Hypertensive disorders in pregnancy: combined screening by uterine artery Doppler, blood pressure and serum PAPP-A at 11–13 weeks

Leona C. Y. Poon, Violeta Stratieva, Silvia Piras, Solmaz Piri and Kypros H. Nicolaides*

Harris Birthright Research Centre for Fetal Medicine, King’s College Hospital, London, UK

Objective To explore if the addition of pregnancy-associated plasma protein-A (PAPP-A) to maternal factors and biophysical markers yields a significant improvement in the detection of hypertensive disorders before the clinical onset of disease.

Methods Prospective screening study for early preeclampsia (PE), late PE and gestational hypertension (GH) in women attending their first hospital visit at 11+0–13+6 weeks of gestation. The performance of screening for PE and GH by combinations of maternal factors, uterine artery with the lowest pulsatility index (L-PI), mean arterial pressure (MAP) and serum PAPP-A was determined.

Results There were 8061 unaffected controls, 37 of whom developed early PE, 128 with late PE and 140 with GH. Compared to the controls, in early PE and late PE MAP and uterine artery L-PI were increased and PAPP-A was decreased. In GH PAPP-A was not significantly different from controls. In screening for a combination of maternal factors, uterine artery L-PI, MAP and PAPP-A the detection rate of early PE was 83.8%, at a 5% false-positive rate. In the prediction of late PE and GH there was no significant improvement from the addition of PAPP-A to the combination of maternal factors, MAP and uterine artery L-PI.

Conclusion Measurement of PAPP-A improves the performance of screening for early PE provided by a combination of maternal factors and biophysical tests at 11–13 weeks. Copyright © 2010 John Wiley & Sons, Ltd.

KEY WORDS: preeclampsia; gestational hypertension; screening; uterine artery Doppler; mean arterial pressure; PAPP-A

INTRODUCTION

Preeclampsia (PE), which affects about 2% of pregnancies, is a major cause of maternal and perinatal morbidity and mortality (American College of Obstetricians and Gynecologists Committee on Practice Bulletins—Obstetrics, 2002; World Health Organization, 2005; Confidential Enquiry into Maternal and Child Health Perinatal Mortality, 2008). Hypertension developing in the second half of pregnancy is subdivided according to the presence or absence of co-existing significant proteinuria into PE and gestational hypertension (GH). Recent evidence suggests that PE can be further subdivided into early PE and late PE with the former being associated with a higher incidence of fetal growth restriction and both short- and long-term maternal mortality and morbidity (Witlin et al., 2000; Irgens et al., 2003; Yu et al., 2008).

Pregnancy-associated plasma protein-A (PAPP-A) has been shown to be a syncytiotrophoblast-derived insulin-like growth factor binding protein protease (Bonomi et al., 1994; Lawrence et al., 1999). There is recent evidence that low first-trimester maternal serum PAPP-A in chromosomally normal pregnancies is associated with an increased risk for subsequent development of PE (Poon et al., 2008). Since insulin-like growth factor is believed to play a significant role in trophoblast invasion, it is not surprising that low-serum PAPP-A is associated with a higher incidence of PE (Irwin et al., 1999).

In the UK, the National Institute for Clinical Excellence (NICE) has issued guidelines on routine prenatal care recommending that at the booking visit a woman’s level of risk for PE, based on factors in her history, should be determined and the subsequent intensity of prenatal care should be based on this risk (RCOG Press, 2008). We have recently demonstrated that the NICE recommendations of screening for PE by maternal characteristics and previous history are potentially useful only when the various factors are incorporated into a combined algorithm derived by multivariate analysis (Poon et al., 2009a). Such an approach made it possible to derive the maternal factor-related a priori risk for early PE requiring delivery before 34 weeks, late PE, and GH based on maternal age, body mass index (BMI), racial origin, history of PE, chronic hypertension and method of conception. The estimated detection rates for early PE, late PE and GH are about 37, 30 and 20%, respectively, at a 5% false-positive rate (Poon et al., 2009a). We have also demonstrated that the combination of maternal factors with biophysical tests comprising mean arterial pressure (MAP) and uterine artery pulsatility index (PI) recorded from the artery with the lowest...
early screening for preeclampsia

PI (L-PI) further improved the detection rates of early PE, late PE and GH to 78, 42 and 36%, respectively, at a 5% false-positive rate (Poon et al., 2009b).

