced an abruption in any of her previous pregnancy, or if women in the non-abruption group had a prior abruption.

The strengths of the study include the prospective nature of the FASTER cohort, standardized data collection across the centers, and all data being manually checked by a data coordination center. Abnormal serum analytes were not utilized to modify the obstetrical management or guide any interventions to prevent the outcome of interest from occurring, so these associations reflect real-life scenarios in contemporary obstetrical practice.

Data on the associations between low PAPP-A and abruption is conflicting. Dugoff and colleagues (17) examined the associations of two first trimester serum analytes, PAPP-A, and β-hCG in relation to obstetrical complications, including abruption, in the FASTER cohort. They showed that the odds of abruption among women with abnormally low PAPP-A ( 5 percentile of the multiples of the median) was 1.8 (95% CI, 1.2–2.8); no association was reported for free β-hCG.

A large study of 137,915 women in California reported that PAPP-A 5 percentile was associated with a 1.6-fold (95% CI, 1.3–2.0) increased risk of abruption (18). In contrast, a hospital-based study in Finland (19) reported no association between low PAPP-A (<1.0 MoM) and abruption (odds ratio 1.09, 95% CI, 0.42–2.82). Similarly, another study from Greece by Pilalis and colleagues (20) reported that the prevalence risks of abruption were similar between women with and without low first trimester PAPP-A. Finally, a third study from Israel (21) also did not find an association between low PAPP-A ( 0.25 MoM) and abruption. These latter studies were perhaps driven by the very few number of abruption cases (17 in the Finland study, 7 in the Greece study, and 2 in the Israel study). PAPP-A has also been shown to be associated with increased risks of other placental dysfunction disorders (22, 23). including stillbirth. In fact, in a multicenter study of 7,934 women, first trimester PAPP-A 5 percentile was associated with over 60-fold (hazard ratio 60.5, 95% CI, 6.1–597.0) increased risk of stillbirth due to abruption (24).

The mechanisms for elevated maternal serum AFP with a structurally normal fetus include disruption of the fetal-maternal-placental barrier, placental vascular damage from early subclinical abruption, or fetal-placental ischemia (25), The associations between high maternal serum AFP and abruption remains inconclusive with two studies showing increased risk (26, 27) and another demonstrating no association (28).

Inhibin is a glycoprotein that is produced by the placenta. Concentrations of circulating dimeric inhibin-A rapidly rise in early pregnancy, fall after 12 weeks of gestation, remain low in the second trimester, and gradually increases in the latter half of pregnancy (29, 30). Previous studies did not report associations of Inhibin-A both at 5th and 95th percentiles in relation to abruption.

While our data suggests increased risk of abruption among women with abnormal PAPP-A, maternal serum AFP, and Inhibin-A levels, the combination of these abnormal analytes substantially increase abruption risk. Despite the strong associations amongst these three analytes and abruption, we can't recommend these multiple maternal serum markers as a population-based screening tools, given the low sensitivity of these serum analytes in predicting abruption (31).

Prediction of abruption has remained an obstetrical challenge as regards prediction and prevention. We hope that future studies aimed at developing prediction models for abruption based on maternal early pregnancy serum biomarkers coupled with Doppler velocimetry profile of the uterine and umbilical arteries or other biomarkers or demographic factors may yield clinically important insights.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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**Table 1**

