

Prediction of adverse pregnancy outcomes by extreme values of first trimester screening markers

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Abstract

Background: To determine the association between extreme values of first trimester markers and adverse pregnancy outcomes.

Methods: A retrospective cohort study of 916 women who underwent first-trimester combined screening during 2015 was performed. Extreme values of NT, pregnancy-associated plasma protein-A (PAPP-A) and free β -hCG, and their association with adverse pregnancy outcomes were analyzed.

Results: Low PAPP-A (<10th percentile) was associated with an increased risk for preeclampsia (adjusted odds ratio (AOR) 4.13), fetal growth restriction (AOR 3.94) and abruptio placentae (AOR 52.63). Abnormally low or high free β -hCG, high PAPP-A or increased NT was not associated with an increased risk for adverse outcomes.

Discussion: PAPP-A <10th percentile could be associated with an increased risk for adverse outcomes. However, the majority of patients with these events do not have abnormal PAPP-A and few patients with PAPP-A <10th percentile will have an adverse outcome.

Keywords

Abruptio placentae, fetal growth, human chorionic-gonadotrophin beta-subunit, nuchal translucency, pregnancy-associated plasma protein-A, preeclampsia

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Introduction

Maternal serum markers obtained in first trimester Down syndrome screening include pregnancy-associated plasma protein-A (PAPP-A) and free beta-human chorionic gonadotropin (free β -hCG). The combined test (sonographic measurement of fetal nuchal translucency (NT) and maternal serum markers) detects 85 percent of Down syndrome fetuses at a five percent false positive rate.^{1,2} Although the primary goal of this screening is to detect these disorders, recent studies describe the association between individual extreme levels of Down syndrome screening markers and adverse pregnancy outcomes, including preterm birth, fetal growth disorders, hypertensive disorders and spontaneous abortion.^{3–15} The aim of this study was to determine the association and predictive ability of extreme values of PAPP-A, free β -hCG and NT with adverse pregnancy outcomes.

Methods

A retrospective cohort study was performed including women with a singleton gestation who underwent first-trimester screening for aneuploidy between 11 weeks 0 days and 13 weeks 6 days of gestation (fetal crown-rump length between 45 and 84 mm) at Alto Minho Local Healthcare Unit, Viana do Castelo, Portugal, during 2015. Women who had a fetal demise before 22 weeks of gestation or whose fetuses were confirmed to have chromosome abnormalities or other malformation were excluded. Likewise, records with incomplete outcome data were not included. The three first-trimester markers PAPP-A level, free β -hCG and NT were evaluated. Values for the two serum markers were obtained by a certificated laboratory and NT measurements were obtained by a maternal fetal medicine specialist with Fetal Medicine Foundation certification. Information on maternal sociodemographics, medical and obstetrical history, gestational age at examination, pregnancy course and delivery outcome were collected. In a primary analysis, extreme values of NT (≥ 2.5 mm), PAPP-A (<1st, 5th and 10th percentiles, >90th, 95th and 99th percentiles) and free β -hCG

(<1st, 5th and 10th percentiles, >90th, 95th and 99th percentiles) were evaluated, as well as their association with adverse pregnancy outcomes. Percentiles were defined using FASTER study⁶ (Table 1). In a second analysis, women with a PAPP-A <10th percentile multiples of median (MoM) were compared to those with a PAPP-A ≥ 10 th percentile. In the final adjusted models, some variables were considered to be confounders for preeclampsia, namely, maternal age, parity and chronic hypertension. Gestational hypertension, chronic hypertension, pregestational diabetes and preeclampsia were considered for fetal growth restriction; and maternal age, parity, gestational hypertension and chronic hypertension, gestational age at delivery and infant sex were considered for abruptio placentae. Performance characteristics, which included the adjusted odds ratios (AOR) and 95% confidence interval (CI), sensitivity, specificity and positive predictive value (PPV) and negative predictive value (NPV) for PAPP-A were estimated for each outcome.