The aim of this study is to examine the performance of screening for hypertensive disorders in pregnancy by the addition of PAPP-A to a model combining maternal factors with biophysical tests at 11–13 weeks.

Methods

This was a prospective screening study for hypertensive disorders in women attending for their routine first hospital visit in pregnancy. In this visit, which is held at 11+0–13+6 weeks of gestation, all women have an ultrasound scan to confirm gestational age from the measurement of the fetal crown-rump length (CRL), to diagnose any major fetal abnormalities, to measure fetal nuchal translucency thickness and maternal serum free β-human chorionic gonadotropin (β-hCG) and PAPP-A as part of screening for chromosomal abnormalities (Snijders et al., 1998; Kagan et al., 2008). We recorded maternal characteristics and medical history, and measured the MAP and lowest uterine artery PI (L-PI) (Poon et al., 2009c,d). Written informed consent was obtained from the women agreeing to participate in the study, which was approved by King’s College Hospital Ethics Committee.

We prospectively examined 9149 singleton pregnancies between March 2006 and November 2007. We excluded 783 (8.6%) because they had missing outcome data (n = 443), there was a major fetal defect or aneuploidy (n = 153), the pregnancies resulted in fetal death or miscarriage before 24 weeks of gestation (n = 139), the pregnancies were terminated for social reasons (n = 15), or when there was at least one episode of hypertension but on the basis of the available data it was not possible to determine if the diagnosis was PE (n = 33). In the remaining 8366 cases, there were 165 (2.0%) that developed PE including 37 that required delivery before 34 weeks (early PE) and 128 with late PE, 140 with GH and 8061 (96.4%) cases that were unaffected by PE or GH.

The blood pressure was taken by automated devices (3BTO-A2, Microlife, Taipei, Taiwan), which were calibrated before and at regular intervals during the study. Recordings were made with the women in the seating position, and the MAP was measured as previously described (Poon et al., 2009d). The PI from both the uterine arteries was measured by transabdominal ultrasound as previously described and the lower PI of the two (L-PI) was used for analysis (Poon et al., 2009c).

Maternal serum PAPP-A was measured using the DELFIA XPRESS analyzer (PerkinElmer Life and Analytical Sciences, Waltham, USA). The variation of the DELFIA XPRESS PAPP-A assay was determined in 20 runs with two replicates using this DELFIA XPRESS system. The calibration curve of the first run was used

**Table 1**—Mean arterial pressure, lowest uterine artery pulsatility index (L-PI) and pregnancy-associated plasma protein-A (PAPP-A) in the four outcome groups

<table>
<thead>
<tr>
<th>Outcome Group</th>
<th>Mean arterial pressure, median (range)</th>
<th>Uterine artery L-PI, median (range)</th>
<th>PAPP-A, median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unaffected</td>
<td>1.00 (0.75–1.38) 84.3 (62.8–138.3)</td>
<td>1.00 (0.43–2.31) 1.40 (0.50–3.60)</td>
<td>1.00 (0.16–5.49) 2.82 (0.20–24.20)</td>
</tr>
<tr>
<td>Early preeclampsia</td>
<td>1.14 (0.94–1.38) 94.5 (80.5–118.0)</td>
<td>1.01 (0.70–2.07) 1.26 (0.95–3.07)</td>
<td>1.60 (0.50–2.70) 2.26 (0.92–3.46)</td>
</tr>
<tr>
<td>Late preeclampsia</td>
<td>1.09 (0.90–1.38) 92.8 (73.5–114.5)</td>
<td>1.00 (0.41–2.70) 1.68 (0.58–3.46)</td>
<td>0.90 (0.25–2.92) 2.63 (0.32–9.88)</td>
</tr>
<tr>
<td>Gestational hypertension</td>
<td>1.07 (0.87–1.31) 92.4 (74.0–116.2)</td>
<td>1.10 (0.40–2.24) 1.51 (0.54–3.88)</td>
<td>0.94 (0.21–3.23) 2.20 (0.24–16.48)</td>
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</table>

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DOI: 10.1002/pd
as a reference curve during the 14-day-period. The intra-assay and inter-assay variations were 1.2 and 2.1% at a PAPP-A concentration of 462 mU/L, 1.4 and 2.3% at 2124 mU/L and 1.3 and 2.5% at 5543 mU/L, respectively.

This study is part of a research programme on the early prediction of pregnancy complications. The data from some of the patients of the present study were published previously, but this is the first study examining the effect of combined screening with maternal risk factors, uterine artery L-PI, MAP and serum PAPP-A (Poon et al., 2008, 2009a,b,c,d).