Maternal and infant characteristics in relation to placental abruption

| Characteristics | Non-abruption (n=35,077) No. (%) | Abruption (n=250) No. (%) | Risk ratio (95% confidence interval) |
|---|---|---|---|
| Maternal age (years)[¶] | 30.1 (5.8) | 31.1 (6.2) | — |
| Primiparity | 27,344 (78.0) | 186 (74.4) | 0.8 (0.6–1.1) |
| Race/ethnicity | | | |
| Non-Hispanic white | 23,749 (67.8) | 191 (76.4) | 1.0 (Reference) |
| Non-Hispanic black | 1,725 (4.9) | 13 (5.2) | 0.9 (0.5–1.6) |
| Hispanic | 7,869 (22.5) | 32 (12.8) | 0.5 (0.4–0.7) |
| Other | 1,711 (4.9) | 14 (5.6) | 1.0 (0.6–1.8) |
| Maternal education (years) | | | |
| <9 | 947 (2.7) | 2 (0.8) | 0.3 (0.1–1.0) |
| 9–12 | 8,355 (23.9) | 49 (19.7) | 0.7 (0.5–1.0) |
| 13–16 | 18,336 (52.4) | 135 (54.2) | 0.7 (0.6–1.2) |
| 17 | 7,388 (21.1) | 63 (25.3) | 1.0 (Reference) |
| Smoking during pregnancy | 1,633 (4.7) | 14 (5.6) | 1.2 (0.7–2.1) |
| Alcohol use | 757 (2.2) | 7 (2.8) | 1.3 (0.6–2.8) |
| Drug use | 354 (1.0) | 0 (0.0) | — |
| Single marital status | 7,481 (21.3) | 40 (16.0) | 0.7 (0.5–1.0) |
| Prepregnancy BMI (kg per m$^2$) [¶] | 25.0 (5.2) | 25.5 (6.0) | — |
| Progesterone supplementation | 1,785 (5.1) | 20 (8.0) | 1.6 (1.0–2.5) |
| Folic acid supplementation | 16,452 (47.1) | 123 (49.2) | 1.1 (0.9–1.4) |
| Assisted reproduction methods | 1,719 (4.9) | 25 (10.0) | 2.1 (1.4–3.2) |
| Diabetes mellitus | | | |
| Gestational diabetes mellitus | 1,216 (3.5) | 16 (6.4) | 1.9 (1.2–3.1) |
| Gestational hypertension | 1,563 (4.5) | 23 (9.2) | 2.2 (1.4–3.3) |
| Preeclampsia | 815 (2.3) | 17 (6.8) | 3.0 (1.9–5.0) |
| Fetal growth restriction | 400 (1.1) | 12 (4.8) | 4.3 (2.4–7.6) |
| Preterm delivery <37 weeks | 2,575 (7.3) | 114 (45.6) | 10.2 (8.0–13.0) |
| Cesarean delivery | 8,283 (23.8) | 118 (48.2) | 3.0 (2.3–3.8) |
| Birthweight (g) [¶] | 3,351 (538) | 2,693 (840) | — |
| Gestational age (weeks) [¶] | 39.2 (2.1) | 36.2 (4.0) | — |

BMI, body-mass index

[¶]Data reported as mean (standard deviation)

**Table 2**

Associations of first and second trimester serum analytes in relation to placental abruption

| Serum analytes multiples of median | No abruption (n=35,077) No. (%) | Abruption (n=250) No. (%) | Risk ratio (95% confidence interval) | |
|---|---|---|---|---|
| | | | Unadjusted | Adjusted |
| **First trimester maternal serum analytes** | | | | |
| **PAPP-A (median, IQR)** | 1.0 (0.7, 1.5) | 1.0 (0.7, 1.4) | P=0.247 | |
| 5% | 1,866 (5.3) | 24 (9.6) | 1.9 (1.2–2.9) | 1.9 (1.2–2.8) |
| 6–10% | 1,738 (5.0) | 10 (4.0) | 0.8 (0.5–1.6) | 0.9 (0.5–1.6) |
| 11–89% | 27,936 (79.6) | 190 (76.0) | 1.0 (Reference) | 1.0 (Reference) |
| 90–94% | 1,754 (5.0) | 12 (4.8) | 1.0 (0.6–1.8) | 1.0 (0.6–1.9) |
| 95% | 1,783 (5.1) | 14 (5.6) | 1.2 (0.7–2.0) | 1.2 (0.7–2.5) |
| **Total β-hCG (median, IQR)** | 1.0 (0.7, 1.4) | 1.0 (0.7, 1.4) | P=0.858 | |
| 5% | 1,727 (5.3) | 13 (5.4) | 1.1 (0.6–1.9) | 1.1 (0.6–1.9) |
| 6–10% | 1,742 (5.3) | 9 (3.8) | 0.7 (0.4–1.4) | 0.7 (0.4–1.4) |
| 11–89% | 26,105 (79.3) | 185 (77.4) | 1.0 (Reference) | 1.0 (Reference) |
| 90–94% | 1,676 (5.1) | 13 (5.4) | 1.1 (0.6–1.9) | 1.1 (0.6–1.9) |
| 95% | 1,653 (5.0) | 19 (8.0) | 1.6 (1.0–2.6) | 1.6 (1.0–2.6) |
| **Free β-hCG (median, IQR)** | 1.1 (0.7, 1.8) | 1.1 (0.6, 1.8) | P=0.611 | |
| 5% | 1,797 (5.1) | 18 (7.2) | 1.4 (0.8–2.2) | 1.5 (0.9–2.4) |
| 6–10% | 1,845 (5.3) | 6 (2.4) | 0.4 (0.2–1.0) | 0.5 (0.2–1.1) |
| 11–89% | 27,922 (79.6) | 205 (82.0) | 1.0 (Reference) | 1.0 (Reference) |
| 90–94% | 1,755 (5.0) | 10 (4.0) | 0.8 (0.4–1.5) | 0.8 (0.4–1.5) |
| 95% | 1,756 (5.0) | 11 (4.4) | 0.9 (0.5–1.6) | 0.9 (0.5–1.6) |
| **Second trimester maternal serum analytes** | | | | |
| **Maternal serum AFP (median, IQR)** | 1.0 (0.8, 1.3) | 1.1 (0.9, 1.4) | P <0.001 | |
| 5% | 1,758 (5.3) | 6 (2.5) | 0.5 (0.2–1.1) | 0.5 (0.2–1.1) |
| 6–10% | 1,589 (4.8) | 3 (1.3) | 0.3 (0.1–0.8) | 0.3 (0.1–0.8) |
| 11–89% | 26,288 (79.7) | 190 (79.5) | 1.0 (Reference) | 1.0 (Reference) |
| 90–94% | 1,667 (5.1) | 17 (7.1) | 1.4 (0.9–2.3) | 1.4 (0.9–2.3) |
| 95% | 1,661 (5.1) | 23 (9.6) | 1.9 (1.2–2.9) | 1.9 (1.3–3.0) |
| Missing | | 11 | | |
| **uE$_3$ (median, IQR)** | 1.0 (0.8, 1.2) | 1.0 (0.8, 1.2) | P=0.810 | |
| 5% | 1,737 (5.3) | 15 (6.3) | 1.2 (0.7–2.1) | 1.1 (0.6–1.9) |
| 6–10% | 1,791 (5.4) | 13 (5.4) | 1.0 (0.6–1.8) | 1.0 (0.6–1.7) |
| 11–89% | 26,038 (79.1) | 185 (77.4) | 1.0 (Reference) | 1.0 (Reference) |
| 90–94% | 1,640 (5.0) | 16 (6.7) | 1.4 (0.8–2.3) | 1.5 (0.9–2.6) |
| 95% | 1,694 (5.2) | 10 (4.2) | 0.8 (0.4–1.6) | 1.0 (0.5–1.8) |
| **Inhibin-A (median, IQR)** | 1.0 (0.8, 1.3) | 1.1 (0.8, 1.5) | P=0.277 | |
| 5% | 1,673 (5.1) | 19 (8.0) | 1.7 (1.1–2.8) | 1.8 (1.1–2.9) |
| 6–10% | 1,659 (4.1) | 11 (4.6) | 1.0 (0.6–1.9) | 1.0 (0.6–1.9) |
| 11–89% | 26,236 (79.8) | 172 (72.0) | 1.0 (Reference) | 1.0 (Reference) |
| 90–94% | 1,683 (5.1) | 14 (5.9) | 1.3 (0.7–2.2) | 1.2 (0.7–2.1) |