Outcome measurements

The outcome measurements examined included preterm birth, gestational hypertension, preeclampsia, third trimester fetal growth restriction, low birth weight, preterm premature rupture of membranes (PPROM), abruptio placentae, gestational diabetes, macrosomia and

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oligohydramnios. Preterm birth was defined, according to World Health Organization, as a delivery occurring before 37 weeks of pregnancy. Gestational hypertension was defined as new onset of hypertension (systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg) at ≥ 20 weeks of gestation, in the absence of proteinuria or new signs of end-organ dysfunction. The blood pressure readings were documented on at least two occasions at least four hours apart, according to the American College of Obstetricians and Gynecologists (ACOG). Preeclampsia was defined as new onset of hypertension and either proteinuria or end-organ dysfunction after 20 weeks of gestation. Criteria for diagnosis were: systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, and proteinuria ≥ 0.3 g in a 24 h urine specimen or protein:creatinine ratio ≥ 0.3 , or signs of end-organ dysfunction (platelet count $< 100,000/\mu\text{L}$, serum creatinine > 1.1 mg/dL or doubling of the serum creatinine, elevated serum transaminases to twice normal concentration), according to ACOG. Third trimester fetal growth restriction was defined as a fetus whose estimated weight was below the 10th percentile for gestational age, calculated by ASTRAIA software, after 27 weeks 0 days of gestation. Low birth weight was defined as a birth weight of a liveborn of less than 2500 g, regardless of gestational age, according to ACOG.

Table 1. Relationship between analytic percentiles and multiples of the median (FASTER trial).

| Percentile | PAPP-A (MoM) | Free β -hCG (MoM) |
|------------|--------------|-------------------------|
| 1st | 0.28 | 0.24 |
| 5th | 0.42 | 0.35 |
| 10th | 0.52 | 0.44 |
| 90th | 2.04 | 2.94 |
| 95th | 2.51 | 3.91 |
| 99th | 3.73 | 6.56 |

MoM: multiples of median; β -hCG: free beta-human chorionic gonadotropin; PAPP-A: pregnancy-associated plasma protein-A.

PPROM was defined as the rupture of the membranes before the onset of labor until 37 weeks of gestation. Abruptio placentae was defined as bleeding at the decidual-placental interface that causes partial or complete placental detachment prior to delivery of the fetus. The diagnosis was primarily clinical and confirmed by ultrasound or intra-operative visualization of placental detachment. Gestational diabetes was diagnosed if fasting glucose level ≥ 92 and < 126 mg/dL at first trimester or at least one value of plasma glucose concentration ≥ 92 , 180 and 153 mg/dL (for fasting, 1- and 2-h post glucose load glucose values, respectively), after performing a 75 g oral glucose tolerance test at 24–28 weeks of gestation.¹⁶ Macrosomia was defined as a birth weight greater than 4500 g. Oligohydramnios was defined as amniotic fluid index ≤ 5 cm or the absence of a single deepest pocket $< 2 \times 1 \text{ cm}^2$.¹⁷

Statistical analysis

Continuous variables were described using median and interquartile ranges and categorical variables using frequencies. Continuous variables were compared between groups using Mann–Whitney *U* test and dichotomous variables using Fisher's exact test or Chi-square test, as appropriate. In the final phase, logistic regression analysis was performed to evaluate possible confounding or adjustment factors. OR and 95% CI were calculated. Statistical analyses were performed with the SPSS package (SPSS Inc., Chicago IL, version 23). Statistical significance was defined as *p* value < 0.05 .

Results

The study population included all women whom PAPP-A level, free β -hCG and NT were available ($N = 1025$). One hundred and nine (10.63%) women were excluded (Figure 1). The patients included in this study did not differ significantly in sociodemographics from those who were excluded and population's characteristics, with relevant patient history, demographic data and obstetric history are summarized in Table 2.