**Outcome measures**

The definitions of PE and GH were those of the International Society for the Study of Hypertension in Pregnancy (Davey and MacGillivray, 1988). In GH the diastolic blood pressure should be 90 mm Hg or more on at least two occasions, at 4 h apart, developing after 20 weeks of gestation in previously normotensive women in the absence of significant proteinuria and in PE there should be GH with proteinuria of 300 mg or more in 24 h or two readings of at least ++ on dipstick analysis of midstream or catheter urine specimens if no 24-h collection is available. In PE superimposed on chronic hypertension significant proteinuria (as defined above) should develop after 20 weeks of gestation in women with known chronic hypertension (history of hypertension before conception or the presence of hypertension at the booking visit before 20 weeks of gestation in the absence of trophoblastic disease).

**Statistical analysis**

The measured MAP, uterine artery L-PI and PAPP-A were converted to multiples of the expected normal median (MoM) corrected for fetal CRL, maternal age, BMI or weight, smoking, parity, racial origin and method of conception as previously described (Kagan et al., 2008; Poon et al., 2009c,d). Comparison of MAP MoM, uterine artery L-PI MoM and PAPP-A MoM between each hypertensive disorder group and the unaffected group was analysed by ANOVA, with post-hoc Bonferroni correction. The risks for early PE, late PE and GH based on combinations of maternal factors, MAP and uterine artery L-PI.

The patient-specific risk for each hypertensive disorder is calculated from the formula: odds/(1 + odds), where odds = $e^y$. The $y$ is derived from logistic regression analysis of log PAPP-A MoM and log transformed a priori risks for early PE, late PE and GH based on combinations of maternal factors, MAP and uterine artery L-PI.

**Early preeclampsia**

Logistic regression analysis demonstrated that in the detection of early PE, there were significant contributions from PAPP-A and combinations of maternal factors, MAP and uterine artery L-PI.

The distribution of PAPP-A MoM in the unaffected, early PE and late PE groups is shown in Figure 1. The median MAP MoM was higher in early PE, late PE and GH than in the unaffected group ($p < 0.0001$), in early PE than in late PE ($p = 0.021$) and in early PE than in GH ($p = 0.001$). The uterine artery L-PI MoM was higher in early PE and late PE than in the unaffected group ($p < 0.0001$), in early PE than late PE ($p < 0.0001$), in early PE than in GH ($p < 0.0001$) and in late PE than in GH ($p = 0.031$). The PAPP-A MoM was significantly lower in early PE than in the unaffected group ($p = 0.001$) and in early PE than in GH ($p = 0.037$) (Table 1).

Pearson correlation between log$_{10}$ uterine artery L-PI MoM, log$_{10}$ MAP MoM and log$_{10}$ PAPP-A MoM in the unaffected controls, PE and GH groups are shown in Table 2.

The statistical software package SPSS 15.0 (SPSS Inc.,Chicago, IL) was used for all data analyses.
Table 2—Pearson correlation between log 10 uterine artery L-PI MoM, log 10 MAP MoM and log 10 PAPP-A MoM in the unaffected controls, preeclampsia (PE) and gestational hypertension (GH) groups

<table>
<thead>
<tr>
<th></th>
<th>Log 10 uterine artery L-PI MoM</th>
<th>Log 10 MAP MoM</th>
<th>Log 10 PAPP-A MoM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unaffected</td>
<td>PE</td>
<td>GH</td>
</tr>
<tr>
<td></td>
<td><strong>Pearson correlation</strong></td>
<td><strong>p</strong></td>
<td><strong>p</strong></td>
</tr>
<tr>
<td>Log 10 uterine artery L-PI MoM</td>
<td>1</td>
<td><strong>&lt; 0.0001</strong></td>
<td><strong>&lt; 0.0001</strong></td>
</tr>
<tr>
<td></td>
<td><strong>&lt; 0.0001</strong></td>
<td>1</td>
<td><strong>&lt; 0.0001</strong></td>
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<td></td>
<td><strong>&lt; 0.0001</strong></td>
<td><strong>&lt; 0.0001</strong></td>
<td><strong>&lt; 0.0001</strong></td>
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</table>

Logistical regression analysis demonstrated that there were significant contributions from PAPP-A and combinations of maternal factors and MAP in the detection of late PE. There was also prediction from the combination of maternal factors, uterine artery L-PI and MAP (Poon et al., 2009b) but this was not improved by the addition of PAPP-A.