| Serum analytes multiples of median | No abruption (n=35,077) No. (%) | Abruption (n=250) No. (%) | Risk ratio (95% confidence interval) | |
| --- | --- | --- | --- | --- |
| | | | Unadjusted | Adjusted |
| 95% | 1,645 (5.0) | 23 (9.6) | 2.1 (1.4–3.3) | 2.0 (1.3–3.1) |

IQR, interquartile range; PAPP-A, pregnancy-associated plasma protein A; hCG, human chorionic gonadotropin; AFP, alpha fetoprotein; uE3, unconjugated estriol

Risk ratios are adjusted for maternal age, age-squared, primiparity, maternal education, single marital status, race-ethnicity, smoking, and assisted reproduction method

**Table 3**

Association of abnormal maternal serum analytes in relation to placental abruption with and without co-occurring ischemic placental disease

| | No IPD | Placental abruption only | | | Abruption with preeclampsia or FGR | | |
|---|---|---|---|---|---|---|---|
| | | | Risk ratio (95% CI) | | | Risk ratio (95% CI) | |
| | No. (%) | No. (%) | Unadjusted | Adjusted | No. (%) | Unadjusted | Adjusted |
| PAPP-A 5 percentile | 1,745 (6.1) | 20 (10.6) | 1.8 (1.2–2.9) | 1.8 (1.2–2.9) | 4 (16.7) | 3.1 (1.1–9.0) | 2.8 (1.0–8.3) |
| Maternal serum AFP 95 percentile | 1,556 (5.8) | 20 (10.4) | 1.9 (1.2–3.0) | 1.8 (1.1–3.1) | 3 (15.0) | 2.9 (0.8–9.8) | 2.7 (0.8–9.2) |
| Inhibin-A 5 percentile | 1,630 (6.0) | 18 (10.2) | 1.8 (1.1–2.9) | 1.8 (1.1–2.9) | 1 (7.1) | 0.5 (0.2–9.2) | 1.3 (0.2–9.8) |
| Inhibin-A 95percentile | 1,484 (5.5) | 15 (8.7) | 1.6 (1.0–2.8) | 1.6 (0.9–2.7) | 8 (38.1) | 10.5 (4.4–25.3) | 8.3 (3.4–21.1) |