Among the 916 women, 31 (3.4%) had a preterm birth, 21 (2.3%) developed gestational hypertension, 12 (1.3%) had preeclampsia, 27 (2.9%) had third trimester fetal growth restriction, 43 (4.7%) had a low birth weight newborn, 10 (1.1%) had a PPRM, 3 (0.3%) had

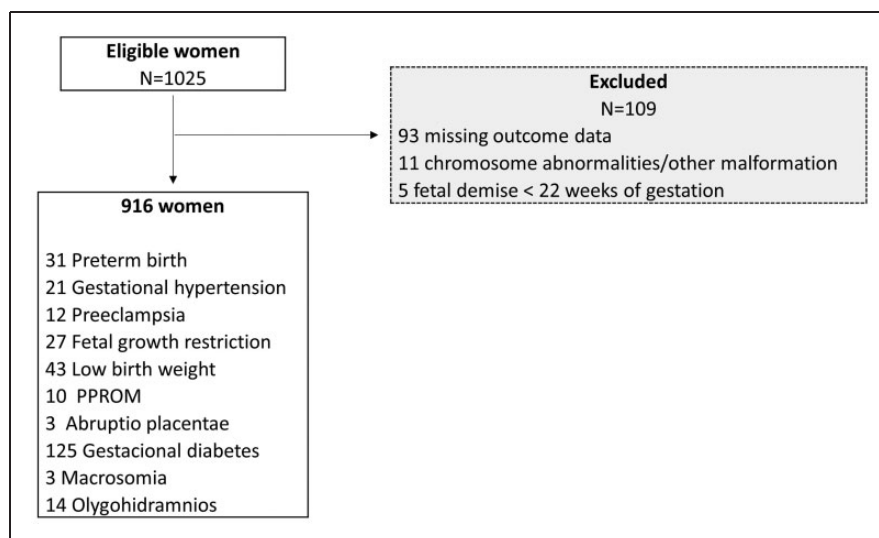


Figure 1. Flow chart of study population selection. PPRM: preterm premature rupture of membranes.

Table 2. Patients' characteristics by PAPP-A <10th percentile MoM versus PAPP-A ≥10th percentile MoM.

| | All (N=916) | PAPP-A <10th percentile (N=103) | PAPP-A ≥10th percentile (N=813) | p-Value |
|--------------------------------------|---------------------|---------------------------------------|---------------------------------------|--------------|
| Maternal age (years) | 31 (28–35) | 31 (29–34) | 31 (28–35) | 0.77 |
| Parity | 1 (0–1) | 1 (0–1) | 1 (0–1) | 0.55 |
| Previous preterm birth | 9 (1%) | 2 (1.9%) | 7 (0.9%) | 0.27 |
| Pregestational diabetes | 8 (0.9%) | 3 (2.9%) | 5 (0.6%) | 0.05 |
| Chronic hypertension | 20 (2.2%) | 3 (2.9%) | 7 (2.1%) | 0.48 |
| Ultrasound marker NT ≥2.5 mm | 70 (7.6%) | 2 (1.9%) | 68 (8.4%) | 0.02 |
| Serum marker Free β-hCG (MoM) | 0.889 (0.608–1.389) | 0.68 (0.49–0.966) | 0.919 (0.629–1.414) | 0.000 |
| First trimester combined risk >1:300 | 26 (2.8%) | 9 (8.7%) | 17 (2.1%) | 0.001 |
| Amniocentesis | 30 (3.3%) | 6 (5.8%) | 24 (3.0%) | 0.14 |
| Delivery | | | | |
| Duration of pregnancy (weeks) | 39 (38–40) | 39 (38–40) | 39 (39–40) | 0.04 |
| Spontaneous labor | 582 (63.5%) | 64 (62.1%) | 518 (63.7%) | 0.75 |
| No operative delivery | 516 (56.3%) | 39 (37.9%) | 456 (56.1%) | 0.75 |
| Male sex | 445 (48.6%) | 64 (62.1%) | 407 (50.1%) | 0.02 |
| Birth weight (g) | 3282.5 (2980–3560) | 3120 (2907.5–3527.5) | 3300 (2990–3571) | 0.02 |
| 1-minute Apgar <7 | 26 (2.8%) | 2 (1.9%) | 24 (3.0%) | 0.42 |
| 5-minute Apgar <7 | 2 (0.2%) | 0 (0.0%) | 2 (0.3%) | 0.78 |

Data are given as frequencies (percent) or median (quartiles).