Y = 0.273 + 2.469 × log_{10} maternal factor-derived *a priori* risk for late PE − 0.964 × log_{10} PAPP-A MoM; Nagelkerke $R^2 = 0.135$, $p < 0.0001$.

Y = 0.447 + 2.580 × log_{10} (risk for late PE based on maternal factor and MAP) − 0.941 × log_{10} PAPP-A MoM; Nagelkerke $R^2 = 0.207$, $p < 0.0001$.

Late preeclampsia

Logistic regression analysis demonstrated that there was no significant additional contribution from PAPP-A and combination of maternal factors, MAP and uterine artery L-PI in the prediction of GH (Poon et al., 2009b).

The areas under the ROC curves and detection rates of early PE, late PE and GH for different false-positive rates in screening by the combinations of maternal factor, MAP, uterine artery L-PI and PAPP-A are given in Table 3. The ROC curves for the prediction of early PE by combinations of maternal factor, MAP, uterine artery L-PI and PAPP-A are shown in Figure 2. The performance of screening for early PE, late PE and GH by risks generated by the specific prediction algorithm for early PE based on maternal factors, MAP, uterine artery L-PI and PAPP-A is given in Table 4.

Example

For example, in a Black woman in her first pregnancy, with no family history of PE, who is 28 years old, has a BMI of 20 kg/m², does not smoke and is at 12 weeks gestation (CRL 65 mm), a uterine artery L-PI of 1.6, her MAP is 85 mmHg, her PAPP-A is 1.0 MoM, the risks of developing early PE, late PE and GH are 0.20, 2.17 and 1.37%, respectively.
Table 3—Comparison of the performance of screening for preeclampsia and gestational hypertension by maternal risk factor, mean arterial pressure (MAP), lowest uterine artery pulsatility index (L-PI) and pregnancy-associated plasma protein-A (PAPP-A)

<table>
<thead>
<tr>
<th>Screening test</th>
<th>Early preeclampsia</th>
<th>Late preeclampsia</th>
<th>Gestational hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal risk factor</td>
<td>0.794 (0.720–0.869)</td>
<td>0.796 (0.761–0.830)</td>
<td>0.721 (0.677–0.765)</td>
</tr>
<tr>
<td>Maternal risk factor plus PAPP-A</td>
<td>0.870 (0.863–0.878)</td>
<td>0.804 (0.795–0.813)</td>
<td>—</td>
</tr>
<tr>
<td>MAP</td>
<td>0.898 (0.845–0.952)</td>
<td>0.854 (0.826–0.882)</td>
<td>0.782 (0.740–0.823)</td>
</tr>
<tr>
<td>Uterine artery L-PI</td>
<td>0.912 (0.863–0.962)</td>
<td>0.812 (0.777–0.847)</td>
<td>0.729 (0.686–0.771)</td>
</tr>
<tr>
<td>Uterine artery L-PI, PAPP-A</td>
<td>0.925 (0.919–0.930)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>MAP, PAPP-A</td>
<td>0.931 (0.925–0.936)</td>
<td>0.863 (0.855–0.870)</td>
<td>—</td>
</tr>
<tr>
<td>MAP, uterine artery L-PI</td>
<td>0.954 (0.919–0.989)</td>
<td>0.863 (0.855–0.870)</td>
<td>0.788 (0.779–0.797)</td>
</tr>
<tr>
<td>All markers</td>
<td>0.960 (0.956–0.964)</td>
<td>—</td>
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<table>
<thead>
<tr>
<th>Detection rate (%) for fixed false-positive rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
</tr>
<tr>
<td>Maternal risk factor</td>
</tr>
<tr>
<td>Maternal risk factor plus PAPP-A</td>
</tr>
<tr>
<td>MAP</td>
</tr>
<tr>
<td>Uterine artery L-PI</td>
</tr>
<tr>
<td>Uterine artery L-PI, PAPP-A</td>
</tr>
<tr>
<td>MAP, PAPP-A</td>
</tr>
<tr>
<td>MAP, uterine artery L-PI</td>
</tr>
<tr>
<td>All markers</td>
</tr>
</tbody>
</table>
with biophysical and biochemical tests (maternal factors with biophysical tests (-----) and maternal factors with biophysical and biochemical tests (-----))

The findings of this study have confirmed the results of several previous studies that low-maternal serum PAPP-A concentration at 11–13 weeks is associated with increased risk for subsequent development of PE (Ong et al., 2000; Smith et al., 2002; Yaron et al., 2002; Dugoff et al., 2004; Spencer et al., 2005, 2007; Pilalis et al., 2007). The results demonstrated that the levels of PAPP-A are substantially lower in those developing early PE rather than late PE.

