CAN FIRST-TRIMESTER MATERNAL SERUM LEVEL OF PREGNANCY-ASSOCIATED PLASMA PROTEIN-A PREDICT SUBSEQUENT FETAL GROWTH RESTRICTION?

Mei-Leng Cheong, Bo-Quing She, Su-Chee Chen1, Fa-Kung Lee2, Ming-Song Tsai*

Prenatal Diagnosis Center, 1Department of Obstetrics and Gynecology, Cathay General Hospital, Taipei, and 2Department of Obstetrics and Gynecology, Cathay General Hospital Hsinchu Branch, Hsinchu, Taiwan.

SUMMARY

Objective: To evaluate whether the maternal serum level of pregnancy-associated plasma protein-A (PAPP-A) in the first trimester can predict pregnancy complicated by low birth weight (LBW) and fetal growth restriction (FGR).

Materials and Methods: This retrospective analysis enrolled 3,089 women with singleton pregnancy who underwent screening for Down syndrome in the first trimester of pregnancy and who delivered at Cathay General Hospital. They were divided into five groups according to the birth weight of their infants: three FGR groups of birth weight less than the 10th, 5th, and 3rd centiles, a LBW group of birth weight less than 2,500 g, and a control group of all other women.

Results: The mean multiples of median (MoM) values of PAPP-A were significantly lower in the LBW group (0.98) and the three FGR groups (< 10th centile, 1.03; < 5th centile, 0.96; and < 3rd centile, 0.99) than in the control group (1.15). Women with PAPP-A less than 0.3 MoM, 0.5 MoM or in the 5th centile (0.32 MoM) also had a significantly higher relative risk of pregnancy complicated by LBW and FGR, but the sensitivity of detection was low. The highest sensitivity using a cut-off at 0.5 MoM was 22.5%.

Conclusion: Our study demonstrated that a low maternal serum PAPP-A level in the first trimester is associated with pregnancy complicated by LBW and FGR, but the sensitivity was low. As a single marker, PAPP-A is not sufficient to predict LBW and FGR. [Taiwanese J Obstet Gynecol 2005;44(2):148-152]

Key Words: fetal growth restriction, low birth weight, pregnancy-associated plasma protein-A

Introduction

Low birth weight (LBW) and fetal growth restriction (FGR) are associated with increased perinatal morbidity and mortality [1], short-term and long-term childhood morbidity [2,3], and a range of cardiovascular and metabolic diseases in later life [4]. Whether we can predict LBW and FGR prenatally is controversial. Several maternal biochemical markers such as pregnancy-associated plasma protein-A (PAPP-A), human placental lactogen, and human chorionic gonadotropin (hCG) are reported to be related to birth weight and gestational age at delivery, but results were not conclusive [5,6]. PAPP-A is a protein derived from trophoblasts in early pregnancy. Since fetal growth is known to be correlated with placental function, there are some reports that low PAPP-A may be associated with pregnancy complicated by LBW and FGR [7,8], although this is controversial [9]. When PAPP-A is combined with maternal age, maternal serum free β-hCG, and fetal nuchal translucency (NT) thickness for prenatal screening of Down syndrome, the accuracy is greater than that of biochemical screening alone in the second trimester. It is reported that the detection rate for Down syndrome is 89% at a 5% false-positive rate [10]. Currently, this test is quite popular in our hospital. The aim of this study...
was to investigate whether maternal serum PAPP-A level in the first trimester can predict LBW and FGR.

Materials and Methods

Sample collection
Between April 1999 and December 2003, we collected data from all non-smoking women with a singleton pregnancy who underwent screening for Down syndrome in the first trimester and who subsequently delivered at the Cathay General Hospital, Taipei. We excluded pregnancies in which any of the following was present: incomplete or incorrect chart record (35 cases), chromosomal abnormalities (9 cases), major structural abnormalities (15 cases), abortion at less than 24 weeks’ gestation (23 cases), and major maternal disease (18 cases). A total of 3,089 pregnancies were enrolled into the study.

First-trimester Down syndrome screening
Screening for Down syndrome at 10–13 weeks of gestation was offered to pregnant women who came to Cathay General Hospital for prenatal care after April 1999. Fetal NT thickness and crown–rump length (CRL) were measured by one of three experienced sonographers. Fetal NT thickness was measured when CRL was between 36 and 76 mm, equivalent to a gestational age of 10 weeks 4 days to 13 weeks 6 days. The procedure followed the criteria published by the UK Fetal Medicine Foundation [11]. Because the discrepancy in gestational age calculated from last menstrual period (LMP) and CRL was quite large in some pregnancies, we converted the CRL to equivalent days of gestational age to define the percentile of birth weight. The equation used, which has been well established in our hospital from women with date discrepancy between LMP and CRL of less than 1 week, is: Predicted gestational age in days = 54.62334 + 0.55155 CRL (mm)

Maternal serum PAPP-A level was determined on the same day as fetal NT measurement, using a microtiter-plate enzyme-linked immunosorbent assay according to the manufacturer’s protocol (Genemed Biotechnologies Inc, South San Francisco, CA, USA). Maternal serum PAPP-A levels are presented as multiples of median (MoM).