Table 3. Relationship between low PAPP-A levels (<1st, 5th and 10th percentiles) and adverse pregnancy outcomes.

| Outcome | 10th percentile N=103 | ≥10th percentile N=813 | p-Value | <5th percentile N=47 | ≥5th percentile N=869 | p-Value | <1st percentile N=10 | ≥1st percentile N=916 | p-Value |
|----------------------|-----------------------------|------------------------------|--------------|----------------------------|-----------------------------|-------------|----------------------------|-----------------------------|-------------|
| Preterm birth | 1 (1%) | 30 (3.7%) | 0.24 | 0 (0%) | 31 (3.6%) | 0.40 | 0 (0%) | 31 (3.4%) | 1.0 |
| GH | 4 (3.9%) | 17 (2.1%) | 0.28 | 4 (8.5%) | 17 (2.0%) | 0.02 | 1 (10%) | 20 (2.2%) | 0.21 |
| Preeclampsia | 4 (3.9%) | 8 (1%) | 0.04 | 1 (2.1%) | 11 (1.3%) | 0.47 | 0 (0%) | 12 (1.3%) | 1.0 |
| FGR | 9 (8.7%) | 18 (2.2%) | 0.002 | 5 (10.6%) | 22 (2.5%) | 0.01 | 2 (20%) | 25 (2.8%) | 0.03 |
| Low birth weight | 8 (7.8%) | 35 (4.3%) | 0.13 | 5 (10.6%) | 38 (4.4%) | 0.06 | 2 (20%) | 41 (4.5%) | 0.08 |
| PPROM | 0 (0%) | 10 (1.2%) | 0.61 | 0 (0%) | 10 (1.2%) | 1.0 | 0 (0%) | 10 (1.1%) | 1.0 |
| Abruptio placentae | 2 (1.9%) | 1 (0.1%) | 0.04 | 1 (2.1%) | 2 (0.2%) | 0.15 | 0 (0%) | 3 (0.3%) | 1.0 |
| Gestational diabetes | 15 (14.6%) | 110 (13.5%) | 0.77 | 6 (12.8%) | 119 (13.7%) | 1.0 | 3 (30%) | 122 (13.5%) | 0.15 |
| Macrosomia | 0 (0%) | 3 (0.4%) | 0.81 | 0 (0%) | 3 (0.3%) | 1.0 | 0 (0%) | 3 (0.3%) | 1.0 |
| Oligohydramnios | 1 (1%) | 13 (1.6%) | 1.0 | 0 (0%) | 14 (1.6%) | 1.0 | 0 (0%) | 14 (1.5%) | 1.0 |

FGR: fetal growth restriction; GH: gestational hypertension; PPROM: preterm premature rupture of membranes. Figures in bold were statistically significant.

abruptio placentae, 125 (13.6%) developed gestational diabetes, 3 (0.3%) had a macrosomic newborn and 14 (1.5%) had oligohydramnios. Only low PAPP-A level was associated with adverse pregnancy outcome. There was a statistically significant association between: PAPP-A <10th percentile and preeclampsia (adjusted odds ratio, AOR, 4.13, CI 1.15–4.80); low PAPP-A (<1st, 5th and 10th percentiles) and third trimester fetal growth restriction (AOR 8.62, 4.76, 3.94, respectively); and PAPP-A <10th percentile and abruptio placentae (AOR 52.63, 1.41–100.0) (Tables 2 and 3). For fetal growth restriction, there was an increased risk for an adverse outcome as the PAPP-A level became increasingly extreme, from 10th to 1st percentile. Because low PAPP-A (<10th percentile) level had the most significant associations with adverse pregnancy outcomes, the

characteristics of two groups were compared (Table 2) and the sensitivity, specificity and positive and NPVs for PAPP-A <0.52 MoM was calculated (Table 3). Concerning PAPP-A <10th percentile, it was observed for preeclampsia 33.3% sensitivity with 3.88% PPV; for third trimester fetal growth restriction 33.3% sensitivity with 8.74% PPV; and for abruptio placentae 66.67% sensitivity, with 1.94% PPV (Table 4).