DISCUSSION

Figure 2—Receiver operating characteristics curves for the prediction of early preeclampsia in screening by maternal factors only (-----) and maternal factors with biophysical tests (-----).

Table 4—Performance of screening for early preeclampsia (PE), late PE and gestational hypertension (GH) by risks generated by the specific prediction algorithm for early PE based on maternal factors, mean arterial pressure, lowest uterine artery pulsatility index and pregnancy-associated plasma protein-A concentration at 11–13 weeks is associated with increased risk for subsequent development of PE (Ong et al., 2000; Smith et al., 2002; Yaron et al., 2002; Dugoff et al., 2004; Spencer et al., 2005, 2007; Pilalis et al., 2007). The results demonstrated that the levels of PAPP-A are substantially lower in those developing early PE rather than late PE.
This study has demonstrated an approach for combining biophysical and biochemical parameters in the first-trimester of pregnancy to predict patient-specific risks for subsequent development of hypertensive disorders. The approach is similar to that used for combining maternal age with sonographic and maternal serum biochemical markers in early screening for chromosomal defects (Snijders et al., 1998; Kagan et al., 2008).

This screening study for hypertensive disorders examined more than 8000 pregnancies including more than 300 cases that developed PE or GH. We firstly applied the previously established prediction algorithms for PE and GH to determine the a priori risks based on maternal factors and biophysical markers, followed by the addition of the measurement of maternal serum PAPP-A to assess its additional value in predicting PE and GH. The risk for early PE was higher in Black than White women and in those with chronic hypertension or a history of PE in previous pregnancies. The risks for late PE and GH increased with maternal age and BMI and were higher for women with a family or prior history of PE. The biophysical components of the combined screening test are impedance to flow in the uterine arteries and MAP. Uterine artery L-PI was significantly increased in those who subsequently developed PE and this was particularly pronounced in those with early PE. In contrast, MAP was significantly increased in both who developed PE and in GH. The estimated detection rate of early PE, for a 5% false-positive rate, is increased from 37% in screening by maternal factors alone to 78% with combined screening by maternal factors and biophysical markers which is further improved to 84% with the addition of maternal serum PAPP-A. However, there is no significant contribution from serum PAPP-A in combination with maternal factors, MAP and uterine artery L-PI in the prediction of late PE and GH. The high detection rate for early PE is important because it is this rather than late PE or GH which is associated with increased risk of perinatal mortality and morbidity and both short- and long-term maternal complications (Withlin et al., 2000; Irgens et al., 2001; von Dadelszen et al., 2003; Yu et al., 2008).

We chose 11–13 weeks as the gestation for screening because this is emerging as the first hospital visit of pregnant women at which combined sonographic and biochemical testing for chromosomal and other major defects is carried out (Snijders et al., 1998; Kagan et al., 2008). At this visit, firstly, a record is made of maternal characteristics, such as age, racial origin, BMI, smoking status and medical and obstetric history. Secondly, an ultrasound scan is carried out to determine the number of fetuses, confirm the gestation from the fetal CRL, exclude major defects, measure the nuchal translucency thickness and other first-trimester markers of chromosomal defects. Thirdly, maternal blood is taken for measurement of free β-hCG and PAPP-A. Given that the measurement of maternal serum PAPP-A is readily available and it would be easy to measure the MAP and uterine artery PI of women in this same visit, the same methodology could then be utilised to calculate the patient-specific risk for both chromosomal defects and hypertensive disorders.

PE is the most common pregnancy complication associated with serious maternal-fetal morbidity and mortality; and at present the only effective treatment is delivery of the placenta. The ability to predict in very early pregnancy those women at risk for PE might decrease maternal and fetal morbidity through closer surveillance by physicians experienced or specialized in high-risk obstetrics, as well as delivery at tertiary care centers (Levine and Lindheimer, 2009). Centralized care of pregnancies at high risk for PE would also lead to a more effective concentration of research activity in an attempt to improve the understanding of the pathophysiology and treatment of the condition.

ACKNOWLEDGEMENTS

This study was supported by a grant from the Fetal Medicine Foundation (Charity No. 1037116).

REFERENCES