Data analysis
After correction of gestational age using the equation above, we divided our study population into the following groups: three FGR groups defined as women with a live born baby below the 10th, 5th, or 3rd centile, respectively, of birth weight at the gestational week of delivery; a LBW group defined as those with infants of birth weight less than 2,500 g; and a control group of all other women.

Statistical analysis
The Chi-squared test and t test were used to compare PAPP-A between subgroups and controls. Multivariate logistic regression models were built to explore the relationship among different variables. Receiver operating characteristic (ROC) curves were drawn to determine the cut-off MoM values for PAPP-A. A p value of less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 11.5 (SPSS Inc, Chicago, IL, USA).

Results
In this study, the mean maternal age was 29.8 years (range, 17–43 years) and 52.1% of women were primigravidae. The mean maternal serum PAPP-A level was significantly lower in the FGR groups (< 10th, 5th, or 3rd centile, respectively), of the LBW group (0.98 MoM, p = 0.002) than in the control group (1.15 MoM) (Table 1).

Table 1. Comparisons of first-trimester maternal serum levels of pregnancy-associated plasma protein-A (PAPP-A) in groups with a low birth weight infant or fetal growth restriction and normal controls

<table>
<thead>
<tr>
<th>Birth weight</th>
<th>n</th>
<th>PAPP-A (MoM)</th>
<th>Median</th>
<th>Mean ± SD</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>2,773</td>
<td>1.04</td>
<td>1.15 ± 0.65</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>&lt; 2,500 g</td>
<td>48</td>
<td>0.93</td>
<td>0.98 ± 0.56</td>
<td>3.03</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>&lt; 3rd centile</td>
<td>92</td>
<td>0.90</td>
<td>0.99 ± 0.60</td>
<td>2.18</td>
<td>0.029</td>
<td></td>
</tr>
<tr>
<td>&lt; 5th centile</td>
<td>155</td>
<td>0.85</td>
<td>0.96 ± 0.57</td>
<td>3.56</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>&lt; 10th centile</td>
<td>312</td>
<td>0.91</td>
<td>1.03 ± 0.59</td>
<td>3.35</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

SD = standard deviation; MoM = multiples of median; t = t test value.
In the ROC curve analyses, we could not determine an adequate cut-off value for FGR prediction (Figure), so we selected 0.3 MoM, 0.5 MoM, and the 5th centile (0.32 MoM) of PAPP-A as cut-offs to calculate the relative risks of pregnancy complicated by FGR. Women with PAPP-A of less than 0.3 MoM or 0.5 MoM had a higher risk of LBW (OR 2.8, \(p < 0.001\), and OR 2.0, \(p = 0.001\)), less than 3rd centile FGR (OR 2.9, \(p < 0.008\), and OR 1.9, \(p = 0.027\)), and less than 5th centile FGR (OR 2.5, \(p = 0.005\), and OR 1.8, \(p = 0.007\)) than the control group. Likewise, women with a PAPP-A of less than the 5th centile also had a higher risk of LBW (OR 2.0, \(p = 0.028\)), less than 3rd centile FGR (OR 2.3, \(p = 0.037\)) and less than 5th centile FGR (OR 2.0, \(p = 0.021\)) than the control group (Table 2). This pattern was not seen in the 10th centile FGR group. The sensitivities of detecting pregnancy complicated by LBW and FGR using 0.3 MoM, 0.5 MoM and the 5th centile of PAPP-A as cut-offs were up to 10.1%, 22.5%, and 10.1%, respectively (Table 3).

**Table 2.** Relative risks of low birth weight and fetal growth restriction at cut-offs for pregnancy-associated plasma protein-A (PAPP-A) of 0.3 multiples of median (MoM), 0.5 MoM, and the 5th centile

<table>
<thead>
<tr>
<th>Birth weight</th>
<th>PAPP-A cut-off</th>
<th>OR</th>
<th>95% CI</th>
<th>(p)</th>
<th>OR</th>
<th>95% CI</th>
<th>(p)</th>
<th>OR</th>
<th>95% CI</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.3 MoM</td>
<td></td>
<td></td>
<td></td>
<td>0.5 MoM</td>
<td></td>
<td></td>
<td>5th centile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 2,500 g</td>
<td>2.8</td>
<td>1.5–4.9</td>
<td>&lt; 0.001</td>
<td></td>
<td>2.0</td>
<td>1.3–3.0</td>
<td>0.001</td>
<td>2.0</td>
<td>1.1–3.6</td>
<td>0.028</td>
</tr>
<tr>
<td>&lt; 3rd centile</td>
<td>2.9</td>
<td>1.4–5.8</td>
<td>0.008</td>
<td></td>
<td>1.9</td>
<td>1.1–3.1</td>
<td>0.027</td>
<td>2.3</td>
<td>1.1–4.7</td>
<td>0.037</td>
</tr>
<tr>
<td>&lt; 5th centile</td>
<td>2.5</td>
<td>1.4–4.5</td>
<td>0.005</td>
<td></td>
<td>1.8</td>
<td>1.2–2.6</td>
<td>0.007</td>
<td>2.0</td>
<td>1.1–3.6</td>
<td>0.021</td>
</tr>
<tr>
<td>&lt; 10th centile</td>
<td>1.2</td>
<td>0.7–2.2</td>
<td>0.446</td>
<td></td>
<td>1.2</td>
<td>0.9–1.7</td>
<td>0.197</td>
<td>1.1</td>
<td>0.6–1.8</td>
<td>0.822</td>
</tr>
</tbody>
</table>