Discussion

The aim of this study was to analyze the association of extreme values of PAPP-A, free β-hCG and NT with adverse pregnancy outcomes.

Table 4. Adverse outcomes associated with PAPP-A <10th percentile (0.52 MoM).

| Outcome | AOR | 95% CI | β -Value | Sensitivity | Specificity | PPV | NPV |
|--------------------------|-------|------------|----------------|-------------|-------------|-----|------|
| Preeclampsia | 4.13 | 1.15–14.80 | 0.03 | 33.3 | 89.1 | 3.9 | 99.0 |
| Fetal growth restriction | 3.94 | 1.68–9.26 | 0.002 | 33.3 | 89.4 | 8.7 | 97.8 |
| Abruptio placentae | 52.63 | 1.41–100.0 | 0.03 | 66.7 | 88.9 | 1.9 | 99.9 |

This study suggests that an unexplained low level of PAPP-A (<10th percentile) during first-trimester can be associated with adverse outcomes, namely preeclampsia, fetal growth restriction and abruptio placentae, as was suggested by previous studies. However, there was not always an increased risk as the PAPP-A level became increasingly extreme and probably the use of <10th percentile threshold can be more clinically useful. In this study, low levels of free β -hCG (<1st, 5th and 10th percentiles) were not associated with adverse outcomes. Other studies demonstrated an association between low levels of free β -hCG (<0.4 or 0.5 MoM) and birthweight below the 5th or 10th percentile (OR 1.6–1.7).^{4,6} If PAPP-A and free β -hCG reflect placentation quality, low levels should be associated with deficient placentation that occurs in preeclampsia and fetal growth restriction. On the other hand, PAPP-A is known to be an insulin-like growth factor-binding protein protease and to increase the bioavailability of insulin-like growth factor (IGF), that plays an important role in fetal growth¹⁸ by mediating trophoblast invasion, and to regulate steroidogenesis and glucose and amino acid transport in the chorionic villi.¹⁹ The mechanism involved with most adverse outcomes such as preeclampsia and fetal growth restriction may be related to the protease activity of PAPP-A affecting free IGF concentrations in early pregnancy, and probably this marker is the best predictor for these outcomes. There was no relationship between high PAPP-A or free β -hCG levels and adverse outcome. These results are in agreement with previous publications.^{4,6,7,10,20} If free β -hCG is increased when oxygen tension is low, as in preeclampsia and fetal growth restriction, this could be a plausible theory to explain adverse outcomes in these women. However, for the time being, there is no known consistent association. Lastly, if impaired establishment of utero-placental circulation during the first trimester may influence the physiological decrease of NT thickness in late first trimester, increased fetal NT measurement should be associated with adverse outcomes. Tsai et al.²¹ conclude that the sensitivity of fetal NT measurement in first trimester is not sufficient as a single marker for predicting the risk of preeclampsia. In this study this association has not been demonstrated probably because NT is a late marker in first trimester and this work included women who underwent first-trimester screening earlier.

Preeclampsia

Previous studies suggested low PAPP-A as a marker for subsequent development of preeclampsia.^{4,6,13,22–24} In this work, the resulting AOR for preeclampsia was significantly higher than the results from other studies, with a fourfold increased risk. Smith et al.⁴ examined the relationship between PAPP-A 5th percentile and preeclampsia and found a statistically significant increased risk (OR 2.3). Dugoff et al.⁶ found an increased risk of preeclampsia (OR 1.34) when PAPP-A was 10th percentile. In the present study, the 10th percentile threshold was the only one statistically significant, probably given the small number of cases in PAPP-A level <5th percentile group. PAPP-A <10th percentile demonstrated low sensitivity and PPV, limiting its clinical utility.