IPD, ischemic placental disease; FGR, fetal growth restriction; PAPP-A, pregnancy-associated plasma protein A; AFP, alpha fetoprotein; CI, confidence interval

Risk ratios are adjusted for maternal age, age-squared, primiparity, maternal education, single marital status, race-ethnicity, and smoking, with "no ischemic placental disease" as the reference group

**Table 4**

Risk of placental abruption in relation to combinations of abnormal first and second trimester maternal serum analytes

| Serum analyte percentile | | | No abruption No. (%) | Abruption No. (%) | Unadjusted risk ratio (95% confidence interval) |
|---|---|---|---|---|---|
| PAPP-A | Maternal Serum AFP | Inhibin-A | | | |
| 11–89% | 11–89% | 11–89% | 17,069 (80.1) | 103 (64.8) | 1.0 (Reference) |
| | | 5% | 1,083 (5.1) | 14 (8.8) | 2.1 (1.2–3.7) |
| | | 95% | 842 (4.0) | 10 (6.3) | 2.0 (1.0–3.7) |
| | 95% | 11–89% | 888 (4.2) | 8 (5.0) | 1.5 (0.7–3.0) |
| | | 5% | 22 (0.1) | 0 (-) | - |
| | | 95% | 162 (0.8) | 4 (2.5) | 4.0 (1.5–10.8) |
| 5% | 11–89% | 11–89% | 976 (4.6) | 14 (8.8) | 2.4 (1.4–4.1) |
| | | 5% | 98 (0.5) | 2 (1.3) | 3.3 (0.8–13.3) |
| | | 95% | 70 (0.3) | 1 (0.6) | 2.4 (0.3–16.6) |
| | 95% | 11–89% | 66 (0.3) | 1 (0.6) | 2.5 (0.4–17.6) |
| | | 5% | 4 (0.02) | 0 (-) | - |
| | | 95% | 36 (0.2) | 2 (1.3) | 8.8 (2.3–34.3) |

PAPP-A, pregnancy-associated plasma protein A; AFP, alpha fetoprotein

**Table 5**

Test characteristics based on combinations of abnormal serum analytes for PAPP-A, MS-AFP, and Inhibin-A on the risk of placental abruption

| Serum analyte percentile | | | Test characteristic (95% confidence interval) | | | |
|---|---|---|---|---|---|---|
| PAPP-A | Maternal Serum AFP | Inhibin-A | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
| 11–89% | 11–89% | 11–89% | - | - | - | |
| | | 5% | 12.0 (6.7–19.3) | 94.0 (93.7–94.4) | 1.3 (0.7–2.1) | 99.4 (99.3–99.5) |
| | | 95% | 8.9 (4.3–14.1) | 95.3 (95.0–95.6) | 1.2 (0.6–2.2) | 99.4 (99.3–99.5) |
| | 95% | 11–89% | 7.2 (3.2–13.7) | 95.1 (94.7–95.4) | 0.1 (0.1–1.8) | 99.4 (99.3–99.5) |
| | | 5% | - | 99.9 (99.8–99.9) | - | 99.4 (99.3–99.5) |
| | | 95% | 3.7 (1.0–9.3) | 99.1 (98.9–99.2) | 2.4 (0.7–6.1) | 99.4 (99.3–99.5) |
| 5% | 11–89% | 11–89% | 12.0 (6.7–19.3) | 94.6 (94.2–94.9) | 1.4 (0.1–2.4) | 99.4 (99.3–99.5) |
| | | 5% | 1.9 (0.0–6.7) | 99.4 (99.3–99.5) | 2.0 (0.0–7.0) | 99.4 (99.3–99.5) |
| | | 95% | 1.0 (0.0–5.2) | 99.6 (99.5–99.7) | 1.4 (0.0–7.6) | 99.4 (99.3–99.5) |
| | 95% | 11–89% | 1.0 (0.0–5.2) | 99.6 (99.5–99.7) | 1.5 (0.0–8.0) | 99.4 (99.3–99.5) |
| | | 5% | - | 100.0 (-) | - | 99.4 (99.3–99.5) |
| | | 95% | 1.9 (0.0–6.7) | 99.8 (99.7–99.9) | 5.3 (0.1–17.8) | 99.4 (99.3–99.5) |

PAPP-A, pregnancy-associated plasma protein A; AFP, alpha fetoprotein; PPV, positive predictive value; NPV, negative predictive value

The 95% confidence intervals were estimated based on the exact binomial proportion method