**OR** = odds ratio; **CI** = confidence interval.
Discussion

We demonstrated that low first trimester maternal serum PAPP-A level was significantly correlated with LBW and FGR. PAPP-A is a maternal serum protein originally isolated in 1974 by Lin et al [12]. It is derived from syncytiotrophoblasts [13] and acts as a protease for binding proteins of insulin-like growth factor (IGFBP-4) [14]. Since it breaks down IGFBP, resulting in elevation of free IGFs, low PAPP-A level indicates low IGF level and, therefore, affects birth weight [14,15]. Maternal PAPP-A level is high in multiple pregnancies, primigravida pregnancies [16], and intrauterine insemination pregnancies [17]. A low PAPP-A level reportedly correlates with smoking [18], abnormal fetal karyotype [19], early pregnancy failure [5,8,20,21], intrauterine fetal death [5,7], LBW [8,18,22], FGR [5,7,23,24], preterm labor [7], and pre-eclampsia [5,25]. However, Morssink et al reported that the concentration of PAPP-A in the first trimester is not associated with subsequent 5th centile FGR compared with controls (0.83 MoM vs 0.98 MoM, \( p = 0.08 \)) [9]. In addition, there is a positive correlation between PAPP-A level and placental weight [6,20].

Yaron et al reported that the relative risks of 5th centile FGR at PAPP-A cut-offs of 0.25 MoM and 0.5 MoM are 3.12 and 3.3, respectively [23]. Similarly, Smith et al reported that the relative risk of 5th centile FGR at a PAPP-A cut-off of the 5th centile is 2.9 [7]. The relative risks of FGR from these two reports were similar but higher than those of this study (2.5, 1.8, and 2.0 at PAPP-A cut-offs of 0.3 MoM, 0.5 MoM, and the 5th centile, respectively).

Although our study showed that a low level of PAPP-A was associated with a higher relative risk of LBW and FGR, the sensitivities according to the cut-offs were quite low. At a PAPP-A cut-off of 0.5 MoM, the sensitivities of detecting subsequent LBW and FGR were between 16.2% and 22.5%, and the specificities were around 86%. However, when the PAPP-A cut-off was 0.3 MoM or the 5th centile, the highest sensitivity of detecting LBW and FGR was only 10.1% with a specificity of around 96%. Our results were consistent with the recent report of Kwik and Morris, in which the sensitivity of detecting 3rd centile and 10th centile FGR were 7.7% and 10.9%, respectively, for a 0.3 MoM cut-off and 23.1% and 32.7% for a 0.5 MoM cut-off [16]. For this reason, the maternal serum PAPP-A level was not sufficient to be a single marker to predict LBW and FGR. Among the cut-offs, 0.5 MoM of PAPP-A seemed to be better at predicting pregnancies complicated by birth weight less than the 5th centile or 2,500 g.

In conclusion, we demonstrated that low maternal serum PAPP-A level in the first trimester was associated with pregnancy complicated by LBW and FGR, but the sensitivity was low. As a single marker, PAPP-A is not sufficient to predict LBW and FGR.

Table 3. Sensitivity and specificity of low birth weight and fetal growth restriction at cut-offs for pregnancy-associated plasma-protein-A (PAPP-A) of 0.3 multiples of median (MoM), 0.5 MoM, and the 5th centile

<table>
<thead>
<tr>
<th>Birth weight</th>
<th>0.3 MoM</th>
<th>0.5 MoM</th>
<th>5th centile</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
<td>Sensitivity</td>
</tr>
<tr>
<td>&lt; 2,500 g (%)</td>
<td>8.9</td>
<td>93.4</td>
<td>22.3</td>
</tr>
<tr>
<td>&lt; 3rd centile (%)</td>
<td>10.1</td>
<td>96.2</td>
<td>22.5</td>
</tr>
<tr>
<td>&lt; 5th centile (%)</td>
<td>8.8</td>
<td>96.3</td>
<td>21.4</td>
</tr>
<tr>
<td>&lt; 10th centile (%)</td>
<td>4.8</td>
<td>96.1</td>
<td>16.2</td>
</tr>
</tbody>
</table>

References

7. Smith GCS, Stenhouse EJ, Crossley JA, Aitken DA, Cameron AD, Connor JM. Early pregnancy levels of pregnancy-associated plasma protein A and the risk of intrauterine...