Fetal growth restriction

Low serum PAPP-A level may represent early onset placental dysfunction. In this study, the resulting AOR for fetal growth restriction was

higher than the results from other studies, with a threefold increase risk. There was an increased risk of fetal growth restriction as the PAPP-A level became increasingly extreme. Dugoff et al.⁶ found an increased risk of fetal growth restriction (OR 2.15) when PAPP-A was <10th percentile and maternal serum free β -hCG was mildly reduced in pregnancies that subsequently developed fetal growth restriction. Goetzinger et al.²⁵ concluded that black race (OR 2.9), β -hCG MoM >90th percentile (OR 1.6), and PAPP-A MoM <5th percentile (OR 2.8) were significant predictors for fetal growth restriction. The association between low PAPP-A levels and fetal growth restriction has been consensual in other studies, however the use of free β -hCG is unsatisfactory until today.^{20,26} PAPP-A <10th percentile demonstrated low sensitivity and PPV. Smith et al.⁴ concluded that the sensitivity of detecting fetal growth restriction for a first trimester PAPP-A level below the 5th percentile is low and PAPP-A as single marker is probably an insufficient screening tool. The same group concluded later that women with low levels of PAPP-A between 10 and 14 weeks and high levels of AFP between 15 and 21 weeks, were more likely to deliver a low birth weight infant, probably reflecting the combined effect of two independent pathophysiologic processes in early placental development.²⁷ In this study, for PAPP-A <1st percentile (<0.28 MoM) and PAPP-A <5th percentile (<0.42 MoM) PPVs were 20% and 10.6%, respectively, similar to the results of Krantz et al.⁷ However, the majority of patients with these adverse outcomes do not have a PAPP-A <5th and these results should be carefully interpreted.

Abruptio placentae

Some authors have questioned if low PAPP-A may be a marker for development of abruptio placentae. In this study, the 10th percentile threshold was the only one statistically significant and the resulting OR for abruptio placentae was very high, with a fiftyfold increase risk, but with only with a low PPV (1.94). Until this study, no significant increase in relative risk has been noted for abruptio placentae.^{24,28} Low levels of PAPP-A in the first-trimester have been associated with abnormal placental morphometry. There is also an evidence linking abnormal trophoblastic invasion of the decidua, thrombotic changes in the spiral arteries and abruptio-induced preterm births.²⁹ Although the majority of studies were not focused on abruptio placentae, low PAPP-A can be associated with this outcome. Blumenfeld et al.³⁰ suggested that first-trimester PAPP-A <5th percentile was associated with placental abruptio (AOR 1.9). In this study, due to the small sample size, there were no possible conclusions, however this association can be analysed in future studies.

No significant increase in relative risk was noted for other adverse outcomes evaluated including: preterm birth; low birth weight; PPROM; gestational diabetes; macrosomia; and oligohydramnios.

Limitations

This study has several limitations. Outcome data were not available for 93 women, but the patients evaluated did not differ significantly from those who were excluded. The median maternal age of this study population was high. However, maternal age was not significantly different between women with low versus high PAPP-A levels. Sample size was insufficient to analyze some rarer outcomes.

Conclusion

This study suggests that women with abnormal PAPP-A level, less than 10th percentile, could have a higher risk for preeclampsia, fetal growth restriction and possibly for abruptio placentae. For fetal growth restriction, the lower the MoM value of PAPP-A, the higher the chances of an adverse outcome. However, the majority of patients with these adverse outcomes do not have a low PAPP-A and, therefore, the sensitivity is low. In addition, few patients with a low PAPP-A actually have an adverse outcome (low PPV). There is no consensus yet as to how these pregnancies should be managed. In the absence of such evidence, no changes in clinical practice are indicated.¹²The Society of Obstetricians and Gynecologists of Canada Genetics Committee recommends that obstetricians should establish a care plan that takes into account the specific risks of each patient, including patient education, ultrasonography to assess fetal growth and amniotic fluid volume, cervical length, second trimester uterine artery Doppler examination and fetal surveillance.¹² Further investigation is needed to determine whether if any type of monitoring and intervention protocol would improve pregnancy outcome when abnormal markers are detected.

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Contributorship

All five authors were involved in writing and reviewing the submitted manuscript.

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